IGF-1, citokini i biokemijski biljezi koštane pregradnje u sinovijalnoj tekućini i serumu bolesnika s primarnim i sekundarnim osteoartritisom kuka

IGF-1, cytokines and biochemical bone turnover markers in synovial fluid and serum of patients with primary and secondary osteoarthritis of the hip

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Sažetak

Cilj: Usporediti koncentracije IGF-1, biljega koštane pregradnje (BSAP, CTX) i citokina u bolesnika s uznapredovalim osteoartritisom kuka te procijeniti povezanosti između tih parametara i etiopatogeneze bolesti.

Materijali i metode: Uzorci zglobne tekućine i seruma prikupljeni su od 17 bolesnika s primarnim osteoartritisom kuka (POA) i 6 bolesnika s avaskularnom osteonekrozom kuka (SOA) podvrgnutih operacijskom zahvatu na kuku. Koncentracije IGF-1, IL-6, IL-8, IL-10, CTX te aktivnosti BSAP mjerene su metodom ELISA.

Rezultati: IGF-1 u serumu bolesnika s osteoartritisom bio je unutar donjeg raspona referentnih vrijednosti, no u bolesnika s osteonekrozom bio je ispod tog raspona. Međutim, koncentracija CTX u serumu bila je značajno viša u bolesnika sa SOA (0,58±0,19) nego u POA (0,39±0,15; P=0,02). IGF-1 u sinovijalnoj tekućini bolesnika sa SOA bio je niži (P=0,008), a CTX viši nego u slučajeva POA (P<0,001). U bolesnika s primarnim osteoartritisom koncentracije IGF-1, CTX, IL-6 i IL-8 u sinovijalnoj tekućini korelirale su s koncentracijama u serumu. U slučajevima osteonekroze utvrđene su slične i naglašene korelacije samo između CTX i IL-8. IGF-1 je u sinovijalnoj tekućini korelirao s aktivnošću BSAP u bolesnika s POA. Pozitivna korelacija je zapažena između CTX i IL-8 u sinovijalnoj tekućini i serumu. U bolesnika s osteonekrozom IGF-1 je u serumu izravno korelirao s IL-10, dok je negativna povezanost nađena između CTX i IL-10.

Zaključci: Koncentracija IGF-1 može biti čimbenikom rizika za predispoziciju za osteoartritis kao i povezana s etiopatogenezom te bolesti. Vrlo niska koncentracija IGF-1 u serumu (PPV>70%) ili sinovijalnoj tekućini može ukazati na nekrozno podrijetlo degenerativne bolesti zglobova. Ovdje izneseni podatci pokazuju da je avaskularna osteonekroza obilježena više kataboličkim stanjem koje se odražava niskim IGF-1 s istodobnim porastom koštane razgradnje i proupalnih pokazatelja.

Ključne riječi: IGF-1, osteoartritis, osteonekroza, koštani metabolizam, interleukini

Abstract

Background: To compare the concentrations of IGF-1, bone turnover markers (BSAP, CTx) and cytokines in patients with advanced hip osteoarthritis and to evaluate associations between these parameters and disease etiopathogenesis.

Materials and methods: Samples of joint fluid and serum were collected from 17 patients with primary hip osteoarthritis (POA) and 6 patients with avascular osteonecrosis of the hip (SOA) who underwent hip surgery. Concentration of IGF-1, IL-6, IL-8, IL-10, CTx and BSAP activity were measured by ELISA.

Results: Patients with osteoarthritis had serum IGF-1 in the lower range of reference values but those with osteonecrosis - below this range. Serum CTx concentration was, however, significantly higher in SOA than in POA cases (0.58±0.19 and 0.39±0.15, respectively, P=0.02). Synovial fluid IGF-1 in SOA patients was lower (P=0.008) and CTx higher than in POA cases (P<0.001). In patients with primary osteoarthritis synovial fluid IGF-1, CTx, IL-6 and IL-8 concentrations correlated with those in the serum. Similar and strong associations, but only for CTx and IL-8, were found in cases with osteonecrosis. IGF-1 in synovial fluid correlated with BSAP activity in POA patients. Positive correlation was observed between CTx and IL-8 in synovial fluid and serum. In patients with osteonecrosis, serum IGF-1 was directly related to IL-10 while negative association was found between CTx and IL-10.

Conclusions: IGF-1 level may constitute a risk factor predisposing to osteoarthritis and may be related to disease etiopathogenesis. Very low IGF-1 concentration in serum (PPV>70%) or synovial fluid may indicate necrotic origin of degenerative joint disease. The data reported here show that avascular osteonecrosis is characterized by a more catabolic state, reflected by low IGF-1 with concomitant increase in bone resorption and pro-inflammatory indices.

Key words: IGF-1, osteoarthritis, osteonecrosis, bone metabolism, interleukins

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Uvod

Osteoartritis, ili drugim nazivom degenerativna bolest zglobova, jest najčešća od svih zglobnih oboljenja (1). Primarni ili sekundarni osteoartritis predstavlja veliki problem u starijih osoba, uz prevalenciju koja je veća u žena nego muškaraca. Etiopatogeneza primarnog osteoartritisa nije jasna. Slabljenje metaboličke ravnoteže između sinteze i razgradnje hrskavice i subhondralne kosti dovodi do prevladavanja kataboličkih nad anaboličkim procesima koje uzrokuje progresivno razaranje zglobnog tkiva (2). Proces obnavljanja je oslabljen ili može dovesti do prebrzog rasta zglobnih struktura (3,4). Tijekom osteoartritisa subhondralna kost i hrskavica mogu imati različitu histološku strukturu i biomehanička svojstva (5). Nedavno je predloženo da bi neujednačena mineralizacija koja se zbiva u subhondralnoj kosti te pojačana koštana pregradnja mogle dovesti do degeneracije i gubitka hrskavice (6). Subhondralna osteonekroza može također prouzročiti promjene u strukturi hrskavice (7,8). Patogeneza osteoartritisa podrazumijeva izmijenjeno međudjelovanje različitih vrsta hondrocita i sastojaka izvanstanične matrice kao što su čimbenici rasta, interleukini i specifični enzimi (9). Neki čimbenici rasta, poput inzulinu sličnog čimbenika rasta 1 (IGF-1) i transformirajućeg čimbenika rasta β (TGF-β), imaju ključnu anaboličnu ulogu u metabolizmu hrskavice i kosti. IGF-1 potiče sintezu proteoglikana i kolagena no u osteoartritisu bi njegovo djelovanje na stanice hrskavice i kosti moglo biti preinačeno (6,10,11). Narušena ravnoteža između IGF-1 i specifičnih veznih proteina (IGFBP) te inhibicijski učinak citokina i mehaničkih čimbenika sudjeluju u razvoju osteoartritisa (12). Osim toga, hondrociti u osteoartritisu su manje osjetljivi na IGF-1 koji nastaju smanjenim izražajem površinskih receptora IGF-1 ili pojačanom aktivnošću citokina (13,14,15). Doprinos svakog mehanizma tijekom osteoartritisa ovisi o fazi bolesti jer je napredovanje bolesti praćeno promjenama hondrocita kojima se očituju različite metaboličke aktivnosti (9,16).
Cilj naše studije bio je usporediti koncentracije biokemijskih biljega, kao što su IGF-1, biljezi koštane pregradnje i citokini, u starijih bolesnika s uznapredovalim primarnim osteoartritisom kuka ili aseptičnom osteonekrozom kuka, te procijeniti povezanosti između tih analita u serumu i sinovijalnoj tekućini i etiopatogeneze bolesti.

Materijali i metode

Uzorci zglobne tekućine i krvi prikupljeni su od 23 bolesnika podvrgnutih operaciji kuka tijekom 2003.–2004. godine u Klinici za ortopediju i traumatologiju Sveučilišne bolnice u Bydgoszczu, Poljska. Operacije su obavljene na 17 kukova (13 žena i 4 muškarca, dob 68±9 godina) zbog primarnog osteoartritisa (skupina POA), te 6 kukova (5 žena i 1 muškarac, dob 68±15 godina) zbog osteonekroze (skupina SOA); svi su bolesnici bili razvrstani na temelju

Introduction

Osteoarthritis, also called degenerative joint disease is the most common of all joint diseases (1). Primary or secondary osteoarthritis constitutes a substantial problem in the elderly, and is more prevalent in women than in men. Etiopathogenesis of primary osteoarthritis is not clear. Loosing the metabolic balance between the synthesis and degradation of the cartilage and subchondral bone leads to predominance of catabolic over anabolic processes that results in progressive destruction of joint tissues (2). The repair process is impaired or may lead to overgrowth of joint structures (3,4). In the course of osteoarthritis, subchondral bone and cartilage may have different histological structure and biomechanical properties (5). Recently, it has been suggested that unequal mineralization, that occurs in the subchondral bone, and increased bone turnover could lead to degeneration and loss of the cartilage (6). Also, subchondral osteonecrosis may cause changes in cartilage structure (7,8). The pathogenesis of osteoarthritis involves altered interactions of different types of chondrocytes and constituents of extracellular matrix such as growth factors, interleukins and specific enzymes (9). Some growth factors like insulin-like growth factor-1 (IGF-1) and transforming growth factor-β (TGF-β) play an essential anabolic role in cartilage and bone metabolism. IGF-1 stimulates proteoglycan and collagen synthesis but its action in osteoarthritis on cartilage and bone cells could be modified (6,10,11). Impaired balance between IGF-1 and specific binding proteins (IGFBPs), inhibitory effect of cytokines and mechanical factors take part in the development of the disease (12). In addition, chondrocytes in osteoarthritis are less sensitive to IGF-1 that may be caused by decreased expression of surface IGF-1 receptors or enhanced activity of cytokines (13,14,15). The contribution of each mechanism in the course of osteoarthritis depends on its stage since the disease progression is accompanied by changes in chondrocytes presenting different metabolic activities (9,16).
The aim of our study was to compare the concentrations of biochemical markers such as IGF-1, bone turnover markers and cytokines in elderly patients with advanced primary hip osteoarthritis or aseptic osteonecrosis of the hip and to evaluate associations between these analytes in serum and synovial fluid in relation to disease etiopathogenesis.

Materials and methods

Samples of joint fluid and blood were collected from 23 patients who underwent hip surgery in years 2003-2004 in the Department of Orthopedics and Traumatology at University Hospital in Bydgoszcz. 17 hips (13 women and 4 men, 68±9 years old) were operated on because of primary osteoarthritis (POA group), and 6 hips (5 women

kliničkih osobina i radiografskih promjena. Krv je prikupljena tijekom tjedna prije operacijskog zahvata, a uzorci seruma čuvani zamrznuti na –70 °C do uporabe. Uzorci sinovijalne tekućine prikupljeni su štrcaljkom prije incizije čahure, centrifugirani i obrađeni hijaluronidazom kao što smo ranije opisali, te pohranjeni na –70 °C do 1 mjesec prije analiza (17).

Informirani pristanak dali su svi sudionici, a istraživačke je postupke odobrio lokalni Bioetički odbor.

U svim su uzorcima analizirani IGF-1, CTX (engl. β-*crosslaps*), BSAP (koštana alkalna fosfataza) i citokini: IL-6, IL-8 i IL-10 uz uporabu komercijalno dostupnih kompleta ELISA. CTX je kao biljeg koštane razgradnje analiziran korištenjem Serum CrossLaps (Osteometer BioTech, Danska), aktivnost BSAP kao biljega koštane izgradnje korištenjem ALKPHASE-B (Metra Biosystems, SAD), IGF-1 pomoću Octeia IGF-1 (IDS, V. Britanija), te koncentracije IL-6, IL-8 i IL-10 korištenjem Bender Medsystems, Austrija.

Statistička analiza

Statistička analiza je provedena korištenjem Studentovog t-testa i Pearsonovog koeficijenta korelacije. Vrijednost $p<0,05$ smatrana je statistički značajnom.

Od mjera dijagnostičke točnosti, izračunate su i prikazane jedino pozitivne prediktivne vrijednosti (PPV).

Rezultati

Bolesnici s avaskularnom osteonekrozom kuka imali su vrlo nisku koncentraciju IGF-1 u serumu (Tablica 1). Srednja koncentracija serumskog IGF-1 u bolesnika s primarnim osteoartritisom kuka bila je unutar normalnog raspona za odrasle osobe. U bolesnika s osteonekrozom srednja koncentracija IGF-1 u serumu bila je niža od 82 μg/L. Pozitivna prediktivna vrijednost serumskog IGF-1 u slučajevima primarnog osteoartritisa kuka bila je 71%, dok je kod avaskularne osteonekroze kuka bila 83%. U našoj je studiji IGF-1 u serumu niži od 82 μg/L bio prihvaćen kao pravi pozitivan rezultat u bolesnika s primarnim i sekundarnim osteoartritisom kuka.

Prosječna koncentracija u serumu ili aktivnost svih mjerenih parametara osim CTX nije se značajno razlikovala između dvije skupine bolesnika.

Utvrdili smo više koncentracije serumskog CTX u slučajevima avaskularne osteonekroze kuka; jedino je u toj skupini srednja vrijednost CTX u serumu bila iznad gornje granice referentnog raspona za zdrave odrasle osobe. Aktivnost BSAP u serumu bila je unutar normalnog raspona u bolesnika iz obje skupine (Tablica 1).

Koncentracije pojedinačnih citokina u serumu bile su slične u obje skupine. Srednja koncentracija IL-6 u serumu bila je niska samo u bolesnika s osteonekrozom, dok je razina IL-8 bila povišena u obje skupine. Prosječna koncentracija IL-10 u serumu bila je unutar referentnog raspona .

and 1 man, 68±15 years old) because of osteonecrosis (SOA group), all classified on the basis of clinical features and radiographic changes. Blood was collected during the week preceding the surgery and serum samples were kept frozen at -70 °C until used. Samples of synovial fluid were collected with a syringe before incising the capsule, centrifuged, treated with hyaluronidase as we previously described and stored at -70 °C for up to 1 month before the analyses (17).

Informed consent was given by all participants and the procedures were approved by the local Bioethics Committee.

All specimens were assayed for IGF-1, CTx (ß-crosslaps), BSAP (bone alkaline phosphatase) and cytokines: IL-6, IL-8 and IL-10 using commercially available ELISA kits. CTx, a bone resorption marker was assayed by Serum CrossLaps (Osteometer BioTech, Denmark), the activity of BSAP, a bone formation marker, by ALKPHASE-B (Metra Biosystems, USA), IGF-1 by Octeia (IGF-1, IDS, UK) and IL-6, IL-8, IL-10 concentrations by Bender Medsystems, Austria.

Statistical analysis

Statistical analysis was done using the t-Student test and Pearson correlation coefficient. P-value < 0.05 was considered statistically significant.

Only positive predictive value (PPV) was calculated as one of the measures of diagnostic accuracy.

Results

Patients with avascular osteonecrosis of the hip had very low serum IGF-1 level (Table 1). Mean serum concentration of IGF-1 in patients with primary hip osteoarthritis was within the normal range for adults. In patients with osteonecrosis, the mean level of IGF-1 in serum was lower than 82 μg/l. Positive predictive value of serum IGF-1 in cases with primary hip osteoarthritis was 71% while in cases with avascular osteonecrosis of the hip was 83%. In our study, serum IGF-1 below 82 μg/l was accepted as true positive result in patients with primary and secondary hip osteoarthritis.

Mean serum concentration or activity of all measured parameters, except CTx, did not differ significantly in both groups.

We found higher concentration of serum CTx in cases with avascular osteonecrosis of the hip and only in this group mean serum CTx value was above the upper reference range for healthy adults. The activity of serum BSAP was within the normal range in patients from both groups (Table 1).

Serum levels of individual cytokines were similar in both groups. Mean serum IL-6 concentration was low only in osteonecrosis patients while IL-8 level was increased in both groups. Mean serum IL-10 was within the reference range.

Tablica 1. Srednje vrijednosti i referentne vrijednosti analita mjerenih u serumu

Table 1. Mean values and reference values of analytes measured in the serum.

	POA group mean ± SD	SOA group mean ± SD	p	Reference values
IGF-1 [µg/L]	86.5 ± 52.9	80.01 ± 35.5	ns	82–221
CTx [ng/mL]	0.39 ± 0.15	0.58 ± 0.19	0.02	F:< 0.556 M:< 0.394
BSAP [U/L]	28.2 ± 11.7	31.7 ± 12.8	ns	F:14.8–43.4 M:15.0–41.3
IL-6 [pg/mL]	4.7 ± 5.1	1.3 ± 0.6	ns	1.4–14.1
IL-8 [pg/mL]	18.5 ± 30.4	19.9 ± 23.3	ns	1.2–16.7
IL-10 [pg/mL]	3.3 ± 1.7	2.9 ± 1.3	ns	0–14.1

POA group – patients with primary hip osteoarthritis, SOA group – patients with avascular osteonecrosis of the hip, F – females, M – males, ns – not significant

Srednja vrijednost IGF-1 u sinovijalnoj tekućini u slučajevima avaskularne osteonekroze kuka bila je značajno niža, a vrijednost CTX viša nego u bolesnika s primarnim osteoartritisom kuka (Tablica 2). Aktivnost BSAP bila je slična u obje skupine. Zabilježena je tendencija prema nižim vrijednostima citokina, osobito IL-6 i IL-10, u sinovijalnoj tekućini bolesnika s avaskularnom osteonekrozom kuka u usporedbi s bolesnicima s primarnim osteoartritisom kuka, no jače je proupalno stanje utvrđeno u osteonekrozi. Omjeri IL-6: IL-10 te IL-8 i IL-10 bili su do triput viši u bolesnika s osteonekrozom.

Zanimljivo je da su koncentracije IGF-1 u sinovijalnoj tekućini (Slika 1) bile, osim u jednog bolesnika, niže u us-

Mean synovial fluid IGF-1 value in cases with avascular osteonecrosis of the hip was significantly lower and CTx was higher than in those with primary hip osteoarthritis (Table 2). Activity of BSAP was similar in both groups. There was a tendency to lower cytokine values, especially for IL-6 and IL-10, in the synovial fluid of patients with avascular osteonecrosis of the hip compared to those with primary hip osteoarthritis; however, more pronounced proinflammatory status was found in osteonecrosis. The quotients IL-6: IL-10 and IL-8: IL-10 were up to 3-fold higher in patients with osteonecrosis.

Interestingly, synovial fluid IGF-1 concentrations (Fig.1) in all patients but one were lower compared with these in

Tablica 2. Srednje vrijednosti parametara određivanih u sinovijalnoj tekućini.

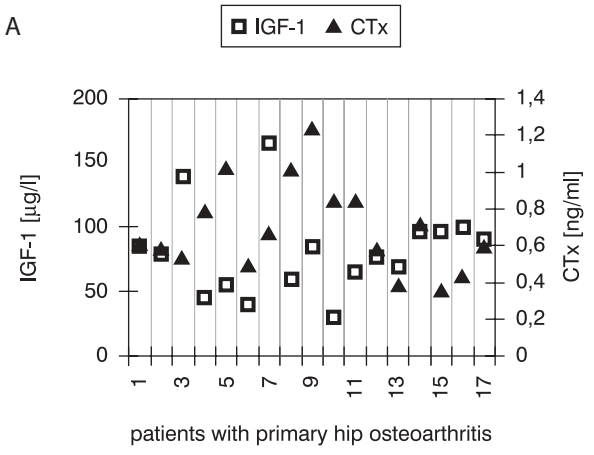
Table 2. Mean values of parameters measured in the synovial fluid.

	POA group mean ± SD	SOA group mean ± SD	p
IGF-1 [µg/L]	81.4 ± 33.9	40.2 ± 6.8	0.008
CTx [ng/mL]	0.69 ± 0.24	1.31 ± 0.46	<0.001
BSAP [U/L]	42.2 ± 26.5	40.2 ± 16.6	ns
IL-6 [pg/mL]	160 ± 120.1	77.6 ± 42.2	ns
IL-8 [pg/mL]	296.3 ± 681.6	265.2 ± 281.3	ns
IL-10 [pg/mL]	21.8 ± 28.6	6.8 ± 4.5	ns

POA group – patients with primary hip osteoarthritis, SOA group – patients with avascular osteonecrosis of the hip, ns – not significant

poredbi s onima u serumu (Slika 2); ta je razlika, međutim, dosegla statističku značajnost samo u slučajevima SOA (Tablica 3).
Nasuprot tome, vrijednosti ostalih biljega mjerenih u zglobnoj tekućini bile su mnogo više nego u serumu u obje skupine. To je prije svega zapaženo kod usporedbe koncentracija citokina u sinovijalnoj tekućini i serumu. U većini slučajeva viši CTX u sinovijalnoj tekućini pratila je niža koncentracija IGF-1.
U bolesnika s primarnim osteoartritisom kuka koncentracije IGF-1, CTX, IL-6 i IL-8, izmjerene u sinovijalnoj tekućini, korelirale su s onima u serumu (Tablica 3). Slične i snažne povezanosti zabilježene su u skupini SOA, no samo za CTX i IL-8. Nije postojala korelacija između aktivnosti BSAP u serumu i sinovijalne tekućine.

serum (Fig.2). However, only in SOA cases this difference reached statistical significance (Table 3).
On the contrary, values of other markers measured in the joint fluid were much higher than in serum in both groups. This was primarily observed when concentrations of cytokines in synovial fluid and serum were compared. In most cases, higher CTx in synovial fluid accompanied low IGF-1 concentration.
In patients with primary hip osteoarthritis IGF-1, CTx, IL-6 and IL-8 concentrations measured in the synovial fluid correlated with those in the serum (Table 3). Similar and strong associations, but only for CTx and IL-8, were noted in the SOA group. There was no correlation between BSAP activity in the serum and synovial fluid.



Slika 1. Pojedinačne vrijednosti IGF-1 i CTX u sinovijalnoj tekućini

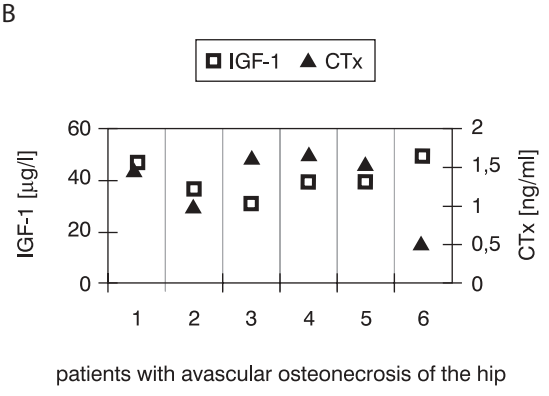
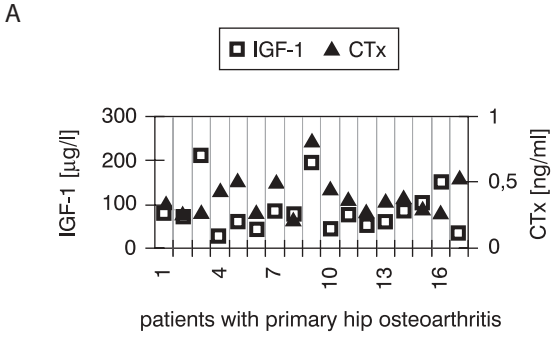


Figure 1. Individual values of IGF-1 and CTx in the synovial fluid



Slika 2. Pojedinačne vrijednosti IGF-1 i CTX u serumu

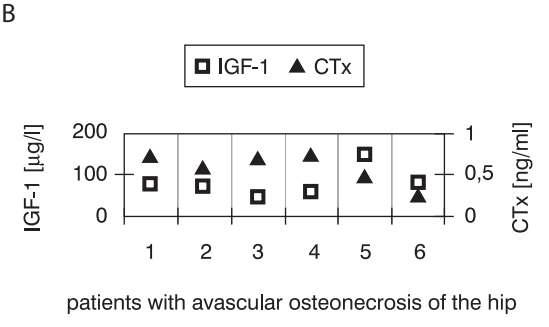


Figure 2. Individual values of IGF-1 and CTx in the serum

Tablica 3. Korelacije između biokemijskih biljega izmjerenih u serumu i sinovijalnoj tekućini.

Table 3. Correlations between biochemical markers measured in serum and synovial fluid.

	IGF-1	
	R	p
POA	0.55	<0.05
SOA	0,26	ns
	CTx	
	R	p
POA	0.52	<0.05
SOA	0.71	<0.05
	BSAP	
	R	p
POA	–0.04	ns
SOA	–0.09	ns
	IL-6	
	R	p
POA	0.67	<0.05
SOA	0.40	ns
	IL-8	
	R	p
POA	0.86	<0.05
SOA	0.99	<0.05
	IL-10	
	R	p
POA	–0.0008	ns
SOA	0.31	ns

POA group – patients with primary hip osteoarthritis, SOA group – patients with avascular osteonecrosis of the hip, ns – not significant

Veze između različitih parametara analiziranih u ovoj studiji prikazane su u tablici 4. Dobra pozitivna korelacija u bolesnika s POA primijećena je prije svega između CTX i IL-8.

IGF-1 u serumu je u skupini SOA korelirao s IL-10, a nađena je i jaka negativna povezanost između CTX u serumu i IL-10 (Tablica 4).

The associations between various parameters analyzed in this study are shown in Table 4. Good positive correlation in POA patients was noted, primarily between CTx and IL-8.

In the SOA group, serum IGF-1 correlated with IL-10, and a strong negative association was found between serum CTx and IL-10 (Table 4).

Tablica 4. Korelacije između biokemijskih biljega u obje skupine bolesnika

Table 4. Associations between biochemical markers in both groups of patients

Patients with primary hip osteoarthritis

	Serum							Synovial fluid					
	IGF-1	**CTx**	**BSAP**	**IL-6**	**IL-8**	**IL-10**		**IGF-1**	**CTx**	**BSAP**	**IL-6**	**IL-8**	**IL-10**
IGF-1	----	R-0.09 ns	R-0.28 ns	R-0.10 ns	R-0.44 ns	R-0.46 ns	IGF-1	----	R-0.01 ns	R-0.51 P<0.05	R-0.11 ns	R-0.07 ns	R-0.49 ns
CTx		----	R-0.42 ns	R0.08 ns	R-0.59 P<0.05	R-0.39 ns	CTx		----	R-0.34 ns	R-0.03 ns	R-0.68 P<0.05	R-0.43 ns
BSAP			----	R-0.48 ns	R0.15 ns	R-0.40 ns	BSAP			----	R-0.46 ns	R-0.12 ns	R-0.12 ns
IL-6				----	R-0.28 ns	R-0.02	IL-6				----	R-0.14 ns	R-0.27 ns
IL-8					----	R-0.27 ns	IL-8					----	R-0.17 ns
IL-10						----	IL-10						----

Patients with avascular osteonecrosis of the hip

	Serum							Synovial fluid					
	IGF-1	**CTx**	**BSAP**	**IL-6**	**IL-8**	**IL-10**		**IGF-1**	**CTx**	**BSAP**	**IL-6**	**IL-8**	**IL-10**
IGF-1	----	R-0.35 ns	R-0.35 ns	R-0.52 ns	R-0.70 ns	R-0.81 P<0.05	IGF-1	----	R-0.08 ns	R-0.17 ns	R-0.64 ns	R-0.54 ns	R-0.74 ns
CTx		----	R-0.35 ns	R-0.57 ns	R-0.79 ns	R-0.86 P<0.05	CTx		----	R-0.42 ns	R-0.12 ns	R-0.05 ns	R-0.81 ns
BSAP			----	R-0.34 ns	R-0.51 ns	R-0.07 ns	BSAP			----	R-0.42 ns	R-0.74 ns	R-0.34 ns
IL-6				----	R-0.09 ns	R-0.37 ns	IL-6				----	R-0.63 ns	R-0.39 ns
IL-8					----	R-0.43 ns	IL-8					----	R-0.26 ns
IL-10						----	IL-10						----

ns - not significant

Rasprava

Nedostatak IGF-1 smatra se ključnim čimbenikom degenerativnih promjena u hrskavici (18,19,20,21). Prethodne su studije pokazale da je lokalna (u sinovijalnoj tekućini) koncentracija IGF-1 niska (22,23,24,25). Hedstrom i sur. izvijestili su o sniženim koncentracijama IGF-1 u serumu bolesnika s prijelomom kuka u usporedbi s osteoartritisom kuka (26). Nedavno je pokazano da su koncentracije IGF-1 u sinovijalnoj tekućini i serumu u bolesnika s olabavljenom aseptičnom protezom niže nego u osteoartritisu (27). Mi smo ustanovili da je koncentracija IGF-1 niska i u serumu i u sinovijalnoj tekućini u starijih bolesnika podvrgnutih operaciji kuka zbog osteoartritisa kuka. Kod većine bolesnika iz obje skupine razina IGF-1 je bila ispod referentnog raspona (PPV 71% ili 83%). Slično tome, Pagura i sur. su za-

Discussion

IGF-1 deficiency is regarded as an essential contributor to degenerative changes in the cartilage (18,19,20,21). Previous reports showed that local (synovial fluid) IGF-1 concentration is low in osteoarthritis (22,23,24,25). Hedstrom et al. reported reduced serum IGF-1 levels in hip fracture patients compared with hip osteoarthritis (26). Recently it was shown that IGF-1 concentrations in the synovial fluid and serum in patients with aseptic prosthesis loosening were lower than in osteoarthritis (27). We found that both serum and synovial fluid concentrations of IGF-1 were low in elderly patients who underwent hip surgery because of hip osteoarthritis. IGF-1 level was in most cases in both groups below the reference range (PPV 71% or 83%). Similarly, Pagura et al. observed lower concentration of

pazili nižu koncentraciju tog čimbenika rasta u serumu i sinovijalnoj tekućini žena predviđenih za artroplastiku koljena nego u kontrolnim ispitanicima (21). Suprotno tome, koncentracije ostalih analiziranih parametara bile su mnogo više lokalno nego u serumu. To zapažanje potvrđuje naše podatke koje smo objavili ranije (17,28,29).

U svojoj studiji Denko i sur. su utvrdili mnogo nižu koncentraciju IGF-1 u sinovijalnoj tekućini nego u serumu bolesnika s osteoartritisom i različitim oblicima reumatoidnog artritisa (25). Naša je pretpostavka da patogeneza osteoartritisa utječe na lokalnu koncentraciju razgradnje hrskavice i pokazatelje koštane pregradnje unutar zgloba. Za srednju koncentraciju u sinovijalnoj tekućini anaboličnog čimbenika kao što je IGF-1 utvrđeno je da je značajno niža u slučajevima avaskularne osteonekroze kuka.

Hilal i sur. su izvijestili o pojačanom odgovoru stanica sličnih osteoblastima nakon stimulacije s IGF-1 i drugim čimbenicima rasta, što rezultira pojačanim izražajem alkalne fosfataze (30). Unatoč tome što smo zapazili izravnu povezanost između IGF-1 i BSAP te niske koncentracije IGF-1, osobito u sinovijalnoj tekućini bolesnika s avaskularnom osteonekrozom kuka, ustanovljena je normalna aktivnost BSAP.

Prema Matsumotu i sur. IGF-1 u serumu je snižen u osteoartritisu s erozijama kosti (19). Utvrdili smo da su niske koncentracije IGF-1 popraćene višim vrijednostima CTX. Međutim, pojačana koštana razgradnja koja ukazuje i na povećanu razgradnju koštanog kolagena bila je potvrđena samo u bolesnika s avaskularnom osteonekrozom. Lajeunesse i sur. su naznačili da bi neravnoteža između koštane razgradnje i izgradnje tijekom koštane pregradnje mogla biti odgovorna za abnormalan metabolizam subhondralne kosti kod osteoartritisa (31). U našoj studiji koštana razgradnja, koju odražava CTX, zaista nije korelirala s koštanom izgradnjom mjerenom kao aktivnost BSAP, čak ni u bolesnika s avaskularnom osteonekrozom kuka.

Do sada je izviješteno da bi koncentracije proupalnih interleukina, osobito IL-8 u sinovijalnoj tekućini, mogle biti povišene u stanjima povezanima s gubitkom kosti kao što su osteoartritis i reumatoidni artritis (32). Unatoč sličnim vrijednostima IL-8 utvrđenima u obje skupine bolesnika, tri puta viši omjer IL-8 i protuupalnog IL-10 u bolesnika s osteonekrozom mogao bi ukazivati na proupalno stanje u potonjoj bolesničkoj skupini. Podatci koji su ovdje izneseni naznačuju mogućnost da bi avaskularna osteonekroza kuka mogla biti više obilježena kataboličnim stanjem koje se ogleda u niskim IGF-1 uz istodoban rast koštane razgradnje i pokazatelja upale.

Ova je studija podložna određenom broju ograničenja, kao što je mali broj slučajeva osteoartritisa kuka te osobito slučajeva avaskularne osteonekroze. Treba, međutim, uzeti u obzir da je dostupnost sinovijalne tekućine kao biološkog materijala za laboratorijske analize često vrlo ograničena.

Koncentracija IGF-1 može predstavljati čimbenik rizika koji ukazuje na predispoziciju za osteoartritis i čini se da je

this growth factor in serum and synovial fluid of females awaiting knee arthroplasty than in controls (21). Contrary to this, the levels of other assayed parameters were much higher locally than in the serum. This observation confirms the data we reported earlier (17,28,29).

In their study, Denko et al. found much lower IGF-1 concentration in the synovial fluid than in the serum of patients with osteoarthritis and different forms of rheumatoid arthritis (25). We suggest that the pathogenesis of osteoarthritis influences the local concentration of cartilage degradation and bone turnover indices within the joint. Mean synovial fluid concentration of an anabolic factor, such as IGF-1, was found to be significantly lower in cases with avascular osteonecrosis of the hip.

Hilal et al. reported increased response of osteoblast-like cells after stimulation with IGF-1 and other growth factors, resulting in augmented expression of alkaline phosphatase (30). Despite the observed direct association of IGF-1 with BSAP and low concentration of IGF-1, especially in the synovial fluid of patients with avascular osteonecrosis of the hip, normal activity of BSAP was detected.

According to Matsumoto et al., serum IGF-1 is decreased in osteoarthritis with bone erosions (19). We found that low IGF-1 concentrations were accompanied by higher values of CTx. However, enhanced bone resorption, indicating increased bone collagen degradation, was demonstrated only in patients with avascular osteonecrosis. Lajeunesse et al. suggested that imbalance between bone resorption and formation during remodeling may be responsible for abnormal metabolism of subchondral bone in osteoarthritis (31). Indeed, in our study bone resorption, reflected by CTx, was not correlated with bone formation, measured as activity of BSAP, even in patients with avascular osteonecrosis of the hip.

It has been reported that the levels of proinflammatory interleukins, especially IL-8 in synovial fluid, may be increased in conditions associated with bone loss such as osteoarthritis and rheumatoid arthritis (32). Despite similar values of IL-8 found in both groups of patients, 3-fold higher ratio of IL-8 compared to anti-inflammatory IL-10 in patients with osteonecrosis may suggest a proinflammatory status in this patient group. The data reported here indicate a possibility that avascular osteonrecrosis of the hip may be characterized by a more catabolic state reflected by low IGF-1 with concomitant increase in bone resorption and proinflammatory indices.

This study suffers from some limitations such as a small number of cases with hip osteoarthritis and, especially, cases with avascular osteonecrosis. However, it should be taken into consideration that the availability of synovial fluid as a biological material for laboratory assays is often very limited.

IGF-1 level may constitute a risk factor predisposing to osteoarthritis and seems to be related to etiopathogenesis

povezan s etiopatogenezom tog oboljenja. Vrlo niske koncentracije IGF-1 u serumu ili lokalno u sinovijalnoj tekućini mogu ukazivati na osteonekrozu.

Zahvale

Ovu je studiju pokrenuo prof. dr. sc. P. J. Bilinski, dr. med., predstojnik Klinike za ortopediju i traumatologiju. Studiju je potpomognuo Collegium Medicum, Sveučilište Nicolaus Copernicus, Bydgoszcz, Poljska, projekt br. BW 14/2002.

of the disease. Very low IGF-1 concentration in serum or locally in synovial fluid may indicate osteonecrosis.

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