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Case Report

# Does Gitelman syndrome really save bone?

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## ABSTRACT

Gitelman syndrome is a renal tubular disease characterized by hypokalemia, hypomagnesemia and hypocalciuria. It has been suggested that Gitelman syndrome may affect bone metabolism by different mechanisms. This case report discusses a young male patient with chronic hypomagnesemia, recurrent fractures, and osteopenia due to Gitelman syndrome.

**Keywords**: Gitelman syndrome, hypomagnesemia, osteopenia, osteoporosis

## INTRODUCTION

Gitelman syndrome is an inherited kidney disease characterized by impaired sodium chloride (NaCl) reabsorption in the distal tubule. Clinically, it is differentiated from other tubulopathies with hypomagnesemia, hypokalemia, normocalcemia and hypocalciuria.[1] There are studies showing that Gitelman syndrome has variable effects on bone metabolism.[2,5]

This case report discusses a patient with Gitelman syndrome who applied to the outpatient clinic with extensive bone pain and recurrent fractures.

## CASE

A twenty-eight-year-old male patient was admitted to the endocrinology outpatient clinic with complaints of joint and bone pain for two years. He had no additional complaints in the physician query. He had two ankle fractures, one finger fracture, and two forearm fractures in his history. All of them occurred in childhood secondary to trauma. But he was investigated due to his history of multiple fractures. The patient was diagnosed with Gitelman syndrome at the age of four. He didn't have growth retardation. Due to Gitelman syndrome, spironolactone intake and magnesium potassium supplementation have been recommended. He did not use the drug because gynecomastia developed after using spironolactone, and he also took magnesium and potassium tablets rarely.

On physical examination, height was 174 cm and weight 62 kg. Blood pressure was 117/87 mmHg, and pulse rate was regular at 101/min. There was no shortening in his height. The patient's laboratory tests showed findings supportive of Gitelman syndrome (Table 1, 2).

**Table 1.** BMD data

| | 2011 | 2022 |
|---|---|---|
| Lumbar 4 z score | -0.6 | -0.7 |
| Femur neck z score | | -1.2 |
| Femur total z score | | -2.2 |

**Table 2.** Laboratory data at the time of application

| | Patients results | Normal ranges |
|---|---|---|
| C. calcium ˜ | 8.86 mg/dl | 8.8-10.6 |
| Sodium | 141 mmol/l | 136-145 |
| Phosphor | 3.3 mg/dl | 2.5-4.5 |
| Albumin | 53 g/l | 35-52 |
| Potassium | 2.85 mmol/l | 3.5-5 |
| Magnesium | 0.54 mmol/l | 0.6-1.07 |
| 25 OH vit D3 | 21.8 qg/l | 30-80 |
| Hemoglobin | 16.5 g/dl | 12.5-16 |
| GFR ¥ | 117.7 ml/dk/1.7 | >90 |
| Creatinine | 0.85 mg/dl | <0.9 |
| Parathormone | 49.3 pg/ml | 15-68.3 |
| Prolactin | 11.2 qg/l | 4.6-21.4 |
| Total testosterone | 541 ng/l | 191-663 |
| DHEA-SO4 § | 198 qg/l | 160-449 |
| TSH | 2.78 mıU/ml | 0.4-4.2 |
| Renin | 21.8 n/ml/hour | 0.1-6.56 |
| Aldosteron | 30.7 ng/dl | >30 |
| 24 hours urine calcium | 17 mg/day | 100-321 |

˜ Corrected calcium, ¥ Glomerüler filtration rate, § Dehidroepiandrosteron sulfat

## DISCUSSION

Hypokalemia, hypomagnesemia and hypocalciuria were observed. The patient's bone mineral densitometry (BMD) measurements were consistent with osteopenia (Femur total Z score: -2.2). Primary or secondary hypogonadism, thyrotoxicosis, primary hyperparathyroidism, vitamin D deficiency, smoking or alcohol use that caused secondary osteoporosis were investigated in the patient. He said he does not smoke or drink alcohol. Intact parathormone(PTH), thyroid stimulating hormone(TSH) and total testosterone levels were normal. But the 25(OH)D level was low. No height loss or chondrocalcinosis was observed in the vertebral radiographs. Oral calcium and vitamin D therapy were given to patient and it was recommended the patient to continue magnesium and potassium oral replacement therapy.

The different effects of electrolyte imbalance observed in patients with Gitelman syndrome on bone metabolism were evaluated in experimental and clinical studies.

Some studies suggested that this syndrome constituted an advantageous condition for bone formation. In a study conducted in mice with homozygous knockout of the NCC gene, it was stated that duodenal calcium absorption and calcium deposition in the bone increased, and osteoblast activity accelerated.[2]

Another study, performed on 45 patients with Gitelman syndrome, reported that the bone mineral density (BMD) of the patients increased compared to the healthy controls in high-resolution peripheral bone tomography. Also, it was found that the trabecular bone structures were thinner but denser.[3] Similar results were found in another study with dual-energy x-ray absorptiometry (DEXA).[4]

However, osteoporosis was also seen in cases with Gitelman syndrome. In a case report presented by Nakamura et al.[5], osteopenia developing in a patient with Gitelman syndrome was associated with hypocalcemia.

In the study of Wan X et al.[6], it was reported that cases with heterozygous mutations in the SLC12A3 gene associated with Gitelman syndrome experienced twice as many fractures as those who did not carry this gene.

Our case applied to the outpatient clinic with complaints of fracture attacks due to trauma and common bone pain. Osteopenia was detected as a result of BMD. According to the study conducted by Gennari et al.[7], the causes of bone loss in men might be related to genetic, environmental, hormonal, and some disease-specific factors. It was reported that about half of men with osteoporosis have alcohol use, hypogonadism, and glucocorticoid intake. In our patient estrogen and testosterone values were in the normal range. There was no glucocorticoid use or alcohol intake. Also the patient wasn't using antiepileptic and immunosuppressive drugs. His PTH and TSH values was normal range. Vitamin D deficiency causes osteoporosis because it causes a decrease in the renewal of bone mineralization and secondary hyperparathyroidism. To protect skeletal health, the 25(OH) D level would be deemed at least 20 ng/ml.[8] In our patient, 25(OH)D vitamin level was 21 ng/ml and the PTH value was within normal limits.

When the drugs he used were questioned, it was learned that he took the potassium and magnesium supplements rarely. According to the laboratory data he had hypomagnesemia and hypokalemia for a long time. Hypomagnesemia, one of the electrolyte imbalances seen in Gitelman syndrome, might also have adverse effects on the bone structure because it was seen that hypomagnesemia might directly play a role in the development of osteoporosis by reducing osteoblastic activity, bone formation, and volume.[9]

A four-year study by Tucker et al.[10] on men revealed that a diet rich in magnesium and potassium was associated with higher bone mineral density and lower bone loss.

In the study of Sara et al.[11] conducted on magnesium and osteoporosis, it was shown that magnesium deficiency caused osteoporosis directly and indirectly. In the body, 60% of magnesium was found in bone, most of which is found on the surface of hydroxyapatite. Hypomagnesemia was associated with decreased bone hardness, decreased osteoblast activity, and increased osteoclast activity due to a reduction in hydroxyapatite crystals. Because the patient did not use magnesium medications regularly, laboratory findings mostly showed hypomagnesemia. So osteopenia and fractures can be connected with hypomagnesemia in our case to. It was also reported that magnesium deficiency, which was used as a cofactor in parathyroid hormone (PTH) synthesis, might lead to a decrease in PTH synthesis and serum vitamin D levels.

Another study conducted by Bigi et al.[12] suggested that collagen in the bone was richer in magnesium and that bone quality might deteriorate in hypomagnesemia.

## CONCLUSION

Although it is known that trabecular bone structures are thinner but denser in patients with Gitelman syndrome, there is not enough data on the frequency of fractures. Although bone density seems to increase in Gitelman syndrome, our patient has osteopenia and multiple fractures. Therefore changes in collagen structure and hypomagnesemia might decrease BMD, increase bone fragility in these patients. So BMD follow-up is recommended in patients with Gitelman syndrome who have long standing hypomagnesemia.

## ETHICAL DECLARATIONS

**Informed Consent:** All patients signed the free and informed consent form.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

## REFERENCES

1. Jeck N, Konrad M, Peters M, Weber S, Bonzel KE, Seyberth HW. Mutations in the chloride channel gene, CLCNKB, leading to a mixed Bartter-Gitelman phenotype. *Pediatr Res.* 2000;48(6):754-758.
2. Hsu YJ, Yang SS, Cheng CJ, et al. Thiazide-sensitive Na+ -Cl- cotransporter (NCC) gene inactivation results in increased duodenal Ca2+ absorption, enhanced osteoblast differentiation and elevated bone mineral density. *J Bone Miner Res.* 2015;30(1):116-127.

3. Qi W, Yin Z, Liang H, et al. Na-Cl Co-transporter (NCC) gene inactivation is associated with improved bone microstructure. *Osteoporos Int*. 2022;33(10):2193-2204.
4. Nicolet-Barousse L, Blanchard A, Roux C, et al. Inactivation of the Na-Cl co-transporter (NCC) gene is associated with high BMD through both renal and bone mechanisms: analysis of patients with Gitelman syndrome and Ncc null mice. *J Bone Miner Res*. 2005;20(5):799-808.
5. Nakamura A, Shimizu C, Nagai S, et al. A rare case of Gitelman's syndrome presenting with hypocalcemia and osteopenia. *J Endocrinol Invest*. 2005;28(5):464-468.
6. Wan X, Perry J, Zhang H, et al. Heterozygosity for a pathogenic variant in SLC12A3 that causes autosomal recessive gitelman syndrome is associated with lower serum potassium. *J Am Soc Nephrol*. 2021;32(3):756-765.
7. Gennari L, Bilezikian JP. Osteoporosis in men. *Endocrinol Metab Clin North Am*. 2007;36(2):399-419.
8. Cesareo R, Iozzino M, D'onofrio L, et al. Effectiveness and safety of calcium and vitamin D treatment for postmenopausal osteoporosis. *Minerva Endocrinol*. 2015;40(3):231-237.
9. Rude RK. Magnesium homeostasis. In: Bilezikian JP, Raisz LG, Martin TJ, eds. Principles of Bone Biology. 3rd ed. Academic Press: 2008:487-513.
10. Tucker KL, Hannan MT, Kiel DP. The acid-base hypothesis: diet and bone in the Framingham Osteoporosis Study. *Eur J Nutr*. 2001;40(5):231-237.
11. Castiglioni S, Cazzaniga A, Albisetti W, Maier JA. Magnesium and osteoporosis: current state of knowledge and future research directions. *Nutrients*. 2013;5(8):3022-3033.
12. Bigi A, Foresti E, Gregorini R, Ripamonti A, Roveri N, Shah JS. The role of magnesium on the structure of biological apatites. *Calcif Tissue Int*. 1992;50(5):439-444.