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Prevalence of Vertebral Fractures and Serum Sclerostin Levels in Acromegaly

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Abstract

Objective

An increased prevalence of vertebral fractures (VFs) has been reported in previous studies. The aim of this study was to evaluate the association between bone mineral density (BMD), bone turnover markers, serum sclerostin levels, and vertebral fractures (VFs) in acromegaly patients. We also evaluated the effects of gonadal status, disease activity, treatment modality, age, sex, and body mass index (BMI) on skeletal endpoints.

Design

Case-control study.

Patients and measurements

Seventy acromegaly patients (M/F:36/34, mean age 45,5±11,9 years) and 70 controls (M/F:31/39; mean age 45.66±11.9 years) were included. VFs, BMD, calcium metabolism, markers of bone turnover, and sclerostin levels were evaluated. BMD was measured by dual-energy X-ray absorptiometry (Hologic QDR 4500). Conventional lateral radiography of the spine was performed and the Genant method was used for the assessment of fractures of T4–L5 vertebrae.

Results

The prevalence of vertebral fractures was higher in acromegalic patients as compared with the control group (72.9% vs. 20%; $p<0.001$). Serum phosphate (P) levels (3.46±0.59 mg/dl vs. 3.11±0.44 mg/dl; $p<0.001$) and b-cross laps (CTx) levels (0.47 µg/l, range 0.04-2.38 vs. 0.28 µg/l, range 0.11-0.80; $p<0.001$) were significantly higher in acromegaly patients than control subjects. Serum sclerostin levels were similar between either acromegaly patients and control subjects or acromegaly patients with VF and without VF. In the means of treatment modality, VFs were more frequent in patients treated with adjuvant gamma-knife radiosurgery (GKS) ($p=0.07$). In the binary logistic regression analysis, the age of the acromegaly patients, the presence of hypogonadism, and GKS treatment were the factors significantly correlated with the occurrence of spinal fractures.

Conclusion

The prevalence of VFs in patients with acromegaly is higher than in control subjects. Since advanced age, the presence of hypogonadism and GKS treatment were the factors predicting VFs in acromegaly; radiological evaluations should be considered as an emerging tool especially in those patients. Although markers of bone turnover elevated in acromegaly, they were not useful for the prediction of fractures. Serum sclerostin levels showed no discrepancy between the two groups and further studies are required for assessment of sclerostin role in this form of secondary osteoporosis.

Introduction

Acromegaly is a rare, chronic endocrine disease usually caused by growth hormone (GH) secreting pituitary adenoma (1). Excessive GH levels and consequent high levels of insulin-like growth factor 1 (IGF-1) are associated with a wide range of systemic complications which lead to increased mortality (1) Vertebral fractures (VFs) are one of these complications associated with high morbidity and low quality of life (QOL) (1). GH and IGF-1 play an important role in the regulation of bone growth and bone metabolism during the lifespan through their effect on osteoblasts and osteoclasts (2). In recent years, acromegaly has been associated with increased bone remodeling which was confirmed with changes in bone turnover markers, calcium kinetics, and bone histomorphometry (3) and has been considered as one of the reasons for secondary osteoporosis (4). GH stimulates osteoblastic transformation, vice versa IGF-1 induces osteoclastogenesis by enhancing the synthesis of receptor activator of nuclear factor _B ligand (RANK-L). Biochemical markers of bone formation and bone resorption increase in favor of bone resorption (3). Mild hyperphosphatemia and hypercalcemia might be seen in acromegaly because of increased levels of calcitriol and direct antiphosphaturic effects of IGF-1 which is independent of parathormone (PTH) action (2). These contribute to the altered bone microarchitecture (2). Thus, bone quality is affected more than bone quantity in acromegalic osteopathy as determined by bone turnover markers (5). Recent studies provided evidence of increased skeletal fragility with high prevalence and incidence of VFs in acromegaly patients despite normal bone mineral density (BMD) (6–10) which was similar to observations in other forms of secondary osteoporosis (11). Bone turnover markers (formation and resorption) also hold promise to predict VF risk in acromegaly (6). The overall median prevalence of VFs in acromegaly is about 40%, a fracture risk which is three- to eight-fold greater compared to control subjects (2, 6). The prevalence of VFs was reported in up to 63% even in remission (12). VF incidence was found to be 20% despite normal BMD (12). The incidence of VFs was estimated as 42% in a prospective follow-up study, which was associated with hypogonadism, femoral neck BMD changes, previous vertebral fractures, and duration of active acromegaly (13). Hypogonadism is found to be associated with VFs towards acromegaly patients in several studies (7–9). However, the data were conflicted considering the association between hypogonadism and VFs, since no relation was shown in a recent study (14).

As the strongest predictor of vertebral fracture is shown to be the subsequent fractures, regardless of disease status; recent acromegaly guidelines suggest performing lateral spine scan imaging to assess VFs in all patients at diagnosis (15).

Sclerostin, a Wnt antagonist derived from osteocytes reduces bone formation by suppressing Wnt signaling in osteoblast precursors and blocks osteoblast differentiation. Also, sclerostin increases osteoclastogenesis by stimulating the expression of RANK-L (16–18). Based on the negative effects of sclerostin on bone, monoclonal antisclerostin antibodies have been developed for osteoporosis treatment (19–20). Nevertheless, the data are limitted focusing on sclerostin and fracture risk association in secondary osteoporosis.

The best approach to predict VFs is an important issue remaining to be clarified because BMD is not useful in acromegaly (6). Bone turnover markers have been addressed in recent studies but serum sclerostin levels were not evaluated in association with VFs in acromegaly patients. This study aimed to evaluate the association between the BMD, bone turnover markers, serum sclerostin levels, and vertebral fractures (VFs) in acromegaly patients given the limited and conflicting studies on this issue. We also assessed the effects of gonadal status, disease activity, treatment modality, age, sex, and body mass index (BMI) on skeletal endpoints.

Material And Methods

Patients:

Seventy acromegaly patients (36M/F:36/34: mean age 45,5 ± 11,9 years) and 70 controls (31M/F:31/39; mean age 45.66 ± 11.9 years) who were followed at the endocrinology clinic of Marmara University Medical School were enrolled. Inclusion criterium was a diagnosis of acromegaly disease with the clinic and biochemical tests in line with the latest guideline. Exclusion criteria were trauma history, osteoporosis treatment other than calcium and vitamin D. The Local Ethics Committee approved the study protocol, and the patients signed informed consent.

Transsphenoidal surgery was performed as the first choice of treatment and followed by adjuvant gamma knife radiosurgery (GKS) if required. GH values at or below 0.4 µg/L after an oral glucose tolerance test and normal age-related IGF-1 levels were defined as remission after surgery and/or irradiation. Biochemical control was defined as normal IGF-1 levels under medication. Both remission and biochemical control groups were classified as ‘controlled disease’. Elevated levels of serum IGF-1 levels after surgery and/or radiosurgery despite medical treatment were defined as active disease. Fifty-three percent of patients had adjuvant radiosurgery (GKS) following transsphenoidal surgery, 45.7% of patients had surgery. Despite surgery and medical treatment, 22.8% of patients had elevated IGF-1 levels. Remission was achieved in 30% of patients. In respect of medical treatment; 37.1% of patients were on somatostatin receptors ligands (SRLs), 28.6% were on SRLs plus dostinex and 4.3% were on SRLs plus pegvisomant treatment after surgery and/or radiosurgery in whom remission could not have been achieved.

Sixteen male patients and 7 female patients had hypogonadotropic hypogonadism and a gonadal replacement was supplied adequately in four of them. Twelve female patients were postmenopausal. The patients on gonadal replacement at least 12 months were considered as eugonadal.

Physical evaluation:

Patients with acromegaly and control subjects were evaluated for their body mass index (BMI) (weight/height squared) and waist circumstances (WC).

Laboratory evaluation:

Serum GH and IGF-1 levels were measured by the Immulite solid-phase, enzyme-labeled chemiluminescent immunometric assay (Roche, Immulate, 2000; The GH intra- and inter-assay variation coefficients: 2.9–4.6% and 4.2–6.6%, respectively, the IGF-1 inter-assay variation coefficient 3.0–7.6%). Thyroid-stimulating hormone (TSH), luteinizing hormone (LH), prolactin (PRL), cortisol, and estradiol in women were measured using electrochemiluminescence immunoassay (ECLIA). Serum-free T4 (fT4, thyroxine), follicle-stimulating hormone (FSH), and testosterone in men were measured using the paramagnetic immunoassays. Hospital laboratory reference values were used. Parameters of calcium and phosphate metabolism (calcium (Ca), P, PTH, and 25-hydroxyvitamin D (25 (OH) vitamin D)) were evaluated. The markers of bone turnover; b-cross laps (CTx) (bone resorption) levels were measured by the electrochemiluminescence immunoassay (Roche Diagnostics, Germany), and osteocalcin (bone formation) levels were measured by an enzyme-labeled chemiluminescent immunometric assay (Siemens, Immulite 2000). Sclerostin levels were measured by Human Sclerostin ELISA Kit (standard range: 0.5–200 ng/ml, intra-assay and inter-assay coefficient of variations: < 8%; < 10%, sensitivity, 0.26 ng/ml; Bioassay Technology Laboratory (BT Lab), Shanghai, China).

Glucocorticoid deficiency was defined as basal serum cortisol values below 3 μg/dL or inadequate response to corticotrophin stimulation test or insulin tolerance test. TSH deficiency was defined as a free T4 level below the normal laboratory reference range. Hypogonadism was evaluated by menstrual cycle history in premenopausal women, decreased gonadotrophin levels in postmenopausal women, and low plasma testosterone levels in men. GH deficiency was not assessed. Patients diagnosed with hypopituitarism were properly treated with levothyroxine, hydrocortisone, testosterone in men, or estrogen replacement in pre-menopausal women.

Bone mineral density (BMD)

BMD was measured at the lumbar spine (L1 to L4) and total hip using dual-energy X-ray absorptiometry (DXA, Hologic QDR 4500, Hologic Inc., Waltham, MA, USA) equipped with reference values based on the National Health and Nutrition Examination Survey (NHANES III). WHO criteria to define osteopenia (T-score between − 1.0 and − 2.5) and osteoporosis (T-score less than − 2.5) were used. The BMD is expressed in grams per square centimeter.

Vertebral fractures:

Conventional lateral radiography of the thoracic and lumbar spine was performed by an experienced radiology technician according to a standardized protocol in all patients. To avoid the overestimation of fractures due to spinal deformities, the radiographs were evaluated by two experienced observers (D.G.Y. and O.B), one of whom is a radiologist, qualified in musculoskeletal radiology. The semi-quantitative method proposed by Genant et al. for the assessment of fractures of T4–L5 vertebrae was used (21). Both physicians were blinded to the patient's characteristics. The fractures were defined as grade 1 (mild fracture), grade 2 (moderate fracture), and grade 3 (severe fracture) based on a height ratio reduction of 20–25%; 25–40%; and > 40%; respectively.

Statistics:

All analyses were performed using commercial statistical software (version 22.0; IBM SPSS). Descriptive statistics were given as the median and range for continuous data, and as percentages and frequency for categorical data. Continuous variables were analyzed for homogeneity of variance using the Kolmogorov-Smirnov test, and those with normal distribution were analyzed with the t-test; while those with uneven distribution were analyzed with the Mann-Whitney U test. The Chi-square test or Fisher's exact test were used to analyze categorical data. Pearson correlation analysis was performed between serum sclerostin and IGF-1, GH, and bone turnover marker. The influence of risk factors for the prevalence of vertebral fractures in patients with acromegaly was assessed using binary logistic regression. P values less than 0.05 were considered statistically significant.

Results

Acromegaly patients and control subjects showed no difference in age, sex, BMI, WC ($p = 0.33, 0.39, 0.57, 0.46$; respectively). Also, there was no difference in serum Ca, PTH, osteocalcin and sclerostin levels between the groups. Serum P levels (3.46 ± 0.59 mg/dl vs. 33.11 ± 0.44 mg/dl; $p < 0.001$) and CTx levels (0.47 µg/l, range 0.04–2.38 vs. 0.28 µg/l, range 0.11–0.80, $p < 0.001$) were significantly higher in acromegaly patients than control subjects. Serum 25 (OH) vitamin D levels were lower in control subjects than acromegaly patients (16.16 ± 12.21 µg/l vs. 22.98 ± 13.25 µg/l; $p = 0.002$). In acromegalic patients, the prevalence of vertebral fractures was higher as compared with the control group (72.9% vs. 20%; $p < 0.001$). Most of the fractures were seen in the thoracic vertebrae(n:32). The VF grade varied from mild to severe (grade 1: 34.3%; grade 2:35.7% grade 3:4.3%) were observed. There was no difference in lumbar spine (LS) Z score between the two groups (0.671 ± 1.821 vs. 0.162 ± 1.153, $p = 0.51$). Contrariwise; the femur neck (FN) Z score was higher in acromegaly patients than the control subjects (0.744 ± 1.035 vs. 0.196 ± 0.909; $p = 0.001$) (Table-1). Serum sclerostin levels showed no correlation with GH ($p = 0.89$), IGF-1($p = 0.92$), Ca ($p = 0.42$), P (0.81), 25 (OH) vitamin D ($p = 027$) ,CTx (0.6), osteocalcin ($p = 0.2$) and PTH ($p = 0.15$) levels in acromegaly patients..

Table-1: Characteristics of Acromegaly and Control Patients

Charecteristics	Acromegaly	Control	P value
n.	70	70	
n. of male/female	36/34	31/39	0.39
n. (%) of fractures	51 (72.9%)	14(20%)	<0.001
Age (years)	45.66±11.9	41.69±9.77	0.33
BMI (kg/m²)	30.35± 5.22	29.81±5.87	0.57
Waist circumference(cm)	99.72±11.51	98.27±11.78	0.46
IGF-1 (ng/ml)	228.25 (44.3-1066)	158.9±61.7	<0.001
Calcium (mg/dl)	9.62±0.51	9.65±0.59	0.63
Phosphate (mg/dl)	3.46±0.59	3.11±0.44	<0.001
PTH (ng/L)	51.87±20.08	52.58±22.39	0.843
25 (OH) vitamin D (µg/l)	22.98±13.25	16.16±12.21	0.002
Osteocalcin (µg/l)	15.6 (range 2.00-54.7)	14.3(range 2.00-34.02)	0.86
CTx (µg/l)	0.47 (range 0.04-2.38)	0.28(range 0.11-0.80)	<0.001
Sclerostin(ng/ml)	10.53±4.59	11.31±5.79	0.46
LS BMD (g/cm²)	1.218±0.218	1.161±0.155	0.78
LS T score	0.671±1.821	0.162±1.153	0.05
LS Z score	0.534±1.805	0.214±1.210	0.22
FN BMD (g/cm²)	1.069±0.144	0.984±0.121	<0.001
FN T score	0.614±1.096	-0.027±1.03	0.001
FN Z score	0.744 ±1.035	0.196±0.909	0.001

Abbreviations: n, number; BMI, body mass index; PTH, parathormone; *CTx, b-cross laps; LS, lumbar spine; FN, femur neck*

Table-2: Characteristics of Acromegaly Patients with and without vertebra fractures

Charecteristics of acromegaly paients	With vertebra fractures	Without vertebra fractures	P value
n (%)	51 (72.9%)	19 (27.1%)	
No. of male/female	27/24	9/10	0.67
Age (years)	48.11 ±11.71	39.05± 9.97	0.01
Disease duration (year)	6.6±5.3	4.4±4.5	0.12
Remission (n)	14 (66.7%)	7 (33.3%)	0.12
BMI (kg/m²)	30.31±0.68	30.49±1.49	0.9
Waist circumference(cm)	99.63±11.96	100.06±13.79	0.89
Hypogonadism (male/female number)	12/15	2/2	0.01
GKS (n/%)	30 (78.9%)	8 (21.9%)	0.07
IGF-1 (ng/ml)	216 (44.3-1066)	260 (57.6-738)	0.68
Calcium (mg/dl)	9.65±0.52	9.52±0.56	0.4
Phosphate (mg/dl)	3.45±0.55	3.50±0.76	0.78
PTH(ng/L)	58.26±23.14	52.17±16.13	0.34
25 (OH) vitamin D(µg/l)	25.49±13.43	18.31±11.61	0.04
Osteocalcin (µg/l)	16.9 (range 2.99-98.2)	15.7 (range2.39-54.7)	0.71
CTx (µg/l)	0.42 (range 0.09-2.38)	0.32 (range0.22-1.58)	0.41
Sclerostin (ng/ml)	11.5±4.48	8.81±3.15	0.31
LS BMD (g/cm²)	1.218±0.220	1.199±0.187	0.76
LS T score	0.66±1.81	0.52±1.68	0.78
LS Z score	0.60±1.84	0.27±1.68	0.53
FN BMD (g/cm²)	1.063±0.144	1.090 ±0.145	0.51
FN T score	0.57±1.09	0.74±1.13	0.59
FN Z score	0.73±1.03	0.76±1.07	0.91

Abbreviations: n, number; BMI, body mass index; PTH, parathormone; CTx, b-cross laps; LS, lumbar spine; FN, femur neck; GKS, gamma knife radiosurgery

In terms of gonadal status, hypogonadal patients showed no significant difference in sex (p = 0.3), active disease prevalence (p = 0.2) and GKS treatment ratios (p = 0.6), IGF-1 levels (203ng/ml; range 44.3–852 vs. 264 ng/ml; range 69.5–1066; p = 0.08) as compared to eugonadal patients. The vertebral fracture prevalence was significantly higher in hypogonadal patients than eugonadal ones (87.1% vs.61.5% p = 0.01). According to laboratory evaluation, PTH levels were higher in hypogonadal patients than eugonadal patients (62.79 ± 23pg/ml vs. 52.46 ± 20.4pg/ml) but the difference was not statistically significant (p = 0.06). The BMD measurements showed no significant difference between the two groups.

No difference was seen in fracture prevalence between active and controlled disease (18.75% vs. 22.2% p = 0.5). Both groups showed no difference in serum Ca, P, PTH, 25 (OH) vitamin D levels, bone turnover markers, sclerostin levels, and BMD measurements (Table 3).

Table 3
Characteristics of acromegaly patients with active and controlled disease

Charecteristics of acromegaly paients	Active disease	Controlled disease	P value
n (%)	54 (77.1%)	16 (22.9%)	0.76
%. of male/female with Fx	33.3/12.5	66.7/87.5	0.08
Age (years)	41.3 ± 8.5	46.9 ± 12.5	0.9
Disease duration (year)	6.4 ± 6.9	5.8 ± 4.6	0.7
BMI (kg/m²)	28.5 ± 4.5	30.8 ± 5.3	0.11
Waist circumference(cm)	95.9 ± 9.7	100.8 ± 11.8	0.13
Hypogonadism (male/female number)	4/1	10/16	0.23
IGF-1 (ng/ml)	439.5 (range268-1066)	197.5 (range44.3-369)	< 0.001
Calcium (mg/dl)	9.51 ± 0.56	9.76 ± 1.0	0.35
Phosphate (mg/dl)	3.66 ± 0.58	3.40 ± 0.59	0.13
PTH(ng/L)	58.26 ± 23.14	52.17 ± 16.13	0.13
25 (OH) vitamin D(µg/l)	25.29 ± 15.58	23.03 ± 12.63	0.55
Osteocalcin (µg/l)	11.5(range 2.99–20.4)	16.9(range2.39-98.2)	0.36
CTx (µg/l)	0.39(range 0.20–0.50)	0.42(range0.09-2.38)	0.37
Sclerostin (ng/ml)	10.42 ± 4.42	11.1 ± 4.4	0.54
LS BMD (g/cm²)	1.264 ± 0.202	1.200 ± 0.215	0.3
LS T score	0.99 ± 1.65	0.53 ± 1.81	0.38
LS Z score	0.83 ± 1.73	0.44 ± 1.82	0.47
FN BMD (g/cm²)	1.082 ± 0.152	1.065 ± 0.143	0.69
FN T score	0.67 ± 1.22	0.60 ± 1.06	0.82
FN Z score	0.73 ± 1.08	0.74 ± 1.02	0.97

Abbreviations: n, number; Fx, fracture; BMI, body mass index; CTx, b-cross laps; LS, lumbar spine; FN, femur neck

The figure shows the prevalence of vertebral fractures in acromegaly patients that were stratified according to disease activity and gonadal status (Figure-1). The highest prevalence of vertebral fracture was seen in the group with active disease and hypogonadism (100%). It was followed by the group with

hypogonadal controlled acromegaly patients (84.6%). The prevalence was decreased in eugonadal active and eugonadal controlled acromegaly patients (63.6% and 57.1%, respectively) (p:0.03).

Patients with vertebral fractures were significantly older than those without fractures (p = 0.01). The disease duration was slightly longer in patients with fracture but did not attain a statistical significance (6.4 ± 5.4 vs. 4.1 ± 4.0 years, p = 0.12). The prevalence of hypogonadism was higher in acromegalic patients with fractures (p = 0.01). In the means of treatment, VFs were more frequent in patients treated with adjuvant GKS compared with patients treated only with transsphenoidal surgery (p = 0.07). Serum IGF-1 levels, Ca, P, PTH, 25 (OH) vitamin D levels, and bone turnover markers showed no significant difference in patients with fracture compared to those without fracture. Neither LS (0.60 ± 1.84 vs. 0.27 ± 1.68) nor FN (0.73 ± 1.03 ± 0.76 ± 1.07) Z-score was significantly different between acromegalic patients with fracture and without fracture (p = 0.53 and p = 0.91, respectively) (Table-2).

In the binary logistic regression analysis, the age of acromegaly patients, the presence of hypogonadism, and GKS treatment were the factors significantly correlated with the spinal fracture occurrence (R^2: 17.5; p = 0.002) (Table 4).

Table 4
Results of logistic regression analyses to predict vertebral fractures in acromegaly patients

	OR	95% CL	P value
Age	1.08	1.016–1.150	.01
Active Acromegaly	0.53	0.125–2.256	.39
Hypogonadism	0.21	0.052–0.917	.03
GKS Treatment	0.25	0.070–0.925	.03
Abbreviations: GKS, Gamma knife radiosurgery			

Discussion

This study confirms that acromegaly patients have a high risk of vertebral fractures despite increased BMD values. The patient's age and hypogonadism were the predictive risk factors of VFs. GKS treatment was also associated with VF occurrence in this study. In terms of calcium metabolism and bone turnover markers, CTx, and serum P levels were elevated in acromegaly patients but did not differ in acromegaly patients with and without fracture. Serum sclerostin levels showed no difference between acromegaly and control groups and no correlation with IGF-1 levels.

Elevated GH/IGF-1 levels in acromegaly are associated with high bone turnover in favor of bone resorption that can result in increased skeletal fragility (3). GH stimulates osteoblastic transformation. The effect of GH on bone is usually mediated by systemic and local IGF-1. On the other hand, IGF-1

induces osteoclastogenesis by enhancing the synthesis of RANK-L. GH increases osteoprotegerin production, which impairs osteoclastogenesis by competing for the RANK-L receptor. IGF-1 stimulates bone activity and impair bone strength by increasing the number of remodeling sites. BMD is not reliable to predict VFs as confirmed several studies showing high prevalence and incidence of VFs despite normal BMD values (7–10). Since it is difficult to diagnose VFs according to the clinic or BMD; morphometric and radiological evaluations are emerging tools for the assessment of VFs, causing increased mortality and morbidity (6, 15). However, the data are limited considering the relationship between vertebral fractures and bone turnover markers. Sclerostin, a Wnt antagonist derived from osteocytes reduces bone formation by suppressing Wnt signaling in osteoblast precursors and blocks osteoblast differentiation. Also, sclerostin increases osteoclastogenesis by stimulating the expression of RANK-L (16–18). Based on the negative effects of sclerostin on bone, monoclonal antisclerostin antibodies have been developed for osteoporosis treatment (19, 20). Nevertheless, studies focusing on sclerostin and bone microarchitecture are limited in secondary osteoporosis. Sclerostin is reported to be elevated in X-linked hypophosphatemia (XLH), characterized by elevated fibroblast growth factor 23 (FGF23) levels; decreased phosphate reabsorption, and skeletal mineralization (20). In contrast to the effects of sclerostin on phosphate metabolism, mild hyperphosphatemia is reported most probably due to elevated calcitriol levels or direct antiphosphaturic effects of IGF-1 in acromegaly (2). A study showed significantly higher serum sclerostin levels in active acromegaly patients compared to controls and sclerostin levels correlated with the GH and IGF-1; nevertheless, VFs and bone turnover markers were not evaluated (22). Other limitation is that the study involved only active acromegaly patients although increased prevalence and incidence of fractures in biochemically controlled acromegaly patients was shown in previous studies (9, 12, 14). İn another study which included active and controlled acromegaly patients, patients with acromegaly had significantly lower sclerostin levels than the control group (23). There was no significant difference in serum sclerostin levels among active and controlled acromegaly patients. Also, no significant correlation was shown between sclerostin level and GH, IGF-I, LS BMD, and FN BMD, respectively (23). We found no significant difference in serum sclerostin levels between nor acromegaly and control groups, neither acromegaly patients with VF and without VF. Sclerostin levels did not differ between active and controlled acromegaly patients and showed no correlation between bone turnover markers, GH, IGF-1 levels.

In contrast to previous case-control studies (9, 13), there was a statistically significant relationship between the patient’s age and the prevalence of VFs. Studies showed men gender predominance in acromegaly patients with fracture (9, 12) however, there was no difference in regards to sex between acromegaly patients with and without VF in this study. Some studies found a correlation between VF and active disease; disease duration; untreated hypogonadism (7, 8, 13). There was no significant difference between acromegaly patients with and without VF in terms of disease activity, disease duration in this study similar to the others (9, 12). When acromegaly patients were classified according to the disease status and gonadal status, the most prevalent fracture rate was seen in hypogonadal active patients. Also, there was a significant correlation between VF occurrence and the presence of hypogonadism in univariate analysis in line with previous studies (7, 9, 12) that persisted in multivariate analysis in this study.

Despite higher levels of serum CTx and P in acromegaly patients compared to controls, no significant difference was found in bone turnover markers and calcium metabolism between patients with VF and without VF as similar to the data on previous studies (9, 12). Serum 25 (OH) vitamin D levels were higher in acromegaly patients compared to controls, and in patients with VF than without VF. This finding confirmed that standard modifications e.g. vitamin D replacement were not adequate in acromegaly-related osteoporosis as they were in primary osteoporosis to prevent VF (24). The role of vitamin D supplements in the prevention of VFs in acromegaly needs to be studied with further studies (15).

Although, there are studies that evaluated the effects of medical treatment on the bone (25), the association between GKS treatment and VFs has not been evaluated so far. We found that the prevalence of VFs is higher in acromegaly patients treated with GKS and there was a significant correlation in multivariate analyses between GKS treatment and VFs. We think that this relation might be associated with secondary hypogonadism or GH deficiency related to GKS but we were not able to analyze the correlation being limited by the small GKS patient size. On the other hand, in a recent study evaluating GKS, the new-onset anterior pituitary deficiency rate was found to be low (26). Further studies are needed for clarification whether GKS; as a modern radiosurgical approach, is associated with a reduced impact on morbidity than conventional radiotherapy (15).

A possible limitation of the present study was the assessment of the VFs with semi-quantitative method instead of quantitative morphometric analysis. To avoid the overestimation of fractures due to spinal deformities, the radiographs were evaluated by two experienced observers, one of whom is a qualified musculoskeletal radiologist.

In conclusion; the prevalence of VFs in acromegaly patients is higher independently of disease activity. Considering morbidity and mortality of VFs and the inability of BMD to predict fracture risk in patients with acromegaly, VF assessment by lateral conventional radiographs of the spine in the screening of patients with acromegaly is important. Since advanced age, the presence of hypogonadism and GKS treatment were the factors predicting VFs in acromegaly; radiological evaluations should be considered as an emerging tool especially in those patients. Although markers of bone turnover elevated in acromegaly patients, they were not useful for the prediction of fractures. Serum sclerostin levels should be investigated with more studies for fracture assessment in this form of secondary osteoporosis. Furthermore, whether GKS treatment per se a risk factor for vertebral fractures or not, is needed to be evaluated to prevent this underestimated clinical comorbidity.

Declarations

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