

# Renal Tubular Acidosis, Sjögren Syndrome, and Bone Disease

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**Background:** There has been disagreement about whether osteomalacia (adult rickets) occurs in adults with type 1 (distal) renal tubular acidosis (RTA1). Therefore, after finding scapular pseudofractures in a patient with RTA1 and Sjögren syndrome, we decided to survey other patients with RTA to learn whether osteomalacia occurred in others and, if it did, whether it was necessarily associated with the presence of Sjögren syndrome.

**Methods:** We examined the hospital records and laboratory findings of 250 patients with codes for RTA, 124 with codes for osteomalacia, and 20 with codes for Sjögren syndrome who were seen at a university-affiliated acute care municipal hospital since 1990. Further detailed survey was then limited to patients older than 15 years and excluded those with potentially confounding

causes of bone disease such as chronic renal insufficiency or sickle cell disease. Seven adults with RTA1 were thereby identified.

**Results:** Two adults with RTA1 had radiological and biochemical findings compatible with osteomalacia, and 1 had findings compatible with Sjögren syndrome. A third patient without Sjögren syndrome had biochemical findings suggestive of osteomalacia.

**Conclusions:** Osteomalacia seems to occur in some adult patients with RTA1, and not only in association with Sjögren syndrome. We found no biochemical evidence of osteomalacia in the patients with Sjögren syndrome who did not have RTA.

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**W** E RECENTLY TREATED a patient who was hospitalized repeatedly for severe weakness due to potassium deficiency caused by type 1 (distal) renal tubular acidosis (RTA1). She also had findings characteristic of Sjögren syndrome, and later review of her x-rays disclosed previously overlooked pseudofractures, consistent with osteomalacia. Osteomalacia (adult rickets) was described in early reports of patients with RTA1,<sup>1(pp227-249),2-4</sup> but the association was later discounted by some authors who attributed the finding of bone disease in patients with renal acidosis without glomerular insufficiency to proximal tubular dysfunction.<sup>5</sup> To learn whether osteomalacia occurred in any of our other adult patients with RTA1, and whether there might be a relationship between such bone disease and Sjögren syndrome, we reviewed the findings in our patients who had diagnoses of RTA1, osteomalacia, or Sjögren syndrome.

## REPORT OF A CASE

A 38-year-old African American woman was seen in March 1996 with a serum sodium

level of 141 mEq/L, potassium level of 3.0 mEq/L, carbon dioxide level of 14 mEq/L, chloride level of 114 mEq/L, urea nitrogen level of 14 mg/dL (5.0 mmol/L), and creatinine level of 0.8 mg/dL (70.7 μmol/L) (**Table 1**), but she did not then undergo treatment or further studies. She was hospitalized for severe muscle weakness in January 1998 with similar laboratory findings (Table 1). Her arterial blood pH was 7.18, PCO<sub>2</sub> was 23 mm Hg, and urine pH was 7.0, confirming a diagnosis of RTA1. Her serum calcium level was 8.2 mg/dL (2.0 mmol/L), and the phosphorus level was 1.7 mg/dL (0.5 mmol/L). The alkaline phosphatase level was 351 U/L (upper reference limit, 115 U/L), and was later shown to be due to elevation of the bone-specific fraction, compatible with osteomalacia. She had a history of cocaine abuse by means of snorting, but denied glue sniffing. She had no symptoms of renal calculi or bone disease then, but later complained of general body aches. She had no goiter or symptoms of thyroid dysfunction, and her thyroxine level was within the reference range at 9.6 μg/dL (123.6 nmol/L). Nevertheless, because her serum thyrotropin level was mildly elevated at 17 mIU/L, and the thy-

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**Table 1. Entry Laboratory Values in a Patient With RTA1, Osteomalacia, and Sjögren Syndrome\***

Date	Site	Serum Levels				
		Urea Nitrogen, mg/dL	Creatinine, mg/dL	Sodium, mEq/L	Potassium, mEq/L	Carbon Dioxide, mEq/L
March 25, 1996	OPD	14	ND	141	3.0	14
January 9, 1998	H	13	0.7	137	2.8	10
September 18, 1998	H	18	0.8	135	1.6	9
January 22, 1999	H	15	0.7	139	2.1	12
June 22, 1999	H	16	0.8	139	2.2	12
April 28, 2000	OPD	ND	ND	ND	ND	ND
August 8, 2000	H	13	0.9	137	3.0	11
April 22, 2001	ED	13	0.9	137	2.9	17

  

Date	Serum Levels						
	Chloride, mEq/L	Calcium, mg/dL	Phosphorus, mg/dL	Alkaline Phosphatase, U/L	Intact Parathyroid Hormone, pg/mL	25-OH-D, ng/mL	1,25-diOH-D, pg/mL
March 25, 1996	114	ND	ND	351	ND	ND	ND
January 9, 1998	126	ND	ND	ND	57	ND	ND
September 18, 1998	123	9.7	2.4	433	ND	ND	ND
January 22, 1999	124	9.0	2.3	363	ND	ND	ND
June 22, 1999	122	8.8	2.0	446	ND	ND	ND
April 28, 2000	ND	ND	ND	ND	ND	ND	15
August 8, 2000	122	9.0	2.5	242	55	6	19
April 22, 2001	116	8.5	2.0	239	ND	ND	ND
Reference range				30-115	10-65	7-52	15-60

Abbreviations: 1,25-diOH-D, 1,25-dihydroxyvitamin D; ED, emergency department; H, hospital; ND, not determined; NR, not reported; 25-OH-D, 25-hydroxyvitamin D; OPD, outpatient department; RTA1, type 1 (distal) renal tubular acidosis.

SI conversion factors: To convert calcium to millimoles per liter, multiply by 0.25; 1,25-diOH-D to picomoles per liter, multiply by 2.6; 25-OH-D to nanomoles per liter, multiply by 2.496; phosphorus to millimoles per liter, multiply by 0.323; urea nitrogen to millimoles per liter, multiply by 0.357.

\*Italicized type indicates values outside the reference range.

roid microsomal antibody titer was 1:6400, she was given levothyroxine sodium, 25 µg/d, without any clinical effect. Her serum was positive for hepatitis C antibody but not cryoglobulins, and results of liver function tests were within the reference range, notably the serum alanine aminotransferase level, which averaged 17.8 ± 10.5 U/L (mean ± SD) over 5 years (21 determinations). Her serum fluorescent anti-nuclear antibody titer was above 1:1280 (speckled nucleolar pattern). She also had high titers of antibodies to Ro and La, compatible with Sjögren syndrome, and later complained of dry mouth and eyes. Her serum total protein level was 7.3 g/dL and globulin level was 4.4 g/dL; on electrophoretic analysis, 22% of the serum protein was polyclonal γ-globulin. Her serum alkaline phosphatase levels were persistently elevated (160-450 U/L), and on subsequent admissions the serum levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D were low or borderline low (Table 1). Serum magnesium level was 1.9 mg/dL (0.8 mmol/L), and the ceruloplasmin concentration was also within the reference range. Computerized tomographic examination of her abdomen showed multiple bilateral renal calculi, and review of her chest x-ray in 1999 showed bilateral scapular pseudofractures, ie, Looser transformation zones, indicative of osteomalacia.<sup>1(pp206-216)</sup>

Her muscle weakness improved rapidly after potassium repletion therapy, and she was urged to continue taking potassium citrate, but did not return for outpatient care and stopped taking potassium. Recurrent muscle weakness prompted 3 further hospitalizations here and at least 2 elsewhere during the next 3 years. Some blood

test results from her first clinic visit and the first day of the other 4 hospitalizations are shown in Table 1.

## METHODS

We reviewed the hospital medical records of 250 patients whose diagnostic codes included RTA, 124 with codes for osteomalacia, and 20 with codes for Sjögren syndrome who were seen during the past 12 years at the Jacobi Medical Center in Bronx, NY, a municipal hospital affiliated with the Albert Einstein College of Medicine, Bronx. The searches were then narrowed by examining information recorded in the hospital's computerized data information system for many of those patients, particularly their hospital discharge summaries and laboratory findings. On that basis we excluded the following patients from detailed medical chart review: (1) patients who had not been hospitalized after 1990 (which did not appear to exclude any with RTA1); (2) those younger than 15 years; (3) those in whom it would not be possible to attribute bone disease, if present, to RTA1 because they had moderate or severe chronic renal failure or sickle cell disease; (4) those with amphotericin-related RTA, who were often quite ill with AIDS, malnourished, and often receiving other potentially nephrotoxic drugs; and (5) 1 patient previously described with Wilson disease and nephrocalcinosis who had proximal and distal tubular dysfunction.<sup>6</sup>

The diagnosis of RTA1 was based on the presence of persistent hyperchloremic acidosis with hypokalemia (except in patient 6), serum urea nitrogen and creatinine concentrations within or near the reference ranges, and urinary pH 6.5 or higher while acidotic. None of the patients had glucosuria on admission, which, if present, would have suggested proximal tubule dysfunction. The diagnosis of osteomalacia was supported by characteristic radiological abnormalities and elevated serum

**Table 2. Clinical Findings in 7 Patients With RTA1**

Patient No./ Sex	Imaging		Serum SS Tests†	Other Diseases
	Osteopenia	Kidneys		
1/F	Looser transformation zones	Extensive calcifications	Positive	Hypothyroid; hepatitis C
2/M	"Codfish" vertebrae and Looser transformation zones	Extensive calcifications; possible medullary sponge kidneys	Negative	Recurrent phlebitis; erythrocytosis
3/F	Not noted	Extensive calcifications	Negative	Asthma
4/F	No	Negative KUB findings	Negative	Hepatitis C
5/F	No	Negative KUB findings; 1 small calculus on sonogram	Negative	Hepatitis C with interferon therapy
6/F	No	Angiomyolipomas but no calcifications	Negative	Tuberous sclerosis
7/F	No	Interstitial nephritis; no calcifications	Positive	Overlap syndrome

Abbreviations: KUB, kidney, ureter, and bladder; RTA1, type 1 (distal) renal tubular acidosis; SS, Sjögren syndrome.

**Table 3. Laboratory Findings in 7 Patients With RTA1\***

Patient No./ Sex	Serum Levels										
	Urea Nitrogen, mg/dL	Sodium, mEq/L	Potassium, mEq/L	Carbon Dioxide, mEq/L	Chloride, mEq/L	Calcium, mg/dL	Phosphorus, mg/dL	Alkaline Phosphatase, U/L	PTH, pg/mL	25-OH-D, ng/mL	1,25-diOH-D, pg/mL
1/F	13	137	<i>2.8</i>	<i>10</i>	<i>126</i>	9.7	2.4	Elevated	57, 55	<i>6</i>	<i>15, 19</i>
2/M	12	137	<i>2.8</i>	<i>13</i>	<i>118</i>	9.1	<i>1.9</i>	Elevated	20, <i>91</i>	15	35-53
3/F	6	133	<i>3</i>	<i>11</i>	<i>111</i>	8.3	<i>1.3</i>	Usually normal	34	ND	ND
4/F	10	139	<i>2.3</i>	<i>18</i>	109	10.5	<i>1.3</i>	Usually normal	19	ND	ND
5/F	10	140	<i>1.4</i>	<i>18</i>	<i>119</i>	9.4	ND	Normal	ND	16	41
6/F	32	134	3.8	<i>15</i>	108	<i>7.5</i>	2.6	Elevated	<i>277</i>	<i>8, † 11</i>	<i>20, † 15</i>
7/F	25	136	3.7	<i>12</i>	<i>118</i>	8.7	4.4	Slightly elevated	42	18	18
									10-65	7-52	15-60

Abbreviations: 1,25-diOH-D, 1,25-dihydroxyvitamin D; normal, within reference range; ND, not determined; 25-OH-D, 25-hydroxyvitamin D; PTH, intact parathyroid hormone; RTA1, type 1 (distal) renal tubular acidosis.

SI conversion factors: See Table 1.

\*Biochemical values were measured at the index admissions. Italicized type indicates values outside the reference range. Multiple values for PTH and vitamin D in some patients denote determinations on different occasions.

†Indicates borderline low value.

bone-specific alkaline phosphatase isoenzyme activity. The diagnosis of Sjögren syndrome was based on symptoms of sicca syndrome associated with positive antibodies to Ro and La.

Most of the 250 patients with codes for RTA actually had moderate or severe chronic renal failure and/or RTA4 rather than RTA1. That left 41 patients with RTA coding whose full medical records we reviewed, of whom 7 (including the index case) had clinical and laboratory findings confirming the diagnosis of RTA1 (**Table 2** and **Table 3**). Patient 6 in Table 2, with tuberous sclerosis, had serum electrolyte levels within the reference range at 27 years of age, mild hyperchloremia several years later, and still later, mild persistent metabolic acidosis with a urine pH of 6.5 to 8.0, but serum potassium levels within the reference range. No patients with incomplete RTA were identified in this survey.

Most of the 124 patients with codes for osteomalacia were children with rickets due to serious dietary inadequacies. Most of the adults in this group had chronic renal insufficiency, and 1 had osteomalacia due to gastrointestinal tract malabsorption and vitamin D deficiency, leaving 6 whose full records were reviewed. One was already included in the RTA1 group, and the other 5 had no findings suggesting RTA1. Twenty patients had coding for Sjögren syndrome, and we reviewed the charts of the 16 who met the criteria noted above. Among those, only 2, who had already been identified, had findings of RTA.

Most of the tests noted were performed in the hospital routine clinical chemistry laboratory; measurements of serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D concentrations were performed by Quest Diagnostics, Teterboro, NJ. We reviewed the x-ray films of 6 of the 7 patients with RTA; only the reports were available for patient 5.

This study was approved by the Institutional Review Board of the Albert Einstein College of Medicine.

## RESULTS

Tables 2 and 3 show some key clinical and laboratory data in the 7 patients with RTA1. Three of them were originally hospitalized mainly for severe weakness due to potassium depletion and hypokalemia (patients 1, 4, and 5), and 3 had nephrocalcinosis or nephrolithiasis (patients 1, 2, and 3). Two had sicca symptoms and serologic evidence of Sjögren syndrome (the index patient and patient 7). Both of these patients had positive fluorescent antinuclear antibody test results (>1:1280), high titers of antibodies to Ro and La, and hyperglobulinemia (see "Comment" section), and the index patient also had laboratory evidence of autoimmune hypothyroid-

ism. Three of the 7 patients had serum antibodies to hepatitis C; 2 of them (patients 4 and 5) had laboratory evidence of liver disease, but neither of them had bone disease or Sjögren syndrome. Although the index patient had antibodies to hepatitis C, she had no evidence of liver disease during 5 years of observation. None of the patients had hepatitis B virus, and none underwent testing for human immunodeficiency virus infection.

Two of the patients had radiological findings compatible with osteomalacia, including patient 1 with Sjögren syndrome who had scapular pseudofractures,<sup>1(pp206-216)</sup> and patient 2 who had femoral pseudofractures and "codfish" vertebrae.<sup>1(pp142-143)</sup> Those 2 patients and a third one (patient 6) also had biochemical findings suggestive of osteomalacia, namely elevated serum alkaline phosphatase levels, with  $\gamma$ -glutamyl transpeptidase levels within the reference range in 2 and elevated bone phosphatase isoenzyme levels in 2. Two of these 3 patients presumed to have osteomalacia had borderline or low serum levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D (patients 1 and 6), but in patient 6 this finding may have been related, at least in part, to long-term anticonvulsant therapy. None of these patients originally complained of bone pain, but the index patient later did. Serum calcium concentrations were usually within the reference range in 6 of the 7 patients (except in patient 6), and 4 of them (including 2 with osteomalacia) had hypophosphatemia on admission. Serum intact parathormone levels were elevated in 2 of the 3 patients with presumed osteomalacia (patients 2 and 6). Patient 2, who had evidence of osteomalacia without Sjögren syndrome, had 24-hour urinary excretions of glucose (121 and 158 mg), phosphate (605-829 mg, n = 3), urate (571-672 mg, n = 4), and glycine (253 mg/g of creatinine) that were low or within the reference range, thus excluding significant proximal tubular dysfunction. The disorder underlying this patient's RTA is medullary sponge kidney. A recent telephone conversation with his mother (who was not examined or included in this series) disclosed that when she had renal colic at about 30 years of age, she was told she had sponge kidneys and, in the past, had been prescribed potassium supplements. She related that another son also has sponge kidneys.

Serum globulin concentrations were elevated only in the 2 patients with Sjögren syndrome (patients 1 and 7, with maximum values of 4.4 and 5.7 g/dL); the others had levels within the reference range, between 2.4 and 3.3 g/dL (mean, 3.04 g/dL). Serum alkaline phosphatase level was within the reference range in the patients with Sjögren syndrome who did not have RTA. Cryoglobulins were not detected in 2 of the 3 patients with hepatitis C virus who underwent testing.

#### COMMENT

We undertook this survey to try to elucidate the relations among RTA1, Sjögren syndrome, and osteomalacia in adults. Our index patient's persistently elevated serum alkaline phosphatase levels had not originally received due attention, and her scapular pseudofractures had been overlooked, so osteomalacia was not diagnosed. Once appreciated, however, this finding seemed inconsistent with

statements in some recent literature that bone disease is uncommon in RTA1,<sup>5</sup> although early articles had described osteomalacia or rickets in several patients.<sup>1(pp227-249),2-4,7</sup> The diagnosis of osteomalacia ultimately rests on the histologic finding of wide uncalcified osteoid seams in bone. However, as in this study, the diagnosis can be inferred by finding characteristic radiological abnormalities such as pseudofractures<sup>1(pp227-249)</sup> and elevation of serum bone-specific alkaline phosphatase levels.

Some cases of RTA1 are associated with genetic abnormalities of the collecting tubule anion exchanger (band 3)<sup>8,9</sup> or of the hydrogen-adenosine triphosphatase pump.<sup>10,11</sup> Other patients with RTA1 have had hyperglobulinemic autoimmune disorders, often Sjögren syndrome as in 2 of our patients,<sup>12-15</sup> and still other cases are due to a toxin such as amphotericin. Results of renal biopsies in several RTA1 patients with and without Sjögren syndrome have revealed absence of the tubule cell hydrogen-adenosine triphosphatase pump.<sup>16-18</sup>

Early reports of RTA1 in adults, which noted the occurrence of osteomalacia, did not record whether those patients also had hyperglobulinemic disorders.<sup>1(pp227-249),2-4</sup> Then, in 1982, Brenner et al<sup>5</sup> surveyed the radiological findings in 44 patients with RTA1 and concluded that none of them had bone disease. They suggested that the apparent association of osteomalacia with RTA1 reported earlier was erroneous and due to failure to identify patients who actually had RTA2 or a mixture of RTA1 and RTA2.<sup>5</sup> On late follow-up, for example, 1 RTA patient with osteomalacia originally described by Albright et al<sup>19</sup> was found to have the renal Fanconi syndrome. However, among 48 patients with RTA seen at the Mayo Clinic, Rochester, Minn, between 1970 and 1980, Harrington et al<sup>20</sup> found bone disease in 9, osteomalacia in 4, and osteoporosis in 5. The RTA was of proximal tubule origin (type 2) in 4 of the 48 patients, and it is unclear whether they or the patients with RTA1 were the ones with osteomalacia. In this regard, our patient 2, who had osteomalacia without Sjögren syndrome, had no evidence of proximal tubular dysfunction.

Bone disease has subsequently been associated with RTA1 in children with familial disease and in adults with hyperglobulinemic disorders, most commonly Sjögren syndrome.<sup>16-18,21-26</sup> Wrong et al<sup>27</sup> found that 11 of 24 acidotic patients with immune-related RTA1 had bone disease, and so did 5 of 17 with familial RTA. The 5 with familial RTA were children who had rickets (the childhood equivalent of osteomalacia), but in 1, bone disease redeveloped during adulthood after alkali therapy was stopped.<sup>8,27</sup> In 2 other groups of RTA patients with anion exchanger (band 3) defects, rickets was common among the children, but the patients who received a diagnosis in adult life apparently did not have bone disease.<sup>8,28</sup> Nilwarangkur et al<sup>29</sup> described 103 Laotian and Thai patients with endemic RTA1. Of these, 24 had bone disease. The etiology of their RTA and nature of the bone disease were not clear, and no band 3 study results or serum vitamin D levels were reported.

Domrongkitchaiporn et al<sup>30</sup> recently described 14 adult Thai patients with RTA1, all with radiological evidence of osteopenia. All underwent bone biopsy, but only one had incompletely mineralized osteoid indicative of

osteomalacia. The authors concluded that the osteopenia in that setting was rarely due to osteomalacia but rather mainly to decreased bone formation. The reports by Nilwarangkur<sup>29</sup> and Domrongkitchaiporn<sup>30</sup> and their colleagues indicate that adults with at least some kinds of RTA1 have bone disease, but what types, and whether the bone disease may differ according to the etiology of the RTA, remains in doubt. In children, the bone disease has been described as rickets. On the basis of the biochemical and radiological findings, we had assumed that our patients had the adult counterpart, osteomalacia, but further bone biopsy studies are clearly needed to answer this question.

Our survey has several shortcomings. We helped treat 3 of the patients described (patients 1, 2, and 7) and identified only 4 other adults with RTA1 from the hospital records. Also, the diagnoses of osteomalacia and Sjögren syndrome were not proved by biopsy. Despite those caveats, we believe the information obtained in this survey provides answers to the 2 questions that prompted the study. First, bone disease occurs in adults with RTA1 (in the Bronx, as well as in Thailand). Two of our patients (patients 1 and 2) had radiological and biochemical evidence of bone disease, likely osteomalacia, and a third (patient 6) had biochemical evidence, although her vitamin D deficiency may also have been a factor. Second, the bone disease seemed primarily related to RTA rather than to Sjögren syndrome, per se, because only 1 of the 3 patients with evidence of bone disease had Sjögren syndrome (patient 1). Also, only 1 of the 2 RTA patients with Sjögren syndrome had bone disease (patient 1), whereas the other one (patient 7) and those with Sjögren syndrome but without RTA did not.

Regarding the diagnosis of Sjögren syndrome, patients 1 and 7 had sicca symptoms and high titers of antibodies to Ro and La, strongly suggesting that diagnosis. Ramos-Casals and colleagues<sup>31</sup> recently reviewed 35 cases of Sjögren syndrome that were "associated with chronic hepatitis C infection," but our index patient, who had antibodies to hepatitis C, had no evidence of active liver disease. In addition, her antibodies to hepatitis C were detected by an enzyme-linked immunosorbent assay, and no confirming recombinant immunoblot assays or polymerase chain reaction analyses were performed. Patient 7, who also had Sjögren syndrome, did not have antibodies to hepatitis C.

At present, there seems no better explanation for the bone disease, presumably osteomalacia, that occurs in RTA1 than some combination of these patients' acidosis and hypophosphatemia, although coexisting vitamin D deficiency, when present, is an aggravating factor. We think that Albright<sup>1</sup> was right again.

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