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# ОГЛЯДИ ЛІТЕРАТУРИ

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DOI 10.29254/2077-4214-2018-4-2-147-11-14

UDC 616.724-018-007.1-02-084:616.314-084

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## PERSPECTIVES OF DEVELOPMENT THE POSSIBLE PREVENTIVE MEASURES OF APPEARANCE OF FLUOROQUINOLONES-INDUCED CHANGES IN THE TEMPOROMANDIBULAR JOINT STRUCTURES

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**Publication relation to planned scientific research projects.** The work is the fragment of SRW of the chair of Anatomy, Operative Surgery and Topographic Anatomy and the chair of Histology, Cytology and Embryology of Zaporizhzhya State Medical University «Lectinohistochemical characteristics of morphogenesis of the organs and tissues in early postnatal period in norm and experiment» (2013-2017, № state registration 0109 U 003986).

The ability of fluoroquinolone antibiotics to adversely affect tendons has been the subject of many articles and case reports in the medical literature for nearly three decades. Clinicians and patients should be aware of the potential risks that fluoroquinolones pose with respect to both cause and potentiation of *tendinopathy*, which is described as the clinical presentation of pain associated with tendon loading [1]. Complications, which arising after fluoroquinolones intake, are able causing temporomandibular joint (TMJ) disorders. This, in turn, reduces the quality of patients' life in the future and can lead to severe consequences and disability. Today is exists the large number of scientific researches, which are devoted to study of mechanisms of development the fluoroquinolones – associated tendino- and arthropathy. However, the correlation between the quinolones intake remains poorly understood. Also, in the literature there are no findings about preventive methods, which are aimed at preventing the development of tendinopathy after fluoroquinolones intake. Especially, it concerns the TMJ, because using the standard methods (temporary immobilization or sparing loads) the above problem is not resolved. This connected with ensuring of vital functions, such as everyday chewing at reception of nutrition, speech etc. All the above indicates the relevance of the issues that we are considering and require further more detailed study the relationship between quinolones therapy and the risk of emergence the temporomandibular joint disorders and necessity development of preventive measures in case of fluoroquinolones-induced tendinopathy.

**The purpose** of this literature review is to discuss the causes of arising and mechanisms of formation the fluoroquinolones-associated tendo- and arthropathy for the further perspectives of development the possible preventive measures of appearance of fluoroquinolones-induced changes in the temporomandibular joint structures.

The first quinolone antibiotic, nalidixic acid, was introduced in the 1960s [2] and this drug has undergone substantial development since then. Oliphant C.M. and Green G.M. shown that fluoroquinolones are effective against both gram-negative and gram-positive bacteria and can be used to treat a range of infections affecting

the respiratory systems and those causing prostatitis, skin soft tissue infections, and sexually transmitted disease. These medicines are well absorbed when taken orally and have a long half-life; thus, dosing once or twice per day can be effective [3]. This group of drugs has a high degree of penetration into tissues and cells and, thus, shows high efficiency in severe forms of infection of different etiology in any localization of the infectious process and in multidrug-resistant diseases [4,5,6,7]. However, the side effects of fluoroquinolones display a high affinity for connective tissue, particularly in cartilage and bone. Authors of experimental studies have shown that these antibiotics may damage juvenile weight-bearing joints; therefore, these drugs are contraindicated in children [8].

The pathways underpinning the tenotoxic effects of fluoroquinolones are unclear [9] but three main mechanisms have been proposed: ischemia, degradation of the tendon matrix, and adverse alteration of tenocyte activity [8]. Matrix metalloproteinases are enzymes with degrading properties that are important in the homeostasis and response to injury of tendon tissue [10,11]. Fluoroquinolones facilitate expression of matrix metalloproteinases in tendon tissue [10] ciprofloxacin (CPX) in particular has been shown to increase the expression of matrix metalloproteinase-3 in human Achilles tendon-derived cells and to reduce collagen synthesis via inhibition of tenocyte proliferation [1]. CPX administration in vitro could induce a weakness-related phenotype in human tenocytes, mainly characterized by decreased ability to cross-link collagen and decreased TIMP-1 levels, possibly leading to higher activity of MMPs in ECM degradation. Therefore, CPX treatment may be responsible for the failure of tenocytes to adequately maintain tendon ECM responses to mechanical loading in vivo. This hypothesis is strengthened by the down-regulation of N-cadherin and CX43, suggesting a reduced ability for the cell-cell communication needed to maintain tissue homeostasis [12,13]. On the basis of these observations, we can hypothesize that after CPX administration a repetitive loading below the injury threshold of the tendon could induce degenerative changes in the composition and organization of tendon ECM, thus leading to a weakness of the tissue and making it more susceptible to rupture [14].

Different studies in this field through extensive cell biology and animal research has partially identified mechanisms by which fluoroquinolones lead to tendon rupture [15,9]. Today it is known several variants of development the effect on fine structures of connective tissue. These medications appear to upregulate multiple matrix metalloproteinases (MMPs) including MMP-1 [9], MMP-2 [9] and MMP-3 [9] resulting to reductions in the diameter

and amount of type I collagen fibrils [15,9]. Also, fluoroquinolones can induce degenerative changes in tenocyte, vacuole formation, organelle dilatation and apoptosis. Collagen constitutes 70% of tendon dry weight, of which 90% is type I collagen and 10% is type III collagen [15]. In the aortic wall, type I and type III are also the dominant forms of collagen [16] thereby suggesting that a medication contributing to tendon ruptures could also lead to aortic aneurysms. Figueiredo B.L., Jaldin R.G. have identified that pathological sections of aortic aneurysms and aortic dissections demonstrate abnormalities of collagen content, fibers allocation and ratios ability [10]. Although aortic aneurysms typically develop slowly, our data suggest that fluoroquinolone prescriptions can contribute acutely to aneurysm progression and rupture [17].

It is known that different types of collagen are the chief structural units of connective tissue and all joints in the human organism. It was found that recent researches detected the joints and tendon damage of limbs after fluoroquinolones therapy. However, in our opinion, side effects after using of fluoroquinolones and associated with this disorders must be considered in the temporomandibular joint. The TMJ and its associated structures play an essential role in guiding mandibular motion and distributing stresses produced by everyday tasks, such as chewing, swallowing, and speaking [18]. Mandibular condylar cartilage plays a crucial role in TMJ function. It facilitates articulation with the TMJ disc and reduces point loads on the underlying bone [19]. It is of the fibrous type and is therefore structurally different from the generally applied hyaline articular cartilage. In accordance with the data of earlier researchers, such as Lunder H.U., Mow V.C. Mizoguchi I., Salo L.A. the cartilage layer on the mandibular condyle is from the articular surface to the underlying bone, composed of several zones: the fibrous, proliferative, mature and hypertrophic. Essentially, the proliferative zone serves as a separating barrier between the fibrocartilaginous fibrous zone and the hyaline-like mature and hypertrophic zones. The fibrous zone is composed of fibroblast-like cells, which have a flat shape. Endoplasmic reticulum of fibrous zone surrounded by a dense intercellular matrix of collagen fibrils and basic substance. The proliferative zone plays an important role as a cell reservoir and reparative source. It has mesenchymal stem cells distributed heterogeneously as chondrocyte precursors for the underlying zones.

The collagen fibers of the fibrocartilage are arranged in several distinct zones, and are considered to provide mainly tensile strength to the cartilage. Shear strength has been suggested to originate from cross-links between the collagen fibers. Mandibular condylar cartilage differs from general articular cartilage by the presence of type I collagen [9]. This is dominant in the superficial zone, though type II collagen (the dominant type in hyaline cartilage) is the main structural compound in the mature and hypertrophic zones. Collagen type III is specific for the superficial zone and collagen type X, was also present in hyaline cartilage. In articular cartilage, collagen forms a three-dimensional network and thus impacts its form, stability and tensile strength and resistance to shear forces. When cartilage is loaded by compression, the low permeability of the collagen impedes the interstitial fluid to flow through the strong collagen network. In the mandibular condylar cartilage, collagen fibers run have optimal orientation to resist antero-posterior shear forces [19,8].

During normal and abnormal function the joints are loaded. This causes its cartilaginous structures to deform. The magnitude of deformation and the resulting stress is, besides the nature of the applied loads, primarily determined by the biomechanical properties of the cartilage, such as stiffness. An understanding of these properties is important for several reasons. First, they determine the role of the cartilage as a stress-distributing and load-absorbing structure [20]. Second, mechanical stress and strain affects the extracellular matrix synthesis in the cartilage [18] resulting in an adaptation of stiffness. Third, the mechanical properties of the cartilaginous structures and their alterations by joint loading will also influence the stresses and strains that occur in the subchondral layers, which are of critical importance for damages on the short term and bone remodeling on the long term. Fourth, precise information about the biomechanical properties of the articular cartilage is required to develop suitable joint simulation models, with the distribution of stress strain in the structures of the joint, were estimated [20]. This will enable prediction of the effects of mechanical manipulation of the joints in the process of prevention or treatment of joint derangements [20]. Today exist the data relatively the MMP-3 expression rate correlated with the degree of joint lesion, while the tissue inhibitor of metalloproteinase – 3 rate showed an opposite trend. These findings clearly indicate that psychological stress may play an important part in the development of TMJ diseases in rats [16].

The dominant factor in relation to cartilage wear is age. Both frequency and severity of the cartilage breakdown appear to increase with aging. For example, degenerative joint disease occurs typically in the fifth and sixth decades of life when articular cartilage usually starts to lose its cellular density and herewith its adaptive capacity [21]. Age-related changes have also been detected in the TMJ components [20]. Also, previous studies relating to fluoroquinolones-associated tendon disorders suggested that the effect of quinolone use on Achilles tendon rupture tended to be greater among older persons [22].

The major direct cause of mandibular condylar cartilage breakdown is overloading. With respect to TMJ-OA, the mechanism of overloading is probably the same as that in the other synovial joints. After CPX administration a repetitive loading below the injury threshold of the tendon could induce degenerative changes in the composition and organization of tendon ECM, thus leading to a weakness of the tissue and making it more susceptible to rupture [23]. Collagen type II is degraded by the first, while aggrecan, the major proteoglycan in TMJ cartilage, is degraded by both. MMP-1, -3 and -9 are abundantly present in cartilage and synovial fluid in joints under pathologic conditions. Cyclic tensile pressure has been demonstrated to up-regulate the expression of MMP-13 [24,1,8].

According to National Institute of Dental and Craniofacial Research in 2011-2016 diseases of the TMJ were the most widespread pathology in the maxillofacial region. Epidemiology reports state temporomandibular joint disorders (TMD) affect up to 25% of the population, yet their etiology and progression are poorly understood. As a result, treatment options are limited and fail to meet the long-term demands of the relatively young patient population. TMD are a class of degenerative musculoskeletal conditions associated with morphological and

functional deformities [18]. Though, in most cases is hard enough to identify causes and symptoms of this pathology [25,21,23].

### Conclusions

1. Analysis of the latest literature shows, that fluoroquinolones treatment leads to appearance of tendino- and arthropathy that refers to temporo-mandibular joint.

2. Pathways that underlie the tendino-toxic effect and mechanisms of development of fluoroquinolone – induced tendino- and arthropathy still are unclear understood.

3. Understanding the issues of arising and formation of fluoroquinolones – induced deformities in the temporomandibular joint, exactly in its structures, allows to predict and development the preventive measures of complications of fluoroquinolones-associated disorders in the temporomandibular joint and, thereby, improve the quality of patients' life during and after quinolones therapy.

**Conflicts of interest:** all authors disclose no financial or personal relationships with other people or organizations that could potentially and inappropriately influence (bias) their work and conclusions.

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### ПЕРСПЕКТИВИ РОЗРОБКИ МОЖЛИВИХ ЗАПОБІЖНИХ ЗАХОДІВ РОЗВИТКУ ФТОРХІНОЛОНІНДУКОВАНИХ ЗМІН В СТРУКТУРАХ СКРОНЕВО-НИЖНЬОЩЕЛЕПНОГО СУГЛОБА

Бурга Ю. О., Маслова І. М., Бурга І. Ю.

**Резюме.** Метою цього огляду літератури, є встановлення причин виникнення та механізмів формування тендо- і артропатій, пов'язаних з терапією фторхінолонами, для визначення подальших перспектив розробки можливих профілактичних заходів, що будуть запобігати розвитку фторхінолон-індукованих змін в структурах скронево-нижньощелепного суглоба. Здатність антибіотиків групи фторхінолонів негативно впливати на сухожилля була предметом численних статей і повідомлень про випадки розривів зв'язок в медичній практиці протягом майже трьох десятиліть. Клініцисти і пацієнти повинні бути інформовані про потенційні ризики, які фторхінолони створюють по відношенню як причини і потенціювання тендінопатій, які описуються клінічно як прояви болю,

пов'язаного з навантаженням на сухожилля. Ускладнення, що виникають після прийому фторхінолонів, здатні викликати розлади в структурах скронево-нижньощелепного суглоба (СНЩС). Це, в свою чергу, знижує якість життя пацієнтів в майбутньому і може призвести до тяжких наслідків і навіть інвалідності. Сьогодні існує велика кількість наукових досліджень, які присвячені вивченню механізмів розвитку фторхінолоніндукованих тендо-і артропатії. Однак кореляція між прийомом хінолонів і розвитком хінолоніндукованих тендо та артропатій СНЩС залишається погано вивченою. Крім того, в літературі немає ніяких висновків про методи профілактики, які спрямовані на запобігання розвитку тендопатій після лікування фторхінолонами. Особливо це стосується СНЩС, так як за допомогою протокольних методів (тимчасової іммобілізації або обмеження навантаження) ця проблема не буде вирішена. Це пов'язано із забезпеченням повноцінної артикуляції для виконання життєво важливих функцій, таких як повсякденне жування при прийомі їжі, мови і т. і. Все вищезазначене вказує на актуальність питань, що розглядаються нами і які вимагають подальшого, більш детального, вивчення взаємозв'язку між терапією фторхінолонами, ризиком виникнення розладів в структурах СНЩС і необхідністю розробки превентивних заходів в разі терапії фторхінолонами.

**Ключові слова:** скронево-нижньощелепний суглоб, фторхінолони, колаген, хрящ, зв'язки, розрив.

### ПЕРСПЕКТИВЫ РАЗРАБОТКИ ВОЗМОЖНЫХ ПРЕВЕНТИВНЫХ МЕР ПРИ РАЗВИТИИ ФТОРХИНОЛОНИНДУЦИРОВАННЫХ ИЗМЕНЕНИЙ В СТРУКТУРАХ ВИСОЧНО-НИЖНЕЧЕЛЮСТНОГО СУСТАВА

**Бурега Ю. А., Маслова И. Н., Бурега И. Ю.**

**Резюме.** Целью данного обзора литературы, является выявление причин возникновения и механизмов формирования тендо- и артропатий для определения дальнейших перспектив разработки возможных профилактических мероприятий, которые будут предотвращать развитие фторхинолон-индуцированных изменений в структурах височно-нижнечелюстного сустава. Способность антибиотиков группы фторхинолонов негативно влиять на сухожилия была предметом многочисленных статей и сообщений о случаях разрывов связок в медицинской практике в течение почти трех десятилетий. Клиницисты и пациенты должны быть осведомлены о потенциальных рисках, которые фторхинолоны создают по отношению к причине и потенцированию тендопатий, которые описывается как возникновение болевого синдрома, связанного с нагрузкой на сухожилие. Осложнения, которые, возникают после приема фторхинолонов, способны вызвать расстройства полноценного функционирования височно-нижнечелюстного сустава (ВНЧС). Это, в свою очередь, снижает качество жизни пациентов в будущем и может привести к тяжелым последствиям и даже инвалидности. Сегодня существует большое количество научных исследований, которые посвящены изучению механизмов развития фторхинолон-индуцированных тендо- и артропатий. Однако корреляция между приемом хинолонов и развитием хинолонассоциированных осложнений остается плохо изученной. Кроме того, в литературе нет никаких выводов о методах профилактики, которые направлены на предотвращение развития тендопатией после приема фторхинолонов. Особенно это касается ВНЧС, так как с помощью стандартных методов (временной иммобилизации или щадящих нагрузок) проблема не может быть решена. Это связано с обеспечением жизненно важных функций, таких как жевание при приеме пищи, речь и т. д. Все вышесказанное указывает на актуальность проблемы, которую мы рассматриваем и требует дальнейшего более детального изучения взаимосвязи между терапией фторхинолонами, риском возникновения нарушений в структурах ВНЧС и необходимостью разработки превентивных мер в случае лечения фторхинолонами.

**Ключевые слова:** височно-нижнечелюстной сустав, фторхинолоны, коллаген, хрящ, связки, разрыв.

### PERSPECTIVES OF DEVELOPMENT THE POSSIBLE PREVENTIVE MEASURES OF APPEARANCE OF FLUOROQUINOLONES-INDUCED CHANGES IN THE TEMPOROMANDIBULAR JOINT STRUCTURES

**Burega Yu. O., Maslova I. M., Burega I. Yu.**

**Abstract.** The purpose of this literature review is to discuss the causes of arising and mechanisms of formation the fluoroquinolones-associated tendo- and arthropathy for the further perspectives of development the possible preventive measures of appearance of fluoroquinolones-induced changes in the temporomandibular joint structures.

The ability of fluoroquinolone antibiotics to adversely affect tendons has been the subject of many articles and case reports in the medical literature for nearly three decades. Clinicians and patients should be aware of the potential risks that fluoroquinolones pose with respect to both cause and potentiation of *tendinopathy*, which is described as the clinical presentation of pain associated with tendon loading. Complications, which are arising after fluoroquinolones intake able to cause temporomandibular joint (TMJ) disorders. This, in turn, reduces the quality of patients' life in the future and can lead to severe consequences and even disability. Today is exists the large number of scientific researches, which are devoted to study of mechanisms of development the fluoroquinolones – associated tendino-and arthropathy. However, the correlation between the quinolones intake and development of quinolones – associated complications remains poorly understood. Also, in the literature there are no findings about preventive methods, which are aimed at preventing the development of tendinopathy after fluoroquinolones intake. Especially, it concerns the TMJ, because using the standard methods (temporary immobilization or limited loads) the above problem is not resolved. This connected with ensuring of vital functions, such as everyday chewing at reception of nutrition, speech etc. All the above indicates the relevance of the issues that we are considering and require further more detailed study the relationship between quinolones therapy and the risk of emergence the temporomandibular joint disorders and necessity of development of preventive measures in case of fluoroquinolones-induced tendinopathy.

**Key words:** temporomandibular joint, fluoroquinolones, collagen, cartilage, tendons, rupture.

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Стаття надійшла 21.11.2018 року*