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ORIGINAL ARTICLE

Renal phosphate handling in Gitelman syndrome—the results of a case–control study

Cristina Viganò · Chiara Amoruso · Francesco Barretta · Giuseppe Minnici · Walter Albisetti · Marie-Louise Syrèn · Mario G. Bianchetti · Alberto Bettinelli

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Abstract
Background Patients with Gitelman syndrome, a hereditary salt-wasting tubulopathy, have loss-of-function mutations in the *SLC12A3* gene coding for the thiazide-sensitive sodium chloride co-transporter in the distal convoluted tubule. Since the bulk of filtered phosphate is reabsorbed in the proximal tubule, renal phosphate wasting is considered exceptional in Gitelman syndrome.
Methods We investigated the renal handling of inorganic phosphate in 12 unselected Italian patients affected with Gitelman syndrome (5 females and 7 males, aged 6.0–18 years, median age 12 years) and in 12 healthy subjects matched for gender and age (controls). The diagnosis of Gitelman syndrome among the patients had been made clinically and confirmed by molecular biology studies.
Results The biochemical hallmarks of Gitelman syndrome, namely hypochloremia, hypokalemia, hypomagnesemia, increased urinary excretion of sodium, chloride, potassium and magnesium and reduced urinary excretion of calcium, were present in the 12 patients. In addition, both the plasma inorganic phosphate concentration (median and interquartile range: 1.28 [1.12–1.36] vs. 1.61 [1.51–1.66)] mmol/L) and the maximal tubular reabsorption of inorganic phosphate (1.08 [0.99–1.22] vs. 1.41 [1.38–1.47] mmol/L) were significantly lower ($P<0.001$) in Gitelman patients than in control subjects. Circulating levels of 25-hydroxyvitamin D, intact parathyroid hormone and osteocalcin were similar in patients and controls.
Conclusions The results of our case–control study disclose a hitherto unrecognized tendency towards renal phosphate

C. Viganò · G. Minnici
Division of Orthopedics, San Leopoldo Mandic Hospital,
Merate, Lecco, Italy

C. Amoruso · A. Bettinelli
Division of Pediatrics, San Leopoldo Mandic Hospital,
Merate, Lecco, Italy

C. Amoruso
Department of Pediatrics, De Ponti Hospital,
University of Insubria,
Varese, Italy

F. Barretta · M.-L. Syrèn
Department of Clinical Sciences and Community Health,
University of Milan,
Milan, Italy

F. Barretta
Epidemiology Unit, Department of Preventive Medicine,
Foundation IRCCS Cà Granda Ospedale Maggiore Policlinico,
Milan, Italy

W. Albisetti
Department of Clinical Orthopedics and Rehabilitation,
University of Milan,
Milan, Italy

M.-L. Syrèn
Laboratory of Medical Genetics, Foundation IRCCS Ca' Granda
Ospedale Maggiore Policlinico,
Milan, Italy

M. G. Bianchetti
Division of Pediatrics, Bellinzona and Mendrisio hospitals,
University of Bern,
Bern, Switzerland

M. G. Bianchetti (✉)
San Giovanni Hospital,
6500 Bellinzona, Switzerland
e-mail: mario.bianchetti@pediatrician.ch

wasting with mild to moderate hypophosphatemia in Gitelman syndrome.

Keywords Gitelman syndrome · Hypokalemia · Hypomagnesemia · Hypophosphatemia · Renal phosphate wasting

Introduction

The kidney plays a key role in the maintenance of inorganic phosphate homeostasis [1, 2]. Since the bulk of filtered inorganic phosphate is reabsorbed in the proximal tubule, renal phosphate wasting is common in proximal renal-tubular disorders [3].

The terms Bartter and Gitelman syndrome are used to denote a group of autosomal-recessive disorders with a unifying pathophysiology consisting of salt loss either by the limb of Henle or the distal convoluted tubule. Affected patients present with low or normal blood pressure, an activated renin–angiotensin–aldosterone system and hypokalemia with or without concurrent hypomagnesemia [4, 5]. Hypophosphatemia is considered rare in Bartter and especially in Gitelman syndrome, the most frequent form of the mentioned salt wasting disorders [6, 7]. We noticed a tendency towards low inorganic phosphate levels in some of our Gitelman patients which led us to investigate the renal handling of this ion in the context of a case–control study. The results of the study indicate a counterintuitive predisposition towards renal phosphate wasting in these patients.

Patients and methods

All patients with Gitelman syndrome on regular follow-up at the renal unit of the Division of Pediatrics, San Leopoldo Mandic Hospital were eligible for enrollment in the trial. Between September and November 2011, a group of 12 Italian patients from nine different families (5 females and 7 males aged 6.0–18 years, median age 12 years) who presented for a scheduled visit and a control group of 12 healthy subjects matched for age and gender (5 females and 7 males aged 6.9–18 years, median age 11 years) entered the study. All patients had history of frequent tetanic episodes, muscular weakness or fatigue, and the diagnosis of Gitelman syndrome was based on the presence of normal or low blood pressure, hypokalemia, hypomagnesemia, inappropriate urinary excretion of chloride and magnesium, hypocalciuria and normal results on renal ultrasound. In addition, biallelic mutations in the gene encoding the thiazide-sensitive sodium chloride co-transporter had been identified in 11 patients (Table 1). All of the mutations have been previously described [8–11], with the exception of those of patient no. 11 who had a frameshift mutation disrupting protein synthesis and a missense mutation that substitutes for the highly conserved residue Arg871.

The study was approved by the Human Subjects Research Committee of Merate–Lecco Hospital. The Gitelman patients, who did not discontinue their medication with potassium chloride (N=11), potassium-sparing diuretics (spironolactone, N=6; amiloride, N=1), indomethacin (N=1) and magnesium (N=1), and the control subjects attended the outpatient clinic after overnight fasting and received a tap water (sodium content <1.0 mmol/L) load of 400 mL [12]. After voiding the bladder, an approximately 2-h urine specimen was collected, and a mid-point blood sample was taken with minimal stasis and without movement of the forearm [12]. Creatinine, sodium, chloride, potassium, total calcium and magnesium and inorganic phosphate were assessed in both the blood and urine samples, urea, bicarbonate, 25-

Table 1 Mutations in the *SLC12A3* gene, located on 16q13 chromosome, coding for the thiazide-sensitive sodium chloride co-transporter in the distal convoluted tubule detected in 11 of the 12 patients enrolled in the study

Patient no.	Family no.	Nucleotide changes	Predicted effects at protein level
1	I	c.[2981G>A]; [506-?_742+?del]	p.[Cys994Tyr]; [Val169_Gln247del]
2	II	c.[2981G>A]; [2981G>A]	p.[Cys994Tyr]; [Cys994Tyr]
3	III	c.[1196_1202dup7bp]; [1424C>G]	p.[Ser402*]; [Ser475Cys]
4	III	c.[1196_1202dup7bp]; [1424C>G]	p.[Ser402*]; [Ser475Cys]
5	IV	c.[1196_1202dup7bp]; [1196_1202dup7bp]	p.[Ser402*]; [Ser402*]
6	IV	c.[1196_1202dup7bp]; [1196_1202dup7bp]	p.[Ser402*]; [Ser402*]
7	V	c.[1175C>T]; [1844C>T]	p.[Thr392Ile]; [Ser615Leu]
8	V	c.[1175C>T]; [1844C>T]	p.[Thr392Ile]; [Ser615Leu]
9	VI	c.[1844C>T]; [1925G>A]	p.[Ser615Leu]; [Arg642His]
10	VII	c.[557G>A]; [1742T>A]	p.[Gly186Asp];[Met581Lys]
11	VIII	c.[283delC]; [2612G>C]	p.[Gln95Argfs*18];[Arg871Pro]

The mutations disclosed in patients from 1 to 10 have been previously reported [8–11]. GenBank accession number NM_000339.2 is used as a reference sequence, in which the A of ATG is number 1. Nomenclature is according to HGVS v.2

hydroxyvitamin D, alkaline phosphatase, intact parathyroid hormone and osteocalcin were assessed only in the blood samples. Creatinine, urea, sodium, bicarbonate, chloride, potassium, total calcium and magnesium and inorganic phosphate were measured on an automated auto-analyzer using colorimetric assays or ion-selective electrodes. Intact parathyroid hormone was measured by a two-site radioimmunometric assay, 25-hydroxyvitamin D using a competitive protein-binding assay and osteocalcin by radioimmunoassay.

The glomerular filtration rate was estimated from height and plasma creatinine [13]. The fractional urinary excretion of sodium, chloride, potassium, calcium, magnesium and inorganic phosphate was calculated from their plasma (P_X) or urinary (U_X) level, as well as from plasma (P_{Cr}) or urinary (U_{Cr}) creatinine as follows [12, 14]:

$$\frac{U_x \times P_{Cr}}{P_x \times U_{Cr}}$$

The maximal tubular reabsorption of inorganic phosphate, the best means of defining the renal tubular handling of this ion, was calculated from plasma (P_{Ph}) or urinary (U_{Ph}) phosphate and plasma (P_{Cr}) or urinary (U_{Cr}) creatinine as follows [12, 14]:

$$P_{Ph} - \left(\frac{U_{Ph} \times P_{Cr}}{U_{Cr}}\right)$$

Blood and urinary levels of sodium, chloride, potassium and magnesium are age and gender-independent [15], and the blood levels of inorganic phosphate and those of its maximal tubular reabsorption significantly vary with age and gender [14, 15]. Hence, the values obtained in our study were also compared with those given in the literature [14] and expressed as the standard deviation score (SDS). Descriptive statistics are presented as median and interquartile range (IQR), which extends from the value at the 25th percentile to the value at the 75th percentile and includes half of the data points. The two-tailed Wilcoxon–Mann–Whitney test for two independent samples and simple linear regressions with the rank correlation coefficient r_s were performed for the analysis. Significance was assumed when $P<0.05$.

Results

Body height and weight were significantly lower in the group of patients affected with Gitelman syndrome than in the control group (Table 2). Blood pressure, heart rate and pubic hair development were not statistically different between the patients (Marshall–Tanner stage ranging from 1 to 5, median 2) and controls (Marshall-Tanner stage ranging from 1 to 4, median 2). Apart from the biochemical hallmarks of Gitelman syndrome, namely hypochloremia, hypokalemia, hypomagnesemia, increased urinary excretion of sodium, chloride, potassium and magnesium, and reduced urinary calcium excretion, the group of patients was found to have some tendency towards total hypercalcemia. However, patients affected with Gitelman syndrome and control subjects did not significantly differ in terms of plasma creatinine and urea levels, estimated glomerular filtration rate and levels of plasma sodium and bicarbonate, serum 25-hydroxyvitamin D, plasma alkaline phosphatase, serum intact parathyroid hormone and serum osteocalcin.

Both the plasma inorganic phosphate concentration and the maximal tubular reabsorption of inorganic phosphate were significantly lower in Gitelman patients than in control subjects, as shown in Table 3. In contrast, the fractional excretion of this analyte was not statistically different between the patients and controls. Figure 1 shows the relationship between the maximal tubular reabsorption of inorganic phosphate and its plasma level in individual Gitelman patients and controls expressed as the SDS. In this figure, the relationship between the maximal tubular reabsorption of inorganic phosphate and its plasma level observed in patients and in controls are compared with age- and sex-specific reference values obtained 30 years ago in Germany. A tendency towards age- and gender-corrected hypophosphatemia was noted in eight of the 12 Gitelman patients. Plasma inorganic phosphate level and the maximal tubular reabsorption of inorganic phosphate were not statistically different in patients with and without potassium-sparing diuretics.

In patients with Gitelman syndrome a significant relationship was noted between the fractional urinary excretion of chloride and potassium, taken as independent values, and that of inorganic phosphate, taken as dependent values (Fig. 2). No significant relationship was noted between circulating magnesium levels or its fractional urinary excretion and the urinary excretion of inorganic phosphate, nor between circulating bicarbonate levels and the urinary excretion of inorganic phosphate.

Discussion

The results of our case–control study in unselected Gitelman patients reveal a hitherto unrecognized tendency towards renal phosphate wasting with mild to moderate hypophosphatemia. At first glance it appears surprising that in Gitelman syndrome, as in Bartter syndrome, the issue of hypophosphatemia has remained so far unrecognized with the exception of two case reports [6, 7]. This is related, in our opinion, to the fact that hypophosphatemia is mild and that many central laboratories do not provide accurate age- and sex-specific reference values.

Table 2 Laboratory findings other than levels and renal handling of inorganic phosphate in the 12 patients affected with Gitelman syndrome and the 12 control subjects

Clinical findings	Patients with Gitelman syndrome[a]	Control subjects[b]	Significance
Body height, m	1.338 [1.158–1.498]	1.433 [1.365–1.528]	$P<0.05$
Body weight, kg	31.0 [21.2–37.0]	41.8 [36.5–49.8]	$P<0.05$
Supine blood pressure, mm Hg	110 [99–120]/60 [49–73]	113 [101–122]/66 [52–74]	NS
Supine heart rate, /min	78 [66–84]	75 [64–86]	NS
Plasma creatinine, μmol/L	49 [40–55]	54 [49–57]	NS
Glomerular filtration rate, mL/min/1.73 m^2	135 [125–144]	132 [126–138]	NS
Plasma urea, mmol/L	5.0 [4.3–6.8]	5.9 [4.6–6.0]	NS
Sodium			
Plasma level, mmol/L	135 [134–136]	136 [135–137]	NS
Fractional excretion, 10^{-2}	0.85 [0.57–10.7]	0.59 [0.30–0.65]	$P<0.05$
Plasma bicarbonate, mmol/L	29 [27–31]	27 [26–29]	NS
Chloride			
Plasma level, mmol/L	97 [95–98]	101 [100–102]	$P<0.001$
Fractional excretion, 10^{-2}	1.57 [1.12–2.09][c]	0.55 [0.40–0.83]	$P<0.001$
Potassium			
Plasma level, mmol/L	3.0 [2.7–3.1]	4.1 [3.9–4.2]	$P<0.0001$
Fractional excretion, 10^{-2}	22 [15–29]	4.9 [3.1–10]	$P<0.001$
Total calcium			
Plasma level, mmol/L	2.52 [2.46–2.54]	2.41 [2.37–2.47]	$P<0.05$
Fractional excretion, 10^{-2}	0.17 [0.12–0.39]	0.84 [0.51–1.45]	$P<0.01$
Total magnesium			
Plasma level, mmol/L	0.69 [0.59–0.71]	0.91 [0.79–0.94]	$P<0.001$
Fractional excretion, 10^{-2}	4.5 [3.5–5.7]	3.2 [2.6–4.0]	$P<0.05$
Serum 25-hydroxyvitamin D, pmol/L	79 [62–110]	79 [55–89]	NS
Plasma alkaline phosphatase, U/L	241 [145–250]	241 [187–284]	NS
Serum intact parathyroid hormone, pmol/L	1.6 [1.2–4.3]	3.2 [1.6–5.3]	NS
Serum osteocalcin, μg/L	49 [36–70]	57 [44–90]	NS

NS, Not significant

Data are presented as the median, with the interquartile range (IQR) given in square parenthesis

[a] Five females, seven males; aged 6.0–18, median 12 years

[b] Five females, 7 males; aged 6.9–18 years, median 11 years

[c] $N=11$

Table 3 Levels and renal handling of inorganic phosphate in the 12 patients affected with Gitelman syndrome and the 12 control subjects[a]

Renal handling of inorganic phosphate	Patients with Gitelman Syndrome	Control subjects	Significance
Plasma inorganic phosphate concentration			
Absolute value, mmol/L	1.28 [1.12–1.36]	1.61 [1.51–1.66]	$P<0.001$
SDS[b]	−2.4 [−3.2 to −1.5]	−0.2 [−0.5–0.1]	$P<0.005$
Maximal tubular reabsorption of phosphate			
Absolute value, mmol/L	1.08 [0.99–1.22]	1.41 [1.38–1.47]	$P<0.001$
SDS[b]	−2.6 [−3.0 to −1.9]	−1.5 [−1.8 to −1.1]	$P<0.01$
Fractional excretion of inorganic phosphate, 10^{-2}	8.8 [6.8–13.8]	11.4 [8.7–12.2]	NS

SDS, Standard deviation score; IQR, interquartile range

Data are presented as the median, with the IQR given in square parenthesis

[a] See footnotes to Table 1 for description of patient and control groups

[b] Calculated from data obtained in healthy German subjects (reference [14])

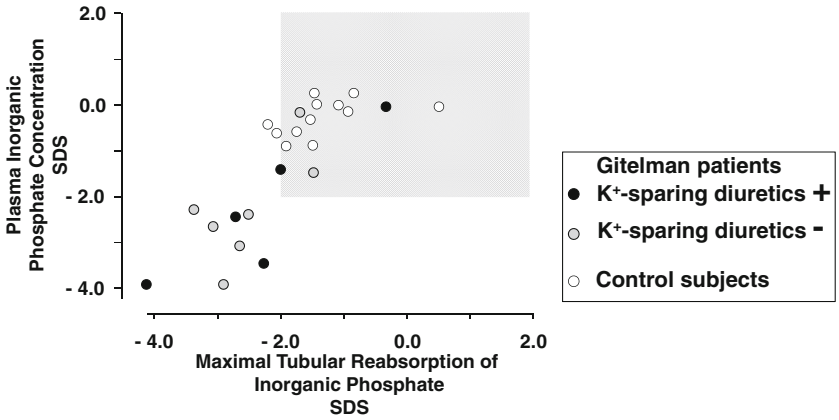

Fig. 1 Relationship between the maximal tubular reabsorption of inorganic phosphate and the corresponding plasma level in 12 Gitelman patients and 12 healthy subjects matched for age and gender. The results are expressed as the standard deviation score (*SDS*). The *shaded area* denotes the reference values obtained from the literature [9]. The plasma inorganic phosphate concentration was normal in the 12 healthy control subjects and reduced in eight of the 12 patients. Patients with (+) and without (−) potassium-sparing diuretics are denoted by *different symbols*

Gitelman syndrome, a salt-wasting tubulopathy, is caused by mutations in the gene coding for the thiazide-sensitive sodium chloride co-transporter [4, 5, 8–11]. This genetic component underlies the profound homology between this tubulopathy and subjects managed with thiazides [4, 5]. There is general agreement with regard to the effects of thiazides on sodium and potassium balance [16, 17]. Relatively little attention has been paid, however, to their effects on phosphate homeostasis [16, 17]. Nevertheless, long-term management with thiazides might cause a tendency towards hyperphosphaturia and hypophosphatemia [16–18].

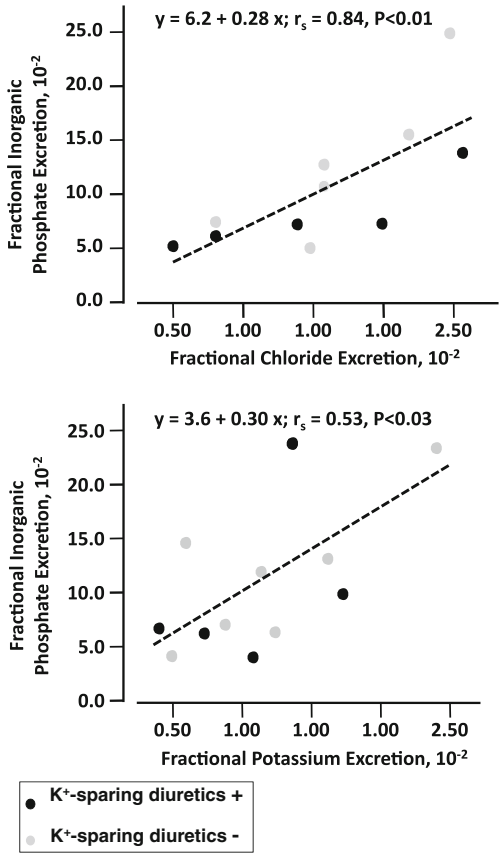

Fig. 2 Relationship between the fractional urinary excretion of chloride (*upper panel*) and potassium (*lower panel*) and that of inorganic phosphate in Gitelman patients. The relationship (*dashed line*) was statistically significant in both cases. The fractional urinary excretion of chloride was not assessed in one case. Patients with (+) and without (−) potassium-sparing diuretics are denoted by *different symbols*

Circulating calcium exists in three forms, namely the form bound to proteins, the form complexed with low-molecular-weight anions, such as bicarbonate, and the ionized form, which is the only biologically active form [1]. In Gitelman syndrome, the amount of circulating calcium bound to proteins or complexed to bicarbonate is increased [19]. As a consequence, in these patients the total circulating calcium level is, on average, slightly increased, as noted in our study, but the level of ionized circulating calcium is normal or slightly reduced [19].

Plasma inorganic phosphate levels are high in children, falling remarkably during and after puberty [14, 15]. In our healthy Italian volunteers, the plasma concentration of inorganic phosphate and its maximal tubular reabsorption were rather low when compared with the corresponding age- and gender-matched reference values obtained more than 30 years ago in Germany [14]. These differences are likely related to both puberty today beginning earlier than it did 30 years ago and Italian children entering puberty earlier than German children [20].

In contrast to the regulation of calcium homeostasis, relatively little is known about the renal regulation of phosphate homeostasis [1, 2, 21–23]. Since extracellular fluid volume expansion increases the excretion of inorganic phosphate, and extracellular fluid volume contraction decreases it, changes in extracellular fluid volume likely do not account for the tendency towards renal phosphate wasting in a salt-wasting

condition such as Gitelman syndrome [1, 2]. There is often a tendency towards metabolic alkalosis in Gitelman syndrome [4, 5]: it is recognized, however, that metabolic alkalosis, contrary to respiratory alkalosis, does not conspicuously modulate phosphate metabolism [1, 2]. There is also an association between hypokalemia and hypophosphatemia in either familial or thyrotoxic hypokalemic periodic paralysis, and between hypomagnesemia and hypophosphatemia in either the treatment of uncontrolled diabetes mellitus or in refeeding. In the latter conditions, however, the electrolyte disturbances result from their shift into cells without renal wasting [1, 2]. Prostaglandin overproduction, a recognized cause of hyperphosphaturia [1, 2], is a constant feature in both classic and neonatal Bartter syndrome. In contrast, Gitelman syndrome patients display a normal urinary excretion of prostaglandin E_2 [24]. Furthermore, our data suggest that in Gitelman disease the tendency towards renal phosphate wasting is not related to an altered circulating level of either 25-hydroxyvitamin D or parathyroid hormone. Finally, the significant relationship between urinary chloride level and phosphate excretion noted in our Gitelman patients might point to some phosphate reabsorption also occurring in the distal segments of the nephron [1].

There is a tendency towards mild to moderate hypophosphatemia in primary hyperaldosteronism and towards hyperphosphatemia upon treatment with potassium-sparing diuretics [2]. For this reason, Gitelman patients receiving treatment with either spironolactone or amiloride were included in our study.

Knowledge of the mechanisms that participate in renal phosphate homeostasis has greatly improved during the past few years following the recognition of phosphaturic hormone fibroblastic growth factor 23 [21–23]. Many disorders associated with low circulating levels of this hormone are characterized by hyperphosphatemia. On the other hand, disorders associated with high circulating levels are characterized by hypophosphatemia [21–23]. The determination of circulating fibroblastic growth factor 23 and 1,25-dihydroxyvitamin and studies investigating the renal handling of inorganic phosphate in Bartter syndrome should therefore be useful in ascertaining the mechanisms underlying hypophosphatemia in Gitelman syndrome.

Conflict of interest None declared.

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