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**Review article**

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# *Current issues of the pathomorphology of foot tissues in diabetic neuroosteoarthropathy, including complicated by osteomyelitis (literature review and results of own research)*

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***Abstract***

**Introduction** Diabetic neuroosteoarthropathy (DNOAP) is a serious medical and social problem, a potentially life-threatening condition associated with increased mortality. **Purpose** Analysis of the literature data on DNOAP complicated by osteomyelitis in terms of pathogenesis and histological diagnostic methods. **Materials and methods** The review considers studies from various information systems (eLibrary.ru, PubMed, etc.) published from 2001 to 2021. **Results** Differential diagnosis of DNOAP and chronic osteomyelitis is a poorly understood issue. The "gold standard" in determining the nature of bone tissue destruction is bone biopsy. An analysis of the literature shows that changes in the structure of the bone in chronic osteomyelitis are of varying severity, and the determination of its boundaries is of considerable difficulty. Histomorphometric diagnostic criteria for chronic osteomyelitis have not been defined. Studies of pathomorphological changes in foot tissues affected by DNOAP are scarce. The most significant pathomorphological changes in the bone tissue in DNOAP are the following: focal necrosis, desolated osteocytic lacunae, endosteal resorption, thinning of the subchondral layer. The inflammatory infiltrate is mild or moderately expressed and is composed by lymphocytes, plasma cells and macrophages, rarely neutrophils and fibroblasts. One of the leading components in the initiation of pathological changes in the tissues of the foot affected by DNOAP is pronounced disorders in the structure of the vessel wall. Degeneration processes are expressed in peripheral nerves. **Conclusion** The pathogenesis of the Charcot foot and pathomorphological changes in the tissues of the foot, depending on etiopathogenetic factors and comorbidity, is not well understood. Histological studies of foot tissues in this pathology are promising for the differential and early diagnosis of Charcot foot, justifying the need for an individual approach to treatment, paying attention to certain morphological changes.

***Keywords***: diabetic neuroosteoarthropathy, Charcot foot, osteomyelitis, pathogenesis, pathomorphology

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Diabetes mellitus is one of the most serious medical, social and economic problems worldwide due to early disability and high mortality from late complications. Diabetic neuroosteoarthropathy is one of the most severe complications of diabetes mellitus that inevitably leads to disability. Diagnosis and treatment of diabetic neuroosteoarthropathy and its complications is one of the most important areas of contemporary medicine [1–4].

**Purpose** To analyze the literature data on diabetic neuroosteoarthropathy complicated by osteomyelitis in terms of pathogenesis and histological diagnostic methods.

## MATERIAL AND METHODS

Various information systems (eLibrary.ru, PubMed and some others) were used to search for studies on the topic under discussion published between 2001 and 2021.

## RESULTS

Diabetic neuroosteoarthropathy (Charcot osteoarthropathy, Charcot foot, Charcot joint) is a non-infectious chronic destruction of the bones and joints of the foot in patients with diabetes mellitus with neurological deficit, leading to irreversible disability if treatment is inadequate [5, 6].

The disease was named "Charcot's foot" in honor of the French neurologist J.M. Charcot, who first established and described in detail the pathogenetic relationship between peripheral neuropathy and ankle joint damage in patients with advanced stages of syphilis [7].

Charcot osteoarthropathy has been also described in patients with alcoholism, leprosy, spinal cord injury, poliomyelitis, and in other conditions associated with peripheral neuropathy [8, 9].

Currently, the most common cause of Charcot osteoarthropathy is diabetes mellitus (diabetic neuropathy). According to the latest data, the number of patients with diabetes mellitus in the world has more than doubled over the past 10 years and exceeded 425 million people by the end of 2017. As estimated by the International Diabetes Federation, about 629 million people will suffer from diabetes by 2045. In Russia, there has been also a significant growth in the number of individuals with this disease. According to the federal diabetes registry, 3.1 % of the population was registered

with dispensaries in the Russian Federation by the end of 2018. The results of the Russian epidemiological study (NATION) state that only 54 % of type 2 diabetes cases have been diagnosed. Thus, the real number of patients with diabetes mellitus is at least 9 million people (about 6 % of the population). Thus, the pathology remains undiagnosed in a significant number of patients; so, they do not receive treatment and have a high risk of complications [10].

Depending on the dominance or combination of the main pathogenetic phenomena in the development of diabetic foot (neuropathy, angiopathy, osteoarthropathy), its main forms are: neuropathic type (trophic foot ulcer, diabetic osteoarthropathy or Charcot foot); ischemic type; and neuroischemic type. Known are neurotraumatic and neurotrophic theories that have long been used to elucidate the pathogenesis of the Charcot foot. The reason for the change in the structure of bone tissue may be a local increase in blood flow in the vessels of the foot due to neuropathy of the fibers of the sympathetic nervous system and / or persistent traumatization due to loss of sensory sensitivity. However, none of these theories gives an exhaustive answer to what causes the skeletal deformity [11–13]. This is due to the small number of studies aimed at studying structural changes in the tissues in patients with diabetic foot.

At present, DNOAP is a serious medical and social problem, as it is a potentially dangerous condition for the limbs. In addition to the emotional and social burden of physical dysfunction, it is associated with increased mortality [14]. During lifetime, 8-15 % of diabetic patients develop trophic foot ulcers that may further develop and the disease can be complicated by gangrene of the limb. Mortality from "high" amputations ranges from 28 to 50 %, and every second patient after "high" amputation dies within 5 years [15, 16].

The most common manifestation of a late complication of diabetic foot is trophic ulcers. They may lead to severe purulent necrotic complications. Up to 60 % of such complications are accompanied by purulent lesions of bones and joints. Osteomyelitis occurs by spreading of infection from the soft tissues due to its contact and is the main cause of non-traumatic amputations of the lower extremities [17, 18].

*Diagnosis of Charcot osteoarthropathy and chronic osteomyelitis* Despite modern advances in medicine, the diagnosis of osteomyelitis in DNOAP is a rather difficult task. Differential diagnosis of Charcot osteoarthropathy and chronic osteomyelitis against the background of purulent necrotic complications of the diabetic foot is a poorly studied issue [2, 3, 17, 19].

*Instrumental methods for diagnosing chronic osteomyelitis and diabetic neuroosteoarthropathy (Charcot foot)* With DNOAP, radiological signs are described in the English literature as symptoms of five "D": joint distension (joint sprain), dislocation, debris (fragments), disorganization (destruction with loss of function), increased density [20, 21]. The radiographic method gives positive diagnosis in the later stages of the disease, with a loss of bone substance of more than 20–40 %, and is ineffective in the early stages of DNOAP [22, 23].

Magnetic resonance imaging is the most informative method for diagnosing DNOAP, as it is able to assess the magnitude of damage to both bones and soft tissues, to differentiate osteomyelitis from diabetic neuroosteoarthropathy, and to assist in planning surgical treatment [24, 25]. New methods for analyzing magnetic resonance imaging data for assessing the Charcot foot have been developed and proposed [26, 27]. Local and systemic decrease in bone mass is reliably determined by densitometry. The most effective, but currently inaccessible, method is skeletal scintigraphy with the introduction of Tc99m [28, 29].

The “gold standard” in determining the nature of bone tissue destruction is the histological method – bone biopsy [30, 31].

*Histological method in the diagnosis of diabetic neuroosteopathy and osteomyelitis* The literature confirms the varying grades of changes in the bone structure in chronic osteomyelitis [17, 23, 32]

Pathological changes in osteomyelitis have been described well enough. Differences between the acute and chronic types of the inflammatory process have been shown. Such pathological signs as foci of osteonecrosis and sequesters, replacement of bone marrow structures with granulation tissue and fibrosis, and inflammatory infiltration are used to formulate a diagnosis of chronic osteomyelitis [17, 33].

The following morphological signs of bone rarefaction are distinguished in osteomyelitis. In compact bone tissue, it is the expansion of Haversian canals, and in cancellous bone tissue, osteoclastic resorption (more characteristic of chronic osteomyelitis). Restructuring of bone tissue is manifested by a change in the structure of bone components. Residual structures are found in osteons such as "fragments" of former osteons. Their enlargement indicates a repeated restructuring. In cancellous bone trabeculae, an increased restructuring manifests itself in a growing number of gluing lines – a layer of bone substance formed during one time period separates from a layer formed in a later period [34].

Characteristic signs of sequestration are empty ostocytic lacunae, empty or pus-filled Haversian canals and bone marrow gaps, serrated edges along the line of separation from the bulk of the bone. Bone microsequesters are sometimes surrounded by giant multinucleated cells. There are lesions of blood vessels and nerves, sclerosis of the walls of the vessels of the microvasculature, perineural sclerosis, and productive vasculitis. The bone marrow gaps are filled with fibrous connective tissue. In soft tissues, there is an overgrowth

of connective tissue with inflammatory infiltrates consisting of lymphocytes and plasmatic cells [34].

In chronic osteomyelitis of the foot, tissue damage is extensive; the infectious process also penetrates the joints [18]. Reports on histological changes in the cartilage tissue of the joints in osteomyelitis are separate descriptions of clinical cases with the development of osteoarthritis and synovitis of large joints [35, 36].

At the border of the subchondral bone, the intensively functioning hypertrophied chondrocytes of the articular cartilage form a chondrohematic barrier that prevents the spread of the osteomyelitic process. In pathological conditions, this "barrier" is broken, and the penetration of blood vessels into the cartilage is noted [37].

The results of our study showed that structural changes in the articular cartilage in chronic osteomyelitis depended on the location of the osteomyelitis nidus. In the calcaneus and talus, when the osteomyelitic focus is distant from the articular surface, the structure of the subchondral bone plate and the basophilic line are not disturbed, the vessels did not penetrate into the cartilaginous tissue. In the presence of an osteomyelitic focus in the subchondral zone, disorders of the structure of the basophilic line and subchondral bone, invasion of cartilage tissue by vessels were revealed. From the side of the articular surface, synovial pannus invades the cartilage matrix. In chronic osteomyelitis of the phalanges and metatarsal bones, in all cases, disorders of the structure of the articular cartilage and subchondral bone, invasion of blood vessels into the cartilage was observed due to the small size of these bones and the contact of the osteomyelitic nidus with the articular cartilage [38].

Chronic osteomyelitis is characterized by stages of its course, alternation of remissions and exacerbations. The literature practically does not reflect the features of the cellular and tissue composition of the substituted bone marrow structures in chronic osteomyelitis in different phases of inflammation (exacerbation, remission).

G.V. Diachkova et al. (2017) analyzed the surgical material harvested from 58 patients with chronic osteomyelitis of the proximal femur and showed the following features characteristic of the active and subacute inflammatory phase: restructuring of the cancellous bone of the femoral head with almost complete destruction of the articular cartilage, trabecular necrosis, thinning of the subchondral bone, replacement of the intertrabecular space with necrotic detritus, accumulations of purulent exudate, immature and mature (fields of fibrosis) granulation tissue. In the active form, there was a large number of segmented leukocytes in the intertrabecular spaces. In the period of remission, in a number of cases, small loose non-caseating granulomas of lymphocytic and macrophage composition were determined, signs of reparative bone formation (layers of newly formed osteoid and layers of osteoblasts on the endosteal surface of the bone trabecular complex) [39].

An important issue is the development of an algorithm for diagnosing osteomyelitis in diabetic foot for possible tactics of treating this pathology. One example of such an algorithm is the diagnostic criteria and recommendations for the treatment of osteomyelitis in patients with diabetic foot proposed in 2008 by the International Diabetic Foot Expert Group (DFSG) of the European Organization for the Study of Diabetes Mellitus (EADS). The authors state that the developed scheme for diagnosing diabetic foot osteomyelitis simplifies the process by using a combination of various diagnostic criteria, including histological ones [40].

J.L. Lázaro-Martinez et al. (2017), having reviewed critically 60 publications, concluded that the diagnosis of osteomyelitis in diabetic foot is not unambiguous due to its heterogeneity. The clinical signs of inflammation along with bone biopsy and radiography have been postulated as the main clinical diagnostic tests for suspected osteomyelitis [41].

A. Tiemann et al. (2014) developed a semi-quantitative histopathological assessment scale for acute and chronic osteomyelitis to determine the phase of the inflammatory process, which included grading bone and soft tissue changes and inflammatory infiltrate from 0 to 3 points [42].

*Pathohistological studies of diabetic neuroosteoarthropathy* Despite current advances of medicine, the problem of differentiated diagnosis of DNOAP and osteomyelitis remains little studied [43, 44, 45].

R.V. Deev et al. (2016) distinguish the following most significant pathomorphological changes in bone tissue in patients with terminal forms of diabetic angio- and neuropathy: focal necrosis, manifested by neglected osteocytic lacunae, endosteal resorption, thinning of the subchondral layer, the phenomenon of free trabeculae; in the intertrabecular space, fibrous and flaky tissue debris without inflammatory infiltrate, signs of reactive osteogenesis are mild and insufficient for complete recovery of the segment [44].

A.A. Dmitrienko et al. (2014), note that the inflammatory infiltrate of the bone tissue in diabetic neuroosteoarthropathy is mild or moderately pronounced and contains mostly lymphocytes, plasma cells and macrophages, rarely neutrophils and fibroblasts. A distinctive feature of osteomyelitis due to DNOAP is a granulation ridge at the border of the necrotic and unchanged bone area [43].

In our earlier study, disorders in the structure and / or complete absence of the subchondral bone was noted in diabetic neuroosteoarthropathy complicated by osteomyelitisdue to the high activity of osteoclasts in the subchodral zone. Signs of reparative bone formation were poorly expressed, the articular surface was covered

with pannus, and invasion of vessels into the cartilage was noted from the side of the pannus and subchondral zone [45].

The pathohistological changes in the bone tissue and articular cartilage, described above, correspond to the pathogenetic mechanisms of the disease. The disorders in the joint structure are accompanied by hypervascularization and resorption of the bone tissue [46]. Osteoclasts play a key role in the course of Charcot arthropathy as exogenous cells responsible for the imbalance of bone metabolism and, ultimately, osteolysis. An increased activity of osteoclasts in Charcot arthropathy leads to an imbalance in permanent remodeling processes [11, 47].

The reason for the increased resorption activity in diabetic neuroosteoarthropathy is unknown. It was suggested that it may be caused by uncontrolled inflammation due to upregulation of pro-inflammatory cytokines and, in particular, tumor necrosis factor α (TNF-α). Further study of the role of pro-inflammatory cytokines is promising in terms of developing new methods for the treatment of diabetic foot [47, 48].

Quantitative experimental studies of bone tissue in diabetes mellitus showed a decrease in bone tissue volume, the number of osteoblasts, and a reduction in the rate of osteoid formation [49].

Histomorphometric studies of bone tissue in patients with diabetic neuroosteoarthropathy showed an increase in the number of empty osteocytic lacunae and Hausship lacunae, what indicated an increase in osteoclastic activity. The number of osteocytes was significantly reduced relative to the control group [50]. In patients with chronic Charcot arthropathy, a significant thinning of bone trabeculae, a decrease in their area, and active osteoblasts were detected on the surface of some trabeculae [51]. It is noted that low bone mineral density is revealed in patients with foot and ankle fractures associated with neuropathic arthropathy [52, 53].

One of the leading factors in initiating pathological changes in foot tissues in DNOAP is a pronounced disruption in the structure of the microcirculatory vessel wall: intimal hyperplasia, thickening of the subendothelial layer, hyalinosis, and calcification of smooth muscle cells [44, 54–56].

The pathogenesis of vascular calcification in diabetes is not fully understood, and high glucose levels and other factors may play an important role in osteogenic transdifferentiation of smooth muscle cells. Further detailed study of the mechanism of vascular calcification in diabetes is necessary to develop effective therapeutic strategies to intervene in this process [57, 58].

A number of metabolic and vascular changes in diabetic neuropathy are interrelated, hyperglycemia being the main factor. Changes include increased oxidative stress, accumulation of advanced glycation end products, activation of pro-inflammatory mechanisms, and ischemia. These processes have a direct and indirect adverse effect not only on neurons and Schwann cells, but also on the blood vessels that supply the nerves. Vascular lesions in the tissues of the foot in diabetic neuroosteoarthropathy that occur at the level of the microvasculature are accompanied by structural changes in peripheral nerves, their degeneration, and a decrease in the number of Schwann cells [59].

O.V. Belov et al. (2017) studied two clinical groups of six patients each. In the first group of patients, ischemic changes prevailed, and neuropathic changes in the second group. The authors revealed the heterogeneity of morphological data. In the first group, severe circulatory disorders, thickening of the walls of microvessels with narrowing of their lumen were found. Changes in the peripheral nerve trunks were characterized by mild demyelination. In the second group, vascular changes were similar to those in the first group; damage to the Schwann sheaths, destruction of myelin up to total demyelination and complete degeneration of the axial cylinders were revealed in the peripheral nerve trunks. Changes in endo- and perineural vessels were thickening of the basement membrane, empty capillaries. Histomorphometry revealed a statistically significant thickening of the walls of precapillary arterioles, a decrease in their inner diameter with a reduction in the internal diameter of capillaries, more pronounced in the first group. The identified morphological features of the manifestations of the neuroischemic type of the diabetic foot substantiate the need for an individual approach to the treatment of patients, paying attention to certain morphological changes [54].

U. Illgner et al. (2019) identified the main semi-quantitative histopathological criteria of the Charcot foot – the Charcot scale (the proposed Charcot scale is based on the principle of the HOES scale of A. Tiemann et al., 2014 [42]). The authors assessed in points (from 0 to 4 points) the severity of tissue necrosis, signs of bone remodeling (detection of osteoblasts, osteoclasts, inflammatory infiltrate), the state of articular cartilage (the severity of signs of destruction and regeneration), and the severity of inflammatory infiltrate in the synovial membrane. A semi-quantitative histopathological score of 11 or more points (maximum score 21) is assessed as Charcot foot. A limitation of the study was a small sample size of 20 patients [60].

## DISCUSSION

Diabetic neuroosteoarthropathy (Charcot foot) is a potentially dangerous complication in patients with diabetes mellitus, leading to significant destruction of bones and joints, foot deformity, and formation of trophic ulcers [5, 6]. Given the high percentage of lower limb amputations and post-amputation mortality

in patients with diabetes mellitus (28–50 %), an early diagnosis of DNOAP is of great importantance [15–18]. The main method for assessing the condition of bones and joints remains radiography that reveals the foci of osteolysis with high reliability, but is ineffective in the early stages of DNOAP [22, 23]. Densitometric methods are being improved currently. The most informative methods for assessing the location and size of the lesion, both in bones and soft tissues, are magnetic resonance imaging [24, 25] and the histological method [30, 31].

The analysis of literature data showed that the problem of differential diagnosis of DNOAP and osteomyelitis remains a poorly studied issue [2, 3, 17, 19].

Quantitative histopathological diagnostic criteria for chronic osteomyelitis have not yet been determined. In a number of cases, there is a need for a reliable diagnosis in the absence of obvious clinical and radiological signs of osteomyelitis to differentiate between diabetic osteoarthropathy and osteomyelitis, when bone tissue destruction is expressed in both cases, or when osteomyelitis is detected as a complication of diabetic osteoarthropathy.

There are three main forms in the development of diabetic foot syndrome: neuropathic, ischemic and neuroischemic. However, none of these theories gives an exhaustive idea of what causes skeletal deformity due to insufficient research on structural tissue changes in patients with diabetic foot [11, 12, 13].

The mechanisms of the Charcot foot pathogenesis and pathomorphological tissue changes in regard to etiological factors and comorbidity have not been not well understood. To date, semi-quantitative histopathological criteria for osteomyelitis and Charcot foot have been developed [42, 60]. The limitation of the presented studies was the small sample size of 52 and 20 patients [42, 60]. Currently, there is no standardized reproducible histological assessment of the surgical material. The results are often presented descriptively and it is difficult for the doctor to work with histopathological results.

## CONCLUSION

The pathogenesis of the Charcot foot and pathological morphological changes in the tissues of the foot, depending on etiopathogenetic factors and comorbidity, is not well understood. Histological studies of the foot tissues in this pathology are promising for the differential and early diagnosis of Charcot foot, justifying the need for an individual approach to treatment, paying attention to certain morphological changes.

## REFERENCES


1. Galchina Iu.S., Karmazanovskii G.G., Paskhalova Iu.S. Osnovnye metody diagnostiki sindroma diabeticheskoi stopy [The main methods of diagnosing the diabetic foot syndrome]. *Meditsinskaia Vizualizatsiia*, 2016, no. 6, pp. 100-117. (in Russian)
2. Minakov O.E., Andreev A.A., Ostroushko A.P. Sindrom diabeticheskoi stopy [The syndrome of diabetic foot]. *Vestnik Eksperimentalnoi i Klinicheskoi Khirurgii*, 2017, vol. 10, no. 2, pp. 165-172. (in Russian) DOI: 10.18499/2070-478X-2017-10-2-165-172.
3. Babushkina Iu.V., Burleva E.P., Galimzianov F.V., Levchik E.Iu. Osobennosti spetsializirovannoi pomoshchi patsientam s diabeticheskoi osteoartropatiei [Particular features of specialized care for patients with diabetic osteoarthropathy]. *Rany i Ranevye Infektsii. Zhurnal imeni prof. B.M. Kostiuchenka*, 2019, vol. 6, no. 2, pp. 6-16. (in Russian) DOI: 10.25199/2408-9613-2019-6-2-6-16.
4. Marmolejo V.S., Arnold J.F., Ponticello M., Anderson C.A. Charcot Foot: Clinical Clues, Diagnostic Strategies, and Treatment Principles. *Am. Fam. Physician*, 2018, vol. 97, no. 9, pp. 594-599.
5. Ulianova I.N., Tokmakova A.Iu., Iaroslavtseva M.V., Ilin A.V., Galstian G.R. Diabeticheskaia osteoartropatiia: sovremennye metody terapii [Diabetic osteoarthropasthy. Current methods of therapy]. *Sakharnyi Diabet*, 2010, vol. 13, no. 4, pp. 70-73. (in Russian) DOI: 10.14341/2072-0351-6061.
6. Galstian G.R., Kaminarskaia Iu.A. Patogenez osteoartropatii Sharko: rol perifericheskoi nervnoi sistemy [Pathogenesis of Charcot osteoarthropathy]. *Endokrinnaia Khirurgiia*, 2014, no. 4, pp. 5-14. (in Russian) DOI: 10.14341/serg20144514.
7. Trepman E., Nihal A., Pinzur M.S. Current topics review: Charcot neuroarthropathy of the foot and ankle. *Foot Ankle Int.*, 2005, vol. 26, no. 1, pp. 46-63. DOI: 10.1177/107110070502600109.
8. Bobrov D.S. Diabeticheskaia osteoartropatiia (stopa Sharko): patogenez, diagnostika i lechenie redkogo oslozhneniia sakharnogo diabeta [Diabetic osteoarthropathy (Charcot foot): pathogenesis, diagnosis and treatment of a rare complication of diabetes mellitus]. *Kafedra Travmatologii i Ortopedii*, 2012, no. 2, pp. 6-12. (in Russian)
9. Mabilleau G., Edmonds M.E. Role of neuropathy on fracture healing in Charcot neuro-osteoarthropathy. *J. Musculoskelet. Neuronal Interact.*, 2010, vol. 10, no. 1, pp. 84-91.
10. Dedov I.I., Shestakova M.V., Maiorov A.Iu., editors. Algoritmy spetsializirovannoi meditsinskoi pomoshchi bolnym sakharnym diabetom: klinicheskie rekomendatsii [Algorithms of specialized medical care for patients with diabetes mellitus: clinical guidelines]. Ed. 9 (updated). *Sakharnyi Diabet*, 2019, vol. 22(S1), pp. 1-212. DOI: 10.14341/DM221S1.
11. Kaynak G., Birsel O., Güven M.F., Oğüt T. An overview of the Charcot foot pathophysiology. *Diabet. Foot Ankle*, 2013, no. 4. DOI: 10.3402/dfa.v4i0.21117.
12. Pinzur M.S. An Evidence-Based Introduction to Charcot Foot Arthropathy. *Foot & Ankle Orthopaedics*, 2018, vol. 3, no. 3, 247301141877426. DOI:10.1177/2473011418774269.
13. Yates T.H., Cooperman S.R., Shofler D., Agrawal D.K. Current concepts underlying the pathophysiology of acute Charcot neuroarthropathy in the diabetic foot and ankle. *Expert. Rev. Clin. Immunol.*, 2020, vol. 16, no. 8, pp. 839-845. DOI: 10.1080/1744666X.2020.1804869.
14. Holmes C., Schmidt B., Munson M., Wrobel J.S. Charcot stage 0: A review and considerations for making the correct diagnosis early. *Clin. Diabetes Endocrinol.*, 2015, vol. 1, pp. 18. DOI: 10.1186/s40842-015-0018-0.
15. Rundo A.I. Sovremennye aspekty etiologii i patogeneza sindroma diabeticheskoi stopy. *Novosti Khirurgii*, 2015, vol. 23, no. 1, pp. 97-104. (in Russian)
16. Gouveri E., Papanas N. Charcot osteoarthropathy in diabetes: A brief review with an emphasis on clinical practice. *World J. Diabetes*, 2011, vol. 2, no. 5, pp. 59-65. DOI: 10.4239/wjd.v2.i5.59.
17. Dmitrienko A.A., Anichkin V.V., Kurek M.F., Vakar A. Diagnostika osteomielita pri sindrome diabeticheskoi stopy (obzor literatury) [Diagnostics of osteomyelitis in diabetic foot syndrome (literature review)]. *Problemy Zdorovia i Ekologii*, 2014, no. 3(41), pp.62-67. (in Russian)

18. Bairamkulov E.D., Vorotnikov A.A., Mozerov S.A., Krasovitova O.V. Kliniko-morfologicheskaia kharakteristika osteomielita pri sindrome diabeticheskoi stopy [Clinical and morphological characteristics of osteomyelitis in diabetic foot syndrome]. *Fundamentalnye Issledovaniia*, 2015, no. 1-1, pp. 23-27. (in Russian)
19. Ergen F.B., Sanverdi S.E., Oznur A. Charcot foot in diabetes and an update on imaging. Diabet. Foot Ankle, 2013, vol. 4. DOI: 10.3402/dfa.v4i0.21884.
20. Storey A.M., Perry C.J., Petrie J.R. Endothelial dysfunction in type 2 diabetes. *Br. J Diabetes & Vascular Dis*., 2001, vol. 1, no. 1, pp. 22-27. DOI: 10.1177/14746514010010010401.
21. Corretti M.C., Anderson T.J., Benjamin E.J., Celermajer D., Charbonneau F., Creager M.A., Deanfield J., Drexler H., Gerhard-Herman M., Herrington D., Vallance P., Vita J., Vogel R.; International Brachial Artery Reactivity Task Force. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. *J. Am. Coll. Cardiol*., 2002, vol. 39, no. 2, pp. 257-265. DOI: 10.1016/s0735-1097(01)01746-6.
22. Markevich P.S., Danilenko S.Iu., Iankin A.V., Plekhanov A.N. Sovremennye metody diagnostiki sindroma diabeticheskoi stopy [Current methods of diagnosing the syndrome of diabetic foot]. *Biulleten VSNTs SO RAMN*, 2012, no. 6(88), pp. 151-155. (in Russian)
23. Diachkova G.V., Diachkov K.A., Kliushin N.M., Larionova T.A., Shastov A.L. A multifaceted osteomyelitis: radiological diagnosis. Genij Ortopedii, 2020, vol. 26, no 3, pp. 385-391. DOI 10.18019/1028-4427-2020-26-3-385-391.
24. Ledermann H.P., Morrison W.B. Differential diagnosis of pedal osteomyelitis and diabetic neuroarthropathy: MR Imaging. *Semin. Musculoskelet. Radiol*., 2005, vol. 9, no. 3, pp. 272-283. DOI: 10.1055/s-2005-921945.
25. Tan P.L., Teh J. MRI of the diabetic foot: differentiation of infection from neuropathic change. *Br. J. Radiol*., 2007, vol. 80, no. 959, pp. 939-948. DOI: 10.1259/bjr/30036666.
26. Meacock L., Petrova N.L., Donaldson A., Isaac A., Briody A., Ramnarine R., Edmonds M.E., Elias D.A. Novel Semiquantitative Bone Marrow Oedema Score and Fracture Score for the Magnetic Resonance Imaging Assessment of the Active Charcot Foot in Diabetes. *J. Diabetes Res*., 2017, vol. 2017, 8504137. DOI: 10.1155/2017/8504137.
27. Berli M.C., Higashigaito K., Götschi T., Pfirrmann C.W.A., Sutter R., Rosskopf A.B. The "Balgrist Score" for evaluation of Charcot foot: a predictive value for duration of off-loading treatment. *Skeletal Radiol*., 2021, vol. 50, no. 2, pp. 311-320. DOI: 10.1007/s00256-020-03541-6.
28. Capriotti G., Chianelli M., Signore A. Nuclear medicine imaging of diabetic foot infection: results of meta-analysis. *Nucl. Med. Commun*., 2006, vol. 27, no. 10, pp. 757-764. DOI: 10.1097/01.mnm.0000230065.85705.b3.
29. Grigoropoulou P., Eleftheriadou I., Jude E.B., Tentolouris N. Diabetic Foot Infections: an Update in Diagnosis and Management. *Curr. Diab. Rep*., 2017, vol. 17, no. 1, pp. 3. DOI: 10.1007/s11892-017-0831-1.
30. Pavlova M.G., Kalashnikova M.F., Gusov T.V., Lavrishcheva N.V. Sovremennye metody diagnostiki i lecheniia sindroma diabeticheskoi stopy [Modern methods of diagnostics and treatment of the syndrome of diabetic foot]. *Klinitsist*, 2007, no. 3, pp. 21-29. (in Russian)
31. Meyr A.J., Singh S., Zhang X., Khilko N., Mukherjee A., Sheridan M.J., Khurana J.S. Statistical reliability of bone biopsy for the diagnosis of diabetic foot osteomyelitis. *J. Foot Ankle Surg*., 2011, vol. 50, no. 6, pp. 663-667. DOI: 10.1053/j.jfas.2011.08.005.
32. Lipsky B.A., Peters E.J., Senneville E., Berendt A.R., Embil J.M., Lavery L.A., Urbančič-Rovan V., Jeffcoate W.J. Expert opinion on the management of infections in the diabetic foot. *Diabetes Metab. Res. Rev*., 2012, vol. 28, no. Suppl. 1, pp. 163-178. DOI: 10.1002/dmrr.2248.
33. Xiao L., Li T., Ding M., Yang J., Rodríguez-Corrales J., LaConte S.M., Nacey N., Weiss D.B., Jin L., Dorn H.C., Li X. Detecting Chronic Post-Traumatic Osteomyelitis of Mouse Tibia via an IL-13Rα2 Targeted Metallofullerene Magnetic Resonance Imaging Probe. *Bioconjug. Chem*., 2017, vol. 28, no. 2, pp. 649-658. DOI: 10.1021/acs.bioconjchem.6b00708.
34. Bodachenko K.A., Rushai A.K., Poliakov K.V. Patomorfologicheskoe obosnovanie kompleksnoi konservativnoi terapii posttravmaticheskogo osteomielita kostei konechnostei [Pathomorphological substantiation of complex conservative therapy of post-traumatic osteomyelitis of limb bones]. *Ukraïnskii Zhurnal Ekstremalnoï Meditsini imeni G.O. Mozhaєva*, 2011, vol. 12, no. 4, pp. 11-15. (in Russian)
35. Ahmad S.S., Kohl S., Evangelopoulos D.S., Krüger A. Silent chronic osteomyelitis lasting for 30 years before outburst of symptoms. *BMJ. Case Rep*., 2013, vol. 2013, bcr2013009428. DOI: 0.1136/bcr-2013-009428.
36. Ellerbrook L., Laks S. Coccidioidomycosis osteomyelitis of the knee in a 23-year-old diabetic patient. *Radiol. Case. Rep*., 2015, vol. 10, no. 1, pp. 1034. DOI: 10.2484/rcr.v10i1.1034.
37. Zaidman A.M., Korel A.V. Srukturno-funktsionalnye osobennosti plastinki rosta tel pozvonka cheloveka v kriticheskie periody rosta [Structural and functional features of the growth plate of human vertebral bodies during critical periods of growth]. *Khirurgiia Pozvonochnika*, 2004, no. 1, pp. 113-120. (in Russian)
38. Stupina T.A., Migalkin N.S., Sudnitsyn A.S. Structural reorganization of the cartilage tissue in chronic osteomyelitis of the foot bones. *Genij Ortopedii*, 2019, vol. 25, no 4, pp. 523-527. DOI 10.18019/1028-4427-2019-25-4-523-527.
39. Diachkova G.V., Kliushin N.M., Migalkin N.S., Larionova T.A., Leonchuk D.S., Diachkov K.A., Begimbetova N.B. Rentgeno-gistologicheskie paralleli stadii khronicheskogo osteomielita [X-ray and histological parallels of the stages of chronic osteomyelitis]. *Vestnik Rossiiskoi Voenno-meditsinskoi Akademii*, 2017, no. 4 (60), pp. 17-22. (in Russian)
40. Berendt A.R., Peters E.J., Bakker K., Embil J.M., Eneroth M., Hinchliffe R.J., Jeffcoate W.J., Lipsky B.A., Senneville E., Teh J., Valk G.D. Diabetic foot osteomyelitis: a progress report on diagnosis and a systematic review of treatment. *Diabetes Metab. Res. Rev*., 2008, vol. 24, no. Suppl. 1, pp. S145-S161. DOI: 10.1002/dmrr.836.
41. Lázaro-Martínez J.L., Tardáguila-García A., García-Klepzig J.L. Diagnostic and therapeutic update on diabetic foot osteomyelitis. *Endocrinol. Diabetes Nutr*., 2017, vol. 64, no. 2, pp. 100-108. (in English, Spanish) DOI: 10.1016/j.endinu.2016.10.008.
42. Tiemann A., Hofmann G.O., Krukemeyer M.G., Krenn V., Langwald S. Histopathological Osteomyelitis Evaluation Score (HOES) – an innovative approach to histopathological diagnostics and scoring of osteomyelitis. *GMS. Interdiscip. Plast. Reconstr. Surg. DGPW*, 2014, vol. 3, Doc08. DOI: 10.3205/iprs000049.
43. Dmitrienko A.A., Anichkin V.V., Kurek M.F., Mishin A.V. Morfologicheskie kriterii differentsialnoi diagnostiki osteoartropatii i osteomielita u bolnykh s sindromom diabeticheskoi stopy [Morphological criteria of differential diagnostics of osteoarthropathy and osteomyelitis in patients with the syndrome of diabetic foot]. *Khirurgiia. Vostochnaia Evropa*, 2014, no. 4, pp. 16-23. (in Russian)
44. Deev R.V., Plaksa I.L., Chekmareva I.A., Galstian G.R., Suchkov I.A., Matveev S.A. Patogistologicheskie izmeneniia tkanei stopy u patsientov s terminalnymi formami diabeticheskoi angio- i neiropatii [Pathological changes in foot tissues of patients with terminal forms of diabetic angio- and neuropathy]. *Vestnik Natsionalnogo Mediko-khirurgicheskogo Tsentra im. N.I. Pirogova*, 2016, vol. 11, no. 2, pp. 69-75. (in Russian)
45. Stupina T.A., Migalkin N.S., Shchudlo M.M., Sudnitsyn A.S., Mezentsev I.N. Mikroskopicheskoe issledovanie komponentov sustavov stopy pri artropatii Sharko, oslozhnennoi osteomielitom [Microscopic investigation of foot joint components in Charcot arthropathy complicated by osteomyelitis]. *Travmatologiia i Ortopediia Rossii*, 2020, vol. 26, no. 4, pp. 112-120. (in Russian) DOI: 10.21823/2311-2905-2020-26-4-112-120.
46. Boulton A.J. The diabetic foot: from art to science. The 18th Camillo Golgi lecture. *Diabetologia*, 2004, vol. 47, no. 8, pp. 1343-1353. DOI: 10.1007/s00125-004-1463-y.
47. Petrova N.L., Petrov P.K., Edmonds M.E., Shanahan C.M. Inhibition of TNF-α Reverses the Pathological Resorption Pit Profile of Osteoclasts from Patients with Acute Charcot Osteoarthropathy. *J. Diabetes Res*., 2015, vol. 2015, pp. 917945. DOI: 10.1155/2015/917945.
48. Jeffcoate W.J., Game F., Cavanagh P.R. The role of proinflammatory cytokines in the cause of neuropathic osteoarthropathy (acute Charcot foot) in diabetes. *Lancet*, 2005, vol. 366, no. 9502, pp. 2058-2061. DOI: 10.1016/S0140-6736(05)67029-8.
49. Creecy A., Uppuganti S., Unal M., Clay Bunn R., Voziyan P., Nyman J.S. Low bone toughness in the TallyHO model of juvenile type 2 diabetes does not worsen with age. *Bone*, 2018, vol. 110, pp. 204-214. DOI: 10.1016/j.bone.2018.02.005.

50. La Fontaine J., Shibuya N., Sampson H.W., Valderrama P. Trabecular quality and cellular characteristics of normal, diabetic, and Charcot bone. *J. Foot Ankle Surg*., 2011, vol. 50, no. 6, pp. 648-653. DOI: 10.1053/j.jfas.2011.05.005.
51. Dharmadas S., Kumar H., Pillay M., Jojo A., Pj T., Mangalanandan T.S., Vivek L., Praveen V.P., Bal A. Microscopic study of chronic Charcot arthropathy foot bones contributes to understanding pathogenesis – A preliminary report. *Histol. Histopathol*., 2020, vol. 35, no. 5, pp. 443-448. DOI: 10.14670/HH-18-162.
52. Hastings M.K., Johnson J.E., Strube M.J., Hildebolt C.F., Bohnert K.L., Prior F.W., Sinacore D.R. Progression of foot deformity in Charcot neuropathic osteoarthropathy. *J. Bone Joint Surg. Am*., 2013, vol. 95, no. 13, pp. 1206-1213. DOI: 10.2106/JBJS.L.00250.
53. Cho J.H., Min T.H., Chun D.I., Won S.H., Park S.Y., Kim K., Yi Y. Bone Mineral Density in Diabetes Mellitus Foot Patients for Prediction of Diabetic Neuropathic Osteoarthropathic Fracture. *J. Bone Metab*., 2020, vol. 27, no. 3, pp. 207-215. DOI: 10.11005/jbm.2020.27.3.207.
54. Belov S.G., Danilova O.V., Taraban I.A., Galata D.I., Gorgol N.I., Potapov S.N. Morfofunktsionalnye osobennosti miagkikh tkanei pri neiroishemicheskoi forme sindroma diabeticheskoi stopy [Morphofunctional features of soft tissues in neuroischemic form of diabetic foot syndrome]. *Novosti Khirurgii*, 2017, vol. 25, no. 2, pp. 140-147. (in Russian)
55. Jeffcoate W. Vascular calcification and osteolysis in diabetic neuropathy – is RANK-L the missing link? *Diabetologia*, 2004, vol. 47, no. 9, pp. 1488-1492. DOI: 10.1007/s00125-004-1477-5.
56. Rogers L.C., Frykberg R.G., Armstrong D.G., Boulton A.J., Edmonds M., Van G.H., Hartemann A., Game F., Jeffcoate W., Jirkovska A., Jude E., Morbach S., Morrison W.B., Pinzur M., Pitocco D., Sanders L., Wukich D.K., Uccioli L. The Charcot foot in diabetes. *Diabetes Care*, 2011, vol. 34, no. 9, pp. 2123-2129. DOI: 10.2337/dc11-0844.
57. Chen N.X., Moe S.M. Arterial calcification in diabetes. *Curr. Diab. Rep*., 2003, vol. 3, no. 1, pp. 28-32. DOI: 10.1007/s11892-003-0049-2.
58. Poetsch F., Henze L.A., Estepa M., Moser B., Pieske B., Lang F., Eckardt K.U., Alesutan I., Voelkl J. Role of SGK1 in the Osteogenic Transdifferentiation and Calcification of Vascular Smooth Muscle Cells Promoted by Hyperglycemic Conditions. *Int. J. Mol. Sci*., 2020, vol. 21, no. 19, pp. 7207. DOI: 10.3390/ijms21197207.
59. Popescu R.M., Cotuţiu C., Graur M., Căruntu I.D. Vascular and nerve lesions of the diabetic foot – a morphological study. *Rom. J. Morphol. Embryol*., 2010, vol. 51, no. 3, pp. 483-488.
60. Illgner U., Mehlhorn A.T., Osada N., Krenn V. Histopathologischer Charcot-Score an intraoperativen Gewebeproben vom Fuß: Prospektive Untersuchung [Histopathological Charcot score on intraoperative tissue samples from the foot: A prospective investigation]. *Orthopade*, 2019, vol. 48, no. 8, pp. 693-703. (in German) DOI: 10.1007/s00132-019-03769-8.

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