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Ferritin in dialysis-related arthropathy: could it be a possible biochemical indicator of articular chronic pain?

Paolo Paparella[1], Massimo Barbieri[2], Maria Concetta Miscia[3], Carlo Rovati[3], Martina Bellini[1]

[1]*Clinical Biochemistry Unit San Carlo Clinic, Paderno Dugnano, Milan, Italy*
[2]*Pain Management Unit San Carlo Clinic, Paderno Dugnano, Milan, Italy*
[3]*Dialysis Unit San Carlo Clinic, Paderno Dugnano, Milan, Italy*

Abstract

Background: The aim of our study was to evaluate laboratory data behaviour in two dialysis populations, with and without dialysis-related arthropathy and pain.

Methods: We produced an elaboration of more than 160,000 items of biochemical data of 25 dialysis-related arthropathy patients with chronic articular pain, and 25 patients asymptomatic for joint pain and arthropathy. The pain visual analogue scale (VAS) was employed for pain intensity determination.

Results: The serum level of β-2 microglobulin was similar in the two groups of patients, while ferritin values were significantly higher in symptomatic patients. We excluded the possibility that the ferritin difference between the two groups was due to different iron storage and to an inflammatory profile. Furthermore, the pain VAS mean value was higher in patients who had higher ferritin and pain than in asymptomatic patients.

Conclusion: It is important to underline that the higher value of ferritin in patients with chronic pain due to dialysis-related arthropathy could represent a new stimulus for a deeper investigation of this indicator, setting a periodic revelation of pain intensity.

Key words: chronic pain, arthropathy; chronic kidney disease, dialysis; pain, biochemical markers, ferritin

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Patients with end-stage chronic kidney disease (CKD) and maintenance haemodialysis treatment often present with an osteoarticular disease called renal osteodystrophy, which includes signs of secondary hyperparathyroidism, osteoporosis, osteosclerosis and osteomalacia [1–6]. Besides this, patients may complain of chronic pain and stiffness, with both large and small joints being affected symmetrically. This condition is called dialysis-related arthropathy. After ten years of dialysis, 80% of patients show stiffness in large joints, 64% show a restriction in movements, and 43% show carpal tunnel syndrome [7, 8]. Less frequent is cubital tunnel syndrome [9]. The known main causes of this condition are beta-2 microglobulin deposits in the joints of patients due to insufficient elimination of this protein during therapy [10]. The deposits, in the form of fibrils, are usually in the synovium, but can also be found in other tissues, including tendons and peripheral nerves [7]. Due to this main cause, dialysis-related arthropathy is as well-known as dialysis amyloidosis [11].

Even though recent literature has focused on β-2 microglobulin deposits, in 1986 Cary et al. [12] presented the hypothesis of iron involvement. They found synovial haemosiderin deposits in stromal macrophages and connective tissue, with smaller amounts in lining cells: the iron deposits may cause arthropathy too. Subsequent scientists have tried to define the role of iron status indicators [13, 14], but they did not consider a complete biochemical panel.

Dialysis-related arthropathy is characterised by severe chronic pain. In the literature, few authors have specifically considered dialysis pain treatment [3, 15–17], and no author

has focused on chronic pain in dialysis-related arthropathy because of the difficulty in defining when the symptoms occur and how to better treat them.

The objective of our study was to investigate the biochemical aspects of patients who suffer from chronic pain due to dialysis-related arthropathy, after an in-depth clinical investigation of patients' conditions.

Our specific question was whether there is a connection between painful joints due to dialysis-related arthropathy and plasma levels of biochemical analytes in dialysis patients. The purpose was to create a basis for identifying a possible biochemical indicator able to predict arthropathy and related pain onset in long-term dialysed patients.

METHODS

PATIENTS

Our cohort consisted of 50 patients who had received haemodialysis for more than ten years (range: 10–30 years) and who had been monitored at the San Carlo Clinic of Paderno Dugnano (Milan) throughout their courses of haemodialysis. We divided them into two groups: a study group (group A), consisting of 25 symptomatic patients with chronic pain and stiffness and surgical or instrumental diagnostic [radiological, sonographic and magnetic resonance] evidence of joint amyloidosis, and a control group (group B), consisting of 25 asymptomatic patients.

LABORATORY EXAMINATIONS

The plasma level of analytes was recorded before each dialysis session from 2001 to 2011 as a routine procedure, for a total of 160,000 determinations. This represents our dialysis panel: albumin, α-1 globulin and α-2 globulin, basophil cells, β-globulin, mean corpuscular haemoglobin concentration (MCHC), reticulocyte haemoglobin content, mean corpuscular haemoglobin (MCH), mean corpuscular volume (MCV), β-2 microglobulin, B_{12} vitamin, C reactive protein, calcitonin, calcium, chloride, total cholesterol, copper, corrected calcium, C peptide, creatine kinase, serum creatinine, creatinine clearance, eosinophils, erythrocyte sedimentation rate, ferritin, folate, gamma gluthamine transferase, haptoglobin, glycated haemoglobin, high density lipoprotein cholesterol, haematocrit, haemoglobin, international normalised ratio, iron, lactate, lactate dehydrogenase, low density lipoprotein cholesterol, lymphocytes, magnesium, monocytes, serum myoglobin, neutrophils, alanine aminotranspherase, aspartate aminotranspherase, parathyroid hormone, pCO_2, glucose, pH, phosphate, platelet, pO_2, potassium, proteins, red cells, sodium, transferrin, triglycerides, troponin I, urate, urea, red cell dispersion width, reticulocytes, urine calcium excretion, urine creatinine, urine, and white cells.

Analytes were measured before the dialysis procedure. Particular attention was focused on β-2 microglobulin and on inflammatory, mineral concentration, iron storage and uremic toxicity parameters.

VISUAL ANALOGUE SCALE

A visual analogue scale [VAS], a psychometric response scale, was used with all 50 patients to record pain intensity when the data was analysed. Pain intensity is referred as 0 to 10, in which 0 = no pain at all and 10 = the worst pain imaginable. We classified pain as mild (1 to 4), moderate (5 to 6), or severe (7 to 10). VAS administration was approved by the ethics committee of the hospital and each patient was informed about the study; written, informed consent was obtained before administration.

STATISTICAL ELABORATION

All statistical analysis and significance of difference between groups were determined by unpaired Student's *t*-test. Mean ± SD is given for quantitative variables.

A P value of < 0.05 was considered statistically significant.

RESULTS

Demographic data is shown in Table 1. Renal insufficiency causes are described in Table 2.

The patients in the two different groups were standardised for age and gender. Median age was 73 ± 16 years, and each group included 15 women and ten men. All patients were Caucasian. The treatment panel was similar for all our patients as shown in Table 3. Pain in group A patients was treated by commonly used analgesics and anti-inflammatory drugs, i.e. paracetamol, tramadol, and ibuprofen.

Table 1. Demographic variables (means ± SD or numbers)

Demographic characteristic	Group A (n = 25)	Group B (n = 25)
Age (years)	72 ± 10	74 ± 8
Sex (male/female)	10/15	10/15
Body mass index (kg m^{-2})	24.5 ± 5.0	25.3 ± 3.2
Dialysis time (months)	75.7 ± 30.7	66.2 ± 40.6

Table 2. Causes of chronic kidney disease (% of patients)

Disease	Group A (n = 25)	Group B (n = 25)
Kidney malformations	8%	8%
Chronic interstitial nephropathy	12%	4%
Bilateral polycystic disease	20%	20%
Vascular nephropathy	16%	12%
Renal calculosis	4%	4%
IgA nephropathy	12%	4%
Diabetic nephropathy	16%	44%
Partial nephrectomy	12%	4%

Table 3. Details of patients' therapy

Groups	Endovenous iron	Erythropoietin	Phosphorus binder	Vitamin D	Cinacalcet	Paricalcitol
A	68%	76%	80%	76%	52%	44%
B	72%	76%	84%	72%	44%	48%

There were six patients who had undergone kidney transplantation in group A and seven in group B. Diabetes was present both in group A (six of 25) and in group B (seven of 25).

Arterial hypertension was very frequent, respectively in 15 of 25 and 16 of 25, and ischaemic heart disease and cerebrovascular disease were seen in group A (n = 6) and in group B (n = 25). Peripheral vascular disease was found in group A (n = 5) and in group B (n = 4). Rheumatic diseases were not present.

Among group A patients who underwent a more specific diagnostic investigation, we found acute monoarthritis or polyarthritis due to periarticular calcification, ruptured tendons from gout or pseudogout, and carpal tunnel syndrome (n = 6, three of these being bilateral). Carpal tunnel syndrome was treated with surgical release of medial nerve. Fractures were present: distal radius fracture in three, bilateral lesions of the rotator cuff in four, femoral fracture in six, and ischiopubic fracture in two.

All patients in group A showed instrumental and surgical evidence of arthropathy. In particular radiological, sonographic, and magnetic resonance images showed signs of periarticular small erosions and subcortical periarticular bone cysts, tendons thickness, and rotator cuff hyper-hypoechogenic deposit.

Patients complained of different levels of pain due to arthropathy. The mean value of VAS in group A was 7 ± 1.7, defined as severe, while in group B the VAS level was 5 ± 1.6, defined as moderate.

Regarding laboratory parameters, the β-2 microglobulin level was normal in both studio and group patients ($P > 0.5$). We observed a statistical difference in serum ferritin mean values ($P < 0.01$), as shown in Table 4.

In the dialysis panel of analytes, only serum ferritin showed a statistically significant difference between the two groups, with an increase of 39% in group A compared to group B.

Due to these results, we decided to investigate the different role of serum ferritin, within an inflammatory and an iron panel. We obtained more accurate results through the elaboration of compared data in a temporal window of seven days.

The iron panel included analytes that are known to be iron status indicators such as mean corpuscular haemoglobin concentration, reticulocyte haemoglobin content, mean corpuscular haemoglobin, haemoglobin, iron itself, and mean corpuscular volume. The inflammatory panel included white cells, lymphocytes, neutrophils, platelet, erythrocyte sedimentation rate, and C reactive protein. Neither of the panels showed any differences in ferritin behaviour. Values are reported in Tables 5 and 6.

Uremic toxicity was evaluated by measurements of serum concentrations of small molecules (urea, creatinine, uric acid, phosphate) and it was excluded in both groups. Secondary hyperparathyroidism affected the totality of the cohort, and it was treated equally in the two groups.

DISCUSSION

Dialysis-related arthropathy commonly affects the shoulders, hips, hands, knees, and wrists, worsening with time and extending to other joints; it is often disabling and can causing severe pain [15].

Chronic pain remains a significant clinical problem in these patients [2] and is not being effectively managed, even if it contributes to functional limitations and/or leads to another clinical problem that worsens patients' quality of life [18]. In fact, joint pain has been shown in at least 50% of dialysis patients [19], with scores of 4 to 7 on the VAS [20].

Currently, the success rate for treating chronic pain in these patients is very low because of the difficult elimina-

Table 4. Ferritin and β-2 microglobulin concentrations in studied groups

Group	Ferritin (ng mL^{-1})				β-2 microglobulin (mg L^{-1})	
	Women		Men			
	n	mean ± SD	n	mean ± SD	n	mean ± SD
A (n = 25)	252	459.9 ± 54.9	349	402 ± 72.1	54	33.2 ± 8.0
B (n = 25)	219	247 ± 53.7	314	295 ± 78.6	60	31.4 ± 0.7
P value		< 0.01		< 0.01		> 0.05

Table 5. Iron panel except ferritin values

Group	Haemoglobin (g L^{-1})		MCV (fL)		MCH (pg)		MCHC (g L^{-1})		Chr (pg)		Iron (μg dL^{-1})	
	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD
A (n = 25)	3,097	11.28 ± 1.4	2,040	91.75 ± 8.27	3,097	29.67 ± 3.28	2,497	32.29 ± 1.49	3,097	32.17 ± 3.24	1,905	54.63 ± 29.7
B (n = 25)	2,320	11.3 ± 1.35	2,320	92.9 ± 6.25	2,320	29.89 ± 2.44	2,320	32.17 ± 1.46	967	32.44 ± 2.6	353	51.64 ± 23.23
P value		> 0.05		> 0.05		> 0.05		> 0.05		> 0.05		> 0.05

Table 6. Inflammatory panel except ferritin values

Group	White cells (G L^{-1})		Lymphocytes (G L^{-1})		Neutrophils (G L^{-1})		Platelet (G L^{-1})		Erythrocyte sedimentation rate (mm h^{-1})		C-reactive protein (mg L^{-1})	
	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD
A (n = 25)	2,497	7.42 ± 2.25	2,092	22.09 ± 5.81	2,092	68 ± 7	2,797	239.38 ± 78	1,905	71.17 ± 28.5	2,040	2.02 ± 3.74
B (n = 25)	2,320	6.88 ± 2.4	1,975	24.42 ± 8.2	1,975	64.8 ± 9.34	2,320	224.84 ± 77	1,535	81 ± 30	1,780	2.08 ± 4
P value		> 0.05		> 0.05		> 0.05		> 0.05		> 0.05		> 0.05

tion of analgesics, their metabolites, and their backlog. In dialysis patients there are more collateral effects, often serious. Currently, there is no specific therapeutic protocol for these patients, due to the unpredictable and abnormal pharmacokinetics in dialysis patients. However, we refer to the World Health Organization three-step analgesic ladder [21].

Though scheduled dialysis sessions allow effective elimination of drugs, this leads to a rapid wash out of analgesics, which in turn causes sudden pain exacerbation during dialysis sessions.

Moreover, pain may come on gradually or fluctuate over a period of weeks, or it may develop suddenly, associated with bone fracture, so targeted therapy is often difficult.

One of the most challenging problems in chronic pain management is the difficulty of making an objectively measurable assessment of pain, since pain is a subjective perception. For these reasons, the possibility of individuating biochemical indicators of joint pain in this population of patients is even more interesting. Furthermore, it is difficult to determine the objective impact of pain and symptoms on health-related quality of life due to complex clinical conditions, which include frequent and periodical hospitalisations and reduced social relationships, including with relatives.

Investigating the role of ferritin in chronic pain due to this condition was our first target, but the dialysis patient is a complex patient. Standardising our two groups was an arduous job. From the clinical point of view, we considered gender, age, years of dialysis, therapy panel, kidney transplantation, comorbidity (diabetes mellitus, arterial hypertension, ischaemic heart disease, cerebrovascular disease, peripheral vascular disease), and then secondary hyperparathyroidism in order to guarantee the best available homogeneity in the two groups. These parameters were similar in both groups. Secondary hyperparathyroidism is known to cause subperiosteal and subchondral reabsorption of bone, leading to erosive arthropathy, and it is also a factor in apatite crystal deposition [5]. It can be a reason for chronic pain subsequent to arthropathy, but the homogeneity of our groups allowed us to exclude secondary hyperthyroidism as a cause of higher ferritin due to inflammation or higher VAS mean value in Group A.

In fact, the serum level of inorganic phosphate, which is related to bone metabolism and to abnormalities in bone mineral density, and is a known disorder in dialysis patients [22, 23], was similar in the two groups.

Rheumatic disease such as rheumatoid arthritis, which may be observed in dialysis patients and which may be a joint pain source [24], was excluded in our cohort. Due to the groups' homogeneity we can exclude the role of the central venous catheter, known to be a potential source of inflammation [25], as a cause of differences in ferritin mean values in the two groups. Pain related to uremic toxicity can be excluded [26].

The common arthropathy dialysis-related indicator β-2 microglobulin [27, 28], was similar in the two groups. There have been different reports regarding the connection of level of β-2 microglobulin and joint symptoms. Chattopadhyay et al. [29] found the β-2 microglobulin level was raised in all examined patients. Nagi et al. [4] found no connection

between the plasmatic level of β-2 microglobulin and detachment of the capsule bone (joint effusion), one of the most important parameters of a painful shoulder in dialysed patients. Baldrati et al. [30] found no connection between the plasmatic level of β-2 microglobulin in patients with dialysis-related amyloidosis and dialysed patents without it. Sethi et al. [31] reported that the plasmatic level of β-2 microglobulin was higher in patients with arthropathy than in dialysed patients without it. Serum β-2 microglobulin seems to be an inconstant indicator of dialysis-related arthropathy.

There have been only a few reports concerning ferritin levels in chronic haemodialysis patients, something we found to be statistically different in our two groups. Brown et al. [14] measured isolated ferritin levels, showing that the four patients in their study with the most severe dialysis arthropathy had higher values. However, Hurst et al. [13] showed that serum ferritin levels had a wide scatter of concentration in patients with large joint chronic synovitis, and these levels were no different to those in patients without synovitis. Ferritin levels seem to be inconstant too, but it is important to underline that no previous researchers have improved a complete iron storage biochemical panel and no one has standardised patients from the clinical point of view.

Our research has some limits. One is the small number of patients (the number will be increased in future research). Second, there is the episodic revelation of pain intensity during the long observation period, and third, the absence of iron deposits demonstrated by articular biopsy. We are currently defining a protocol of investigations for dialysis patients, which includes periodic VAS evaluation and functional evaluation of joints before taking blood samples.

Even with these limitations, we are the first to describe a complete panel to investigate biochemical and clinical characteristics of this kind of patient, leading us to speculate that the different ferritin behaviour in our symptomatic patients is independent of iron storage and inflammatory aspects.

This result opens a new area of research for future investigation. This work allowed us to re-evaluate the role of ferritin as a biochemical indicator of iron deposits in arthropathy associated with dialysis. Moreover, serum ferritin will be evaluated as a possible indicator of articular chronic pain. This is relevant in view of our future multidisciplinary approach. We will extend our research to two more populations with articular chronic pain, and we will correlate each serum sample with pain VAS administration in a prospective trial. Thus, the future aim of our research is to collect more evidence of ferritin as a possible serum indicator that can be used to identify and quantify arthropathic pain in dialysis patients, and then to consider different populations of patients.

Knowing how and when we can treat dialysis arthropathy pain is necessary to improve the quality of life for these patients because pain is a significant problem and is not being effectively managed at present. From the perspective of more complete research, the individualisation of indicators of chronic articular pain could open up the possibility of the improvement of actual treatment protocols and of personalised pain therapy.

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Corresponding author:
Martina Bellini, MD
Clinica San Carlo
Paderno Dugnano (Milan), Italy
+393289252670
e-mail: Bellini_martina@libero.it

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