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Hyperostosis frontalis interna and association of disease control with frontal bone thickness in acromegaly

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Abstract

Purpose Studies investigating hyperostosis frontalis interna (HFI) in acromegaly are limited. We aimed to investigate HFI and the association of disease control with frontal bone thickness (FBT) in acromegaly.

Methods Adult patients with acromegaly were grouped according to the presence of HFI on the baseline MRI: Group 1 absent, Group 2 present. We measured FBT, parietal bone thickness (PBT) and occipital bone thickness (OBT) in the mid-sagittal plane on MRI. The changes between first and last measurements were analyzed. We grouped the patients as controlled vs. uncontrolled acromegaly, and as established disease control for at least 5-year vs. 1-5-years.

Results Group 1/Group 2 comprised of 23/29 patients, female/male ratio was 34/18, and mean age 55.41(± 14.21) years. Median follow-up duration was 108 months (6-408). FBT^{first} ($p=0.001$), FBT^{last} ($p<0.001$), PBT^{last} ($p=0.025$), and OBT^{last} ($p=0.028$) were higher in Group 2 than in Group 1. FBT^{change}, PBT^{change}, and OBT^{change} were positive in Group 2 ($p<0.001$, $p=0.008$, and $p=0.008$; respectively). The ratio of patients with FBT(increased) was higher in Group 2 than in Group 1 ($p=0.001$). FBT^{first}, FBT^{last}, PBT^{first}, PBT^{last}, OBT^{first}, OBT^{last}, FBT^{change}, PBT^{change} and OBT^{change} were similar in controlled or uncontrolled acromegaly groups. FBT^{change} and OBT^{change} were positive in patients with disease control established for at least 5 years ($n=30$) ($p=0.027$ and $p=0.002$, respectively).

Conclusion HFI was common in patients with acromegaly. HFI is associated with a continuous increase in FBT, PBT and OBT. HFI, bone thickness, or increase in bone thickness seems independent of disease activity. Since headaches can be related to an increase in bone thickness, patients should be evaluated and graded during baseline imaging.

Keywords Acromegaly, Hyperostosis, Hyperostosis frontalis Interna, Bone, Frontal bone

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Introduction

Acromegaly is usually caused by a pituitary tumor producing growth hormone (GH), which secondarily leads to a high level of insulin-like growth factor 1 (IGF-1) [1, 2]. In addition to the classical physical features associated with acromegaly, excess GH and IGF-1 can lead to rapid changes in bone structure, including increased bone turnover and loss, with a greater impact on vertebral bones, which may lead to an increased risk of vertebral fractures [3, 4].

Hyperostosis frontalis interna (HFI) is characterized by irregular thickening of the endocranial part of the frontal bone and usually asymptomatic incidental finding detected by cranial imaging performed for another reason [5]. Although the pathogenesis of HFI has not been fully elucidated, it has been suggested that obesity, virilism, diabetes mellitus, toxic goiter, prolonged estrogen stimulation, menopause, hypogonadism, neurological and mental disorders might be associated with the development of HFI [6, 7, 8, 9]. It may be a part of Morgagni-Stewart-Morel or Troell-Junet syndrome [6, 7].

Studies investigating the association of HFI with acromegaly are limited in the literature. In one study, the frequency of HFI was found to be higher in patients with acromegaly than in controls [10]. The frontal bone thickness was also higher in acromegaly [10]. Similar findings were reported also in another study [11]. HFI was presented as an incidental finding on magnetic resonance imaging (MRI) in an old female patient with acromegaly [12]. In our study, we aimed to investigate the frequency of HFI, and the association of disease control with frontal bone thickness in patients with acromegaly.

Materials and methods

Study population

Adult patients with acromegaly who were admitted to our clinics between January 2010 and December 2022 were included in this study. This observational, retrospective cohort study was approved by the Clinical Researches Ethics Committee of Zonguldak Bülent Ecevit University Medical Faculty (Approval number:2023/01), and was performed in accordance with the ethical standards specified in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants.

Adult patients who were diagnosed with acromegaly were included in the study. Those for whom data were lacking were excluded from the study. Patients with any disease involving the cranial bones, such as metabolic or neoplastic bone diseases, were not included in the study. Patients with a history of cranial surgery, except for transsphenoidal pituitary surgery, or major cranial trauma were also excluded from the study.

Data collection

Demographic (age, age at diagnosis of acromegaly, sex), clinical (duration of follow-up, previous history of type 2 diabetes, hypothyroidism or hypogonadism, treatment modality [medical vs. surgical and medical]), laboratory (serum insulin-like growth factor 1 [IGF-1], fasting plasma glucose [FPG], growth hormone [GH], prolactin, cortisol, and HbA1c) and cranial MRI findings (size of pituitary adenoma at the diagnosis [microadenoma vs. macroadenoma], frontal, parietal and occipital bone evaluation, HFI) were recorded from the written and electronic files.

Diagnosis of acromegaly

The diagnosis of acromegaly was based on phenotypic characteristics, excessive GH secretion with elevated serum IGF-1 levels, the absence of suppression of GH to <1.0 μg/L after documented hyperglycemia maintained by oral glucose load, and the presence of pituitary adenoma on MRI, as described in the previous guideline [13].

Laboratory evaluation

In the previous acromegaly guideline, biochemical target goal for acromegaly was reported as an age-normalized serum IGF-1 value, which indicates control of acromegaly [13]. We grouped the patients according to the IGF-1 level measured at the follow-up as follows: controlled acromegaly, if the IGF-1 level was within the specific reference range for at least the previous year; uncontrolled acromegaly, if the IGF-1s level measured in the previous year were above the specific reference range. We also grouped the patients with controlled acromegaly as follows: established disease control for at least 5-year vs. disease control for 1-5-years.

Blood samples were obtained from the patients at 08.00 AM after an overnight fasting for at least 8 h. GH and IGF-1 levels were measured by an automated two-site, solid-phase enzyme-linked chemiluminescent immunoassay on an Immulite 2000 system (IMMULITE 2000; Siemens Medical Diagnostics, Germany). The measurement of IGF-1 at the last follow-up was labeled as "last", and the measurement at the time of acromegaly diagnosis was labeled "first". We analyzed FPG, GH, prolactin, cortisol, and HbA1c levels measured at the last follow-up. FPG was measured by an enzymatic method via an ADVIA 2400 automated autoanalyzer (Bayer Diagnostics, Tarrytown, NY, USA). HbA1c was measured in National Glycohemoglobin Standardization Program (NGSP) units by high-performance liquid chromatography. Serum PRL and cortisol levels were measured by chemiluminescence using a Dxl 800 system (Beckman Coulter, Inc., Fullerton, CA, USA).

Radiological evaluation

All patients underwent MRI at the time of diagnosis and during the follow-up period. MRI images obtained at the time of diagnosis and at the last follow-up were examined.

HFI was evaluated based on MRI performed at the time of acromegaly diagnosis. The last MRI was also evaluated for the presence or type of HFI. The diagnosis and classification of HFI was based on the studies of Hershkovitz et al. [5, 14]. According to these studies, the extent of involvement, appearance, border type, shape, and location of nodular growth on the endocrinal surface of the frontal bone were examined and classified as follows: patients with single or multiple, unilateral or bilateral isolated elevated bony island(s), which were generally < 10 mm in size and commonly found on the anteromedial aspect of the frontal bone, were classified as type A; those with nodular bony overgrowths, without discrete margins and with only slight elevation identified on less than 25% of the frontal bone classified as type B; those with more extensive nodular bony overgrowth, associated with irregular thickening of up to 50% of the frontal endocranial surface classified as type C; and those with continuous bony overgrowth, involving more than 50% of the frontal endocranial surface, or the entire region with irregular elevation with sharp, clearly demarcated borders, were classified as type D.

Frontal, parietal and occipital bone thicknesses were measured in the mid-sagittal plane of MRI. Frontal bone thickness was measured at the end point of the frontal sinus on the frontal bone and was recorded as frontal bone thickness (FBT). Parietal bone thickness (PBT) was measured at the mid-point of union of right and left parietal bones. Occipital bone thickness (OBT) was measured at the point just above the external occipital protuberance. Bone thickness was measured based on MRI both at the time of diagnosis and at the time of last follow-up. Measurements of bone thickness at the last follow-up were labeled as "last", and the measurements at the diagnosis of acromegaly were labeled as "first". The changes between first and last measurements were defined as: "change=(last measurement)-(first measurement)".

Patient groups

Patients were divided into two main groups on the basis of the presence of HFI on the baseline MRI performed at the time of diagnosis. Group 1 was defined as the absence of HFI, and Group 2 was defined as the presence of HFI.

Statistical analysis

For the data analysis, SPSS software (ver. 26.0; IBM Corporation, Armonk, NY, USA) was used. The Shapiro-Wilk test was used to assess the normality of the data. When two independent groups were compared in terms of quantitative measures, independent samples t tests for parametric tests and Mann–Whitney U tests for nonparametric tests were used. Pearson's Chi-square tests were used to compare categorical variables. Wilcoxon signed rank test was used to assess the change in frontal, parietal and occipital bone thicknesses between the first and last measurements. Quantitative variables are reported as the median (minimum-maximum) and X(± Standard deviation) in the tables. Categorical variables are reported as numbers (n) and percentages (%), and p-values < 0.05 were taken to indicate statistical significance.

Results

A total of 52 patients were included, female/male ratio was 34/18. The mean age was 55.41(± 14.21) years. Median duration of follow-up was 108 months (6-408). Group 2 comprised of 29 (55.8%) patients. FBT^{first} ($p = 0.001$), FBT^{last} ($p < 0.001$), PBT^{last} ($p = 0.025$), and OBT^{last} ($p = 0.028$) were higher in Group 2 than in Group 1 (Table 1). Most frequent HFI Type was Type A ($n = 15$, 51.7%) (Table 2). The ratio of presence of HFI did not change throughout the course of the disease. All patients with HFI at the time of acromegaly diagnosis had the same type of HFI at the last follow-up. HFI was not detected at the last follow-up in any of the patients without HFI at the time of acromegaly diagnosis (data not shown in the tables).

FBT^{first}, FBT^{last}, PBT^{first}, PBT^{last}, OBT^{first} and OBT^{last} were similar in controlled or uncontrolled acromegaly groups (Table 3). FBT^{change}, PBT^{change}, and OBT^{change} were significantly positive in Group 2 ($p < 0.001$, $p = 0.008$, and $p = 0.008$; respectively), but not significant in Group 1. FBT^{change}, PBT^{change}, and OBT^{change} were similar in controlled and uncontrolled acromegaly groups (Table 4).

FBT^{change} and OBT^{change} were significantly positive in patients with disease control established for at least 5 years ($n = 30$) ($p = 0.027$ and $p = 0.002$, respectively) (Table 5). FBT increased more frequently in Group 2 than in Group 1 ($p = 0.001$) (Table 6).

Discussion

We found that HFI was present in more than half of the patients with acromegaly. Frontal, parietal, and occipital bone thickness significantly increased during the follow-up period in the HFI group. Disease control was not associated with HFI, bone thickness, or increased bone thickness.

The frequency and severity of HFI have been shown to be associated with an increased age [15, 16]. We found that HFI was present in more than half of the patients with acromegaly. The frequency of HFI in our study was higher than that reported in the general population but seems to be similar to that reported in previous acromegaly studies [5, 11]. However, in a recently published

Table 1 Comparison of numerical variables according to the presence of HFI

Numerical Variable	Group 1 (*n* = 23) HFI absent	Group 2 (*n* = 29) HFI present	Total (*n* = 52)	*p*
	Median (min.-max.)			
Age (year)	56 (30–83)	59 (24–82)	58 (24–83)	0.412
Age at diagnosis (year)	44 (24–75)	44 (21–74)	44 (21–75)	0.775
Duration of follow-up (month)	96 (12–252)	120 (6-408)	108 (6-408)	0.184
	X (± SD)			p
FBT^{first}(mm)	7.30 (1.80)	10.04 (3.10)	8.82 (2.93)	**0.001**
FBT^{last}(mm)	7.21 (1.64)	11.17 (3.13)	9.42 (3.24)	**< 0.001**
PBT^{first}(mm)	6.09 (1.81)	6.78 (1.84)	6.48 (1.84)	0.128
PBT^{last}(mm)	6.33 (1.68)	7.57 (2.29)	7.02 (2.11)	**0.025**
OBT^{first}(mm)	5.86 (1.64)	6.77 (2.16)	6.37 (1.98)	0.092
OBT^{last}(mm)	6.06 (1.34)	7.33 (2.26)	6.77 (2.00)	**0.028**
FPG (mg/dL)	112.78 (21.21)	122.68 (44.26)	118.30 (35.97)	0.978
HbA1c (%)	6.14 (0.77)	6.39 (1.54)	6.28 (1.26)	0.832
IGF-1^{first}(ng/mL)	476.73 (215.89)	580.51 (296.67)	534.61 (266.72)	0.281
IGF-1^{last}(ng/mL)	186.63 (82.07)	207.30 (98.87)	198.16 (91.60)	0.549
GH (ng/mL)	1.21 (1.25)	1.45 (2.07)	1.35 (1.75)	0.652
Prolactin (ng/mL)	8.18 (7.34)	8.88 (7.78)	8.57 (7.52)	0.541
Cortisol (µg/dL)	9.43 (5.47)	9.80 (5.78)	9.64 (5.59)	0.768

HFI: hyperostosis frontalis interna FBT: Frontal bone thickness PBT: Parietal bone thickness OBT: Occipital bone thickness FPG: Fasting plasma glucose IGF-1: Insulin-like growth factor 1 GH: Growth hormone

Table 2 Comparison of categorical variables according to the presence of HFI

Categorical Variable	Group 1 (*n* = 23) HFI absent	Group 2 (*n* = 29) HFI present	Total (*n* = 52)	*p*
	n(%)			
Sex (female)	16(69.6)	18(62.1)	34(65.4)	0.571
HFI Type				
A	N/A	15(51.7)	N/A	N/A
B		6(20.7)		
C		6(20.7)		
D		2(6.9)		
T2D (absent/present)	14(60.9)/9(39.1)	13(44.8)/16(55.2)	27(51.9)/25(48.1)	0.249
Hypothyroidism (absent/present)	16(69.6)/7(30.4)	18(62.1)/11(37.9)	34(65.4)/18(34.6)	0.571
Hypogonadism (absent/present)	11(47.8)/12(52.2)	18(62.1)/11(37.9)	29(55.8)/23(44.2)	0.304
Treatment Modality				
Medical	4(17.4)	3(10.3)	7(13.5)	0.461
Both surgical and medical	19(82.6)	26(89.7)	45(86.5)	
Microadenoma/Macroadenoma	1(4.3)/22(95.7)	4(13.8)/25(86.2)	5(9.6)/47(90.4)	0.233
Disease Control				
Controlled	17(73.9)	19(65.5)	36(69.2)	0.513
Uncontrolled	6(26.1)	10(34.5)	16(30.8)	

HFI: hyperostosis frontalis interna T2D: Type 2 Diabetes mellitus 1 N/A: Not applicable

report, HFI was found at a frequency of 22% in patients with acromegaly [10]. They reported that the age at diagnosis of acromegaly was greater in patients with HFI than in those without HFI. It might be a confounding factor, based on the previous studies suggesting the association of age with the occurrence of HFI [15, 16]. We showed that the mean age at diagnosis was over 40 years and was similar in acromegaly patients with or without HFI in the present study. Additionally, we found that more than half of the acromegaly patients with HFI were female, which is consistent with the findings of previous studies [5, 10]. In previous studies, the frequency of HFI was shown to be 11.8% in women aged of 20–29, and 44.2% in those > 80-year-old [14, 17]. 90% of acromegaly patients with HFI were female according to a recent report [10]. However, we found no differences in the ratio of female sex between patients with HFI and those without HFI.

Table 3 Comparison of bone measurements according to disease control for at least last-year

	Controlled (*n* = 36)	Uncontrolled (*n* = 16)	*p*
	X (± SD)		
FBT^{first}	8.33 (2.47)	9.94 (3.61)	0.171
FBT^{last}	8.84 (2.68)	10.71 (4.04)	0.142
PBT^{first}	6.37 (1.82)	6.71 (1.92)	0.445
PBT^{last}	6.70 (2.10)	7.76 (2.03)	0.071
OBT^{first}	6.09 (1.85)	7.00 (2.18)	0.194
OBT^{last}	6.60 (1.76)	7.17 (2.46)	0.545

FBT: Frontal bone thickness PBT: Parietal bone thickness OBT: Occipital bone thickness

We found that the predominant type of HFI was type A in patients with acromegaly. HFI typing was based on the extension of nodular bony growth on the endocranial surface [14]. In previous studies investigating HFI, type A HFI was also the most common type of HFI both in patients with acromegaly and in the general population [10, 14, 18]. Indeed, type A, as the mildest form of HFI, may already be expected to be the most frequent type in the general population. On the basis of the present and previous studies, acromegaly does not seem to affect the proportion of types of HFI compared with the general population [10, 14]. A positive effect of IGF-1 on bone metabolism has been revealed in previous studies [19, 20]. It was shown that bone turnover was accelerated, and bone formation and resorption markers were increased in acromegaly [21]. The frequency of vertebral fractures was shown to increase in acromegaly, but bone turnover markers were not shown to be significant predictors of vertebral fractures [21, 22]. These studies may suggest that acromegaly leads to a decrease in bone quality in addition to bone density [21, 22]. HFI is associated with the formation of cancellous bone. We can argue that acromegaly might be associated with the occurrence of HFI, but the effect of acromegaly on bone metabolism seems not to increase the severity of HFI compared with that of HFI in the general population or associated with other causative factors [5, 10, 14]. The possible factors more directly associated with the extension of the HFI should be elucidated in future studies.

Acromegaly results in the enlargement of long bone ends and facial bones. This growth is often associated with periosteal bone deposition, and bone quality may differ from normal, as increased density is frequently accompanied by irregular mineralization. The skull and facial bones have distinct embryological origins; most cranial bones develop through intramembranous ossification derived from the neuroectoderm, whereas facial

Table 5 Changes in bone thickness measurements in patients with established disease control for at least 5 years

	Established disease control for at least 5 years (*n* = 30)	
	Median (min.-max.)	*p* value
FBT^{change}	0.6 (-1.80–3.0)	**0.027**
PBT^{change}	0.35 (-3.0–3.3)	0.198
OBT^{change}	0.65 (-2.90–3.50)	**0.002**

FBT: Frontal bone thickness PBT: Parietal bone thickness OBT: Occipital bone thickness

Table 6 Changes in bone thickness measurements according to duration of disease control and presence of HFI

	FBT (increased)	PBT (increased)	OBT (increased)
Disease Control	***n* (%)**		
Controlled for > 5-year (***n* = 30**)	20 (66.7)	20 (66.7)	22 (73.3)
Controlled for < 5-year (***n* = 6**)	4 (66.7)	4 (66.7)	1 (16.7)
Uncontrolled (***n* = 16**)	11 (68.8)	12 (75)	10 (62.5)
p value	0.989	0.835	**0.031**
HFI	**n (%)**		
Group 1 (HFI absent) (*n* = **23**)	10 (43.5)	14 (60.9)	13 (56.5)
Group 2 (HFI present) (*n* = **29**)	25 (86.2)	22 (75.9)	20 (69)
p value	**0.001**	0.245	0.355

HFI: hyperostosis frontalis interna FBT: Frontal bone thickness PBT: Parietal bone thickness OBT: Occipital bone thickness

Table 4 Comparison of changes in bone measurements according to presence of HFI and disease control for at least last-year

	Group 1 HFI absent (*n* = 23)	Group 2 HFI present (*n* = 29)	pDifference (Group1-2)	Controlled (*n* = 36)	Uncontrolled (*n* = 16)	pDifference (Controlled-Uncontrolled)	Total (*n* = 52)
	Median(min.-max.)/ *p* value			Median(min.-max.)/ *p* value			Median(min.-max.)/ *p* value
FBT^{change}	-0.10(-1.80–1.80)/ 0.637	1.10(-1.50–3.10)/**<0.001**	**< 0.001**	0.50(-1.80–3.00)/**0.012**	0.70(-0.90–3.10)/**0.031**	0.648	0.50(-1.80–3.10)/**0.001**
PBT^{change}	0.30(-2.30–3.3)/0.115	1.00(-3.00 - 3.20)/**0.008**	**0.039**	0.35(-3.00–3.30)/0.125	1.05(-0.80–3.20)/**0.003**	0.083	0.50(-3.00–3.30)/**0.003**
OBT^{change}	0.20(-2.90–2.20)/0.338	0.50(-1.40–3.50)/**0.008**	0.310	0.55(-2.90–3.50)/**0.007**	0.25(-1.40–1.70)/0.438	0.279	0.45(-2.90–3.50)/**0.008**

HFI: hyperostosis frontalis interna FBT: Frontal bone thickness PBT: Parietal bone thickness OBT: Occipital bone thickness

bones predominantly originate from neural crest cells [23, 24]. These embryological differences may explain the growth patterns and degrees of involvement in acromegaly. For instance, while periosteal reactions are observed in both conditions, pachydermoperiostosis is a genetic disorder characterized primarily by skin and soft tissue thickening, usually without any associated hormonal abnormalities. These distinctions play a critical role in understanding the impact of embryological origin and pathophysiological mechanisms on bone growth [25]. Another disease affecting bone growth is conditions such as McCune-Albright syndrome. The primary difference from the mechanism in acromegaly lies in the pathogenesis. In acromegaly, excessive stimulation of periosteal growth leads to the widening of long bones and soft tissue enlargement, even after the closure of the epiphyseal plate [26]. In contrast, McCune-Albright Syndrome (MAS) results from a mosaic activating mutation in the GNAS gene, leading to continuous activation of the cAMP pathway and the formation of fibrous dysplasia in bones. This results in weak, irregular fibrous tissue replacing normal bone. Growth in acromegaly is generally homogeneous and hormone dysfunction-driven, whereas in MAS, growth is asymmetrical and localized, caused by a genetic mutation. Although pathological bone growth is observed in both conditions, their mechanisms operate through distinct biological pathways [27]. Furthermore, patients with MAS were excluded from this study due to the absence of café-au-lait spots, commonly associated with McCune-Albright disease, in our patient group.

Coexistence of hypogonadism or adrenal insufficiency or over- or undertreatment with glucocorticoids also has a substantial effect on the interaction between acromegaly and bone metabolism [21, 28]. Testicular atrophy and a decrease in androgen stimulation with age in men and menopause have been suggested to be associated with HFI [5, 18]. We detected no association between hypogonadism and the presence of HFI in the present study. In HFI group, we observed an increase in bone thickness during the follow-up. The process occurred in acromegaly patients with HFI might lead to an increase in bone thickness during the follow-up despite the management of acromegaly, and it may differ in those without HFI. It is difficult to propose the exact mechanism of the formation and extension of the HFI and the increase in cranial bone thickness in acromegaly patients with HFI. In previous studies, hypogonadism, menopause, female sex and thyroid disease were shown to have some impact on the development of HFI [14, 29, 30]. In our study, we showed that hypothyroidism or diabetes was not associated with the presence of HFI in patients with acromegaly.

May et al. reported diffuse increases in the thickness of calvarial bones in postmenopausal women with HFI [31]. In a previous study investigating HFI in acromegaly patients, frontal bone thickness was significantly greater in the acromegaly group than in the control group; however, parietal and occipital bone thicknesses were similar between the acromegaly and control groups [10]. Hershkovitz et al. showed an increase in frontal bone thickness in HFI [14]. We showed that bone thickness was higher in patients with HFI than in those without HFI. Additionally, temporary changes in FBT, PBT, and OBT were examined in acromegaly patients in the present study. Our findings suggest that FBT, OBT and PBT increased throughout the course of acromegaly in the presence of HFI. We showed that frontal, parietal or occipital bone thickness; changes in bone thickness; and the presence of HFI were not associated with disease control in patients with acromegaly. The pathogenesis of HFI in acromegaly may involve factors other than IGF-1, or HFI may occur after pre- and postdiagnosis exposure to high IGF-1 levels for a longer time than the disease duration we examined. In addition, the effectiveness of medical or surgical treatment for acromegaly and impaired drug adherence might affect the association of IGF-1 with HFI [13, 32, 33]. We showed that no patients without HFI at the time of diagnosis had HFI during the course of acromegaly and that the type of HFI did not change in those with HFI. Although the frequency of HFI might be increased in acromegaly, the process of HFI seems to be initiated before the diagnosis of acromegaly and can be monitored throughout the disease course.

Strength and limitations

Studies investigating bone thickness and HFI in acromegaly are scant. We analyzed HFI and bone thickness, and changes in frontal, parietal and occipital bone thickness in a considerable number of patients with acromegaly. We could not include a control group. The present study was retrospective-designed study. We could not obtain cranial CT images of the patients.

Conclusion

More than half of acromegaly patients were found to have HFI, a condition that appears to be independent of disease activity and duration. Our study demonstrated that frontal, parietal, and occipital bone thickness increased over the course of the disease in patients with HFI, despite treatment of acromegaly. However, disease control does not seem to influence the occurrence of HFI, bone thickness, or changes in bone thickness. Given the potential association between HFI and headache in acromegaly patients, HFI should be evaluated and appropriately graded during baseline imaging. While our findings suggest a link between acromegaly and HFI, the exact mechanisms underlying this association remain to be elucidated.

Abbreviations

HFI	Hyperostosis frontalis interna
FBT	Frontal bone thickness
PBT	Parietal bone thickness
OBT	Occipital bone thickness
GH	Growth hormone
IGF-1	Insulin-like growth factor 1
MRI	Magnetic resonance imaging
FPG	Fasting plasma glucose

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Author contributions
All authors contributed to the study conception and design. Study design, material preparation, data collection and analysis were performed by Ömercan Topaloğlu, İhsan Ayhan, and Taner Bayraktaroğlu. The first draft of the manuscript was written by Ihsan AYHAN, and co-authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This observational, retrospective cohort study was approved by the Ethics Committee of our institution (Clinical Researches Ethics Committee of Zonguldak Bülent Ecevit University Medical Faculty with an Approval number: 2023/01) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants.

Consent for publication
Not applicable.

Informed consent
Written informed consent was given by all the participants included in the study.

Conflict of interest
All authors declare that they have no conflict of interest. No funding was taken during the whole process of study, writing of the article or preparation of manuscript.

Competing interests
The authors declare no competing interests.

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References

1. Vilar L, Vilar CF, Lyra R, Lyra R, Naves LA. Acromegaly: clinical features at diagnosis. Pituitary. 2017;20(1):22–32.
2. Dineen R, Stewart PM, Sherlock M, Acromegaly. QJM: Int J Med. 2017;110(7):411–20.
3. Mazziotti G, Lania AGA, Canalis E. Management of endocrine disease: bone disorders associated with acromegaly: mechanisms and treatment. Eur J Endocrinol. 2019;181(2):R45–56.
4. Sorohan MC, Poiana C. Vertebral fractures in acromegaly: A systematic review. J Clin Med. 2022;12(1):164.
5. Topaloğlu Ö, Bayraktaroğlu T, Tekin S, Topaloğlu SN, Şahin İ, Cantürk Z. Hyperostosis frontalis Interna. Turkish J Endocrinol Metabolism. 2022;26(4):213–6.
6. Moore MT. The Morgagni-Stewart-Morel syndrome: report of a case with Pneumoencephalographic findings. Arch Intern Med. 1944;73(1):7–12.
7. Moore S. The Troell-Junet syndrome. Acta Radiol. 2010;39(6):485–93.
8. She R, Szakacs J. Hyperostosis frontalis Interna: case report and review of literature. Ann Clin Lab Sci. 2004;34(2):206–8.
9. Alvarez LA, Corrigan W, Gardner S. A case report of hyperostosis frontalis Interna. Cureus. 2022;14(5).
10. Mutlu U, Telci Caklili O, Barburoglu M, Yarman S. Frequency of hyperostosis frontalis Interna in patients with active acromegaly: is there a possible role of GH excess or hyperprolactinemia in its etiopathogenesis? Hormones. 2022;1:1–8.
11. Fulton JD, Shand J, Ritchie D, McGhee J. Hyperostosis frontalis Interna, acromegaly and hyperprolactinaemia. Postgrad Med J. 1990;66(771):16–9.
12. Mönnich H, Böhm BO, Weidenbach H. 82-year old patient with hyperostosis frontalis, prognathism, makroglossia and cutis gyrata. Internist (Berl). 2004;45(7):815–9.
13. Katznelson L, Laws ER, Melmed S, Molitch ME, Murad MH, Utz A, et al. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(11):3933–51.
14. Hershkovitz I, Greenwald C, Rothschild BM, Latimer B, Dutour O, Jellema LM, et al. Hyperostosis frontalis Interna: an anthropological perspective. Am J Phys Anthropol. 1999;109(3):1096–8644.
15. Nikolić S, Djonić D, Živković V, Babić D, Juković F, Djurić M. Rate of occurrence, gross appearance, and age relation of hyperostosis frontalis Interna in females: A prospective autopsy study. Am J Forensic Med Pathol. 2010;31(3):205–7.
16. Cvetković D, Nikolić S, Brković V, Živković V. Hyperostosis frontalis Interna as an age-related phenomenon– Differences between males and females and possible use in identification. Sci Justice. 2019;59(2):172–6.
17. Chen OI, Murthy AS. Benign hyperostotic mass of the frontal bone. J Craniofac Surg. 2012;23(1):e27–30.
18. Raikos A, Paraskevas GK, Yusuf F, Kordali P, Meditskou S, Al-Haj A, et al. Etiopathogenesis of hyperostosis frontalis Interna: A mystery still. Annals Anat - Anatomischer Anzeiger. 2011;193(5):453–8.
19. Locatelli V, Bianchi VE. Effect of GH/IGF-1 on bone metabolism and osteoporosis. Int J Endocrinol. 2014;2014.
20. Vaňuga P, Kužma M, Stojkovičová D, Smaha J, Jackuliak P, Killinger Z, et al. The Long-Term effects of growth hormone replacement on bone mineral density and trabecular bone score: results of the 10-Year prospective Follow-up. Physiol Res. 2021;70(Suppl 1):S68.
21. Anthony JR, Ioachimescu AG. Acromegaly and bone disease. Curr Opin Endocrinol Diabetes Obes. 2014;21(6):476–82.
22. Uygur MM, Yazıcı DD, Buğdaycı O, Yavuz DG. Prevalence of vertebral fractures and serum sclerostin levels in acromegaly. Endocrine. 2021;73(3):667–73.
23. Siismets EM, Hatch NE. Cranial neural crest cells and their role in the pathogenesis of craniofacial anomalies and coronal craniosynostosis. J Dev Biol. 2020;8(3):18.
24. Roth DM, Bayona F, Baddam P, Graf D. Craniofacial development: neural crest in molecular embryology. Head Neck Pathol. 2021;15(1):1.
25. Alaya Z, Amri D, Baccouche K, Zaghouani H, Bouzaouach M, Belghali S, et al. AB0930 the Pachydermoperiostosis: clinical and radiologic characteristics (About 6 Cases). Ann Rheum Dis. 2015;74(Suppl 2):1211–1211.
26. Melmed S. Acromegaly pathogenesis and treatment. J Clin Invest. 2009;119(11):3189–202.
27. Lung H, Hsiao EC, Wentworth KL. Advances in models of fibrous Dysplasia/McCune-Albright syndrome. Front Endocrinol (Lausanne). 2020;10.
28. Bolanowski M, Daroszewski J, Mędraś M, Zadrozna-Śliwka B. Bone mineral density and turnover in patients with acromegaly in relation to sex, disease activity, and gonadal function. J Bone Min Metab. 2006;24(1):72–8.
29. Yamakawa K, Mizutani K, Takahashi M, Matsui M, Mezaki T. Hyperostosis frontalis Interna associated with hypogonadism in an elderly man. Age Ageing. 2006;35(2):202–3.
30. May H, Peled N, Dar G, Abbas J, Medlej B, Masharawi Y, et al. Hyperostosis frontalis Interna and androgen suppression. Anat Record: Adv Integr Anat Evolutionary Biology. 2010;293(8):1333–6.
31. May H, Mali Y, Dar G, Abbas J, Hershkovitz I, Peled N. Intracranial volume, cranial thickness, and hyperostosis frontalis Interna in the elderly. Am J Hum Biology. 2012;24(6):812–9.

32. Shin MS, Yu JH, Choi JH, Jung CH, Hwang JY, Cho YH, et al. Long-term changes in serum IGF-1 levels after successful surgical treatment of growth hormone-secreting pituitary adenoma. Neurosurgery. 2013;73(3):473–9.
33. Fleseriu M, Biller BMK, Freda PU, Gadelha MR, Giustina A, Katznelson L, et al. A pituitary society update to acromegaly management guidelines. Pituitary. 2021;24(1):1–13.

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