Evaluating distal renal tubular acidification function in primary hyperparathyroidism and its effects on bone mineral density

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Abstract

Background: Primary hyperparathyroidism (PHPT) is a common endocrinopathy that may increase fracture risk and decrease bone mineral density (BMD). Some patients develop distal renal tubular acidification dysfunction under conditions of hyperchloraemia or hyperchloraemic acidosis. To examine whether this dysfunction influences the clinical outcome, we explored the distal renal tubular acidification function in patients with PHPT and its effects on the clinical manifestations of the disease.

Methods: We retrospectively analysed 75 PHPT patients with regard to renal tubular acidification and blood gas analysis. The patients were divided into two groups, the renal tubular acidification dysfunction group and normal function group.

Results: Serum phosphate level and total hip bone density were significantly decreased and 25OHD level was significantly increased in the renal tubular acidification dysfunction group in comparison to the normal function group. Female patients in the renal tubular acidification dysfunction group showed significantly decreased femoral neck and total hip BMD and increased susceptibility to fracture. However, there were no such differences in male patients between the two groups.

Conclusions: About 54.6% of PHPT patients in our study population had abnormal distal renal tubular acidification. PHPT patients with abnormal distal renal tubular acidification may have lower hip bone density. Female PHPT patients with abnormal distal renal tubular acidification showed increased susceptibility to fractures and the development of osteoporosis.

Keywords: Primary hyperparathyroidism, Distal renal tubule, Acidification function, Bone mineral density

Background

Chronic acid retention may decrease bone mineral density (BMD). Studies [1, 2] showed that dysfunction of distal renal tubular acidosis may cause bone loss. Patients with abnormal distal renal tubular acidification may not manifest in significant systemic acidosis, however, the increased of acid loading may trigger the release of alkali in the bone, resulting a greater absorption of bone [3]. Sromicki et al. reported that 23% of osteopenia/osteoporosis patients may have abnormal distal renal tubular acidification, which may lead to chronic acid retention [4]. Primary hyperparathyroidism (PHPT) is the third most common endocrine disease. Although the incidence of proximal renal tubular acidification dysfunction is known to be higher in PHPT patients, there have been few studies regarding distal renal tubular acidification dysfunction in PHPT [5–7]. Therefore, the aim of the retrospective study was to explore distal renal...
Methods
Subjects
The study population consisted of 75 patients, 21 men aged 36–74 years and 54 women aged 29–83 years, with a diagnosis of PHPT [8] according to the following criteria: (1) increased serum calcium above the upper limit of normal range of 2.55 mmol/L, excluding other causes of hypercalcemia; (2) increased PTH above the upper limit of normal range of 7.63 pmol/L; (3) decreased serum phosphorus; and (4) combined with clinical symptom and characteristic radiographic features. The exclusion criteria were as following: patients with multiple endocrine adenoma, secondary or tertiary hyperparathyroidism were excluded from this study. All subjects were hospitalized patients first treated in Tianjin Medical University General Hospital between 2013 and 2019.

Statistical methods
Data were analysed using SPSS 25.0 (SPSS, Chicago, IL, USA). The results are presented as the mean ± SD. Analysis of the categorical variables was performed by χ² or Fisher’s test, and comparisons between the two groups were performed using the independent samples t test. The continuous variables of non-normal distribution expressed by M (P25, P75) and the non-parametric test were used for comparisons between the groups. In all analyses, P < 0.05 was taken to indicate statistical significance.

Results
Gender distribution, age, BMI, course of disease, blood gas analysis indicators, bone turnover indicators, AKP, blood and urine electrolytes (except serum phosphate) were not significantly different between the renal tubular acidification dysfunction group and normal function group. Urine PH was significantly increased, urine ammonium ion and titratable acid were significantly decreased in renal tubular acidification dysfunction group (P < 0.01). Serum phosphate was significantly decreased and 25OHD was significantly increased in the renal tubular acidification dysfunction group compared with the normal function group (P < 0.05). The renal tubular acidification dysfunction group showed decreased serum potassium level and increased parathyroid hormone (PTH) level but these differences were not significant (both P > 0.05). There were no differences in the incidence of kidney stones and fractures between the renal tubular acidification dysfunction group and the normal function group (both P > 0.05). (Table 1).

Total hip BMD was significantly decreased in the renal tubular acidification dysfunction group compared with the normal function group (P < 0.05). There were no differences in the proportions of patients with osteoporosis at any site between the two groups (P > 0.05). (Table 2).
Table 1: Comparison of clinical data of the renal tubular acidification dysfunction group and the normal function group (X±S)

| Variable                                      | Abnormal acidification group | Normal acidification function group | P         |
|-----------------------------------------------|------------------------------|-------------------------------------|-----------|
|                  | (41)                          | (34)                               |           |
| Sex (male/female)                             | 13/28                        | 8/26                                | 0.432 (χ²) |
| Medical history (y)                           | 0.25 (1, 5.5)                | 0.33 (1, 5)                         | 0.881 (Non-parametric) |
| Age, y                                        | 61.1 ± 12.0                  | 56.8 ± 11.0                         | 0.116     |
| BMI, kg/m²                                    | 24.2 ± 4.85                  | 24.74 ± 3.84                        | 0.602     |
| Albumin, g/L                                  | 41.24 ± 3.86                 | 40.79 ± 3.54                        | 0.604     |
| Albumin-corrected serum calcium, mmol/L       | 2.80 ± 0.39                  | 2.84 ± 0.31                         | 0.635     |
| Serum phosphate, mmol/L                       | 0.69 ± 0.17                  | 0.79 ± 0.18                         | 0.017     |
| Serum potassium, mmol/L                       | 3.85 ± 0.50                  | 4.08 ± 0.51                         | 0.061     |
| Serum chloride (mmol/L)                       | 107.55 ± 3.45                | 107.23 ± 3.99                       | 0.717     |
| Serum sodium (mmol/L)                         | 141.06 ± 2.70                | 142.24 ± 1.71                       | 0.062     |
| Serum magnesium (mmol/L)                      | 0.83 ± 0.11                  | 0.86 ± 0.07                         | 0.220     |
| Serum creatinine, umol/L                      | 58 (47.5, 73)                | 58 (42.75, 73.25)                   | 0.447 (Non-parametric) |
| AkP (U/L)                                     | 125 (91.5, 231.5)            | 103.5 (67, 157.75)                  | 0.075 (Non-parametric) |
| PTH (pmol/L)                                  | 59.4 (24.65, 130)            | 36.1 (17.17, 64.02)                 | 0.061 (Non-parametric) |
| 25OHD (nmol/L)                                | 34.5 (21.4, 64.02)           | 25.5 (20.45, 32.66)                 | 0.020 (Non-parametric) |
| Urine PH (4.5-6.5)                             | 6.67±0.45                    | 5.78±0.42                           | 0.000     |
| Urine HCO3 (0-12.44mmol/L)                    | 5.50 (3.35, 10.90)           | 4.50 (2.87, 5.90)                   | 0.231 (Non-parametric) |
| Urine TA (9.57-150mmol/L)                     | 4.45 ± 2.83                  | 11.91 ± 4.39                        | 0.000     |
| Urine NH₄⁺(25.84-200mmol/L)                   | 16.48 ± 5.57                 | 25.62 ± 5.89                        | 0.000     |
| Blood gas PH (7.35-7.45)                      | 7.40 ± 0.28                  | 7.40 ± 0.21                         | 0.266     |
| PCO₂ (mmHg)                                   | 36.76 ± 5.12                 | 37.51 ± 4.84                        | 0.519     |
| HCO₃⁻ (mmol/L)                                | 23.20 ± 3.15                 | 23.87 ± 2.63                        | 0.327     |
| BE (mmol/L)                                   | -1.80 (-13.3, 0.82)          | -0.77 (-19.2, 1.00)                 | 0.165 (Non-parametric) |
| Urinary calcium, (mmol/24h)                   | 8.30 ± 3.30                  | 7.98 ± 3.64                         | 0.280     |
| Urinary phosphate, (mmol/24h)                 | 18.8 ± 7.34                  | 20.4 ± 8.34                         | 0.389     |
| Urinary potassium, (mmol/24h)                 | 18.65 ± 7.11                 | 20.40 ± 8.34                        | 0.331     |
| Urine sodium (mmol/24h)                       | 138.46 (93.01, 205.75)       | 197.6 (157.59, 238.51)              | 0.161 (Non-parametric) |
| Urine magnesium (mmol/24h)                    | 2.85 (1.84, 3.63)            | 2.7 (2.19, 3.48)                    | 0.898 (Non-parametric) |
| OC (ng/ml)                                    | 60.06 (29.49, 125.25)        | 59.61 (33.58, 131.30)               | 0.903 (Non-parametric) |
|CTX (ng/ml)                                    | 0.99 (0.65, 1.86)            | 1.18 (0.80, 2.49)                   | 0.225 (Non-parametric) |
|PINP (ng/ml)                                   | 70 (45.28, 125.25)           | 74.28 (41.09, 103.80)               | 0.709 (Non-parametric) |
|Kidney stones (with/without)                   | 19/22                        | 12/22                               | 0.333 (χ²) |
|Fracture (with/without)                        | 13/28                        | 10/24                               | 0.830 (χ²) |
On stratification according to sex, serum phosphate level, femoral neck and total hip BMD were significantly decreased, while the proportion of patients with bone fractures and osteoporosis at any site were significantly increased in female patients in the renal tubular acidification dysfunction group compared with the normal function group. However, there were no such differences in male patients between the two groups. The comparison of the other parameters between the two groups was the same as before the gender stratification. (Tables 3 and 4)

**Discussion**

Abnormal renal tubular acidosis may affect bone metabolism. Results of former study [3] showed that patients with abnormal distal renal tubular acidification may not manifest in significant systemic acidosis, this persistent acid load may trigger the release of the alkali in the bone, resulting in greater bone loss. Other study found that patients with osteoporosis or reduced BMD have a strong relationship with incomplete distal renal tubular acidosis [11]. It has been reported that patients with PHPT are prone to renal tubular dysfunction [12, 13].

### Table 2 Comparison of bone mineral density in the renal tubular acidification dysfunction group and the normal function group (X±S)

| Variable (BMD)                  | Distal renal tubular dysfunction group   | Distal renal tubular normal group   | P    |
|--------------------------------|-----------------------------------------|-----------------------------------|------|
| L1-L4 (g/cm²)                  | 0.837 ± 0.206                           | 0.923 ± 0.210                     | 0.166|
| Femoral neck (g/cm²)           | 0.661 ± 0.173                           | 0.727 ± 0.130                     | 0.112|
| Total hip (g/cm²)              | 0.676 ± 0.177                           | 0.770 ± 0.139                     | 0.030|
| Osteoporosis at any site (n, %)| 23(62.1%)                               | 11(44%)                           | 0.159(χ²) |

### Table 3 Comparison of bone mineral density between female patients in the renal tubular acidification dysfunction group and the normal function group (X±S)

|                        | Distal renal tubular dysfunction group (28) | Distal renal tubular normal group (26) | P    |
|------------------------|--------------------------------------------|---------------------------------------|------|
| Age, y                 | 60.21 ± 13.4                               | 57.6 ± 11.2                           | 0.436|
| BMI (kg/m²)            | 23.82 ± 5.16                               | 24.19 ± 3.93                         | 0.770|
| Premenopausal/postmenopausal | 4/24                                 | 3/23                                  | 0.112|
| Albumin, g/L           | 40.89 ± 4.11                               | 40.50 ± 3.56                         | 0.710|
| Albumin-corrected serum calcium, mmol/L | 2.80 ± 0.42                           | 2.85 ± 0.31                           | 0.615|
| Serum phosphate, mmol/L | 0.71 ± 0.19                                | 0.82 ± 0.18                          | 0.034|
| Serum sodium (mmol/L)  | 140.92 ± 3.05                              | 141.7 ± 2.63                         | 0.371|
| Serum magnesium (mmol/L)| 0.81 ± 0.12                                | 0.86 ± 0.08                          | 0.149|
| PTH (pmol/L)           | 64.9 (25.1, 145.25)                        | 30.15 (18.95, 65.92)                 | 0.083 (Non-parametric) |
| 25OHD (nmol/L)         | 29.5 (20.4, 41.8)                          | 24.99 (20.23, 32.61)                 | 0.272 (Non-parametric) |
| Urinary calcium, mmol/24h | 8.01 ± 3.13                              | 9.86 ± 6.21                          | 0.169|
| Urinary phosphate, mmol/24h | 17.84 ± 6.15                           | 19.51 ± 8.85                         | 0.421|
| Urine sodium (mmol/24h) | 159.12 (97.65, 208)                       | 187.2 (101.4, 223.0)                 | 0.683 (Non-parametric) |
| Urine magnesium (mmol/24h) | 3.3 (2.17, 4.06)                        | 2.7 (2.19, 3.50)                     | 0.486 (Non-parametric) |
| L1-L4 (g/cm²)          | 0.787 ± 0.195                              | 0.863 ± 0.187                        | 0.214|
| Femoral neck (g/cm²)   | 0.604 ± 0.163                              | 0.719 ± 0.129                        | 0.023|
| Total hip (g/cm²)      | 0.604 ± 0.159                              | 0.756 ± 0.128                        | 0.002|
| Fracture (with/without) | 12/16                                     | 4/22                                 | 0.038 (Fisher) |
| Kidney stones (with/without) | 11/17                               | 5/21                                 | 0.107 (χ²) |
| Osteoporosis at any site (n, %) | 19 (67%)                              | 9 (34%)                              | 0.015 (χ²) |
So we carried out this retrospective study try to find whether the dysfunction of renal tubular acidification may affect the PHPT patients’ outcomes. The cut-off rate we used to define acidification function is from our lab. We found about half of the PHPT patients (54.6 %) had distal renal tubular acidification dysfunction. Although the impaired titratable acid and ammonia ion secretion in the distal renal tubules did not cause body acid-base imbalance, we found that total hip bone density was significantly decreased in the patients with this abnormal acidification. Stratification according to gender showed that female patients with abnormal distal tubular acidification function had lower femur neck and total hip BMD and were more susceptible to bone fracture compared to those in the normal function group. However, there were no such differences in male patients between the two groups. Castellano et al. [14, 15] reported that sex and menopausal status may affect the clinical presentations of PHPT. They found that postmenopausal female PHPT patients were more prone to osteoporosis compared with male patients. Cheng et al. [16] reported that sex and age can modify skeletal manifestations in an experimental model of hyperparathyroidism, and found that high PTH levels reduced trabecular bone mass in female mice but had the opposite effect in male mice. Our results were consistent with these studies, in the condition of increasing acid loading, female PHPT patients appeared to have increased susceptibility to osteoporosis and bone fracture.

With the exception of serum phosphate and plasma 25OHD levels, serum calcium, alkaline phosphatase, PTH, bone turnover indices and electrolyte in urine were similar between the groups with and without acidification disorders. Therefore, we speculated that decreased secretion of acid in the distal renal tubular may directly affect bone mass.

The pathogenesis of distal renal tubular acidification dysfunction in PHPT patients is not clear. It has been suggested that hypercalciuric renal tubular damage may induce dysfunction of the distal renal tubular epithelium [6, 12]. However, we found no significant differences in urinary calcium levels between the groups with and without acidification dysfunction in the present study. Other groups have suggested that the long duration of the disease is responsible for renal interstitial calcification, which causes tubular acidification

| Table 4 Comparison of bone mineral density between male patients in the renal tubular acidification dysfunction group and the normal function group (X±S) |
|---------------------------------|---------------------------------|---------------------------------|
| Age, y                          | 63.5 ± 8.7                      | 54.25 ± 13.7                    | 0.081 |
| BMI (kg/m²)                     | 24.94 ± 4.2                     | 26.51 ± 3.09                    | 0.373 |
| Albumin, g/L                    | 42.25 ± 3.30                    | 41.75 ± 3.49                    | 0.750 |
| Albumin-corrected serum calcium, mmol/L | 2.80 ± 0.32                     | 2.79 ± 0.34                     | 0.968 |
| Serum phosphate, mmol/L         | 0.66 ± 0.13                     | 0.72 ± 0.17                     | 0.402 |
| PTH (pmol/L)                    | 54.15 (25.2, 112.75)            | 41.25 (15.52, 62.8)             | 0.217 (Non-parametric) |
| 25OHD (nmol/L)                  | 40.05 (20.0, 48.1)              | 31.4 (23.8, 32.4)               | 0.554 (Non-parametric) |
| Serum sodium (mmol/L)           | 141.9 ± 1.28                    | 141.85 ± 1.95                   | 0.957 |
| Serum magnesium (mmol/L)        | 0.87 ± 0.07                     | 0.86 ± 0.07                     | 0.866 |
| Urinary calcium, mmol/24h       | 9.07 ± 3.83                     | 9.23 ± 6.37                     | 0.944 |
| Urinary phosphate, mmol/24h     | 20.56 ± 9.25                    | 23.28 ± 5.99                    | 0.473 |
| Urine sodium (mmol/24h)         | 110.61 (68.41, 183.39)          | 209.8 (141.18, 259.26)          | 0.093 (Non-parametric) |
| Urine magnesium (mmol/24h)      | 2.12 (1.52, 3.49)               | 2.82 (2.23, 4.39)               | 0.258 (Non-parametric) |
| L1-L4 (g/cm²)                   | 1.004 ± 0.165                   | 1.076 ± 0.213                   | 0.441 |
| Femoral neck (g/cm³)            | 0.797 ± 0.118                   | 0.781 ± 0.133                   | 0.798 |
| Total hip (g/cm³)               | 0.823 ± 0.134                   | 0.835 ± 0.163                   | 0.870 |
| Kidney stones (with/without)    | 3/10                            | 2/6                             | 1.000 (Fisher) |
| Fracture (with/without)         | 8/5                             | 7/1                             | 0.336 (Fisher) |
| Osteoporosis at any site(n,%)   | 3(23%)                          | 1 (12.5%)                       | 0.549 (Fisher) |
Conclusion

In summary, our study found PHPT patients with abnormal distal renal tubular acidification may have lower hip bone density. Female PHPT patients with distal renal tubular acidification dysfunction showed increased susceptibility to fractures and the development of osteoporosis.

Our study is a real-world study, it is retrospectively analysis the data from the hospitalized patients. The test to evaluate the renal tubular acidification has been used in the Nephrology Department of our hospital for more than 20 years. However this method is not standardized and wildly accepted. The relatively small-scale of this study may affect its strength. So further larger scale and multi-center study are needed to confirm our findings.

Abbreviations

250HD: 25 hydroxyvitamin D; PHPT: Primary hyperparathyroidism; PTH: Parathyroid hormone; BMD: Bone mineral density; AKP: Alkaline phosphatase; TA: Titratable acid; OC: Osteocalcin; CTX: Type I collagen cross-linked C-telopeptide; PINP: Procollagen type I N-terminal propeptide

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Authors’ contributions

HWJ, BPW, and CLD conceived and devised the study. WNT, YC, TL and HW collected the data and WNT analyzed the data. All authors contributed to the interpretation of the data. WNT drafted the article, and all authors reviewed and edited the manuscript, approved the version to be published and agreed to be accountable for all aspects of the work. WNT and CLD accept full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish it.

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Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This is a retrospective study based on data collected from the Endocrinology and Metabolism Disease Department of TJMUG Hospital. The paper was reported after the approval of Institutional Review Board (IRB)/Ethical Committee of TJMUG Hospital.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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