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NEPHROLOGY - REVIEW

Gitelman syndrome: an analysis of the underlying pathophysiologic mechanisms of acid–base and electrolyte abnormalities

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Abstract Gitelman syndrome is the most common inherited tubular disease resulting from mutations of the SLC12A3 gene that encodes the thiazide-sensitive sodium–chloride cotransporter in the early distal convoluted tubules. The review presents the underlying pathophysiologic mechanisms of acid–base and electrolyte abnormalities observed in patients with Gitelman syndrome. The syndrome is usually characterized by hypokalemic metabolic alkalosis in combination with hypomagnesemia and hypocalciuria. Additionally, increased chloride excretion and renin/aldosterone levels, hypophosphatemia (occasionally), hyponatremia (rarely) and glucose intolerance/insulin resistance have been reported. The knowledge of the pathophysiologic mechanisms is useful for the treatment of patients with Gitelman syndrome as well as for the understanding of other tubular diseases.

Keywords Gitelman syndrome · Pathophysiology · Electrolytes · Acid–base · Potassium

Introduction

Gitelman syndrome (familial hypokalemia–hypomagnesemia) is the most common inherited tubular disease resulting from mutations of the SLC12A3 gene encoding the thiazide-sensitive sodium–chloride cotransporter (NCC), which is responsible for NaCl reabsorption in the early distal convoluted tubules. The syndrome is transmitted as an autosomal recessive trait and is characterized by hypokalemic metabolic alkalosis in combination with hypomagnesemia and hypocalciuria (Table 1) [1–3].

Aim of this review is the presentation of the underlying pathophysiologic mechanisms of acid–base and electrolyte abnormalities observed in patients with Gitelman syndrome (Table 1).

Hypokalemia and kaliuria

Hypokalemia (serum potassium concentration <3.5 mEq/L) owing to renal potassium wasting (potassium to creatinine ratio in a random urine specimen >18 mEq/g creatinine) is a cardinal manifestation of Gitelman syndrome. The underlying mechanisms of kaliuria include (Fig. 1):

1. Increased distal flow rate as a result of the decreased sodium chloride reabsorption in the early distal convoluted tubules leads to increased potassium secretion due to diffusion gradient through enhanced “big” or “maxi” potassium channels activity [4–6].
2. Volume depletion-induced increased aldosterone levels lead to increased potassium secretion through the renal outer medullary potassium (ROMK) channels. Additionally, the aldosterone-induced increased sodium reabsorption in the late distal convoluted and cortical collecting tubules by the epithelial sodium channel [ENaC] is associated with increased potassium excretion through an increased electronegativity of the lumen resulting in an elevated electrical gradient favoring potassium secretion [4–8].

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Table 1 Gitelman syndrome: main laboratory findings

Serum analyses
Hypokalemia (serum potassium <3.5 mEq/L)
Metabolic alkalosis
Hypomagnesemia (serum magnesium <1.4 mEq/L)
Increased renin and aldosterone levels
Hypophosphatemia (occasionally)
Hyponatremia (rarely)
Glucose intolerance/insulin resistance (rarely)
Urine analyses[a]
Renal potassium wasting (potassium/creatinine in a random urine specimen >18 mEq/g creatinine)
Renal magnesium wasting (fractional magnesium excretion >4%)
Hypocalciuria (calcium/creatinine in a random urine specimen <0.07 mg/mg)
Increased chloride excretion (fractional chloride excretion >0.5%)

[a]Fractional excretion (FE) of a substance (s) is determined by the equation: $FEs = 100 \times \frac{Surine \times CREATININEserum}{Sserum \times CREATININEurine}$

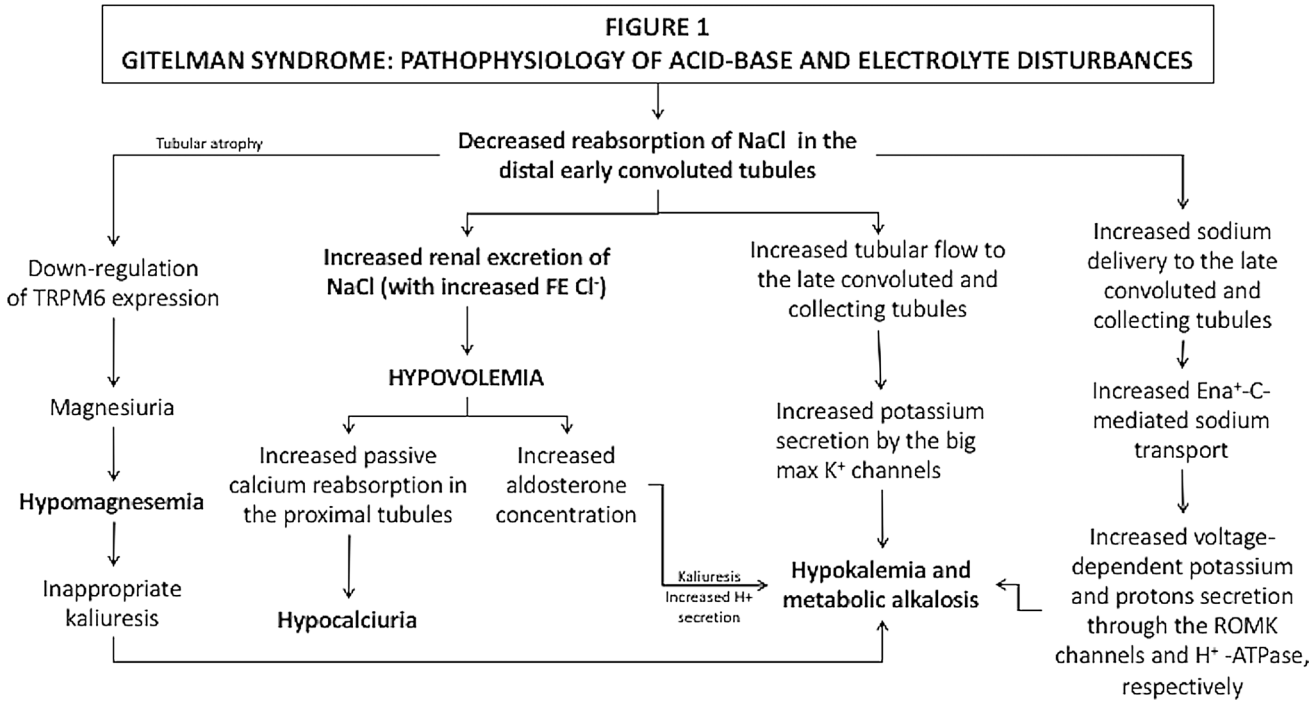

Fig. 1 Gitelman syndrome: Pathophysiology of the associated acid–base and electrolyte abnormalities. *TRMP6* epithelial magnesium channel transient receptor potential cation channel subfamily M member 6, *FE* fractional excretion, *ENaC* epithelial sodium channel, *ROMK* renal outcome medullary potassium channel

3. Hypomagnesemia is also associated with inappropriate kaliuresis and can contribute to the development of hypokalemia [9, 10].

Increased excretion of chloride

The decreased sodium and chloride reabsorption in the early distal convoluted leads to increased fractional excretion of chloride. Indeed, a fractional excretion of chloride >0.5% is among the diagnostic criteria proposed for the diagnosis of Gitelman syndrome [1]. However, increased chloride excretion is also observed in other genetic tubulopathies (such as Bartter syndrome) or diuretics surreptitious intake [11, 12]. It has been proposed that a thiazide test can be useful for the diagnosis of the Gitelman genotype in patients with normotensive hypokalemic alkalosis. Thus, in cases of Gitelman syndrome 3 h after the administration of 50 mg of hydrochlorothiazide fractional chloride clearance increases by less than 2.3% [13].

Metabolic alkalosis

Hypokalemia is commonly associated with metabolic alkalosis. The underlying mechanisms of metabolic alkalosis are shown in Fig. 2. Hypokalemia is associated with redistribution of potassium out of the cells resulting in entry of H^+ into cells. This intracellular acidosis in the renal tubular cells is associated with increased H^+ secretion in both proximal and distal tubules along with increased bicarbonate reabsorption. Furthermore, increased potassium depletion-associated ammoniogenesis in the proximal renal tubules may also play a role in the development of alkalosis. Finally, hypokalemia is also associated with induction of the H^+–K^+–ATPase in the a-intercalated tubular cells in the collecting tubules resulting in increased excretion of H^+, which can also contribute to the development of metabolic alkalosis [14].

Hypocalciuria

Hypocalciuria, defined as a spot urine calcium to creatinine ratio <0.07 mg/mg (0.2 mmol/mmol) in adults, is a common finding in patients with Gitelman syndrome [1]. It has been reported that the decreased calcium excretion is related to the extracellular volume contraction-mediated compensatory increase in sodium reabsorption in the proximal renal tubules leading to an increased passive calcium paracellular transport through an increase in the electrochemical gradient [15–17]. In fact, it is well known that in the proximal renal tubules calcium reabsorption is coupled tightly to sodium chloride reabsorption [15]. It has been proposed that increased calcium reabsorption at the thiazide-sensitive site in the distal convoluted tubules may contribute to the hypocalciuria [7, 18] though this mechanism has not been confirmed [16]. In fact, in the distal tubules the reduced NCC expression is associated with reduced intracellular sodium levels leading to increased calcium exit across the basolateral membrane through the Na^+–Ca^{2+} exchanger 1. The resulting low intracellular calcium leads to increased apical calcium entry into the cells through the transient receptor potential cation channel subfamily V member 5 (TRPV5) channels. Alternatively, the decreased magnesium reabsorption in the distal convoluted tubules results in reduced intracellular magnesium concentration leading to increased TRPV5-mediated calcium reabsorption [18].

It has been also reported that increased sodium chloride transport in the thick ascending loop of Henle (TAL) through the K^+–Na^+–$2Cl^-$ cotransporter is observed in these patients as a result of tubular adaptation to renal sodium loss [19, 20]. This process is associated with an increase in transepithelial voltage along the TAL leading to paracellular calcium reabsorption along this segment [19]. It has recently been reported that the thiazide-sensitive NCC gene inactivation in experimental animals is associated with increased duodenal calcium absorption as well as osteoblast differentiation and bone calcium storage [21]. These findings may explain the higher bone mineral density observed in patients with Gitelman syndrome but also in thiazide-treated patients [22].

Hypomagnesemia

Hypomagnesemia (serum magnesium <1.2 mEq/L) associated with inappropriate magnesiuria (fractional magnesium excretion >4%) [23] is a characteristic feature of patients with Gitelman syndrome [1]. In these patients, the underlying mechanisms of magnesiuria are not well delineated.

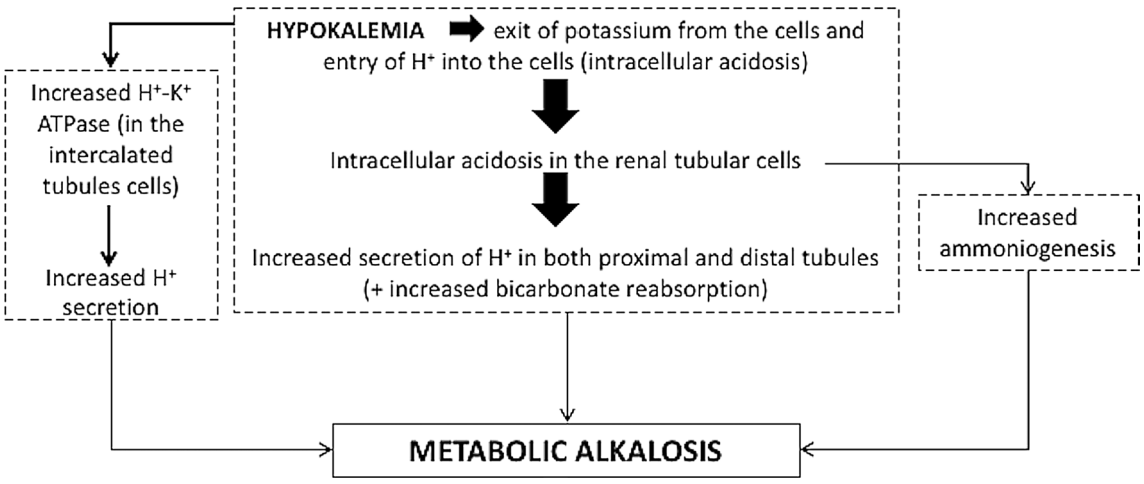

Fig. 2 Mechanisms of metabolic alkalosis in patients with Gitelman syndrome

However, it has been suggested that hypomagnesemia is related to downregulation of the epithelial magnesium channel transient receptor potential cation channel subfamily M member 6 (TRMP6), which is expressed along the apical membrane of the distal convoluted tubules and is responsible for the active transcellular transport of magnesium [15, 24]. The underlying mechanisms of this downregulation are not clear, but atrophy of the early distal convoluted cells observed in mice not expressing the NCC in the apical membrane of the distal convoluted cells may be responsible [16]. Additionally, increased aldosterone levels observed in these patients have been shown to be related to magnesiuria possibly through downregulation of TRMP6 channels. Thus, spironolactone is useful in these patients since it can reduce urinary magnesium excretion and increase magnesium levels 1 [25]. Finally, hypokalemia may also play a role in the development of hypomagnesemia since it is also associated with renal magnesium wasting [9]. It should be mentioned that hypomagnesemia in combination with hypokalemia can lead to a prolonged QT interval and cardiac arrhythmias [26, 27]. Thus, patients with these electrolyte derangements should avoid drugs prolonging the QT interval.

Hypophosphatemia

Hypophosphatemia due to renal phosphate wasting has been occasionally reported in patients with Gitelman syndrome. The underlying mechanisms are not clear though hypophosphatemia may be due to increased aldosterone levels or to the coexistent metabolic derangements (hypokalemia and metabolic alkalosis) [28, 29].

Hyponatremia

Hyponatremia is rarely reported in patients with Gitelman syndrome [30]. A NCC blockage-induced syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been proposed, especially in case of an impaired renal tubular dilutional capacity owing to inability to decrease distal tubular Na^+ and Cl^- concentration, similar to thiazide-induced hyponatremia mechanism [31]. Additionally, extracellular volume contraction seen in patients with Gitelman syndrome due to urinary Na^+ loss may increase antidiuretic hormone release. Patients with Gitelman syndrome exhibit decreased free water clearance [19], a factor that increases the risk of hyponatremia if other contributing factors ensue, such as a substantial increase in free water intake [30, 32], renal tubular salt wasting [32] or pneumonia-induced antidiuretic hormone inappropriate secretion [33].

Mechanisms of blood pressure control and carbohydrate metabolism abnormalities

Even though these patients exhibit hypovolemia-induced elevated angiotensin II and aldosterone levels, their blood pressure tends to be normal or even low. The absence of hypertension is related to renal sodium wasting but also to the increased concentration of angiotensin-converting enzyme 2 (ACE-2), which converts angiotensinogen to angiotensin_1-7 that possess vasodilatory effects. However, hypertension in adulthood is common in patients with Gitelman syndrome possibly due to the chronic elevated levels of angiotensin II and aldosterone [34–36].

Both increased and decreased insulin resistance have been described in patients with Gitelman syndrome. Glucose intolerance and insulin resistance are possibly related to chronic hypokalemia/hypomagnesemia [36]. Additionally, impaired insulin secretion compared with healthy subjects has been reported in Gitelman patients [37]. However, increased insulin sensitivity along with reduced oxidative stress as well as improved endothelial function possibly due to reduced angiotensin II signaling have also been found [38–40].

Conclusions

Gitelman syndrome is usually characterized by hypokalemic metabolic alkalosis in combination with hypomagnesemia and hypocalciuria, but increased chloride excretion and renin/aldosterone levels, hypophosphatemia (occasionally), hyponatremia (rarely) and glucose intolerance/insulin resistance can be also observed. The knowledge of the associated pathophysiologic mechanisms is useful for the treatment of patients with Gitelman syndrome as well as for the understanding of clinical and laboratory manifestations of other tubular diseases.

Compliance with ethical standards

Conflict of interest Professor MS Elisaf reports personal fees from ASTRA ZENECA, Grants and personal fees from MSD, personal fees from PFIZER, ABBOTT, SANOFI, BOEHRINGER INGELHEIM, ELI LILLY, GSK. The authors have given talks and attended conferences sponsored by various pharmaceutical companies, including Bristol-Myers Squibb, Pfizer, Lilly, Abbott, Amgen, AstraZeneca, Novartis, Vianex, Teva and MSD.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Blanchard A, Bockenhauer D, Bolignano D, Calo LA, Cosyns E, Devuyst O, Ellison DH, Karet Frankl FE, Knoers NV, Konrad M, Lin SH, Vargas-Poussou R (2017) Gitelman syndrome: consensus and guidance from a kidney disease: improving global outcomes (KDIGO) controversies conference. Kidney Int 91:24–33. doi:10.1016/j.kint.2016.09.046
2. Knoers NV, Levtchenko EN (2008) Gitelman syndrome. Orphanet J Rare Dis 3:22. doi:10.1186/1750-1172-3-22
3. Riveira-Munoz E, Chang Q, Bindels RJ, Devuyst O (2007) Gitelman's syndrome: Towards genotype-phenotype correlations? Pediatr Nephrol 22:326–332. doi:10.1007/s00467-006-0321-1
4. Subramanya AR, Ellison DH (2014) Distal convoluted tubule. Clin J Am Soc Nephrol 9:2147–2163. doi:10.2215/CJN.05920613
5. Palmer BF (2015) Regulation of potassium homeostasis. Clin J Am Soc Nephrol 10:1050–1060. doi:10.2215/CJN.08580813
6. McCormick JA, Ellison DH (2015) Distal convoluted tubule. Compr Physiol 5:45–98. doi:10.1002/cphy.c140002
7. Reilly RF, Ellison DH (2000) Mammalian distal tubule: physiology, pathophysiology, and molecular anatomy. Physiol Rev 80:277–313
8. Alfandary H, Landau D (2017) Future considerations based on the information from Barrter's and Gitelman's syndromes. Curr Opin Nephrol Hypertens 26:9–13. doi:10.1097/MNH.0000000000000285
9. Solomon R (1987) The relationship between disorders of K^+ and Mg^+ homeostasis. Semin Nephrol 7:253–262
10. Huang CL, Kuo E (2007) Mechanism of hypokalemia in magnesium deficiency. J Am Soc Nephrol 18:2649–2652. doi:10.1681/ASN.2007070792
11. Stolting G, Fischer M, Fahlke C (2014) CLC channel function and dysfunction in health and disease. Front Physiol 5:378. doi:10.3389/fphys.2014.00378
12. Wu KL, Cheng CJ, Sung CC, Tseng MH, Hsu YJ, Yang SS, Chau T, Lin SH (2017) Identification of the causes for chronic hypokalemia: importance of urinary sodium and chloride excretion. Am J Med. doi:10.1016/j.amjmed.2017.01.023
13. Colussi G, Bettinelli A, Tedeschi S, De Ferrari ME, Syren ML, Borsa N, Mattiello C, Casari G, Bianchetti MG (2007) A thiazide test for the diagnosis of renal tubular hypokalemic disorders. Clin J Am Soc Nephrol 2:454–460. doi:10.2215/CJN.02950906
14. Lee Hamm L, Hering-Smith KS, Nakhoul NL (2013) Acid–base and potassium homeostasis. Semin Nephrol 33:257–264. doi:10.1016/j.semnephrol.2013.04.006
15. Blaine J, Chonchol M, Levi M (2015) Renal control of calcium, phosphate, and magnesium homeostasis. Clin J Am Soc Nephrol 10:1257–1272. doi:10.2215/CJN.09750913
16. Nijenhuis T, Vallon V, van der Kemp AW, Loffing J, Hoenderop JG, Bindels RJ (2005) Enhanced passive Ca^{2+} reabsorption and reduced Mg^{2+} channel abundance explains thiazide-induced hypocalciuria and hypomagnesemia. J Clin Invest 115:1651–1658. doi:10.1172/JCI24134
17. Ellison DH (2000) Divalent cation transport by the distal nephron: insights from Bartter's and Gitelman's syndromes. Am J Physiol Renal Physiol 279:F616–F625
18. Reilly RF, Huang CL (2011) The mechanism of hypocalciuria with NaCl cotransporter inhibition. Nat Rev Nephrol 7:669–674. doi:10.1038/nrneph.2011.138
19. Favre GA, Nau V, Kolb I, Vargas-Poussou R, Hannedouche T, Moulin B (2012) Localization of tubular adaptation to renal sodium loss in Gitelman syndrome. Clin J Am Soc Nephrol 7:472–478. doi:10.2215/CJN.00940111
20. Ellison DH (2012) Adaptation in Gitelman syndrome: "we just want to pump you up". Clin J Am Soc Nephrol 7:379–382. doi:10.2215/CJN.01060112
21. Hsu YJ, Yang SS, Cheng CJ, Liu ST, Huang SM, Chau T, Chu P, Salter DM, Lee HS, Lin SH (2015) Thiazide-sensitive Na^+–Cl^- cotransporter (NCC) gene inactivation results in increased duodenal Ca^{2+} absorption, enhanced osteoblast differentiation and elevated bone mineral density. J Bone Miner Res 30:116–127. doi:10.1002/jbmr.2306
22. Nicolet-Barousse L, Blanchard A, Roux C, Pietri L, Bloch-Faure M, Kolta S, Chappard C, Geoffroy V, Morieux C, Jeunemaitre X, Shull GE, Meneton P, Paillard M, Houillier P, De Vernejoul MC (2005) 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 20:799–808. doi:10.1359/JBMR.041238
23. Elisaf M, Panteli K, Theodorou J, Siamopoulos KC (1997) Fractional excretion of magnesium in normal subjects and in patients with hypomagnesemia. Magnes Res 10:315–320
24. Viering DH, de Baaij JH, Walsh SB, Kleta R, Bockenhauer D (2016) Genetic causes of hypomagnesemia, a clinical overview. Pediatr Nephrol. doi:10.1007/s00467-016-3416-3
25. Colussi G, Rombola G, De Ferrari ME, Macaluso M, Minetti L (1994) Correction of hypokalemia with antialdosterone therapy in Gitelman's syndrome. Am J Nephrol 14:127–135
26. Malafronte C, Borsa N, Tedeschi S, Syren ML, Stucchi S, Bianchetti MG, Achilli F, Bettinelli A (2004) Cardiac arrhythmias due to severe hypokalemia in a patient with classic Bartter disease. Pediatr Nephrol 19:1413–1415. doi:10.1007/s00467-004-1611-0
27. Foglia PE, Bettinelli A, Tosetto C, Cortesi C, Crosazzo L, Edefonti A, Bianchetti MG (2004) Cardiac work up in primary renal hypokalaemia–hypomagnesaemia (Gitelman syndrome). Nephrol Dial Transpl 19:1398–1402. doi:10.1093/ndt/gfh204
28. Vigano C, Amoruso C, Barretta F, Minnici G, Albisetti W, Syren ML, Bianchetti MG, Bettinelli A (2013) Renal phosphate handling in Gitelman syndrome—the results of a case–control study. Pediatr Nephrol 28:65–70. doi:10.1007/s00467-012-2297-3
29. Katopodis K, Elisaf M, Siamopoulos KC (1996) Hypophosphataemia in a patient with Gitelman's syndrome. Nephrol Dial Transpl 11:2090–2092
30. Ganguli A, Veis JH (2017) Hyponatremia—a rare complication of Gitelman's syndrome. Indian J Nephrol 27:74–77. doi:10.4103/0971-4065.177208
31. Hwang KS, Kim GH (2010) Thiazide-induced hyponatremia. Electrol Blood Press 8:51–57. doi:10.5049/EBP.2010.8.1.51
32. Schepkens H, Stubbe J, Hoeben H, Vanholder R, Lameire N (2001) Severe hyponatraemia and hypouricaemia in Gitelman's syndrome. Nephrol Dial Transpl 16:2250–2252
33. Ali A, Masood Q, Yaqub S, Kashif W (2013) A case of Gitelman syndrome with severe hyponatraemia and hypophosphataemia. Singap Med J 54:e18–e20
34. Ariceta G, Rodriguez-Soriano J (2006) Inherited renal tubulopathies associated with metabolic alkalosis: effects on blood pressure. Semin Nephrol 26:422–433. doi:10.1016/j.semnephrol.2006.10.002
35. Calo LA, Schiavo S, Davis PA, Pagnin E, Mormino P, D'Angelo A, Pessina AC (2010) ACE2 and angiotensin 1–7 are increased in a human model of cardiovascular hyporeactivity: pathophysiological implications. J Nephrol 23:472–477
36. Berry MR, Robinson C, Karet Frankl FE (2013) Unexpected clinical sequelae of Gitelman syndrome: hypertension in adulthood is common and females have higher potassium requirements. Nephrol Dial Transpl 28:1533–1542. doi:10.1093/ndt/gfs600

37. Yuan T, Jiang L, Chen C, Peng X, Nie M, Li X, Xing X, Li X, Chen L (2017) Glucose tolerance and insulin responsiveness in Gitelman syndrome patients. Endocr Connect 6:243–252. doi:10.1530/EC-17-0014
38. Calo LA, Maiolino G, Naso A, Davis PA (2015) The association of systemic oxidative stress with insulin resistance: mechanistic insights from studies in Bartter's and Gitelman's syndromes. Clin Endocrinol (Oxf) 83:994–995. doi:10.1111/cen.12817
39. Davis PA, Pagnin E, Semplicini A, Avogaro A, Calo LA (2006) Insulin signaling, glucose metabolism, and the angiotensin II signaling system: studies in Bartter's/Gitelman's syndromes. Diabetes Care 29:469–471
40. Calo LA, Maiolino G, Alessi M (2017) Magnesium, cardiovascular-renal disease and the Gitelman's syndrome paradox. J Hypertens 35:1122–1124. doi:10.1097/HJH.0000000000001314