Dijlah Journal of Medical Sciences (DJMS) Vol. 1, No. 3, May, 2025, pp. 84-90
P-ISSN: 3078-3178, E-ISSN: 3078-8625, paper ID: 11

Acromegaly and Osteoporosis: A Review of the Paradox of Increased Bone Turnover and Fragility – Pathophysiology, Diagnosis, and Management

Isam Noori Salman, Omar Yasir Shakir, Safaa Ehssan Atta* and Baydaa Ahmed Abed
National Diabetes Center, Mustansiriyah University, Baghdad, Iraq.

Article Info

Article history:

Received February, 14, 2025
Revised March, 12, 2025
Accepted April, 25, 2025

Keywords:

Acromegaly,
IGF-1,
Osteoporosis,
Growth Hormone,
Bone Health

ABSTRACT

A rare endocrine condition called acromegaly is brought on by an overabundance of growth hormone (GH) and like growth factor 1 (IGF-1), usually due to pituitary adenoma. Even though bone density is elevated, increased IGF-1 levels in acromegaly patients (AC-PTs) can lead to musculoskeletal disorders such as osteoporosis and structurally weak bone. Nevertheless, GH in acromegaly is necessary for maintaining bone health. The excessive secretion of these hormones in AC-PTs may lead to bone turnover and osteoporosis. Despite Acromegaly's higher bone turnover, the condition is paradoxically linked to compromised bone microarchitecture and increased fracture risks, frequently unrelated to bone mineral density (BMD) levels. BMD testing bone health in AC-PTs might fail to determine remodeling dynamics and bone quality. The effects of osteoporosis in AC-Pts result from impaired osteoblast function, osteoclast activity, and disrupted bone remodeling, which leads to bone fragility, weakened bone, and elevated risks of fractures. An overall monitoring of bone turnover, bone microarchitecture, clinical assessment, and advanced imaging are important for determining bone health. In contrast, calcium and vitamin D3 supplements are necessary to support bones in acromegaly. The pathophysiological processes, diagnostic difficulties, and treatment approaches for osteoporosis in acromegaly are examined in this article.

Corresponding Author:

***** Safaa Ehssan Atta
National Diabetes Center, Mustansiriyah University, Baghdad, Iraq
safaaehssan@uomustansiriyah.edu.iq

1. INTRODUCTION

Acromegaly progresses slowly, with specific somatic and systemic features brought on by hypersecretion of GH and IGF-1 [1, 2]. Although skeletal abnormalities such as prognathism and enlarged extremities are widely known, little is known about the connection between acromegaly and bone health, especially osteoporosis. Despite appearing to have normal or elevated bone mineral density, osteoporosis in acromegaly is linked to a higher incidence of vertebral fractures, which raises concerns regarding the quality of bone microarchitecture [3].

The Insulin-like growth factor 1 (IGF-1) and Growth hormone (GH) are essential modulators of bone remodeling and have intricate functions in bone health [4, 5]. Although these hormones are necessary for preserving bone strength and density, dysregulation of them, as observed in diseases like acromegaly, can result in osteoporosis and a higher risk of fracture. In Bone Health, Normal IGF-1 and GH Physiology directly affect bone formation by promoting osteoblast differentiation and proliferation [6]. It also promotes the synthesis of IGF-1, which mediates many of the effects of growth hormone on bone. GH promotes bone mineralization by increasing calcium

reabsorption in the kidneys and absorption in the intestines. One such factor is insulin-like growth factor 1 (IGF-1). IGF-1 acts locally in bones and is mainly produced in the liver when growth hormone is stimulated. It increases collagen synthesis, stimulates osteoblast activity, and encourages the synthesis of bone matrix [6, 7]. In order to preserve the equilibrium between bone formation and resorption, IGF-1 also inhibits osteoclast activity [8, 9].

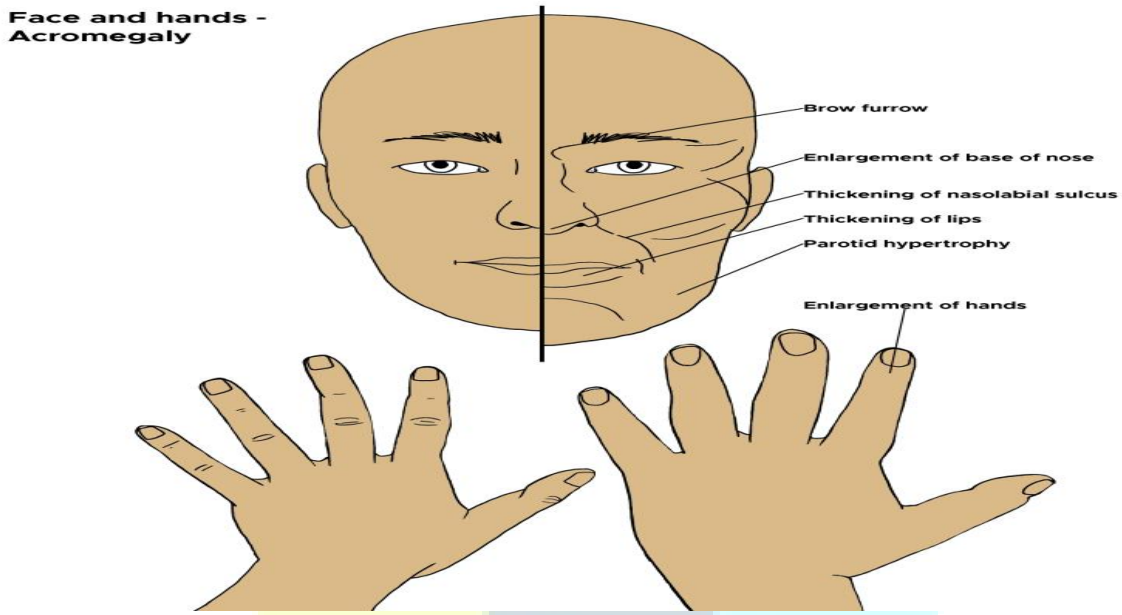

Figure 1. Physical attributes of face and hands of acromegaly [9]

According to several endocrinologists, there is no unanimity on the recommended process for handling and evaluating bone health in AC-PTs, leading to alternative practices [10, 11]. A recent study shows AC-PTs have a 2.5-fold higher risk of vertebral fractures than the normal population despite often having increased or normal bone mineral density (BMD) [12]. This contradiction focuses on the weakness of BMD evaluations in asses the health of bone in AC-PTs, which is a warning condition for physicians to consider the substitutional diagnostic patterns. In synopsis, there is a considerable gap between acromegaly and osteoporosis in knowledge mechanisms, diagnostic strategies, and management challenges. The pathophysiology, diagnostic methods, and treatment approaches for osteoporosis in patients with acromegaly are the main topics of this review, which explores the intricate relationship between GH/IGF-1 and bone health.

PATHOPHYSIOLOGY ROLE IN OSTEOPOROSIS

Acromegaly, which is characterized by a persistent elevation of GH and IGF-1, throws off the equilibrium of bone remodeling. The effects of IGF-1 and GH Overproduction on bone remodeling are dysregulated in osteoporosis, which leads to poor-quality bone, abnormal mineralize and microarchitecture of bone [13]. Increased Bone Turnover of Osteoblasts and osteoclasts are overstimulated by GH and IGF-1, which results in increased bone turnover [14, 15]. In contrast, influence on Cortical Bone Although cortical bone may thicken, increased porosity weakens its overall structure. Trabecular bone deterioration leads to too much turnover, which weakens bones by interfering with trabecular connectivity. Poor microarchitecture increases fracture risk, especially in vertebrae, even in normal or elevated bone mineral density (BMD) [16]. Inadequate GH or GH deficiency (GHD) in adults was involved in Decreased Bone Formation. Lower GH and IGF-1 levels impact osteoblast activity and bone formation [17]. Moreover, lower bone mineral density and poorer bone remodeling are associated with increased fracture risk, especially in the trabecular-rich spine [18]. In bone health, IGF-1 plays a role in osteoporosis, and its physiological levels preserve bone integrity and encourage bone growth at normal levels. Excessive levels of prolonged elevation, such as in acromegaly, cause microarchitectural fragility and interfere with remodeling [19, 20]. Vertebral fractures associated with acromegaly are common, primarily due to factors like cortical porosity, trabecular disruption, and increased bone turnover. It's crucial to understand that measuring bone mineral density (BMD) alone doesn't provide a complete picture of bone quality [21]. This quality is affected by both growth hormone (GH) and insulin-

like growth factor 1 (IGF-1). Therefore, using additional methods, such as high-resolution imaging or the trabecular bone score (TBS), is essential for a more accurate assessment of bone health [22]. Insulin-like growth factor 1 (IGF-1) and Growth hormone (GH) are remarkable factors in bone growth and remodeling. GH directly stimulates the differentiation and proliferation of osteoblasts, the cells responsible for bone formation, while IGF-1 promotes osteoblast activity and the synthesis of bone matrix [8, 23]. Although IGF-1 is primarily produced in the liver, it is also generated locally in bone tissue. Acromegaly, a condition characterized by excessive levels of GH and IGF-1, leads to uncoupled bone remodeling, resulting in increased bone turnover. This elevation in GH and IGF-1 can cause the deterioration of trabecular bone microarchitecture, which leads to structural fragility, while cortical bone mass often increases [24, 25, 26]. The effect on bone health can be significant in several ways, such as increased bone turnover and microarchitectural integrity of trabecular bone by disrupting trabecular connectivity. In cortical bone, although thickening may occur, it is often accompanied by increased porosity, which ultimately weakens the bone. Additionally, vertebral fractures are pretty common, and this high incidence suggests that bone quality, rather than density, is the primary concern when evaluating bone health [27].

DIAGNOSIS

Osteoporosis in acromegaly is often asymptomatic until fractures occur, with patients potentially experiencing persistent back pain due to vertebral fractures, as well as kyphosis or a loss of height. To measure bone mineral density (BMD), dual-energy X-ray absorptiometry (DXA) is used; however, since BMD measurements do not assess bone quality, they may underestimate the fracture risk in patients with acromegaly [28, 29]. Interestingly, some patients may have normal or even elevated BMD, particularly in areas with high cortical density. Advanced imaging techniques, such as Trabecular Bone Score (TBS), enhance DXA by evaluating trabecular microarchitecture, while High-Resolution Peripheral Quantitative CT (HR-pQCT) provides detailed information regarding bone strength and microarchitecture [30]. Additionally, it is common to find elevated levels of bone turnover markers, such as serum osteocalcin and bone-specific alkaline phosphatase, in affected individuals [31].
The microstructure appearance in bone was scanned with various technologies such as computed tomography (CT) that reported reduced thickness and trabecular number in addition to more porous cortical bone, elucidating increased vertebral fractures up to 40–50% [32].

MANAGEMENT

Several studies have suggested that AC-PTs have unique biochemical profiles due to their hyper-production of IGF-1 and GH, which may considerably affect treatment results and bone health [19, 33, 34].
Effective therapy considerations include managing growth hormone (GH) and insulin-like growth factor 1 (IGF-1) levels, as normalizing these hormones through medical or surgical interventions can decrease bone turnover and reduce fracture risk [35]. In cases of osteoporosis, mainly where fractures are present, it may be necessary to use pharmacological agents such as denosumab or bisphosphonates to support bone health. Additionally, patients with acromegaly or growth hormone deficiency (GHD) should be monitored through advanced imaging techniques to assess their bone microarchitecture and ensure optimal bone health [36, 37].

OSTEOPOROSIS CONTROL

The normalization of GH/IGF-1 involves Bone turnover, and when hormonal balance is achieved, fracture risk is decreased. Denosumab and bisphosphonates slow down bone resorption as Pharmacological Interventions. Nonetheless, Teriparatide may be used to promote bone formation, but caution should be exercised when using it in conditions with high turnover. Several factors include vitamin D, sufficient calcium consumption, lifestyle changes, exercise involving weight bearing to strengthen bones, prognosis, and long-term care. At the same time, some potential protective effects may derive from somatostatin such as pasireotide, octreotide, and lanreotide medications in addition to vitamin D_3 supplementation, independently from the disorder state [32, 38].

Although effective GH/IGF-1 regulation enhances bone quality, fracture risk is not entirely eliminated fracture Risk Reduction. Routine follow-up with DXA, TBS, and IGF-1 levels is essential for monitoring and controlling bone health and disease progression [39]. In AC-PTs, treating GH levels by surgery or somatostatin medications was important to reduce osteoporosis. In contrast, typical osteoporosis covers bone-reinforcement therapies like bisphosphonates and bone mineral density, whereas normal IGF-1 and GH levels in acromegaly are required to save bone health from osteoporosis and reduce fracture risk in acromegaly [40]. Acromegaly treatment reduces bone problems, and GH and IGF-1 levels must return to normal. The first line of treatment for pituitary adenomas is surgical resection [41]. Medical therapy for conditions such as acromegaly includes dopamine agonists, growth

hormone (GH) receptor antagonists (like pegvisomant), and somatostatin analogs (such as octreotide and lanreotide) [42]. Radiotherapy is typically reserved for cases that do not respond to these other treatments [43]. In terms of osteoporosis management, pharmacological treatments play a crucial role. Bisphosphonates can help lower the risk of fractures by preventing osteoclast-mediated bone resorption. Additionally, denosumab and teriparatide are effective therapies; teriparatide is a monoclonal antibody that lowers bone turnover by targeting RANKL [44].

2. CONCLUSION

The levels of GH and IGF-1 are essential for bone health because they control mineralization, turnover, and remodeling. Osteoporosis can result from dysregulation, whether in excess (acromegaly) or deficiency (GHD). Understanding their effects on bone remodeling and quality is essential for managing bone health and fracture risks in these conditions. Pituitary adenomas-induced acromegaly pose special difficulties for bone health, especially when it comes to treating osteoporosis. Because of the paradox of elevated BMD but poor bone quality, it is crucial to assess bone microarchitecture in these patients. Early detection, efficient pituitary adenoma management, and focused osteoporosis treatment are vital to lowering the risk of fractures and enhancing general quality of life. Enhances bone quality without totally removing the risk of fracture. the Observation of control bone health and disease progression, routine monitoring of DXA, TBS, and IGF-1 levels is essential.

ACKNOWLEDGEMENTS

We want to express our thankfulness to Mustansiriyah University/National Diabetes Center for its support and resources during this review article. We also appreciate special thanks to our center's endocrinologists, mentors, and all contributors to this study for their valuable insights on acromegaly.

REFERENCES

[1] Esposito, D., et al. (2024). Diabetes mellitus in patients with acromegaly: Pathophysiology, clinical challenges, and management. Nature Reviews Endocrinology, 20(9), 541-552.

[2] Bogusławska, A. (2024). The auxological and genetic analysis in patients with acromegaly—The call for the algorithm of an early diagnosis of tall stature and growth hormone excess.

[3] Mazziotti, G., et al. (2015). Bone turnover, bone mineral density, and fracture risk in acromegaly: A meta-analysis. The Journal of Clinical Endocrinology & Metabolism, 100(2), 384-394.

[4] Evaluation of the activity of arginase and some biochemical parameters in sera of patients with acromegaly. (2024). Baghdad Science Journal, 21(12), 3709-3715. https://doi.org/10.21123/bsj.2024.8784

[5] Saadi, M. T., Mohammed, N. U. G., Abed, B. A., Farhan, L. O., & Salman, I. N. (2024). Validity of galactin-3 in acromegaly: Comparison with traditional markers. Irish Journal of Medical Science, 193(4), 1837-1841. https://doi.org/10.1007/s11845-024-03674-w

[6] Mazziotti, G., Lania, A. G., & Canalis, E. (2022). Skeletal disorders associated with the growth hormone–insulin-like growth factor 1 axis. Nature Reviews Endocrinology, 18(6), 353-365.

[7] Liu, H., et al. (2024). Effect of gut hormones on bone metabolism and their possible mechanisms in the treatment of osteoporosis. Frontiers in Pharmacology, 15, 1372399.

[8] Fang, J., et al. (2023). The role of insulin-like growth factor-1 in bone remodeling: A review. International Journal of Biological Macromolecules, 238, 124125.

[9] Adigun, O. O., Nguyen, M., Fox, T. J., & Anastasopoulou, C. (2023). Acromegaly. In StatPearls [Internet]. StatPearls Publishing.

[10] Bennett, M. J., Center, J. R., & Perry, L. (2024). Establishing consensus recommendations for long-term osteoporosis care for patients who have attended an Australian fracture liaison service: A Delphi study. Osteoporosis International, 35(3), 373-389.

[11] Bennett, M. J., Center, J. R., & Perry, L. (2023). Exploring barriers and opportunities to improve osteoporosis care across the acute-to-primary care interface: A qualitative study. Osteoporosis International, 34(7), 1249-1262.

[12] Maione, L., & Chanson, P. (2022). Acromegaly. In Pituitary Adenomas: The European Neuroendocrine Association's Young Researcher Committee Overview (pp. 127-171). Springer.

[13] Kyriakakis, N. (2021). Exploring the morbidity and mortality in acromegaly. University of Leeds.

[14] Mohamad, N.-V., Razali, N.-S. C., & Shamsuddin, N.-A. M. (2024). Dehydroepiandrosterone and bone health: Mechanisms and insights. Biomedicines, 12(12), 2780.

[15] Salman, I. N., Mohammed, N. U. G., Atta, S. E., Abed, B. A., & Omran, H. H. (2024). Evaluations of bone turnover in a sample of Iraqi postmenopausal hypertensive obese women. Cardiometry(32), 55-59.

[16] Turcotte, A.-F., et al. (2021). Association between obesity and risk of fracture, bone mineral density, and bone quality in adults: A systematic review and meta-analysis. PLOS ONE, 16(6), e0252487.

[17] Wydra, A., Czajka-Oraniec, I., Wydra, J., & Zgliczyński, W. (2023). The influence of growth hormone deficiency on bone health and metabolism. Reumatologia, 61(4), 239.

[18] Stürznickel, J., Hinz, N., Delsmann, M. M., Hoenig, T., & Rolvien, T. (2022). Impaired bone microarchitecture at distal radial and tibial reference locations is not related to injury site in athletes with bone stress injury. The American Journal of Sports Medicine, 50(12), 3381-3389.

[19] Umur, E., et al. (2024). Exploring the role of hormones and cytokines in osteoporosis development. Biomedicines, 12(8), 1830.

[20] Salman, I. N., Mohammed, N. U. G., Al-Ghanny, R. J. A., Abed, B. A., & Mutar, S. A. (2024). Evaluation of Collagen Triple Helix Repeat Containing-1 protein in postmenopausal women with osteoporosis. Al-Kindy College Medical Journal, 20(3), 245-249. https://doi.org/10.47723/hr739z61

[21] Frara, S., et al. (2022). High prevalence of vertebral fractures associated with preoperative GH levels in patients with recent diagnosis of acromegaly. The Journal of Clinical Endocrinology & Metabolism, 107(7), e2843-e2850.

[22] Bioletto, F., et al. (2023). Trabecular bone score as an index of bone fragility in patients with acromegaly: A systematic review and meta-analysis. Neuroendocrinology, 113(4), 395-405.

[23] Malek, F. K., Abbas, S. A.-R., & Abed, B. A. (2024). Measurement of arginase activity in sera of Iraqi acromegaly patients with diabetes. Al-Mustansiriyah Journal of Science, 35(1), 44-49.

[24] Yang, J., & Ma, Z. (2021). Research progress on the effects of nickel on hormone secretion in the endocrine axis and on target organs. Ecotoxicology and Environmental Safety, 213, 112034.

[25] Jawiarczyk-Przybyłowska, A., Halupczok-Żyła, J., Syrycka, J., Zembska, A., Kuliczkowska-Płaksej, J., & Bolanowski, M. (2022). Trabecular bone score and osteoprotegerin as useful tools in the assessment of bone deterioration in acromegaly. Frontiers in Endocrinology, 13, 862845.

[26] Atta, S. E., Salman, I. N., Mohammed, N. U. G., Abed, B. A., & Salim, R. (2024). Serum visfatin in patients with type 2 diabetes mellitus and diabetic retinopathy. Сахарный диабет, 27(5), 480-486.

[27] Lems, W., et al. (2021). Vertebral fracture: Epidemiology, impact, and use of DXA vertebral fracture assessment in fracture liaison services. Osteoporosis International, 32, 399-411.

[28] Golding, P. H. (2022). Dual-energy X-ray absorptiometry (DXA) to measure bone mineral density (BMD) for diagnosis of osteoporosis—Experimental data from artificial vertebrae confirms significant dependence on bone size. Bone Reports, 17, 101607.

[29] Alvarez, M., et al. (2024). Osteoporosis and fractures in patients with acromegaly: A two-center cross-sectional study.

[30] El Miedany, Y., Elwakil, W., Abu-Zaid, M. H., & Mahran, S. (2024). Update on the utility of trabecular bone score (TBS) in clinical practice for the management of osteoporosis: A systematic review by the Egyptian Academy of Bone and Muscle Health. Egyptian Rheumatology and Rehabilitation, 51(1), 18.

[31] Schini, M., Vilaca, T., Gossiel, F., Salam, S., & Eastell, R. (2023). Bone turnover markers: Basic biology to clinical applications. Endocrine Reviews, 44(3), 417-473.

[32] Frara, S., Acanfora, M., Franzese, V., Brandi, M. L., Losa, M., & Giustina, A. (2024). Novel approach to bone comorbidity in resistant acromegaly. Pituitary, 1-11.

[33] Gatto, F., et al. (2019). Current perspectives on the impact of clinical disease and biochemical control on comorbidities and quality of life in acromegaly. Reviews in Endocrine and Metabolic Disorders, 20(3), 365-381.

[34] Mazziotti, G., Lania, A. G., & Canalis, E. (2019). Management of endocrine disease: Bone disorders associated with acromegaly—Mechanisms and treatment. European Journal of Endocrinology, 181(2), R45-R56.

[35] Tausendfreund, O., et al. (2024). Growth hormone treatment in aged patients with comorbidities: A systematic review. Growth Hormone & IGF Research, 101584.

[36] Oryan, A., & Sahvieh, S. (2021). Effects of bisphosphonates on osteoporosis: Focus on zoledronate. Life Sciences, 264, 118681. https://doi.org/10.1016/j.lfs.2020.118681

[37] Cianferotti, L., et al. (2023). Bone quality in endocrine diseases: Determinants and clinical relevance. Journal of Endocrinological Investigation, 46(7), 1283-1304.

[38] Hatta, N. N. K. N. M., Firdaus, M. K. Z. H., & Hasan, M. K. C. (2023). Enhancing bone health in aging populations to prevent fragility fractures. International Journal of Care Scholars, 6(3), 1-6.

[39] Wei, H., Zhao, Y., & Xiang, L. (2023). Bone health in inflammatory bowel disease. Expert Review of Gastroenterology & Hepatology, 17(9), 921-935.

[40] Freda, P. U. (2024). Impact of medical therapy for hormone-secreting pituitary tumors on bone. Pituitary, 27(6), 860-873.

[41] Bray, D. P., Mannam, S., Rindler, R. S., Quillin, J. W., & Oyesiku, N. M. (2022). Surgery for acromegaly: Indications and goals. Frontiers in Endocrinology, 13, 924589.

[42] Lim, D. S. T., & Fleseriu, M. (2022). Personalized medical treatment of patients with acromegaly: A review. Endocrine Practice, 28(3), 321-332.

[43] Chandra, R. A., Keane, F. K., Voncken, F. E., & Thomas, C. R. (2021). Contemporary radiotherapy: Present and future. The Lancet, 398(10295), 171-184.

[44] Matsumoto, T., & Endo, I. (2021). RANKL as a target for the treatment of osteoporosis. Journal of Bone and Mineral Metabolism, 39, 91-105.

ضخامة الأطراف وهشاشة العظام: مراجعة لمفارقة زيادة معدل دوران العظام وهشاشتها – الفسيولوجيا المرضية والتشخيص والإدارة

الخلاصة

تعد ضخامة الأطراف من الحالات النادرة التي تسببها إضطرابات الغدد الصم عن طريق زيادة هرمون النمو (GH) وعامل النمو الشبيه بالإنسولين ١ (IGF-1)، وعادة ما يكون ذلك نتيجة ورم في الغدة النخامية. وعلى الرغم من زيادة كثافة العظام، فإن زيادة مستويات IGF-1 في مرضى الأكروميجالي (AC-PTs) قد تؤدي إلى اضطرابات عضلية هيكلية مثل هشاشة العظام وضعف العظام الهيكلية. ومع ذلك، فإن هرمون النمو في الأكروميجالي ضروري للحفاظ على صحة العظام.

قد يؤدي الإفراز المفرط لهذه الهرمونات في مرضى الأكروميجالي إلى دوران العظام وهشاشة العظام. على الرغم من أن الأكروميجالي يرتبط بزيادة دوران العظام، فإن الحالة مرتبطة بشكل متناقض بالميكروهندسة الهيكلية الضعيفة للعظام وزيادة خطر الكسور، وغالبًا ما تكون غير مرتبطة بكثافة المعادن العظمية (BMD). قد يفشل اختبار BMD في تقييم صحة العظام لدى مرضى الأكروميجالي بسبب عدم قدرته على تحديد ديناميكيات الترميم وجودة العظام.

إن تأثيرات هشاشة العظام في مرضى الأكروميجالي ناتجة عن ضعف وظيفة الخلايا العظمية (أوستيوبلست) ونشاط الخلايا العظمية المدمرة (أوستيوكلاست)، واضطراب تجديد العظام، مما يؤدي إلى هشاشة العظام وضعف العظام وزيادة خطر الكسور.

يعتبر المراقبة الشاملة لدوران العظام، والميكروهندسة العظمية، والتقييم السريري، والتصوير المتقدم أمرًا مهمًا لتحديد صحة العظام. في المقابل، فإن مكملات الكالسيوم وفيتامين D_3 ضرورية لدعم العظام في الأكروميجالي. تم فحص العمليات الفيزيولوجية المرضية، والصعوبات التشخيصية، وأساليب علاج هشاشة العظام في الأكروميجالي في هذه الدراسة.