www.ThePharmaJournal.com

The Pharma Innovation

ISSN: 2277- 7695
TPI 2017; 6(1): 89-92
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www.thepharmajournal.com
Received: 16-11-2016
Accepted: 17-12-2016

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Evolution of pro-and anti-inflammatory cytokines rates as well as inflammatory markers in patients with osteoarthritis depending on the age comorbidity rate and on the treatment

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Abstract
Objective: To study age aspects of comorbidity development in patients with osteoarthritis (OA) and evolution of pro- and anti-inflammatory cytokines as well as inflammatory markers during a three month conventional treatment.
Material and methods: Dynamic observations conducted in 90 patients aged 37-76 years with OA of the first-third radiographic stages by Kellgren-Lawrence (K-L). Methods: clinical, ELISA (interleukins 1β, 4, tumor necrosis factor α), biochemical, instrumental ones.
Results: It was found that patients in the age group of 50 years had manifestations of oligoosteoarthritis of the first-second stages by K-L, as well as 2-3 comorbid diseases with moderate symptoms. The patients of the age group 51-60 years were suffering from polyosteorthritis with moderate symptoms and from 4-5 comorbid diseases 4-5 in more than two systems. In patients aged over 60, OA became more systemic, it was mainly of the third radiographic stage by K-L, there were 6-8 comorbid diseases, dominated by those of the cardiovascular system and metabolism.
All age groups showed an increasing imbalance of pro- and anti-inflammatory cytokines as well as inflammatory markers and their worse reversibility during the treatment. The most negative influence on the symptoms of reversibility torpidity of these changes was observed in comorbid second-third degree obesity, type 2 diabetes and in OA of the third stage by K-L.
Conclusions: Patients suffering from OA, while ageing, are experiencing more systemic and pronounced changes in their joints, in the number and severity of comorbid diseases. These phenomena are accompanied by a progressing imbalance of pro- and anti-inflammatory cytokines as well as inflammatory markers rates and are characterized by an increasing resistance to reversibility during the treatment.

Keywords: Osteoarthritis, comorbidity, pro- and anti-inflammatory cytokines, inflammatory markers, treatment

1. Introduction
Comorbidity has been recognized as one of the leading problems in the modern medicine [1, 2]. Osteoarthritis (OA) is the most common disorder in the musculoskeletal system, which is characterized by high rates of comorbidity [3]. Until recently, a degenerative process in articular structures was thought to be a pathogenetic basis for OA. However, in recent years it has been proved to be also characterized by inflammation [4, 5], which is implemented through an imbalance of the cytokine regulation link [5-8]. Among the most common comorbid diseases in OA are those of atherosclerotic origin, obesity, diabetes and metabolic syndrome phenomena in which we also found signs of low-level inflammation and cytokine imbalance [9-13]. Therefore, in OA patients with these comorbid processes, low-level inflammation phenomena have different origins, but a common pathogenetic link both of OA progression and comorbid processes. It is possible to clarify the role of certain cytokines in this complex process by fulfilling a certain stage of treatment of the underlying disease while comparing the evolution of changes in pro-and anti-inflammatory cytokines and clinical manifestations of OA as well as comorbid processes.

1.1 Objective: To study age features of comorbidity development in patients with OA and evolution of pro- and anti-inflammatory cytokines as well as inflammatory markers in the blood in the course of a three month conventional treatment.

2. Materials and methods Investigation

The observations involved 90 patients aged 37-76 predominantly women (71 individuals- 78, 90%) with OA at the first-third radiographic stage by I.Kellgren-I.Lawrence (K-L) in the period of exacerbation. The diagnosis of OA was made by EULAR criteria [14], and that of comorbid diseases was made according to the recommendations of leading European professional associations and confirmed by appropriate specialists. OA patients received standard treatments recommended by EULAR: nonsteroid anti-inflammatory drugs (NSAIDs), chondroprotectors (CP), a local treatment on the affected joints and a gastro protector. For the comorbid diseases as it was recommended by specialists, we used antihypertensive, anti-ischemic, antioxidant, if necessary - lipid-lowering, antidiabetic agents. The blood was tested for proinflammatory cytokines rate: tumor necrosis factor-α (TNF-α), interleukin 1β (IL-1 β), anti-inflammatory cytokine interleukin-4 (IL-4) using the kits of the company «Bender Med Systems» (Austria) by a solid-phase method «Platinum ELISA» according to the manufacturer's instructions for enzyme-linked immunosorbent analyzer «StatFax 300" (USA). We also studied inflammatory markers in the blood-C-reactive protein (CRP) and peripheral blood indices by conventional methods. The examinations were conducted at the time of hospitalization, and after 1 and 3 months of treatment.

To compare these blood parameters we examined a group of practically healthy individuals (PHI) (30) of the same age and sex. The studies were approved by the local committee on bioethics. All the patients gave an informed consent to participate in the study.

Statistical data manipulation was made using the program «Microsoft Excel, version 7".

3. The Received Results and their Discussion

To study the age features of comorbid process development in patients with OA, they were divided into three groups: those being under 50 years old, those being 51-60 and those being over 60 years old. The results are presented in table 1.

Table 1: Age features of poly- and comorbid diseases in patients with osteoarthritis (n, %)

Nosology	Age group 50 years n=17	Age group 51-60 years n=32	Age group over 60 years n=41
Without comorbid diseases	4 (23,53%)	-	-
I degree arterial hypertension	5 (29,41%)	3 (9,37%)	2 (4,88%)
II degree arterial hypertension	-	14 (43,75%)	31 (75,61%)
IHD, moderate forms	-	4 (12,5%)	10 (24,39%)
IHD, severe forms (with heart failure or arrhythmia)	-	-	4 (9,76%)
I degree obesity	3 (17,65%)	6 (18,75%)	3 (7,32%)
II-III degree obesity	-	9 (28,12%)	28 (68,29%)
Diabetes mellitus type 2	-	2 (6,25%)	8 (19,51%)
Steatohepatosis	-	11 (34,37%)	29 (70,73%)
Cerebral forms of the I-II degree atherosclerosis	-	3 (9,37%)	6 (14,63%)
Gastritises, duodenitises	8 (47,06%)	18 (56,25%)	25 (60,97%)
Cholecystitises	7 (41,18%)	20 (62,50%)	30 (73,17%)
Pancreatitises	-	7 (21,87%)	11 (26,83%)
Enterocolonopathies	-	6 (18,75%)	15 (36,58%)

Notes: IHD – ishemic heart disease

As table 1 shows, the patients in the age group under 50 years had a minimum level of comorbidity (2-3 diseases with moderate or mild symptoms, while 4 out of 17 patients did not experience any comorbid processes) and lesions in the first and second groups of joints (the first and second degree oligoosteoarthritis). In the age group of 51-60 years there were 4-5 comorbid processes in two or more body systems with more prominent clinical manifestations, and OA was characterized by more pronounced systemic nature (mainly the second radiographic degree polyosteoarthritis and less frequently it was of the third degree). After 60 years there were 6-8 comorbid processes and polyarthritis of mostly the third radiographic degree, less frequently of the second degree. Clinical forms and the course of OA in patients aged under 50 years were mild, after 50, especially 60 years they were moderate ones with a clear tendency to progression. In all groups of patients with OA lesions of supporting joints were dominant, as to the comorbid processes they were progressive, with age, disorders of the cardiovascular system.

Features of disorders in pro- and anti-inflammatory cytokines in these age groups of patients and their evolution during a three month treatment are presented in table 2.

Table 2. Evolution of indices of pro- and anti-inflammatory cytokines, blood inflammatory markers in patients with osteoarthritis depending on the age rate of comorbidity and on a conventional treatment for 1 and 3 months (M+m)

Parameters under study			TNF-α, pg/ml	IL-1β, pg/ml	IL-4, pgr/ml	CRP, mg/л	White blood cells, x 10^9/l	ESR, mm / h
Practicaly healthy individuals, n=30			41,3±3,74	38,2±3,62	33,6±2,12	2,8±0,22	6,34±0,38	7,2±0,43
≤50 years, minimum comorbidity, n=17	Before treatment		61,2±4,20*	62,43±5,56*	44,2±3,18*	6,4±0,48*	7,3±0,36	8,4±0,36
	After treatment	After 1 month	45,3±3,09**	46,2±3,48**	42,2±3,28nr	4,03±0,26*/**	6,3±0,28nr	7,6±0,74nr
		After 3 months	43,8±4,12#	44,2±3,16#	37,6±3,22	3,1±0,28#	6,4±0,48nr	6,6±0,36#
51-60 years,	Before treatment		86,4±5,38*	76,2±5,84*	37,6±3,66	8,8±0,56*	9,4±0,42*	16,6±1,14*

moderate comorbidity, n= 32	After treatment	After 1 month	74,6±4,68$^{*/nr}$	65,4±4,46$^{*/nr}$	41,3±4,12^{nr}	7,4±0,43$^{*/nr}$	7,2±0,64**	10,8±1,16$^{*/**}$
		After 3 months	69,6±4,14$^{\#*}$	54,5±4,22$^{\#*}$	43,2±3,66^{nr}	5,1±0,32$^{*/\#}$	6,8±0,38$^{\#}$	8,6±0,62$^{\#}$
>60 years, pronounced comorbidity, n=41	Before treatment		89,6±6,12*	83,4±6,38*	38,4±4,74^{nr}	10,2±0,62*	11,24±0,82*	18,4±0,94*
	After treatment	After 1 month	81,2±5,66$^{*/nr}$	74,2±5,38$^{*/nr}$	40,1±4,88^{nr}	8,4±0,46$^{*/nr}$	8,2±0,78**	14,2±0,66$^{*/**}$
		After 3 months	75,4±5,48$^{*/nr}$	64,4±4,36$^{*/\#}$	42,6±3,18$^{*/nr}$	6,2±0,41$^{*/\#}$	7,1±0,43$^{\#}$	10,8±0,66$^{\#}$

Notes: *- reliability of the difference between parameters in the group compared to the same ones in PHI (p<0,05-0,001); ** - reliability of the difference between parameters in the group before and after a month treatment (p<0,05); # - reliability of the difference between parameters in the group before and after a three month treatment (p<0,05-0,01); nr – the difference between the parameters before and after the treatment is not reliable.

According to table 2, in the period of OA exacerbation pro-inflammatory cytokines TNF-α, IL-1β and the CRP rate, as a marker of inflammatory process, are reliably elevated compared to healthy people in all age groups and it tends to grow with an age-related comorbidity increase more systemic manifestations of OA. However, in the course of treatment in the age group under 50 years within a month we reached a clinical remission, which is accompanied by a reliable reduction of TNF-α, IL–4 and CRP rates almost to the level of practically healthy people and tends to become normal by the third month of treatment.

Patients in the age group 51-60years reached the clinical condition of partial remission after two months, but the downward trend in levels of TNF-α and IL-1β even after three months was still insufficient (their levels were reliably higher than in practically healthy people). Inconsistency of regression of OA clinical manifestations is particularly noticeable in patients older than 60 years, in a state of incomplete clinical remission of OA after 2 months TNF-α levels dropped unreliably and was higher than in PHI, although the performance of CRP and ESR decreased reliably.

Anti-inflammatory cytokine IL-4 in patients aged under 50 years in OA remission only decreased reliably after three months; in the group of 51-60 years with decreased manifestations of OA during this period there was its unreliable rise, although the level of CRP and ESR decreased reliably. This trend was more clearly expressed in OA patients older than 60 years.

Assessment of cytokine disbalance was more demonstrative regarding the essence of pathological processes according to their ratio in the blood of the patients under study (table3).

Table 3: Evolution of pro- and anti-inflammatory cytokines ratio in the blood of patients with osteoarthritis depending on their comorbidity and on conventional treatment after 1 and 3 months

Ratios under study	≤ 50 years, n=17			51-60 y., n=32			>60 y., n=41			PHI, n=30
	Before treatment	after 1 mthc	after 3 mths	Before treatment	After 1 mth	After 3 mths	Before treatment	After 1 mth	After 3 mths	
TNF-α/IL-4	1,38 ↑ by 1,1tp	1,12	1,16	2,29 ↑ by 1,9 t	1,81 ↑ by 1,5 t	1,61 ↑ by 1,34t	2,33 ↑ by 1,94 t	2,02 ↑ by 1,68 t.	1,77 ↑ by 1,47tp	1,2
IL-1β/IL-4	1,57 ↑ by 1,4 t	1,17	1,18	2,02 ↑ by 1,8 t	1,58 ↑ by 1,4 t	1,26 ↑ by 1,13t	2,16 ↑ by 1,93 t	1,85 ↑ by 1,65t	1,51 ↑ by 1,35 t	1,12

As we can see from the materials in table 3, there is a moderate disbalance of pro- and anti-inflammatory cytokines in patients, belonging to the age group under 50 years only in case of OA exacerbation, in the age group 51-60 years it surpasses its ratio in PHI by 1, 9 – 1, 8 times reducing to 1, 5-1, 4 times a month after the treatment and to 1, 34-1, 13 three months after it. This dynamics proved to be even more torpid in patients with OA aged over 60: in exacerbation the cytokine disbalance surpasses the ratio in PHI by 1,94 times, after a month- by 1, 65- 1-68 times and after three months – by 1, 47 – 1, 35 times.

To sum up, in case of a significant decrease of OA clinical manifestations with increasing age and severity of comorbid processes, there is a tendency to stability or torpidity of the regression of pro- and anti-inflammatory cytokines disbalance, especially at the age over 60 years. This tendency may be caused by comorbid diseases. An individual assessment of pro- and anti-inflammatory cytokines evolutionin the treatment of patients suffering from OA with manifestations of the second and third degree obesity, expressed atherosclerosis and type 2 diabetes mellitus (DM) in which this torpidity was the most pronounced prove this fact.

Since the curability of such diseases as type 2 diabetes, obesity, various manifestations of atherosclerosis is questionable, nonspecific inflammatory effects of low-intensity inflammation and stable cytokine imbalance, which characterize these processes, are both one of the additional parts of the formation, progression of OA and reduce the results of the treatment of these patients. Other comorbid processes like lesions of the digestive system, characterized by their better reversibility during the treatment were less pronounced, and might be less, additional sources of cytokine imbalance, therefore, their pathogenetic role in the formation and progression of OA should be considered minimal.

4. Conclusions

1. Patients with osteoarthritis are characterized by an age increase of comorbid processes. 2. An imbalance in pro- and anti-inflammatory cytokines in these patients is due to osteoarthritis and comorbid diseases and is a nonspecific link in their progression. 3. In the comprehensive treatment of patients with osteoarthritis of the high comorbidity it is advisable to use drugs on comorbid processes and low level inflammation inhibitors.

The authors declare no conflict of interests.

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