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Role interleukin 18 in the course and progression of osteoarthritis in patients with obesity

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Abstract: *musculoskeletal disorders are an extremely common pathology. They are the most common cause of chronic pain and disability: every minute, more than 30% of adults suffer from joint pain or limited physical activity. These diseases significantly affect the psychosocial status of patients, their families, and caregivers. The course of joint diseases leads to loss of mobility, social autonomy; such patients have higher rates of hospitalization and mortality. That is, the quality of life significantly deteriorates, and the financial costs of health care for patients and society increase. It is proved that one of the predictors of arthrosis is overweight. In the pathogenesis of osteoarthritis and obesity, proinflammatory cytokines play an important role, the excess synthesis of which leads to the progression and chronicity of the process. Therefore, the aim of our study was to determine the dependence of interleukin-18 activity in patients with osteoarthritis, which occurs on the background of obesity and without it. The study presents the study of interleukin-18 in 75 people with osteoarthritis (OA), which occurred on the background of obesity (main group), and 50 patients with isolated OA (comparison group). The control group consisted of 37 healthy individuals. The diagnosis of OA was established based on the order of the Ministry of Health of Ukraine of 12.10.2006 “On medical care for patients with osteoarthritis”, unified diagnostic criteria of the Association of Rheumatologists of Ukraine (2004), and the criteria of the American College of Rheumatologists. The presence and severity of obesity were assessed according to the criteria of the International Diabetes Federation (IDF, 2005) based on the calculation of body mass index (BMI) according to the Kettle formula. When determining the level of IL-18 in the main group, it was found that the content of this cytokine was almost two times higher than the reference values ($p < 0.05$). In the comparison group, the activity of IL-18 increased 1.6 times ($p < 0.05$). Comparison of the content of IL-18 between the study groups allowed us to determine its increase in the presence of obesity by almost 1.2 times. The increase in IL-18 content depended on the radiological stage of joint damage: the maximum value was recorded in patients of the main group with stage 2 symptoms. Apparently, such results are a consequence of the predominance of the inflammatory reaction in the progression of the pathology due to the comprehensive involvement of extra-articular components (ligaments, tendons, bags, etc.). Slightly lower levels of IL-18 in stage 1 OA are likely to be due to the involvement of a limited portion of joint tissue, while the 3rd radiological stage is characterized by a predominance of dystrophic processes. In patients with osteoarthritis, an increase in the content of IL-18 in the serum is determined, which is associated with the development of the inflammatory process in the components of the joint. The content of IL-18 has a direct correlation with overweight / obesity and the radiological stage of the process*

in the joints. Increased proinflammatory cytokine IL-18, which is a component of the immune system and simultaneously synthesized by adipocytes of adipose tissue, can be considered a factor that will contribute to the preservation of chronic pain and progression of the pathology. Dynamic control of IL-18 activity should be used as an indicator of the effectiveness of therapy.

Key words: osteoarthritis, obesity, interleukin-18, overweight, body mass index.

Introduction

Cytokines are considered endogenous immunomodulators: they have a universal significance in the regulation of all organ systems. Compared to exogenous modulators (chemical, bacterial, or plant origin), cytokines effect through specific receptors and are natural regulators of the functional activity of different cell types. Interleukin-18 (IL-18) in a number of monoregulatory mediators have a special place due to its key position among other cytokines involved in the formation of congenital and acquired immune response Rex, D., Agarwal, N., Prasad, T., Kandasamy, R. K., Subbannayya, Y., & Pinto, S. M. (2020), Min, H. K., Kim, S., Lee, J. Y., Kim, K. W., Lee, S. H., & Kim, H. R. (2021).

Almost 20 years later, the main properties of this cytokine were determined. Thus, it was found that IL-18 stimulates the production of IFN- γ , GM-CSF, IL-1, IL-2, adhesion molecules and apoptosis factors Fas / FasL. At the same time, IL-18 is involved in the activation of cytotoxic T lymphocytes, NK cells, macrophages, dendritic cells and promotes the formation of an effective anti-infective and antitumor immune response. IL-18 is able to activate cellular immunity, which allows us to consider it a potential inducer of protective immunity in cancer and infectious processes (viral and bacterial) Mansoori, M. N., Shukla, P., Kakaji, M., Tyagi, A. M., Srivastava, K., Shukla, M., Dixit, M., Kureel, J., Gupta, S., & Singh, D. (2016), Min, H. K., Won, J. Y., Kim, B. M., Lee, K. A., Lee, S. J., Lee, S. H., Kim, H. R., & Kim, K. W. (2020).

IL-18, originally identified as an IFN- γ -inducing factor, also stimulates both congenital and adaptive lymphocyte-mediated responses (Th1 and Th2), increasing NK cell activity and apoptosis (Bhaumik, S., & Basu, R., 2017). In general, it should be noted that due to the presence of various directions of action of this cytokine, it is involved not only in the body's

protective reactions but also in the pathogenesis of many diseases accompanied by chronic inflammation, autoimmune component, and tissue destruction. It has been proved that the excess of IL-18 in vitro can stimulate the expression of adhesion molecules (ICAM-1 and VCAM), i.e. it is involved in the infiltration of tissue by immunocompetent cells (Jung, Y. K., Kang, Y. M., & Han, S., 2019).

However, because IL-18, like many other immunoregulatory cytokines, is pleiotropic, its biological effects may, in some cases, be undesirable or unpredictable Fields, J. K., Günther, S., & Sundberg, E. J. (2019). For example, in the literature, there are ambiguous data on the ability of IL-18 to stimulate Tx1 or Tx2 type; the use of recombinant IL-18 in infectious or oncological processes, leads to increased production of proinflammatory cytokines and adhesion molecules, which along with the stimulatory effect on the formation of a protective immune response can have negative consequences, as this protein can cause inflammation or metastasis Gracie, J. A., Forshey, R. J., Chan, W. L., & McInnes, I. B. (1999).

In general, it should be noted that due to the presence of such diverse activity in this cytokine, it is involved in the pathogenesis of many diseases.

Thus, the ability of IL-18 to stimulate the activity of IL-1, one of the sites of formation of which are adipocytes, may serve to determine its receipt in obese patients Gracie, J. A., Forshey, R. J., Chan, W. L., & McInnes, I. B. (1999).

Aim

These theses were the basis for a study aimed at establishing the clinical and prognostic value of interleukin-18 activity in patients with osteoarthritis, which occurs against the background of obesity.

Materials and methods

The study involved 75 patients with osteoarthritis with overweight or obesity (main group)

and 50 patients with isolated OA (comparison group). The study groups were identical in age, sex, and history of OA. Thus, the average age of patients in the main group was (30.92 ± 0.546) years, among them were 48 (64%) men and 27 (36%) women; in the comparison group - (30.95 ± 0.545) years, including 32 (64%) men and 18 (36%) women. Thus, the groups were comparable in age and gender.

All the patients involved in the study signed a voluntary consent to participate in the study in accordance with the provisions of the Helsin Declaration (2000) and European Society Directive 86/609 on human participation in biomedical research.

The diagnosis of OA was established following the order of the Ministry of Health of Ukraine of 12.10.2006 "On medical care for patients with osteoarthritis", unified diagnostic criteria of the Association of Rheumatologists of Ukraine (2004) and the criteria of the American College of Rheumatologists Hochberg, M. C., Altman, R. D., April, K. T., & Tugwell, P., (2012). Stages of OA were determined taking into account changes in radiographs of joints according to the classification of H. Kellgren and RS Lawrence Kellgren, J. H., & Lawrence, J. S. (1957).

The presence and severity of obesity were assessed according to the criteria of the International Diabetes Federation (IDF, 2005) based on the calculation of body mass index (BMI) according to the Kettle formula: $BMI = \text{body weight (kg)} / \text{height (m}^2)$ Hochberg, M. C., Altman, R. D., April, K. T., & Tugwell, P., (2012).

The activity of IL-18 (pg/ml) was determined in fasting serum by enzyme-linked immunosorbent assay (ELISA) - sets of reagents VectorBEST A-8870, China.

Statistical analysis was performed using the software package "Statistica 10.0" and Excel 2010. To quantify the characteristics, the results were provided in the form of medians (Me) with quarter quartile interval [Q25%; Q75%], taking into account the lack of normal distribution. Quantitative and order changes were compared using the Mann-Whitney test. In all procedures of statistical analysis, the level of significance and p were taken to be equal to or less than 0.05 ($p < 0.05$).

Results and discussion

According to the localization of joint damage, patients with OA and obesity were distributed as follows: involvement in the disease of the knee joints (gonarthrosis) was observed in 30 people (40%); moreover, unilateral lesions were found in 10 cases. OA of the hip joints (coxarthrosis) was registered in 12 patients (16%); unilateral and bilateral joint damage occurred with the same frequency - 6 patients. Combined lesions of the knee and hip joints were observed in 25 patients (33%). Simultaneous involvement in the pathology of large and small joints was determined in 8 people (11%).

Among patients in the comparison group, the "joint" distribution corresponded to the following: 34 people (68%) were diagnosed with gonarthrosis (unilateral lesions were found in 26 people), 10 patients (20%) - coxarthrosis (unilateral lesions - 7 patients). Combined lesions of the knee and hip joints were observed in 4 patients (8%); additional involvement in the process of small joints was recorded in 2 people (4%).

According to the duration of the disease, patients of the main group were divided into 4 subgroups (table 1).

Table 1. Distribution of the studied patients with OA according to the anamnesis

Duration of anamnesis with OA (years)	Examined patients	
	Main group	Comparison group
up to 3	28 (37,4%)	20 (40 %)
4 - 6	30 (40 %)	19 (38%)
7 - 10	13 (17,3 %)	6 (12 %)
More than 10	4 (5,3 %)	5 (10 %)

According to the Kettle index, the largest number of patients had grade I obesity (BMI - 30-34.9 kg / m²) and 22 people were in the groups with increased body weight (BMI - 25-29.9 kg / m²) and obesity II degree (BMI - 35-39.9 kg / m²).

According to the changes in radiographs and the classification of H. Kellgren and RS Lawrence, patients with OA and obesity were divided into 3 groups (table 2).

In the comparison group, the radiological stage of osteoarthritis corresponded to the following: I st. determined in 9 cases (18%), II st. - in 34

Table 2. Distribution of patients in the main group with osteoarthritis by radiological stages and body mass index

Examined patients (n = 75)		Distribution of patients by BMI					
		Overweigh (n=22)		Stage I obesity (n=31)		Stage II obesity (n=22)	
		Abs.	%	Abs.	%	Abs.	%
Radiological stages of osteoarthritis	I (n=21)	5	23,8	13	61,9	3	14,3
	II (n=38)	17	44,7	18	47,4	3	7,9
	III (n=16)	-	-	-	-	16	100

(68%) and III st. - in 7 (14%). Patients with stage IV radiological OA were not involved.

In order to obtain control indicators, a group of 37 healthy individuals of the same age (30.95 ± 0.545 years), sex (24 (64.9%) men and 13 (35.1%) women) and normal BMI.

When determining the level of IL-18 in the main group, it was found that the content of this cytokine was almost two times higher (99.46 ± 1.8 pg / ml) than in the control group (53.23 ± 1.4

pg / ml), p <0.05. In the comparison group, the activity of IL-18 also significantly exceeded the control index (86.53 ± 1.86 pg / ml, p <0.05), but was lower than in the main group of patients. At the same time, when determining the level of IL-18, taking into account the stage of obesity, the following results were obtained (table 3).

We can assume that with overweight, an increase of IL-18 may be the result of stressful effects of fat cells on periarticular tissues. Apparently, in the 1st stage of obesity, there is a relative control of this process, which inhibits the activity of IL-18 compared to people with overweight; while in the 2st obesity begins a powerful synthesis of this cytokine by adipocytes, as well as active involvement in the process of periarticular tissues.

We analyzed and proved the dependence of IL-18 activity on the degree of cartilage degradation (table 4).

In our opinion, the probable increase in IL-18 in patients with stage 2 radiological OA is the result of the predominance of inflammatory re-

Table 3. The content of proinflammatory cytokine IL- 18 in the serum of patients with OA depending on BMI

BMI	The content of IL-18 (pg/ml)
Control group (n=37)	53,23 ± 1,4
Overweight (n=22)	99,95 ± 2,8 * "
Stage I obesity (n=31)	94,82 ± 2,4 *
Stage II obesity (n=22)	105,49 ± 4,1 *

Note: p <0.001 * - relative to the control group; p <0.05 "- for a group of patients with stage II obesity.

Table 4. The content of IL-18 (pg / ml) depending on the radiological stage of osteoarthritis in overweight and obese patients

Control group (n=37)	Radiological stages of osteoarthritis	BMI		
		Overweigh (n=22)	Stage I obesity (n=31)	Stage II obesity (n=22)
53,23 ± 1,4 (K)	I	89,95±4,97 (A)	90,66±3,7 (B)	91,86±3,02 (C)
	II	102,89±3,04 (D)	97,83±3,08 (E)	144,33±5,48 (F)
	III	-	-	102,77±3,05* (G)

Notes: A , B , C , D , E , F , G , K - are marked and the groups are presented in table 4.

p <0.05 - probability of differences and is statistically significant between groups .

p A , G <0,05 - probability of difference between groups of patients with osteoarthritis and overweight and osteoarthritis and stage II obesity;

pK, A <0.05 - the probability of the difference between the control group and the group of patients with osteoarthritis and overweight.

actions due to the participation of extra-articular tissues (ligaments, tendons, bags, etc.) in inflammatory processes, in contrast to stage 1, where the processes of inflammation of these tissues are somewhat limited. At the same time, the 3rd radiological stage is characterized by a predominance of dystrophic processes.

Thus, the course of OA is accompanied by an increase in the content of IL-18 relative to normal, which confirms the presence of an active inflammatory process and is natural, both in terms of inflammation in periarticular tissues and the overall involvement of the immune system in this process. At the same time, in patients of the main group, the activity of this cytokine was more pronounced, which is the result of its additional synthesis by adipocytes of adipose tissue. The accumulation in the serum of IL-18 in patients with OA with altered BMI can be considered as a negative factor in immune disorders, which contributes to disease progression and its chronicity due to the involvement of periarticular tissues with a chronic inflammatory response due to the constant synthesis of this cytokine by adipose tissue.

Conclusions

In patients with osteoarthritis, there is an increase in the activity of interleukin-18 as a result of the participation of the proinflammatory part of the immune system in the systemic response.

The development of osteoarthritis on the background of obesity is accompanied by a probable increase in IL-18 both in relation to the control and the comparison group, which may be due to the active participation of adipocytes in its synthesis.

The activity of IL-18 in patients with osteoarthritis depends on the stage of obesity and the degree of radiological changes in cartilage: it was maximum at the 2 st. of the specified parameters.

The dynamics of the content of IL-18 can be used as a control during long-term monitoring of osteoarthritis.

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This study was not funded.

Conflict of interest

There was no conflict of interest during the study.

Consent to publication

Litynova Anastasiia agreed to the publication.

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of article

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Роль інтерлейкіну 18 в перебігу й прогресуванні остеоартриту в хворих з ожирінням

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Анотація: захворювання опорно-рухового апарату є надзвичайно поширеною патологією. Вони є найбільш частою причиною хронічного болю та інвалідності: щомиті понад 30% дорослих людей потерпають від болю в суглобах або обмеження рухової активності. Дані захворювання суттєво впливають на психосоціальний статус пацієнтів, їх родин та осіб, які здійснюють догляд. Перебіг захворювань суглобів призводить до втрати рухливості, соціальної автономності; такі хворі мають більш високі показники госпіталізації і смертності. Тобто, значно погіршується якість життя, збільшуються фінансові витрати на охорону здоров'я з боку як пацієнта, так і суспільства. Доведено, що одним із предикторів формування артрозів є надлишкова маса тіла. В патогенезі остеоартроза та ожиріння важливу роль набувають прозапальні цитокіни, надлишок синтезу яких призводить до прогресування та хронізації процесу. Тому, метою нашого дослідження було визначення залежності активності інтерлейкіну-18 у хворих на остеоартрит, що перебігає на тлі ожиріння та без нього. В роботі представлено дослідження інтерлейкіну-18 у 75 осіб з остеоартритом (ОА), що перебігав на тлі ожиріння (основна група), та 50 пацієнтів на ізольований ОА (група порівняння). Контрольну групу склали 37 практично здорових осіб. Діагноз ОА встановлювали спираючись на наказ МОЗ України від 12.10.2006 року «Про надання медичної допомоги хворим із остеоартрозом», уніфікованих діагностичних критеріїв Асоціації ревматологів України (2004) та критеріїв Американської колегії ревматологів. Наявність та тяжкість ожиріння оцінювали згідно з критеріями International Diabetes Federation (IDF, 2005) на підставі розрахунку індексу маси тіла (ІМТ) за формулою Кетле. При визначенні рівню ІЛ-18 у осіб основної групи було встановлено, що вміст даного цитокіну майже у 2 рази перевищував референтні значення ($p < 0,05$). В групі порівняння активність ІЛ-18 збільшувалася у 1,6 разів ($p < 0,05$). Порівняння вмісту ІЛ-18 між досліджуваними групами дозволило визначити його підвищення при наявності ожиріння майже в 1,2 рази. Збільшення вмісту ІЛ-18 залежало від рентгенологічної стадії ураження суглобів: максимальне значення реєстрували у хворих основної групи з 2-ю стадією ознак. Мабуть, такі результати є наслідком

переважання запальної реакції при прогресуванні патології через всебічне залучення поза-суглобових складових (зв'язок, сухожиль, сумок тощо). Декілька менші показники ІЛ-18 при 1-ї стадії ОА, ймовірно, є результатом участі обмеженої частини тканин суглобів; в той час, як для 3-ї рентгенологічної стадії є характерним переважання дистрофічних процесів. У хворих на остеоартрит визначається збільшення вмісту ІЛ-18 у сироватці крові, що пов'язано з розвитком запального процесу в компонентах суглоба. Вміст ІЛ-18 має пряму кореляційну залежність з надлишковою масою тіла/ожирінням та рентгенологічною стадією процесу у суглобах. Збільшення прозапального цитокіну ІЛ-18, який є одним із складових імунної системи та одночасно синтезується адипоцитами жирової тканини, можна розглядати в якості фактора, що буде сприяти збереженню хронічного болю та прогресуванню патології. Динамічний контроль активності ІЛ-18 доцільно використовувати в якості показника ефективності терапії.

Ключові слова: остеоартрит, ожиріння, інтерлейкін-18, зайва вага, індекс маси тіла.



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