

β 2-Microglobuline Plasma Level and Painful Shoulder in Haemodialysed Patients

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ABSTRACT

Painful shoulder in patients on chronic haemodialysis is most often associated with dialysis arthropathy or accumulation of deposits containing modified fibrils of β 2- microglobuline especially in bones and joints due to insufficient elimination during the therapy. The aim of this study is to investigate whether there is connection between painful shoulder and plasma level of β 2-microglobuline and to corroborate that with morphologic parameters found in proved amyloidosis. It has to be emphasized that even other causes may contribute the development of painful shoulder. Real time sonography and conventional plain radiographs of the 108 shoulders were performed in 54 patients receiving chronic haemodialysis as a treatment of terminal renal failure (without previous history of rheumatoid arthritis), 27 symptomatic with persistent pain and stiffness in both shoulders and lasting for more than 6 weeks and restriction of movements in various degree and 27 asymptomatic. Plasma level of β 2-microglobuline, CRP and uric acid were taken periodically as routine procedure during a one year prospective trial, as well as plasma level of calcium, phosphor and alkaline phosphatase. Plasmatic level of β 2-microglobuline is strongly connected with painful shoulder in dialyzed patients, as well as CRP as sign of acute inflammation. That is proved by morphologic parameters associated with histological proved amyloidosis in patients on long term dialysis, more then 10 years.

Key words: β 2-microglobuline, painful shoulder, dialysis

Introduction

Chronic shoulder pain in patients on chronic haemodialysis is most often associated with dialysis arthropathy, bacterial arthritis, gout and pseudogout. The term dialysis related arthropathy is associated with accumulation of deposits containing modified fibrils of β 2-microglobuline especially in bones and joints due to insufficient elimination during the therapy. Early symptoms are connected with shoulder and it is often the first involved with morphologic changes¹. Dialysis related arthropathy with stiffness and movement reduction is related to the long term dialysis (more then ten years). Painful shoulder

is, however, noticed even in patients receiving shorter term dialysis. The usage of high resolution ultrasound in clinical practice revealed the morphologic changes in patients receiving short term dialysis or even in asymptomatic patients¹.

After ten years of dialysis in 80% of patients a stiffness in large joints are registered, in 64% restriction of movements, and in 43% carpal tunnel syndrome².

Characteristic radiologic signs are periarticular small erosions and subcortical periarticular bone cysts, espe-

cially in the head of humerus³⁻⁶. These symptoms and radiologic changes are associated with duration of dialysis and age of patients, confirmed with post mortal studies.

However, a presence of β 2- microglobulin fibrils deposits are registered in joints of 21% of patients receiving 2 year long dialysis, and in 90% of patients after 7 year long dialysis⁷.

Radiologic, sonographic and magnetic resonance studies of shoulders in patients on long term dialysis set up some morphologic parameters associated with pathologic proved dialysis related amyloidosis, such as small erosions and subcortical cysts of the humeral head. These signs are late signs and are associated with duration of dialysis lasting more than 10 years^{3,4,6}.

Sonographic and magnetic resonance findings in those cases includes joint effusion^{8,9}, rotator cuff thickness, biceps tendon thickness, biceps tendon sheet effusion¹⁰⁻¹⁴, subdeltoid bursa effusion^{1,13,15}, hyper-hypoechoic deposits of rotator cuff and bursae and inhomogeneity of the tendon texture¹⁵⁻¹⁷.

Our study includes even symptomatic patients with painful shoulder on short term dialysis, shorter than 10 years, as well as asymptomatic. The aim of this study is to investigate whether there is connection between painful shoulder and plasma level of β 2-microglobuline and to corroborate that with morphologic parameters found in proved amyloidosis. Of course it has to be emphasized that even other causes may contribute the development of painful shoulder.

Materials and Methods

Patients and variables

Real time sonography of the 108 shoulders with linear transducer of 10 MHz was performed in 54 patients receiving chronic haemodialysis as a treatment of terminal renal failure (without previous history of rheumatoid arthritis), 27 symptomatic with persistent pain and stiffness in both shoulders and lasting for more than 6 weeks and restriction of movements in various degree and 27 asymptomatic. Each group of patients consisted of 17 males and 10 females., mean age 57.6 \pm 14.8 in symptomatic and 51.9 \pm 14.2 in asymptomatic. In 108 shoulders thickening of tendon of m. supraspinatus were examined. The thickness of supraspinatus was measured in both longitudinal and transversal view, in neutral position of the shoulder and in the adduction, hyperextension and internal rotation of the arm. The mean values between transversal and longitudinal view in both positions are calculated as follows:

1. Transverse view: superior of the head of humerus, just above the bicipital groove, taken mid-point between symmetrical lateral narrowing of the tendon,

2. Longitudinal view: measured at point where tendon emerges beneath acromial shadow.

Diameter of the biceps tendon sheet was measured in the level of the superior margin of the bicipital groove, in both transverse and longitudinal view.

Glenohumeral joint effusion (bone-capsule distance) was measured in transaxillar scan approaching the part of the humerus head not covered with rotator cuff.

Subdeltoid bursa effusion and biceps tendon sheet effusion were also noticed.

During examination texture of the tendons, especially inhomogeneity, hyperechoic amyloid deposits, small calcium deposits supraspinatus tendon ruptures were observed.

Supraspinatus tendon was defined as homogenous if the fibrillar structure was preserved and border towards subdeltoid bursa clearly defined. Tendon was defined as inhomogeneous if the fibrillar structure was modified without clear border towards subdeltoid bursa.

Conventional plain radiographs in standard positions were analysed looking for presence of calcifications of the tendons and bursa, eventual subcortical bone cystic changes or periarticular small bone erosions, metastatic calcifications and generalised osteopenia. Osteoarthritis of acromioclavicular and glenohumeral joint were noticed as well as sclerosis of the greater tuberosity of humerus and acromial osteophytes.

Laboratory examinations

Plasma level of β 2- microglobuline, CRP and uric acid were taken periodically as routine procedure during a one year prospective trial, as well as plasma level of calcium, phosphorus and alkaline phosphatase.

Data analysis

The software package Statistica 6. was used.

To estimate statistical significant difference between numeric parameters, T test and Mann Whitney test were used. Correlation between categorical variables between groups was estimated by χ^2 -test.

Results

Plasma level of β 2- microglobuline and CRP in symptomatic patients was significantly higher than in asymptomatic dialyzed. There was no significant difference between groups in plasma level of uric acid (Table 1), calcium, phosphorus and alkaline phosphatase.

Thickness of supraspinatus tendon, diameter of biceps tendon sheet and capsule-bone distance in both shoulders in symptomatic dialyzed patients were significantly higher than in asymptomatic ones (Table 2).

Inhomogeneity of the supraspinatus tendon was found in significantly more shoulders in symptomatic than in asymptomatic dialyzed patients ($\chi^2=57.22$; $p\leq 0.001$).

Hypo-hyperechoic deposits in rotator cuff and bursae were found only in symptomatic dialyzed patients in 12 shoulders (22%) (Figure 1).

TABLE 1
PLASMA LEVEL OF β 2-MICROGLOBULINE, CRP AND URIC ACID IN SYMPTOMATIC AND ASYMPTOMATIC DIALYZED PATIENTS

		symptomatic N=27	asymptomatic N=27	p
β 2-microglobuline (mg/L)	\bar{X} ±SD	34.8±10.2	18.99±6.46	<0.001
	median	31.4	17.2	
	min-max	23.2–68.2	8.1–38.5	
CRP (mg/L)	\bar{X} ±SD	23.37±19.68	11.05±8.96	<0.001
	median	16.0	11.0	
	min-max	2.4–76.0	1.3–47.0	
Uric acid (μ mol/L)	\bar{X} ±SD	430.6±58.56	388.6±75.6	0.073
	median	430.0	393.0	
	min-max	337.0–540.0	242.0–534.0	
Mann Whitney				

TABLE 2
METRIC PARAMETERS OF PAINFUL SHOULDER IN SYMPTOMATIC AND ASYMPTOMATIC DIALYZED PATIENTS

		symptomatic N = 27	asymptomatic N = 27	p
thickness of supraspinatus tendon (left)(mm)	\bar{X} ±SD	7.97±1.07	7.28±0.74	0.008
	median	7.8	7.2	
	min-max	5.8–10.1	6.0–8.8	
thickness of supraspinatus tendon (right)(mm)	\bar{X} ±SD	7.68±1.07	6.92±0.68	<0.001
	median	7.8	6.9	
	min-max	5.5–10.4	5.6–8.8	
diameter of biceps tendon sheet (left)(mm)	\bar{X} ±SD	6.37±1.11	5.19±1.12	<0.001
	median	6.51	4.8	
	min-max	4.3–8.7	3.6–7.9	
diameter of biceps tendon sheet (right)(mm)	\bar{X} ±SD	6.28±1.35	5.18±1.02	<0.001
	median	6.35	4.95	
	min-max	4.3–9.6	3.4–7.2	
capsule-bone distance (left)(mm)	\bar{X} ±SD	3.96±0.92	2.75±0.52	<0.001
	median	4.2	2.6	
	min-max	2.4–5.3	2.1–3.9	
capsule- bone distance (right)(mm)	\bar{X} ±SD	3.72±0.91	2.59±0.55	<0.001
	median	4.0	2.3	
	min-max	2.2–5.5	1.8–3.9	
T test				

Partial ruptures were found only in symptomatic patients in 17 shoulders (31%) (Figure 2), as well as total ruptures in 5 shoulders (9%).

Biceps tendon sheet effusion is found in significantly more shoulders in symptomatic than in asymptomatic dialyzed patients ($\chi^2=23.34$; $p<0.001$) (Figure 3).

Subdeltoid bursa effusion was found only in symptomatic dialyzed patients in 31 shoulders (57%) (Figure 4).

Osteoarthritis of acromioclavicular joint was found in significantly more shoulders in symptomatic than in asymptomatic dialyzed patients ($\chi^2=13.50$; $p<0.001$) as well as sclerosis of greater tuberosity of humerus ($\chi^2=4.6$; $p<0.05$).

Osteoarthritis of glenohumeral joint was found only in symptomatic patients in 16 shoulders (29%).

Periarticular subcortical cysts were found in 3 shoulders (5%), and periarticular small bone erosions in 15 shoulders (27%) only in symptomatic patients.

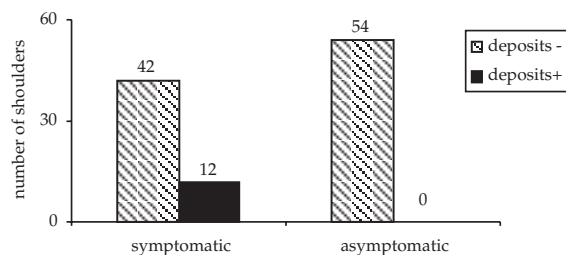


Fig 1. Presence of hypo-hyperchogenic deposits of rotator cuff and bursae in symptomatic and asymptomatic dialyzed patients.

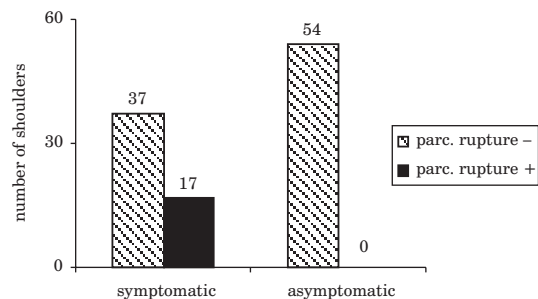


Fig 2. Partial ruptures of supraspinatus tendon in symptomatic and asymptomatic dialyzed patients.

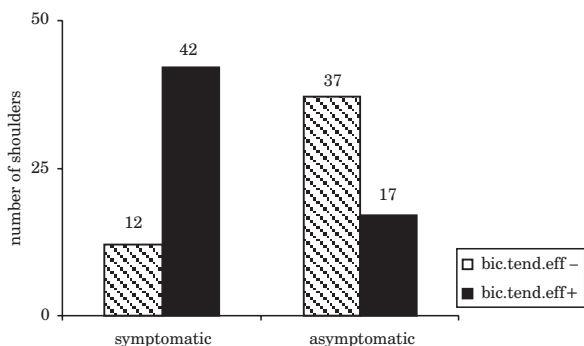


Fig 3. Biceps tendon sheet effusion in symptomatic and asymptomatic dialyzed patients.

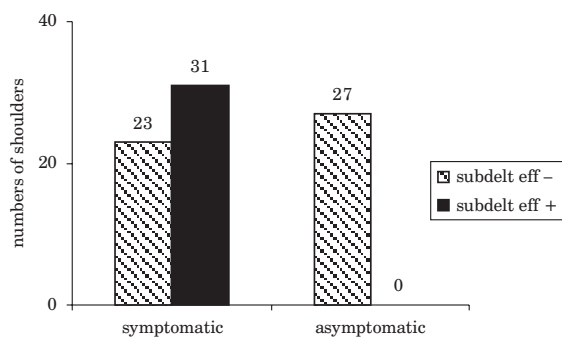


Fig 4. Subdeltoid bursa effusion in symptomatic and asymptomatic dialyzed patients.

Metastatic calcifications were found in 10 shoulders (18%) in symptomatic patients.

There was no significant difference between symptomatic and asymptomatic dialyzed patients concerning the presence of calcifications in supraspinatus tendon of both shoulders ($\chi^2=2.01$; $p\leq 0.2$), acromial osteophytes reducing the subacromial space ($\chi^2=2.74$; $p\leq 0.1$) and diffuse osteopenia of the shoulder ($\chi^2=1.16$; $p\leq 1$).

Discussion

Dialysis related arthropathy with stiffness and movement restriction is associated with long term dialysis.

Painful shoulder is, however, found in patients who are shorter time on this therapy either¹.

There are different reports regarding the connection of level of β 2-microglobuline and joint symptoms. Nagi et al. found no connection between plasmatic level of β 2-microglobuline and distance capsule-bone (joint effusion), one of the important parameter of the painful shoulder in dialyzed patients¹².

Baldrati et al. found no connection between plasmatic level of β 2-microglobuline in patients with dialyzed related amyloidosis and dialyzed patients without it. They even found no correlation between plasmatic level of β 2-microglobuline and dialysis duration⁶.

Sethi et al. reported that plasmatic level of β 2-microglobuline was higher in patients with arthropaty then dialyzed patients without it (57.3 mg/L versus 50.7 mg/L), but without statistical significance, as well as plasmatic level of parathormon⁷.

Aulisa et al. investigated 11 symptomatic long term dialyzed patients with painful shoulder with rendgenologic characteristic signs of dialysis related amyloidosis and 9 asymptomatic. They found significantly higher plasmatic level of β 2-microglobuline in a group of symptomatic¹⁸.

In our previous investigations we applied machine learning based analysis.

Machine learning algorithm extracted β 2-microglobulin plasma levels as well as sonographic inhomogeneity of the right shoulder rotator cuff and duration of dialysis as the parameters that with 97.4% accuracy discriminate symptomatic (with painful shoulder due to presumptive amyloidosis) from asymptomatic patients. The cut off value of β 2-microglobulin plasma level was 15.9 mg/L¹⁶.

Kazama et al. point out that plasmatic level of β 2-microglobulin decreases after renal transplantation, influencing the diminishing the joint symptoms¹⁹. Joint deposits don't disappear but inflammation around them does^{19,20}.

Considering those facts today is in use so called »adsorbent column« for β 2-microglobulin, decreasing its plasmatic level. Diminishing the joint symptoms was noticed, but radiologically detected oosteroarticular lesions remained^{21,22}.

Chatzimichail et al. have investigated two groups of dialyzed patients. In first group there were 10 patients with painful shoulder on 14 year long dialysis. In second group there were 12 asymptomatic patients on 4 years long dialysis. Clinical, radiological and biochemical examinations were performed (β 2-microglobulin, albumins, parathormon). In a group of symptomatic patients there were higher levels of β 2-microglobulin (41 mg/L) then in group of asymptomatic (32 mg/L). There were no statistic significance in values of albumin or parathormon²³.

In our investigations β 2-microglobulin plasma level was significantly higher in symptomatic (31.4 mg/L) then in asymptomatic patients (17.2 mg/L). This is in accor-

dance with Sethi's and Chatzimichailz's reports as well as our previous investigations¹⁶.

C reactive protein (CRP) is also associated with dialyzed arthropathy. Sethi et al. reported its higher plasma level in symptomatic patients (18.6 mg/L) than asymptomatic (11.4 mg/L) which suggested inflammatory background⁷. In our patients CRP plasma level was statistically significant higher in symptomatic patients, almost twice.

Increase plasma level of uric acid is connected with dialysis and gout is sometimes cause of painful shoulder²⁴. Although plasma level does not need to be important sign in acute attack of gout, it is significant that there was no difference in plasma level of uric acid between symptomatic and asymptomatic patients.

Thickening of the rotator cuff, specially the supraspinatus tendon, higher diameter of biceps tendon sheath and higher capsule-bone distance as indicator of intra-articular effusion are strongly associated with dialysis arthropathy from the beginning of high resolution diagnostic ultrasound use^{1,8-14}. In our patients symptomatic had higher values than asymptomatic.

Calcification of supraspinatus tendon surprisingly showed no difference between groups. Metastatic calcifications, subacromial space reducing, occurred in few symptomatic patients suggesting secondary parathyroidism²⁵.

Inhomogeneity of the supraspinatus tendon is established as very important morphologic parameter for painful shoulder in dialyzed patients. All symptomatic patients had inhomogeneity of the supraspinatus tendon in various degree and significantly more than in asymptomatic patients. Inhomogeneity was mentioned in the report of Sommer end associated in the investigation of histological proven amyloidosis in patients under long term dialysis, more than ten years, and without history of rheumatoid arthritis¹⁵.

Hyper-hypoechogenic deposits were found only in group of symptomatic dialyzed patients and it is very significant parameter of dialysis arthropathy as specific sign found in histological proven dialysis related amyloidosis^{9,13,16,26}.

Partial ruptures of supraspinatus tendon were found only in symptomatic patients (31%) as well as total ruptures in 5 shoulders (9%). Ruptures may be consequence of tendon structure modification due to visible or non-visible amyloid deposits¹⁵, or some other causes of painful shoulder not associated with dialysis^{27,28}.

Biceps tendon effusion is present as a parameter connected with dialysis arthropathy^{1,9,10,13,14,16,27,28}, although may be present in inflammatory conditions like rheumatoid arthritis or in impingement syndrome because repetitive tendon pressure. Our results were similar and showed that this parameter is strongly associated with painful shoulder of dialyzed patients implicating inflammatory component as cause.

Subdeltoid bursa effusion is present almost only in group of dialyzed patients. This morphologic parameter is in literature associated with dialysis arthropathy as sign of inflammation^{1,9-14,16,27} but also can be present in rheumatoid arthritis²⁹, and even rarely in gout affecting shoulder²⁴.

Other relevant parameters analysed radiographically are acromioclavicular osteoarthritis and sclerosis of greater tuberosity of the humerus, strongly connected with rotator cuff disease³⁰. Those parameters are non-specific as well as glenohumeral osteoarthritis.

Specific periarticular subcortical cysts were present only in few cases, as late sign of dialysis related amyloidosis³⁻⁷.

Plasmatic level of β 2- microglobuline is strongly connected with painful shoulder in dialyzed patients, as well as CRP as sign of acute inflammation. That is proved by morphologic parameters associated with histological proven amyloidosis in patients on long term dialysis, more than 10 years, such as joint effusion, thickness of supraspinatus tendon, biceps tendon effusion, subdeltoid bursa effusion and hypo-hyperechogenic deposits of rotator cuff and bursa. Also inhomogeneity of the supraspinatus tendon and partial ruptures of modified tendon should be considered as important signs. Although the patients had no previous history of rheumatoid arthritis we have to admit that similar signs except deposits may be found in that disease. In addition, although acromial osteophytes as sign strongly connected with impingement syndrome showed no importance, partial ruptures, osteoarthritis of acromioclavicular joint and sclerosis of greater tuberosity of the humerus are signs of rotator cuff disease of different origin. That suggests that cause of painful shoulder in dialyzed patients is multifactorial and shoulder has to be diagnostically treated comprehensively. In spite of this, plasmatic level of β 2-microglobuline should be considered as important sign and procedures that diminish it should take important part in painful shoulder prevention.

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PLAZMATSKA RAZINA β 2-MIKROGLOBULINA I BOLNO RAME BOLESNIKA NA HEMODIJALIZI

SAŽETAK

Bolno rame u bolesnika na kroničnoj hemodijalizi je često povezano s dijaliznom artropatijom ili akumulacijom depozita koji sadrže modificirane fibrile β 2-mikroglobulina poglavito u kostima i zglobovima, zbog njegove smanjene eliminacije tokom terapije. Svrha istraživanja je da ispita vezu između bolnog ramena i plazmatske razine β 2-mikroglobulina i to dokažu morfološkim parametrima pronađenim kod dokazane amiloidoze. Treba naglasiti da postoje i drugi uzroci koji mogu dovesti do bolnog ramena. Ultrazvučni i radiografski pregledi učinjeni su kod 108 ramena u 54 bolesnika na kroničnoj hemodijalizi (bez reumatoidnog artritisa u povijesti bolesti), 27 simptomatskih s perzistentnom boli i stezanjem u ramenima u trajanju najmanje 6 tjedana i s restrikcijom pokreta, te 27 asimptomatskih. Plazmatska razina β 2-mikroglobulina, CRP i urati su mjereni periodično kao rutiski postupak tokom jedne godine, kao i plazmatska razina kalcija, fosfora i alkalne fosfataze. Plazmatska razina β 2-mikroglobulina je jako povezana s bolnim ramenom u dijaliziranih bolesnika, kao i CRP kao znak akutne upale. To je potvrđeno morfoloških parametrima povezanim s histološki dokazanom amiloidozom kod bolesnika na dugotrajnoj dijalizi, dužoj od 10 godina.