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## **Spontaneous tendon ruptures in patients with end-stage renal disease**

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## **ABSTRACT**

Spontaneous tendon ruptures in patients with end-stage renal disease (ESRD) have been reported rarely. We describe the largest own group of patients with spontaneous rupture of major tendons. Rupture of 16 tendons occurred in 9 patients. Mean patient age was 52.78 years; 77.7 % were male. Four patients were treated with hemodialysis, four received renal transplant and one was treated with automated peritoneal dialysis. Bilateral rupture was found in 5 patients (3 quadriceps, one Achilles and one supraspinatus and subscapularis tendon rupture). Distal brachial biceps tendon rupture, Achilles tendon rupture, unilateral quadriceps, and rupture of the oblique internal abdominal muscle tendon were developed by one patient each. Patients were treated with renal replacement therapy for 3 to 21 years (mean 12.89). Five patients were treated with steroids and 6 patients received quinolone antibiotic before the tendon rupture. All patients had laboratory and clinical signs of hyperparathyroidism. A patient who was treated with APD for 3 years had primary hyperparathyroidism with nephrolithiasis as the cause of ESRD.

Our results demonstrated that patients with hyperparathyroidism are at increased risk for development of spontaneous tendon ruptures, and the risk is further amplified when they receive quinolone antibiotics and/or steroids.

**Key words: tendon rupture, end-stage renal disease, dialysis, renal transplantation, hyperparathyroidism, fluoroquinolones, steroids**

## **INTRODUCTION**

Spontaneous tendon rupture is a rare complication which severely disables patient's activity. It generally occurs in association with different chronic metabolic disorders such as diabetes mellitus, systemic lupus erythematosus, rheumatoid arthritis, chronic renal failure, gout and obesity (1). Especially rare are simultaneous, spontaneous, bilateral ruptures which mostly occur in the weight bearing tendons (the quadriceps femoris, Achilles and patellar tendon) (2). Only a few cases of spontaneous bilateral tendon ruptures have been reported in the literature to date (3-13). Tendon ruptures may be attributed to degenerative changes in tendons or changes at their attachments to the bone. However, the pathogenesis of spontaneous tendon rupture in uremic patients is a matter of controversy. Some authors advocate duration of dialysis with subsequent malnutrition, insufficient dialysis and  $\beta$ 2-amiloidosis as the main etiologic factor (14), while other considered accumulation of uremic toxins as the causative factor of tendon weakness and spontaneous ruptures (15). Secondary hyperparathyroidism has been suggested as the main reason for tendon ruptures in patients on chronic hemodialysis (16-18). Other factors that may predispose to tendon injury in CRF patients include corticosteroid treatment and floroquinolone antibiotics (19,20).

In the present study we evaluated clinical characteristics of 9 patients with the end-stage renal disease treated with different renal replacement therapies (RRT) that developed spontaneous tendon ruptures.

## **PATIENTS AND METHODS**

All patients treated at Department of dialysis University Hospital Zagreb or University Hospital Rijeka who required RRT and developed spontaneous tendon rupture were eligible for investigation. Investigation was approved by the Ethic committee of the School of medicine, University of Zagreb.

Age, gender, body mass index, primary renal disease, duration of renal disease, history of diabetes, hepatitis B and C status, duration and kind of renal replacement treatment, mechanism of injury, method of treatment and tendon that ruptured were recorded. Laboratory parameters included calcium, phosphorus, alkaline phosphatase, iPTH, albumin, and C-reactive protein.

Body mass index was calculated as body weight (kg) / height (m)<sup>2</sup>.

Immunosuppressive protocol in renal transplant recipients included daclizumab 2 mg/kg in 2 doses (day 0 and day 14 after transplantation), cyclosporine A (trough levels 150-200 µg/L during the first several months), mycophenolate mofetil and steroids. Doses of steroids and use of fluoroquinolone antibiotics were recorded.

## **RESULTS**

From June 2006 to October 2008, 16 spontaneous tendon ruptures occurred in 9 patients. There were 7 male and two female patients. Ruptures occurred after normal activity in all patients. The main symptom of tendon rupture was pain accompanied with function impairment. Diagnosis was obtained based on clinical and ultrasound examination.

Clinical characteristics are presented in Table 1.

Table 1.

Age of the patients ranged from 43 to 69 (mean 52.78 years). Most of them required renal replacement treatment for long time. Average time on RRT was 12.89 years (range 3-21). Four patients were treated with hemodialysis, four patients received a renal allograft from deceased donor, and one patient was treated with automated peritoneal dialysis combined with one hemodialysis session per week. The most common tendon that ruptured was quadriceps femoris tendon, followed by Achilles tendon. We describe for the first time spontaneous ruptures of supraspinatus and supscapularis tendons, rupture of obliquus abdominis internus tendon and tendon of the short head of the biceps brachii tendon in patients with ESRD.

Body mass index ranged from 17 to 32 (mean 24.01) kg/m<sup>2</sup>. Two patients were hepatitis B positive, and 4 patients had chronic HCV infection. Patient 7 was treated with pegylated interferon prior to transplantation, and had negative HCV RNA at the time of transplantation. Four transplanted patients received steroids as part of their immunosuppressive protocol. None of them experienced acute rejection which would require increased doses of steroids. Steroids were also used in patient 5. Six patients were treated with ciprofloxacin prior to development of spontaneous tendon rupture. Two patients received simvastatin for treatment of dyslipidemia. All

patients had hyperparathyroidism, and one of them had primary form of the disease which caused end-stage renal disease because of kidney stones formation. Laboratory data are presented in Table 2.

Table 2.

CaxP product ranged from 2.59 to 7.61 (mean 4.58)  $\text{mmol}^2/\text{L}^2$ , iPTH from 58.8 to 281.4 (mean 201.9) pg/mL, and alkaline phosphatase from 40 to 471 IU (mean 148.3). Signs of malnutrition were present in 2 patients and obesity in one patient. C-reactive protein was elevated in four patients, probably as the consequence of the urinary tract infections that were treated with ciprofloxacin. Serum albumin was within the normal range in 7 patients, while 2 patients had low albumin levels.

The dominant arm was affected by the distal biceps tendon rupture in patient 1. Patient 2 developed avulsion of obliquus abdominis internus tendon insertion to the pelvis after the episode of allergic cough. She was treated surgically with reattachment of tendon and improved completely. Patient 5 had a history of long-term renal disease. After treatment with hemodialysis and renal transplantation with graftectomy due to renal vein thrombosis, she started with peritoneal dialysis. After 3 years on peritoneal dialysis she developed severe encapsulating sclerosing peritonitis with malnutrition. She was switched back to hemodialysis and started treatment with tamoxifen and steroids. Tamoxifen was discontinued after 2 years because of the liver toxicity, and she remained on steroids. In June 2008 she developed spontaneous rupture of right supraspinatus and subscapularis muscle, and 4 months later rupture of the same tendons on the opposite side. She could not ingest phosphate binders due to severe bowel problems. We believe that tamoxifen did not add to increase the risk for development of tendon rupture. This case is interesting while it raises the awareness of multiple complications in patients with sclerosing peritonitis who could not ingest phosphate binders. Patient 9 was relatively short on dialysis compared to the rest of the group. However, he had primary hyperparathyroidism and had developed ESRD due to nephrolithiasis. He was treated with automated peritoneal dialysis and one hemodialysis session per week according to his own wish. None of the patients had diffuse calcifylaxis.

Tendon ruptures were treated surgically with tendon reinsertion. Unfortunately, tendon biopsies were not performed during the surgical procedure. It is possible that some of the patients had calcifying tendonitis. The main problem after surgical treatment was impaired wound healing in all renal transplant recipients. One of them needed prolonged drainage and antibiotic treatment after operation. Patients also experienced delayed recovery and needed prolonged physical therapy. Treatment resulted in significant improvement in all patients.

## **DISCUSSION**

The advent of dialysis and renal transplantation has resulted in improved survival of patients with chronic renal failure and subsequent development of numerous disease complications. Spontaneous tendon ruptures are rare, but potentially serious complications in this group of patients. However, the causal relation between chronic renal failure and spontaneous tendon rupture is not well understood. We collected the largest own series of patients with spontaneous tendon rupture. Patients were treated with different renal replacement therapies: one patient with automated peritoneal dialysis, four patients with hemodialysis, and four received a renal transplant.

Ruptures seen in patients with CRF occur at younger age than in patients with other etiologies (2). Average age of patients from our series was 52.78 years what is in concordance with previous reports. It was suggested that the uremic environment could predispose development of tendon ruptures. Chronic acidosis with the consequent degenerative changes (21,22), hyperparathyroidism with weakness of bone-tendon junction (23) and amyloidosis (10,14) may all contribute to development of spontaneous tendon ruptures in patients with chronic renal failure. Additionally, many of the patients described in previous reports had been treated with corticosteroids or fluoroquinolone antibiotics (24-28). Most of the reports proved relationship between the length of time on dialysis and occurrence of spontaneous tendon ruptures (12,13,23). Our results demonstrate that although most of the patients received renal replacement therapy for more than 10 years, spontaneous tendon rupture may occur in patients who were relatively short on dialysis, as was the case with patient 9.

Statins are widely prescribed for treatment of dyslipidemia in renal transplant recipients. Besides the relatively common and well-known side effects as are rhabdomyolysis or mild liver lesion,



statins may rarely cause tendonitis or even tendon rupture (29). Their contribution to tendon rupture in uraemic patients remains unclear. Two of our patients received statins, one of them was treated with hemodialysis and one was transplanted.

Corticosteroids were found to be associated with tendinopathies more than 40 years ago, with majority of cases consisted of tendon ruptures, predominantly of the Achilles tendon (24). All our renal transplant recipients received steroids, but none of the patients who developed spontaneous tendon rupture was exposed to the boluses of steroids for treatment of acute rejection. Besides the renal transplant recipients, steroids could be an important additive factor for tendon injury in patient 5.

Two thirds of our patients who developed spontaneous tendon rupture had chronic hepatitis C infection. It is unclear whether hepatitis C infection increase the risk for spontaneous tendon rupture, or is merely coincident finding associated with long-term renal disease and treatment with blood transfusions before the introduction of erythropoietin for treatment of renal anemia. Microscopic tendon lesions occurred with reovirus infection, and resulted in tenosynovitis with progressive tendon fibrosis in chicken (30). Case reports demonstrated association of hepatitis C infection with necrotizing (31) and vacuolar myopathy (32). However, there is no data about the possible involvement of hepatitis C virus in tendon injuries.

High incidence of spontaneous tendon ruptures in renal transplant recipients occurred after joining of Croatia to Eurotransplant, an international organization for organ allocation. Previous allocation system that was primarily based on HLA matching was changed to an allocation scheme with emphasis on the length of dialysis. This resulted in high number of renal transplantations performed in the long-term dialysis patients with significant comorbidities. Most of these patients had evidence of poorly controlled secondary hyperparathyroidism with high levels of iPTH and alkaline phosphatase. Additive effect of high-dose steroids and use of ciprofloxacin for treatment of urinary tract infections resulted in spontaneous ruptures with prolonged hospitalization and mobility limitations.

Hyperparathyroidism was common to all patients in the primary, secondary or tertiary form as demonstrated in the Table 2. CaxP product ranged from 2.59 to 7.61 mmol<sup>2</sup>/L<sup>2</sup> (mean 4.58), iPTH from 58.8 to 281.4 (mean 201.9) pg/mL, and alkaline phosphatase from 40 to 471 IU (mean 148.3). Renal transplant recipients had low CaxP product due to phosphorus wasting during the immediate posttransplant allograft recovery and to the “hungry” bones. The importance of

hyperparathyroidism in development of spontaneous tendon injury is clear from the case of patient 9 who had tendon rupture only 3 years after he started with dialysis, but had primary hyperparathyroidism.

Treatment results were good. Patients needed prolonged physical therapy after surgical treatment. Significant problems with wound healing occurred in renal transplant recipients who received immunosuppressive therapy.

In conclusion, our results demonstrated that patients with hyperparathyroidism are at increased risk for development of spontaneous tendon ruptures, and the risk is further amplified when they receive fluoroquinolone antibiotics and/or steroids. Hyperparathyroidism should be treated before renal transplantation. Fluoroquinolone antibiotics should be avoided in patients with hyperparathyroidism, especially at early stages after transplantation when they receive high doses of steroids. These patients may be candidates for steroid-free immunosuppressive protocols.

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Table 1. Clinical parameters of patients with spontaneous tendon ruptures. Gend – gender (f - female, m - male), PRD – primary renal disease (DM II – diabetes mellitus type II, GN – chronic glomerulonephritis without biopsy, MPGN – mesangioproliferative glomerulonephritis), RRT (yrs) – time on renal replacement therapy, last RRT –treatment modality at the time of tendon rupture, BMI – body mass index, HBV – hepatitis B status, HCV – hepatitis C status, FQ – recent history of fluoroquinolone antibiotic treatment, HD – haemodialysis, APD – automated peritoneal dialysis, Tx – renal transplantation.

| Patient | Age | Gend | PRD               | RRT (yrs) | Last RRT | Tendon                                    | BMI   | HBV | HCV | Ster | Stat | FQ |
|---------|-----|------|-------------------|-----------|----------|---|-------|-----|-----|------|------|----|
| 1       | 69  | m    | DM II             | 13        | HD       | m. biceps brachii                         | 28.05 | +   | -   | -    | -    | -  |
| 2       | 53  | f    | GN chr            | 12        | HD       | m. obliquus abd. internus                 | 22.86 | -   | +   | -    | -    | +  |
| 3       | 52  | m    | GN chr            | 7         | HD       | m. quadriceps bil                         | 32.45 | -   | -   | -    | +    | +  |
| 4       | 44  | m    | Hypoplasia        | 21        | Tx       | m. quadriceps bil.                        | 28.36 | -   | +   | +    | -    |    |
| 5       | 54  | f    | Pyeloneph.        | 15        | HD       | m. supraspinatus and m. subscapularis bil | 17.06 | +   | -   | +    | -    | +  |
| 6       | 62  | m    | GN chr            | 7         | Tx       | Achils tendon bil                         | 26    | -   | -   | +    | -    | +  |
| 7       | 43  | m    | MPGN              | 18        | Tx       | Achilles tendon                           | 28.4  | -   | +   | +    | -    | +  |
| 8       | 55  | m    | GN chr            | 20        | Tx       | m. quadriceps                             | 26.5  | -   | +   | +    | +    | -  |
| 9       | 43  | m    | Primary hyperpara | 3         | APD + HD | m. quadriceps bil                         | 26.43 | -   | -   | -    | -    | -  |

Table 2. Laboratory parameters of patients with spontaneous tendon ruptures. Normal ranges are indicated in parentheses. CaxP – calcium x phosphorus product, iPTH – intact parathyroid hormone, AIP – alkaline phosphatase

| Patient | Ca x P<br>(mmol <sup>2</sup> /L <sup>2</sup> ) | iPTH (pg/mL)<br>(20-120) | AIP (IU/L)<br>(54-119) |
|---------|--|--------------------------|------------------------|
| 1       | 3.91   | 281.4                    | 40                     |
| 2       | 6.48   | 258.3                    | 43                     |
| 3       | 7.61   | 127.3                    | 471                    |
| 4       | 2.59   | 135                      | 128                    |
| 5       | 3.94   | 378.9                    | 143                    |
| 6       | 5.97   | 234.6                    | 114                    |
| 7       | 3.56   | 172.2                    | 105                    |
| 8       | 2.74   | 58.8                     | 127                    |
| 9       | 4.47   | 170.6                    | 164                    |