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FERRITIN IN JOINT ARTHROPLASTY: CAN IT BE A POSSIBLE BIOCHEMICAL INDICATOR OF ARTICULAR PAIN?

FERITIN U ARTROPLASTICI ZGLOBA: MOŽE LI BITI BIOHEMIJSKI POKAZATELJ BOLOVA U ZGLOBOVIMA?

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Summary

Background: A retrospective study was undertaken to investigate the biochemistry data of a restricted cohort of patients. The aim of our study was to evaluate laboratory data behavior and the VAS pain scale before and after joint replacement.
Methods: We produced an elaboration of the biochemical data of 90 orthopedic patients, collected from 2011 to 2013. These 90 patients were divided into 2 groups: one group of 45 patients who claimed severe postoperative pain and one group of 45 patients who showed no or mild postoperative pain. A student's t-test was applied, considering a P value less than 0.05 as statistically significant. Pearson correlation was applied. The pain visual analog scale [VAS] was employed.
Results: Significant and relevant unexpected biochemical differences were found between the two groups of patients. The serum level of ferritin was significantly higher in men who claimed postoperative pain. We excluded the possibility that the ferritin difference between the two groups was due to different iron storage or to an inflammatory profile.
Conclusions: The correct use of a biochemical database could permit identification of significant values which must be correlated with clinical data: these results confirmed what has been found in a dialysis cohort.

Keywords: chronic pain, arthropathy, biochemical panel, indicator, joint replacement

Kratak sadržaj

Uvod: Ova retrospektivna studija preduzeta je kako bi se istražili biohemijski podaci jednog ograničenog skupa pacijenata. Cilj studije bio je da se proceni »ponašanje« laboratorijskih podataka i skala bola VAS pre i posle zamene zgloba.
Metode: Predstavili smo elaboraciju biohemijskih podataka 90 ortopedskih pacijenata, prikupljenih od 2011. do 2013. godine. Ovih 90 pacijenata podeljeno je u dve grupe: grupu od 45 pacijenata s jakim postoperativnim bolovima i grupu od 45 pacijenata bez bolova ili s blagim postoperativnim bolovima. Primenjen je Studentov t-test, pri čemu je statistički značajnom smatrana P vrednost manja od 0,05. Pearsonova korelacija je upotrebljena i korišćena je Vizuelno-analogna skala bola (VAS).
Rezultati: Otkrivene su značajne i relevantne, neočekivane biohemijske razlike između dve grupe pacijenata. Nivo feritina u serumu bio je značajno viši kod muškaraca koji su osećali postoperativne bolove. Isključili smo mogućnost da je razlika u feritinu između dveju grupa nastala zbog različitih zaliha gvožđa i zbog inflamatornog profila.
Zaključak: Pravilna upotreba biohemijske baze podataka mogla bi omogućiti identifikaciju značajnih vrednosti koje moraju korelisati s kliničkim podacima: ovi rezultati su potvrdili ono što je otkriveno u skupu pacijenata na dijalizi.

Ključne reči: hronični bol, artroplastika, biohemijski panel, pokazatelj, zamena zgloba

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Introduction

Joint replacement surgery is a safe and effective procedure (1); it is generally conducted to relieve arthritis pain or fix severe physical joint damage.

Knee replacement surgery, also known as knee arthroplasty, is regarded as a modern surgical procedure that entails restoring the weight bearing facade of the knee joint that is damaged, worn out, or diseased to relieve pain and movement disability (2). Hip replacement is a surgical procedure in which the hip joint is replaced by a prosthetic implant. Hip replacement surgery can be performed as a total replacement or a hemi (half) replacement. A total hip replacement consists of replacing both the acetabulum and the femoral head, while hemiarthroplasty generally only replaces the femoral head (3).

Some patients who have had joint replacement suffer chronic pain after the surgery. Causes of postoperative pain are various after knee arthroplasty: complex regional pain syndrome type 1 (characterized by pain, swelling, stiffness and skin changes), intra-articular causes such as infection, aseptic loosening, soft-tissue impingement and arthrofibrosis (4, 5). After hip replacement, pain can arise if the iliopsoas rubs against the edge of the acetabular cup (5, 6). Even though hip replacement surgery is the second most common joint replacement procedure, closely following knee replacements, and even though hip and knee arthroplasty are useful to reduce pain, often pain management can be difficult.

The objective of our study was to investigate the biochemical aspects of patients undergoing a joint replacement that suffer from pain due to joint arthropathy, after an in-depth clinical investigation of the patients' conditions. Our specific question was whether there is a connection between painful joints and plasma levels of biochemical analytes. The purpose is to create a basis for identifying a possible biochemical indicator able to predict arthropathy and related pain onset in joint replacement patients.

Materials and Methods

Patients

Our cohort consists of 90 patients who have received joint replacement at the San Carlo Clinic of Paderno Dugnano (Milan). We have divided them into two groups: Group A, consisting of 45 patients who claim severe and moderate pain (VAS score 45–100) after joint replacement, and Group B, consisting of 45 patients with mild or no pain (0–44) (7) after joint replacement. The common cause of arthroplasty is knee arthritis. Demographic data are shown in *Table I*.

The patients in the two different groups were standardized for age and gender. Median age is 55±10 years for men and 62±9 for women, and each group includes 23 women and 22 men. All the patients are Caucasian. The treatment panel is similar for all our patients: before the joint replacement we administered Cefazolin and Enoxaparin sodium, while after the joint replacement we administered Amoxycillin and Enoxaparin sodium. Pain was treated by commonly used analgesics and antiinflammatory drugs, i.e. paracetamol, tramadol, and ibuprofen. Patients, before and after joint replacement, are not treated with erythropoietin, blood transfusions or antineoplastic drugs. No rheumatic disease and autoimmune disorders were found.

Table I Demographic variables.

Demographic characteristic	Group B	Group A
N	45	45
Age (years)	72±10	74±8
Sex (male/female)	10/15	10/15
Body mass index –BMI kg/m^2	23.5±4.0	22.3±5.2

Arterial hypertension was found in 38/45 in the group A and 39/45 in the group B; high serum blood cholesterol was treated in 25/45 patients in the group A and 28/45 in the group B; diabetes mellitus was found in 12/45 patients in the group A and 14/45 in the group B.

Postoperative complications were excluded: prosthesis infection, aseptic loosening, venous thromboembolism, severe anemia with peripheral tissue hypoxia and prosthesis dislocation. Neurologic problems, including spinal stenosis, neurogenic clacudication, and lumbar radiculopathy were also excluded. Complex regional pain syndrome type 1, previously known as reflex sympathetic dystrophy, was excluded as the cause of postoperative pain.

Laboratory examinations

A large computerized hospital database containing extensive clinical, laboratory and pathological information has been consulted.

The plasma level of analytes was recorded before and after joint replacement from 2011 to 2012 as a routine procedure. Analytes that represent our panel: albumin, alpha-1-globulin and alpha-2-globulin, basophil cells, beta-globulin, mean corpuscular hemoglobin concentration, reticulocyte hemoglobin content, mean hemoglobin, mean volume, B12 vitamin, C reactive protein, calcitonin, calcium, chloride, total cholesterol, copper, corrected calcium, correction ratio, C peptide, creatine kinase, serum creatinine, creatinine clearance, eosinophils, erythrocyte sedimentation rate, ferritin, folate, gamma glu-

tamyl transferase, haptoglobin, glycated hemoglobin, high density lipoprotein cholesterol, hematocrit, hemoglobin, international normalized ratio, iron, lactate, lactate dehydrogenase, low density lipoprotein cholesterol, lymphocytes, magnesium, monocytes, serum myoglobin, neutrophils, alanine aminotransferase, aspartate aminotransferase, 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.

The analytes were measured before and after joint replacement. Particular attention was focused on inflammatory and iron storage parameters.

Statistical analysis

All the statistical analyses and the significance of differences between groups were determined by unpaired student's t-test. A P value of <0.05 was considered statistically significant. Mean±standard deviation is given for quantitative variables.

Pearson correlation was calculated.

Visual Analog Scale

The visual analog scale [VAS], a psychometric response scale, was used with all the 50 patients to record pain intensity when the data were analyzed. Pain intensity is referred to as 0 to 10, in which 0 = no pain at all and 10 = the worst pain imaginable. We classified pain as mild [5 to 44], moderate [45 to 74], or severe [75 to 100]. 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.

Results

Patients complained about different levels of pain before and after joint replacement. The mean value of VAS before joint replacement in Group A was 75±1; in Group B, the VAS level before joint replacement was 77±1.1. The mean value of VAS after joint replacement in Group A was 40±1.2; in Group B, the VAS level after joint replacement was 60±1. The different types of joints do not influence the VAS mean value: total hip replacement showed VAS mean values of 70, partial hip replacement 70 and knee replacement 65, after surgery. Regarding the laboratory parameters, a statistical difference in serum ferritin mean values [$P<0.01$] was observed in men before and after surgery, as shown in *Table II*.

Table II Iron panel.

Before joint replacement	Ferritin, pmol/L				MCHC, g/dL		Chr × 10^9/L		MCH, pg/cell		Hemoglobin, mmol/L		Iron, µmol/L		MCV, fl	
	Female		Male													
	Mean ± SD	*N*	*Mean ± SD*	*N*	*Mean ± SD*	*N*	*Mean ± SD*	*N*	*Mean ± SD*	*N*	*Mean ± SD*	*N*	*Mean ± SD*	*N*	*Mean ± SD*	*N*
A *(n=45)*	575.32±170	23	685.33±173	22	29.52±2.34	45	31.42±1.3	45	28.98±1.45	45	6.18±0.93	45	8.57±3.7	45	90.9±4.25	45
B *(n=45)*	631.4±165	23	959.7±167	22	30.34±1.58	45	30.16±2.3	45	24.56±2.67	45	7.36±0.66	45	9.54±4.5	45	90.75±3.27	45
P value																
A VS B	>0.01		<0.01		>0.05		>0.05		>0.05		>0.05		>0.05		>0.05	
After joint replacement	Ferritin, pmol/L				MCHC, g/dL		Chr × 10^9/L		MCH, pg/cell		Hemoglobin, mmol/L		Iron, µmol/L		MCV, fl	
	Female		Male													
	Mean ± SD	*N*	*Mean ± SD*	*N*	*Mean ± SD*	N	*Mean ± SD*	N	*Mean ± SD*	N	*Mean ± SD*	N	*Mean ± SD*	N	*Mean ± SD*	N
A (n=45)	577.47±127	23	649±144	22	31.15±2.36	45	30.44±2.3	45	26.85±1.44	45	6.18±0.69	45	8.54±3.4	45	90.9±5.25	45
B (n=45)	662.8±134	23	900±156	22	31.29 ±1.36	45	31.17±2.24	45	26.64±2.28	45	6.16±0.72	45	8.7±3.8	45	90.55±6.23	45
P value																
A VS B	<0.05		<0.01		>0.05		>0.05		>0.05		>0.05		>0.05		>0.05	

Table III Inflammatory panel, except ferritin values.

Before joint replacement	White cells × 10^9/L		Lymphocytes × 10^9/L		Neutrophils × 10^9/L		Platelet × 10^9/L		ESR		CRP nmol/L	
	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N
A *(n=45)*	6.75±1.8	45	0.022±0.0072	45	0.059±0.00834	45	218.84±80	45	79±26	45	19.33±37	45
B *(n=45)*	6.42±2.5	45	0.021± 0.0068	45	0.065± 0.0076	45	219.38±78	45	74.17±27.5	45	19.81±34.39	45
P value												
A VS B	>0.05		>0.05		>0.05		>0.05		>0.05		>0.05	
After joint replacement	White cells × 10^9/L		Lymphocytes × 10^9/L		Neutrophils × 10^9/L		Platelet × 10^9/L		ESR		CRP nmol/L	
Mean ± SD	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N
A *(n=45)*	5.78±2.1	45	0.022± 0.0074	45	0.0625±0.00814	45	214.74±78	45	80±29.8	45	18.86±30.4	45
B *(n=45)*	6.32±2.5	45	0.021± 0.0062	45	0.063±0.0067	45	219.48±76	45	70.17±30.5	45	17.33±25.7	45
P value												
A VS B	>0.05		>0.05		>0.05		>0.05		>0.05		>0.05	

Table IV Hemoglobin and red cells values.

Before joint replacement	Hemoglobin, mmol/L				Red cells x10^{12}/L			
	Women		Men		Women		Men	
	Mean±SD	N	Mean±SD	N	Mean±SD	N	Mean±SD	N
A (n=45)	6.87±1.26	23	7.5±0.72	22	4.03±0.9	23	4.18±1.1	22
B (n=45)	6.06±0.96	23	6.64±1.14	22	3.87±0.7	23	4.09±0.9	22
P value								
A VS B	>0.05		>0.05		>0.05		>0.05	
After joint replacement	Hemoglobin, mmol/L				Red cells x10^{12}/L			
	Women	Men	Women	Men				
	Mean±SD	N	Mean±SD	N	Mean±SD	N	Mean±SD	N
A (n=45)	6,72±0.66	23	6.9±0.6	22	3.98±0.7	23	3.98±1.2	22
B (n=45)	6.66±0.84	23	6.84±0.9	22	3.78±0.9	23	3.99±1	22
P value								
A VS B	>0.05		>0.05		>0.05		>0.05	

In the dialysis panel of analytes, only serum ferritin showed a statistically significant difference between the two groups, with an increase of 40 percent in the men of Group B compared to Group A before surgery, and with an increase of 39 percent in the men of Group B compared to Group A after surgery.

Due to these results, we decided to investigate the different role of serum ferritin within an inflammatory and an iron panel. The iron panel includes the analytes that are known to be iron status indicators such as mean corpuscular hemoglobin concentration, reticulocyte hemoglobin content, mean hemoglobin, hemoglobin, iron itself, and mean volume. The inflammatory panel includes white cells, lymphocytes, neutrophils, platelet, erythrocyte sedimentation rate, and C reactive protein. Neither of the panels showed any differences in ferritin behavior. Values are reported in *Table II* and *III*. Hemoglobin values were not relevant, as show in *Tables IV.*

We had the panel evaluated in particular men: higher ferritin level was not related with iron storage and inflammatory status. The value of Pearson correlation R is 0.37 (*Table V*).

Table V Pearson correlation value.

Before joint replacement				
	VAS		Ferritin, pmol/L	
	Women	Men	Women	Men
	Mean	Mean	Mean±SD	Mean±SD
N	70	80	575.32±170	685.33±173
A	70	85	631.4±165	959.7±167
After joint replacement				
	VAS		Ferritin, pmol/L	
	Women	Men	Women	Men
	Mean	Mean	Mean±SD	Mean±SD
N	35	45	257±58.1	289±65.8
A	75	55	295±61.2	402±71.3
Pearson correlation R	0.37			

Discussion

Laboratory tests for orthopedic patients are not diagnostic in the case of mechanical failure such as dislocation, periprosthetic fracture, or component disassociation. In the face of painful arthroplasty, laboratory tests are essential to establish a definitive diagnosis and notably to rule out or to ascertain an infectious complication or a hypersensitivity reaction. Laboratory tests in arthroplasty may be helpful in the diagnosis of an infected joint replacement, but patients may have normal laboratory results in spite of a deep infection (8). Specific tests that may be useful include a complete blood count with differential, erythrocyte sedimentation rate, and C-reactive protein.

No previous researcher has improved the complete iron storage biochemical panel and no one has considered ferritin outside its inflammatory and iron storage role. In fact, recently, Enko et al. (9) and Schleiffenbaum et al. (10) described the role of ferritin in major orthopedic surgery patients to describe anemia, Galliera et al. (11) described ferritin as a marker of postoperative joint infection inside the iron storage panel and Fotland et al. (12) hypothesized that iron status and ferritin could predict transfusion requirement after joint replacement.

Knowing how and when we can treat joint pain is necessary to improve the quality of life for patients, because pain is a significant problem and is often not being effectively managed at present. Pain may come gradually or fluctuate over a period of weeks, or it may develop suddenly, so targeted therapy is often difficult.

The individualization of biochemical indicators of articular pain could open up the possibility for improvement of actual treatment protocols and for personalized pain therapy.

Investigating the role of ferritin in joint pain is the primary outcome. Standardizing our patients was our first target. From the clinical point of view, we considered gender, age, therapy panel, comorbidity [diabetes mellitus, arterial hypertension, ischemic heart disease, cerebrovascular disease], in order to guarantee the best available homogeneity. Our group has investigated the role of ferritin in dialysis related arthropathy and pain (13): dialysis-related arhtropathy is severe, often disabling and causing severe pain (14) and it remains a significant clinical problem in dialysis patients (15).

If it contributes to functional limitations and/or leads to another clinical problem that worsens the patient's quality of life (16–18), it is not being effectively managed. In fact, joint pain was shown in at least 50 percent of dialysis patients (19), with scores of 4 to 7 on the VAS (20), with a very low success rate, and there is no specific therapeutic protocol for these patients, due to the unpredictable and abnormal pharmacokinetics in dialysis patients.

In our cohort, we observed a statistical difference in serum ferritin mean values [$P<0.01$] between patients with and without pain, after groups standardization.

These results were partially confirmed in our study on joint replacement and pain, because we found a statistically relevant ferritin increase in men who claimed higher levels of pain after surgery, while women did not show this kind of results.

Although technically a positive correlation, the Person correlation coefficient shows that the relationship between our variables is weak, but close to 0.4, that means moderate correlation. Pearson correlation will be reevaluated in a prospective study to minimize this kind of error.

Our research has some limits. One is the small number of patients. Second, there is the episodic revelation of pain intensity during the long observation period. We are currently defining a protocol of in-

vestigations for joint replacement patients, which includes periodic VAS evaluation and functional evaluation of joints before taking blood samples. Even with these limitations, our results lead us to speculate that the different ferritin behavior in our symptomatic patients is independent of iron storage and inflammatory aspects.

One of the most challenging problems in pain management is the difficulty of making an objectively measurable assessment of pain, since pain is a subjective perception. For these reasons, the possibility to individuate biochemical indicators of joint pain is even more interesting. Due to our results, we will proceed with a prospective study, to confirm the hypothesis of the relationship of pain and ferritin's levels. We will extend our research to more populations with articular pain and we will correlate each serum sample with pain VAS administration in a prospective trial.

Conflict of interest statement

The authors stated that they have no conflicts of interest regarding the publication of this article.

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