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ORIGINAL PAPER

# Prevalence and densitometric characteristics of incomplete distal renal tubular acidosis in men with recurrent calcium nephrolithiasis

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**Abstract** The aim of this study was to assess the prevalence of incomplete distal renal tubular acidosis (idRTA) in men with recurrent calcium nephrolithiasis and its potential impact on bone mineral density. We conducted a retrospective analysis of 150 consecutive, male idiopathic recurrent calcium stone formers (RCSFs), which had originally been referred to the tertiary care stone center of the University Hospital of Berne for further metabolic evaluation. All RCSFs had been maintained on a free-choice diet while collecting two 24-h urine samples and delivered second morning urine samples after 12 h fasting. Among 12 RCSFs with a fasting urine pH >5.8, a modified 3-day ammonium chloride loading test identified idRTA in 10 patients (urine pH >5.32, idRTA group). We matched to each idRTA subject 5 control subjects from the 150 RCSFs, primary by BMI and then by age, i.e., 50 patients, without any acidification defect (non-RTA group) for comparative biochemistry and dual energy X-ray absorptiometry (DEXA) analyses. The prevalence of primary idRTA among RCSFs was 6.7% (10/150). Patients with idRTA had significantly higher 2-h fasting and 24-h urine pH (2-h urine pH:  $6.6 \pm 0.4$  vs.  $5.2 \pm 0.1$ ,  $p = 0.001$ ; 24-h urine pH:  $6.1 \pm 0.2$  vs.  $5.3 \pm 0.3$ ,  $p = 0.001$ ), 24-h urinary calcium excretion ( $7.70 \pm 1.75$  vs.  $5.69 \pm 1.73$  mmol/d,  $p = 0.02$ ),

but significantly lower 24-h urinary urea excretion ( $323 \pm 53$  vs.  $399 \pm 114$  mmol/d,  $p = 0.01$ ), urinary citrate levels ( $2.32 \pm 0.82$  vs.  $3.01 \pm 0.72$  mmol/d,  $p = 0.04$ ) and renal phosphate threshold normalized for the glomerular filtration rate (TmPO<sub>4</sub>/GFR:  $0.66 \pm 0.17$  vs.  $0.82 \pm 0.21$ ,  $p = 0.03$ ) compared to non-RTA patients. No significant difference in bone mineral density (BMD) was found between idRTA and non-RTA patients for the lumbar spine (LS BMD (g/cm<sup>2</sup>):  $1.046 \pm 0.245$  SD vs.  $1.005 \pm 0.119$  SD,  $p = 0.42$ ) or femoral neck (FN BMD (g/cm<sup>2</sup>):  $0.830 \pm 0.135$  SD vs.  $0.852 \pm 0.127$  SD). Thus, idRTA occurs in 1 in 15 male RCSFs and should be sought in all recurrent calcium nephrolithiasis patients. Bone mineral density, however, does not appear to be significantly affected by idRTA.

**Keywords** Incomplete renal tubular acidosis · Metabolic acidosis · Recurrent nephrolithiasis · Bone mineral density

## Abbreviations

idRTA	Incomplete distal renal tubular acidosis
Non-RTA	Non-idRTA recurrent stone formers
BMD	Bone mineral density
LS	Lumbar spine
FN	Femoral neck
DEXA	Dual energy X-ray absorptiometry
SD	Standard deviation

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## Introduction

The skeleton serves as a reservoir of labile calcium that can be mobilized in response to humoral mechanisms for the defense of blood pH and the maintenance of the ionic calcium concentration. Several reports have underlined the

negative impact of chronic metabolic acidosis on bone mineral composition. Studies by others and us have suggested a link between renal stone formation and osteoporosis [1–4].

Distal renal tubular acidosis is a syndrome of systemic hyperchloremic acidosis with alkaline urine pH, hypocitraturia and hypercalciuria due to reduced secretion of  $H^+$  ions by the cells of the collecting tubules [5, 6]. Overt metabolic acidosis in distal renal tubular acidosis contributes as a predisposing factor to recurrent nephrolithiasis and bone loss [7, 8]. In contrast, patients with incomplete distal renal tubular acidosis (idRTA) have a persistently high urine pH, but are able to maintain net acid excretion under basal conditions. Thus, idRTA does not manifest in overt systemic acidosis, but may cause recurrent positive acid loads in periods of increased protein intake or catabolic stress triggering alkali release from the bone and thus leading to greater bone resorption [9, 10]. Patients with idRTA frequently suffer from recurrent nephrolithiasis, mainly with calcium phosphate stones, due to the combination of hypercalciuria, low urine citrate, and high urine pH which favors calcium phosphate crystallization [11].

Studies on an association between idRTA and calcium nephrolithiasis are scarce. Population-based studies reported incidence rates of idRTA of 2–8% in patients with nephrolithiasis, but were not able to establish a correlation between idRTA and low bone mineral density (BMD) [12, 13]. In patients with reduced bone mass, however, prevalences of idRTA as high as 22% have been reported in smaller studies, and a strong relationship between osteoporosis or reduced BMD and idRTA has been described in adults [10, 14]. In children, idRTA is known to cause skeletal growth retardation [15].

The aim of this study was to retrospectively assess the prevalence of idRTA in men with recurrent calcium nephrolithiasis and its potential impact on bone mineral density.

## Materials and methods

### Study population

After institutional review board approval, a retrospective analysis of 150 consecutive, male idiopathic recurrent calcium stone formers (RCSFs) who had originally been referred to the tertiary care stone centre of the University Hospital of Berne for further metabolic evaluation was performed. An RCSF was defined as a person who had passage or had had removal of at least two calcium-containing stones, established by either by stone analysis or conventional radiogram findings.

RCSFs with a history of hyperthyroidism, hyperparathyroidism or sarcoidosis were excluded. Past and present smoking status, alcohol intake and corticosteroid use were documented, and the patients' weight and height were recorded. According to our standard diagnostic protocol [11], all RCSFs had been maintained on a free-choice diet while making two 24-h urine collections (in the absence of urinary tract infections).

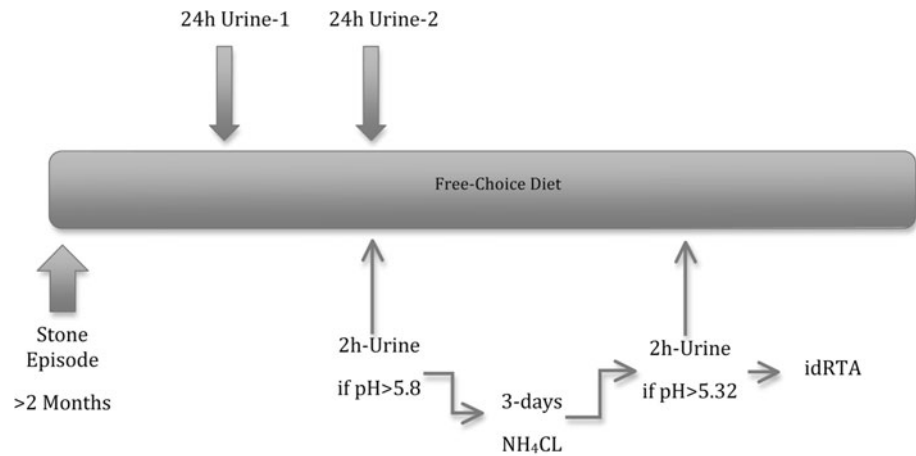
Among 12 RCSFs with urine pH values  $>5.8$  after 12 h of fasting, a modified 3-day ammonium chloride loading test (see biochemistry) had identified idRTA in 10 patients who formed the idRTA group. We matched to each idRTA subject 5 control subjects from the above-mentioned original 150 RCSFs, primary by BMI (due to the known influence of weight on bone mineral density) and then by age, i.e., 50 patients without an acidification defect.

These 50 RCSFs served as a non-RTA group for comparative laboratory and densitometric analyses. The exact findings regarding stone composition were known in 9/10 idRTA patients (7 calcium phosphate/calcium oxalate stones, 2 calcium oxalate stones) and in 24/50 control patients (22 calcium oxalate, 2 calcium oxalate/calcium phosphate). In the remaining patients, diagnosis was based on the radio-opaque stone findings from conventional radiograms.

### Biochemistry

Plasma from fasting venous blood was analyzed for creatinine, total calcium, phosphate and alkaline phosphatase activity using autoanalyzer techniques. In whole blood, ionized calcium was measured by an ion-selective electrode (Ciba Corning Diagnostics Corp., Medford, MA, USA) and venous bicarbonate by a Ciba Corning 278 blood gas system immediately after sampling without compression. None of the study subjects had systemic acidosis based on the venous BGA analysis. Serum intact PTH (normal values 10–65 pg/mL) and 25-OH-Vitamin D (normal range 6–40 ng/mL) were measured using radioimmunoassay (Nichols Institute, San Juan Capistrano, CA, USA). All study subjects had two 24-h urine collection under free-choice diet. On evaluation day sampling of venous blood and a 2-h fasting urine after 12 h without eating and 8 h without drinking were performed in all patients (Fig. 1). In 2-h fasting urine (2nd morning urine), pH was measured by a Metrohm 654 pH-meter (Metrohm, Herisau, Switzerland). Fasting urine was analyzed for calcium and creatinine using autoanalyzer techniques, and hydroxyproline was determined using a kit (Organon Teknica, Boxtel, The Netherlands). Patients with an urinary pH  $>5.8$  in the 2-h fasting urine underwent a modified ammonium chloride loading test using a lower dose of ammonium chloride, as originally established by Hess et al.

**Fig. 1** Protocol for urine evaluation of recurrent renal stone formers. All study subjects had two 24-h urine collection under free-choice diet (24-h urine-1 and 24-h urine-2: 24-h urine collections no. 1 and 2). On evaluation day a 2-h fasting urine after 12 h without eating and 8 h without drinking were performed in all patients (2-h urine). Patients with an urinary pH >5.8 in the 2-h fasting urine underwent the modified ammonium chloride loading test, as previously established by Hess et al. [11]



[11]. In 24-h urine, creatinine and calcium were measured by autoanalyzer techniques, and citrate was determined using the citrate lyase method [11]. The 24-h urine samples were collected in a 3-l plastic bottles containing 10 g boric acid as preservative. In collaboration with the central laboratory of the University Hospital in Berne, we had previously extensively studied the influence of 10 g of boric acid on pH from 24-h urine collections in the 3-l urine containers. We found that pH values were not significantly altered. All individual 24-h urine values are the mean of two urine collections.

The modified, “more physiologic” ammonium chloride loading test consisted of sampling venous blood and 2-h fasting urine after 12 h without eating and 8 h without drinking on day 0. From then on, ammonium chloride (total of 0.05 g/kg body weight/day or 0.95 mEq/kg body weight/day) was added to the free-choice diet for 3 days, given in capsules (Streuli Pharma, Uznach, Switzerland) in three divided doses 20 min before each meal. On day 3, sampling of fasting venous blood and 2-h urine was repeated.

#### Bone mineral density measurements

We routinely perform DEXA scans on recurrent calcium stone formers during metabolic evaluation. 50 control patients, without any acidification defect, were selected (non-RTA group) for comparative DEXA analyses versus the idRTA group. BMD measurements of the lumbar spine (LS; L2–L4) and of the non-dominant (or non-fractured) femoral neck (FN) were assessed by DEXA (Hologic, Bedford, MA, USA).

Scans had been performed according to the manufacturer’s guidelines and analyzed according to ISCD rules with respect to exclusion of vertebrae that had been affected by local structural changes or artefacts [REF International Society for Clinical Densitometry (ISCD) official positions 2007; available at <http://www.iscd.org/Visitors/positions/officialPositionsText.cfm>. BMD was

expressed in grams per square centimeter of hydroxyapatite and as *T*-scores (standard deviation [SD] from the mean of a healthy young reference population) and *Z*-scores (SD from the mean of the reference population of the same age). When vertebrae had to be excluded, the BMD of the remaining vertebrae was used to derive the *T*- and *Z*-scores, i.e., three vertebrae instead of four, or two instead of three, were used, respectively. Local normal values were derived from 400 healthy white women and men living in the area of Berne, Switzerland. Quality control was performed daily (anthropometric spine phantom supplied by the manufacturer) with an overall precision error of 0.3% in vitro and a mean precision error in our hands of 1.1% in vivo.

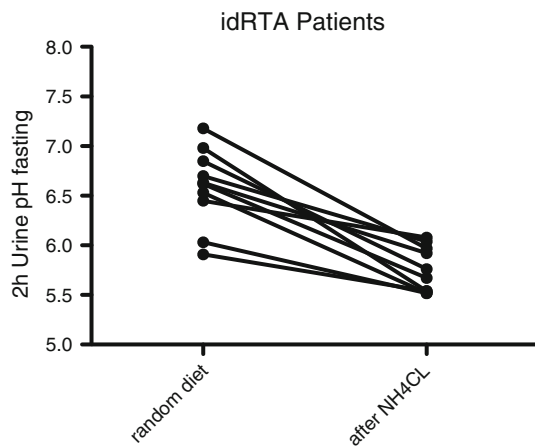
#### Statistical analysis

The data are presented as mean  $\pm$  SD. Normality of the data was assessed by Kolmogorov–Smirnov test. Student’s *t* test was used as appropriate for the comparison of the group means and proportions. Statistical analyses were done using Prism 4.0; GraphPad Software Inc., San Diego, CA. A *p* value <0.05 was considered statistically significant.

#### Results

Two-hour fasting urine pH, measured in all 150 male RCSFs, exceeded 5.8 in 12 cases. Ammonium chloride loading was abnormal in 10 cases, i.e., the fasting urine pH after ammonium chloride loading did not fall below 5.32 (Fig. 2). In the absence of systemic metabolic acidosis upon ammonium chloride loading, these 10 RCSFs were diagnosed as having idRTA. Thus, the prevalence of idRTA in 150 male RCSFs was 6.7%.

Biometric data and serum and urinary results in idRTA and non-RTA groups are summarized in Table 1 and Fig. 3. There were no significant differences between the



**Fig. 2** Line diagram of 2-h fasting urine pH under free choice diet and after  $\text{NH}_4\text{Cl}$  test in idRTA subjects

two groups, except for higher 2-h fasting and 24-h urine pH (2-h urine pH:  $6.6 \pm 0.4$  vs.  $5.2 \pm 0.1$ ,  $p = 0.001$ ; 24-h urine pH:  $6.1 \pm 0.2$  vs.  $5.3 \pm 0.3$ ,  $p = 0.001$ ), 24-h urinary calcium excretion ( $7.70 \pm 1.75$  vs.  $5.69 \pm 1.73$  mmol/d,  $p = 0.02$ ), but significantly lower 24-h urinary urea excretion ( $323 \pm 53$  vs.  $399 \pm 114$  mmol/d,  $p = 0.01$ ), urinary citrate levels ( $2.32 \pm 0.82$  vs.  $3.01 \pm 0.72$  mmol/d,  $p = 0.04$ ) and renal phosphate threshold normalized for the glomerular filtration rate ( $\text{TmPO}_4/\text{GFR}$ :  $0.66 \pm 0.17$  vs.  $0.82 \pm 0.21$ ,  $p = 0.03$ ) compared to non-RTA patients.

Densitometric data are given in Table 2. Bone mineral density in  $\text{g}/\text{cm}^2$ , Z-scores as comparative references values and T-scores did not differ significantly between the idRTA and the non-RTA groups, either for the LS or FN. In particular, the clinically most widely used T-scores were not different, either for the LS ( $-0.4 \pm 1.8$  in idRTA vs.  $-0.7 \pm 0.8$  in non-RTA,  $p = 0.41$ ) or FN ( $-0.9 \pm 1.1$  in idRTA vs.  $-0.7 \pm 1.0$  in non-RTA,  $p = 0.60$ ). Figure 4 shows a box-plot of T- and Z-scores for the LS (L2–L4) and FN for both groups.

## Discussion

This study investigated two issues: (1) the prevalence of idRTA in male recurrent calcium stone formers (RCSFs); and (2) the impact of idRTA on bone mineral density (BMD).

The prevalence of RTA in the general population in Switzerland is not known because no epidemiological study has ever investigated this issue. We found that 6.7% of 150 male RCSFs had idRTA, i.e., 1 out of 15 male RCSFs can be expected to have idRTA. This is similar to the findings of previous epidemiological studies in endemic areas with a known high prevalence of idRTA [13, 16]. We

**Table 1** Demographic and laboratory data of idRTA and non-RTA groups

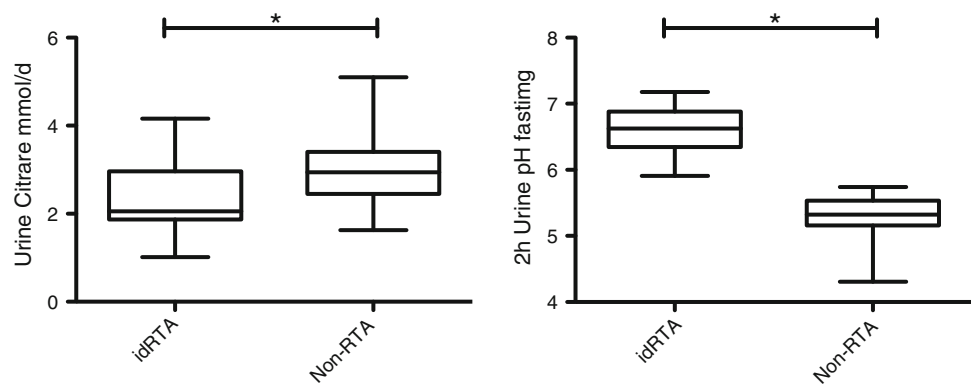
Groups	idRTA (n = 10)	Non-RTA (n = 50)	p value
Age (years)	$53 \pm 12$	$46 \pm 11$	0.10
BMI ( $\text{kg}/\text{cm}^2$ )	$26 \pm 3$	$26 \pm 3$	0.97
S-Bicarbonate (mmol/l)	$26 \pm 3$	$28 \pm 2$	0.15
S-Bicarbonate after $\text{NH}_4\text{Cl}$ (mmol/l)	$23 \pm 1$		
S-creatinin (mmol/l)	$86.4 \pm 13$	$92.3 \pm 14$	0.28
S-total $\text{Ca}^{2+}$ (mmol/l)	$2.3 \pm 0.1$	$2.4 \pm 0.1$	0.10
S-ion $\text{Ca}^{2+}$ (mmol/l)	$1.2 \pm 0.1$	$1.3 \pm 0.1$	0.22
S-phosphate (mmol/l)	$0.9 \pm 0.1$	$0.9 \pm 0.2$	0.82
S-Alk-Phos (U/l)	$69 \pm 13$	$78 \pm 24$	0.27
PTH (pg/ml)	$27 \pm 13$	$31 \pm 11$	0.32
S-25(OH)VitD <sub>3</sub> (nmol/ml)	$92 \pm 6$	$71 \pm 23$	0.06
2-h urine pH fasting	$6.6 \pm 0.4$	$5.2 \pm 0.1$	<b>0.001</b>
2-h urine pH after $\text{NH}_4\text{Cl}$	$5.8 \pm 0.3$		
24-h urine pH	$6.1 \pm 0.2$	$5.3 \pm 0.3$	<b>0.001</b>
U-HProl/creat (nmol/mmol)	$0.01 \pm 0.01$	$0.01 \pm 0.01$	0.98
U-Ca (mmol/d)	$7.70 \pm 1.75$	$5.69 \pm 1.69$	<b>0.02</b>
U-citrate (mmol/d)	$2.32 \pm 0.82$	$3.01 \pm 0.72$	<b>0.04</b>
U-anion-gap	$78 \pm 21$	$67 \pm 24$	0.29
U-uric acid ( $\mu\text{mol}/\text{d}$ )	$2,982 \pm 1,297$	$3,397 \pm 1,016$	0.38
U-urea (mmol/d)	$323 \pm 53$	$399 \pm 114$	<b>0.01</b>
$\text{TmPO}_4/\text{GFR}$	$0.66 \pm 0.17$	$0.82 \pm 0.21$	<b>0.03</b>

Bold values indicate  $p < 0.05$  was considered statistically significant S serum, S-ion  $\text{Ca}^{2+}$  serum ionized calcium concentration, S-Alk-Phos serum alkaline phosphatase, PTH serum parathormone, S-25(OH)VitD<sub>3</sub> serum 25(OH)Vitamin D<sub>3</sub>, U urinary, 2-h fasting urine pH under free-choice diet, 24-h urine pH under free-choice diet, 2-h urine pH after  $\text{NH}_4\text{Cl}$  ammonium chloride loading test, U-HProl/creat urinary hydroxyproline/creatinine ratio, U-Ca 24-h urinary calcium excretion, U-citrate: 24-h urinary citrate excretion,  $\text{TmPO}_4/\text{GFR}$ : renal phosphate threshold normalized for the glomerular filtration rate

thus believe that idRTA is generally underdiagnosed due to the lack of routine screening, including ammonium chloride loading, in patients with recurrent nephrolithiasis or suspected low bone mineral density. Our study also confirmed the well-known increased urinary calcium and decreased urinary citrate excretion in RCSFs with idRTA [11]. The difference in urinary citrate is statistically significant, although not in the expected magnitude. This may be attributable to the limited sample size of idRTA patients and due to the fact that urinary citrate in both groups was performed under free choice diet and not under standardized conditions.

Chronic acid retention in idRTA increases the release of calcium phosphate from bone and reduces tubular reabsorption of calcium and phosphate. As a consequence,

**Fig. 3** Box-plots of 24-h urinary citrate excretion and from 2-h fasting urine pH, both for idRTA and non-RTA groups



hypercalciuria, a known risk factor for stone formation develops and the precipitation of calcium phosphate crystals is further favored by the persistently high urine pH in idRTA [6, 17]. Moreover, idRTA reduces the urinary excretion of citrate, because intracellular acidosis in proximal renal tubular cells—as in idRTA—favors the tubular reabsorption of citrate. Because citrate is an important inhibitor of the precipitation of stone-forming calcium salts in urine, hypocitraturia together with hypercalciuria and elevated urinary pH additionally predispose patients with idRTA to calcium phosphate stone formation [6]. Similarly, chronic dietary acid loads were shown to result in significant and reversible negative calcium balance [18]. On the other hand, partial neutralization of an acidogenic western diet with exogenous potassium citrate or potassium bicarbonate can improve calcium balance, reduce bone reabsorption, and increase the rate of bone formation [19, 20].

Our study was not able to detect a significant impact of idRTA on BMD in the LS or FN. According to BMD values and *T*- and *Z*-scores, the skeletal scores were not significantly different between our idRTA and non-RTA groups. Findings on the clinical nature and impact of idRTA on bone density are inconsistent. In accordance with our findings, a recent report by Pongchaiyakul et al. [13] found no association between idRTA and lower bone mass in a community-based study on endemic RTA in Thailand. After a follow-up period of 24 months, no significant difference in bone loss between idRTA subjects and controls was found, providing additional support for the hypothesis that idRTA may have at most a minor impact on BMD. Considering the differences in genetic background, population characteristics and dietary habits, however, it may be inappropriate to extrapolate findings from Thailand to our Swiss study population.

Renal tubular dysfunction after kidney transplantation inducing RTA has been described by Keven et al. [21] in over 30% of allograft recipients. Nevertheless, the prevalence of osteopenia or osteoporosis appeared not to be different between allograft recipients with RTA and those

**Table 2** Densitometric characteristics of idRTA and non-RTA groups

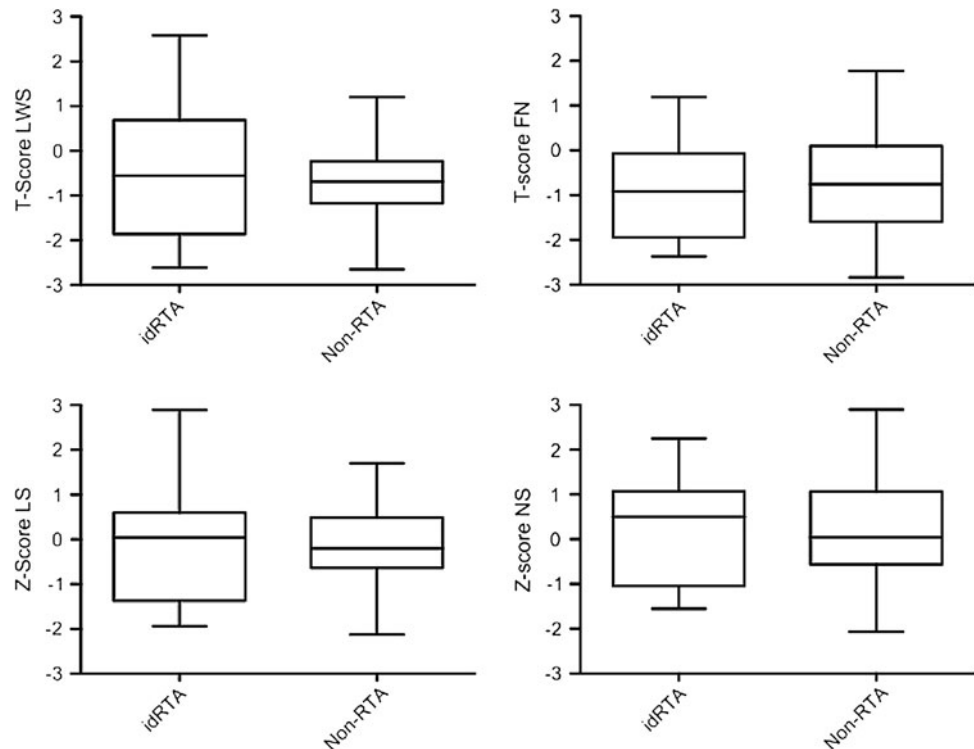
	idRTA ( <i>n</i> = 20)	Non-RTA ( <i>n</i> = 50)	<i>p</i> value
Lumbar spine			
BMD (g/cm <sup>2</sup> )	1.046 ± 0.245	1.005 ± 0.119	0.42
<i>T</i> -score (SD)	−0.4 ± 1.8	−0.7 ± 0.8	0.41
<i>Z</i> -score (SD)	0.3 ± 1.8	−0.1 ± 0.9	0.26
Femoral neck			
BMD (g/cm <sup>2</sup> )	0.830 ± 0.135	0.852 ± 0.127	0.61
<i>T</i> -score (SD)	−0.9 ± 1.1	−0.7 ± 1.0	0.60
<i>Z</i> -score (SD)	0.3 ± 1.2	0.3 ± 1.5	0.92

without. A major limitation of this study, however, was the lack of acid loading tests and the absence of information on a history of renal osteodystrophy or pre-transplant BMD status.

The studies by Weger et al. [10] and Deutschmann et al. [14] in patients with osteoporosis contrast sharply with our findings and those of others. The incidence of idRTA in these studies was up to 22%. However, there was a fundamental difference from our approach and that of others: both studies did not evaluate kidney stone patients, but selected primarily patients with osteoporosis for further evaluation of osteoporosis risk factors. Indeed, Deutschmann et al. [14] found a significant correlation between the number of identified risk factors and severity of bone disease, but did not find a direct correlation between idRTA and BMD. Furthermore, they did not measure urinary excretion of citrate before or after ammonium chloride loading.

We offer a hypothetical explanation for the differences observed in BMD between idRTA patients primarily affected by kidney stone disease and those suffering from osteoporosis. Chronic acid retention in idRTA might mobilize extracellular buffers in two different ways: on the one hand, renal stone patients with idRTA might preferentially buffer retained acid in renal tubular cells, resulting in a rise in citrate uptake (hypocitraturia) and reduced renal

**Fig. 4** Box-plots of Z- and T-scores of lumbar spine (LS) and femoral neck (FN) for both idRTA and non-RTA groups



tubular calcium reabsorption (hypercalciuria); on the other hand, osteoporosis patients with idRTA might rather use bone tissue for extracellular buffering, which in turn would result in a progressive loss of bone mass.

In conclusion, one in 15 male recurrent calcium stone formers exhibit idRTA. However, idRTA in men with recurrent calcium stone disease does not appear to significantly affect BMD in the lumbar spine and femoral neck in comparison with stone formers without idRTA.

**Conflict of interest** The authors declare that they have no competing interests.

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