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REVIEW PAPER

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The effect of diabetes on the connective tissue and the bone-joint system

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ABSTRACT

Introduction. Diabetes is associated with a number of complications, including renal disease, peripheral neuropathy, retinopathy, and vascular events.

Aim. Article presents the research results reported in the scientific literature about the influence of diabetes on connective tissue and the bone-joint system.

Material and methods. Analysis of literature.

Conclusion. Due to its multi-systemic nature, the development of additional manifestations, such as musculoskeletal complications, is possible including, for example diabetic osteopathy, limited joint mobility, joint disorders, and other, many of which are subclinical and correlated with the disease duration and its inadequate control. They should be recognized and treated properly, because their management improves the patients' quality of life.

Keywords. diabetes mellitus, diabetic osteopathy, limited joint mobility, joint disorders

Introduction

Concomitant metabolic disorders affect many organs and systems including the motor organs – bones, joints, and soft tissues. These changes are related to other disorders: angiopathy and neuropathy.[1] Changes in motor organs have a diversified picture.

As opposed to vascular complications, musculoskeletal manifestations of diabetes are common, but not life threatening. They are an important cause of morbidity, pain, and disability. They usually occur in patients with poorly controlled diabetes of long duration and in those who suffer from other more serious complications.[2]

Among the musculoskeletal complications of diabetes, two basic groups can be identified:[3]

- effects of diabetes on the muscle tissues
- effects of diabetes on joints and the connective tissue.

An extensive discussion of these diseases has been presented by Brazilian authors.[4]

The review of these musculoskeletal manifestations in diabetic patients has been also presented by Polish authors.[5] In this paper we wish to recall some of these musculoskeletal manifestations based on the literature data and our own observations.

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Diabetic osteopathy

Even though studies on the pathogenesis of diabetic osteopathy have a considerably long history, there are many mechanisms leading to metabolic disorders of bones in diabetes mellitus that have not been explained. As a consequence of diabetes, processes of rebuilding and creation of bones are both disordered. There are experimental studies on rats conducted, aimed to explain mechanisms of metabolic disorders of bones in diabetes mellitus.[6] Both types 1 and 2 of diabetes mellitus constitute a risk factor for bone fractures.[7]

Based on a meta-analysis comprising long-term studies on the risk of bone fracture in diabetic patients, Adami stated that in patients with type 1 diabetes, an increased risk of fracture is associated with a decreased BMD level, while in patients with type 2 diabetes this risk exists despite a correct or increased BMD level.[8] The author presented the results of an overview of relevant literature data from January 1970 to November 2008, relating to the correlation between the bone mass and an increased risk of fragility fracture in patients with diabetes.

The same observations are described by other authors. An important difference, however, is that in type 1 diabetes, the risk of fracture is associated with a lower level of bone mineral density, while patients with type 2 diabetes usually have a correct or even increased BMD level.[9]

Many researchers confirm that the risk of fracture occurs in patients with type 2 diabetes despite a BMD level within the normal range.[10,11]

Much attention is devoted to pathophysiology of bone changes in diabetes.[12]

An extensive discussion of this issue has been recently presented by Ferrari.[13] The author analyzes mechanisms that may lead to an increased risk of fractures in diabetic patients.

The risk of bone fracture concerns especially patients with uncontrolled diabetes.[14,15]

Some scientists claim that the loss of bone mass occurs both in patients with type 1 and type 2 diabetes. Other authors state that osteopathy in young patients with type 1 diabetes is in fact a diabetes-related complication, whereas in older patients with type 2 diabetes it is actually gerontic osteoporosis, and diabetes only plays a role of and enhancer of this process.

In the opinion of the majority of researchers, the patient's age when diabetes is diagnosed has a great effect on the occurrence of bone lesions. It seems that patients with diabetes diagnosed in their growth period, prior to skeletal maturation, are particularly predisposed.

Additionally, the role of calcitonin secretion disorders, diagnosed in diabetic patients, has not been explained yet. Considering the vitamin D insufficiency as one of the causes of diabetic osteopathy, as well as potential vitamin D metabolism disorders at the final stages of its transformation, is controversial, although it seems that a decrease of the biological activity of this metabolite or a drop in the number of receptors in the target tissue are more possible than the deficiency of 1,25(OH)2D. Opinions about the PTH secretion in diabetic patients and its relevance to the occurrence of diabetic osteopathy are differentiated.

In recent years, a whole series of studies on bones density and bones turnover in patients, mainly in children and adolescents with type 1 diabetes, were published.[16-18]

It was stated that the bone status of adolescents with type 1 diabetes mellitus assessed with QUS differs from that of their healthy peers and is dependent on long-term metabolic control.[19]

Results of these investigations are equivocal. Most of them state that bone density in patients with diabetes is lower than in their healthy peers; however, this decrease concerns unequally individual cases of bone meshwork (cortical bone, spongy bone).

The most frequently observed changes did not reveal any association with the stage of metabolic balance in diabetes mellitus; however, Valerio et al., who studied the effect of diabetes on the bone density and the resorption processes in 27 juvenile patients (aged 13.1 ± 1.7) with type 1 diabetes lasting 6.9 ± 3.0 years, concluded that incorrect metabolic control in diabetes mellitus in puberty may constitute a risk factor of the osteopathy progression in adult age, whereas optimized metabolic control in growing children may prevent the osteoporosis occurrence in their later life.[20]

It is assumed that an increased tendency for the occurrence of VF (vertebral fracture) in diabetic patients with a correct level of BMD (bone mineral density) is an effect of concomitant obesity and hyperglycemia, which was proven in Japanese studies conducted in a group of male patients with type 2 diabetes.[21]

Japanese authors propose a range of factors that may prove important in the risk assessment of fractures in patients with type 2 diabetes. It was shown that the serum level of the insulin-like growth factor-I (IGF-I) may be useful in the assessment of the intensification of vertebral fractures (VFs).[22]

Another factor considered by authors as useful in the risk assessment of vertebral fractures is the OC/BAP coefficient (osteocalcin/bone-specific alkaline phosphatase). The OC/BAP ratio could be clinically useful for assessing the risk of vertebral fractures regardless of BMD. [23]

Authors indicate the usefulness of the serum adiponectin level for the BMD evaluation in patients with type 2 diabetes.[24] The correlation between the state of bones and the level of adiponectin was investigated also by Polish authors.[25]

The authors conducted a study on the effect of metabolic control of diabetes on selected bone turn-

over markers, the bone mineral density, and serum adiponectin concentrations in post-menopausal women with newly diagnosed Type 2 diabetes. They found that the level of adiponectin is inversely correlated with the bone mineral density of the entire body.

Osteoporotic fractures may be affected by medications applied in the course of diabetes treatment. It is assumed that such an influence may be exerted by thiazolidinediones (TZD). It was stated that the application of these medications may increase the risk of fracture. In vitro studies suggest to the contrary that incretin medications have a positive effect on the metabolism of bones.[9,26]

Currently, studies on the effect of metformin on the metabolism of bones are being conducted. Further randomized trials are required concerning this issue.[27]

During the First International Symposium on Diabetes and Bone in Rome in November 2014, the risk of the increased incidence of fractures due to a rapid rise in the number of diabetic patients was considered as a serious problem, also from the financial perspective.[28]

Limited joint mobility syndrome - LJMS

The LJM - limited join mobility syndrome is a diabetes complication well known for a long time, but recently it is getting more interesting to scientists.[29] Many diabetes complications are induced by changes in the collagen structure.[30,31] Probably, changes in the collagen structure induce the LJM syndrome, and advanced glycation end-products may play a role in this process.[32]

In the opinion of many scientists, symptoms of LJM may be far ahead of other chronic diabetes complications; therefore, they could be used as their risk factor.

The LJM syndrome results in the limited joints mobility that affects the metacarpal-phalanx joints and the interphalangeal joint of the 5th finger, usually in the beginning. Afterwards, changes progress gradually through the carpal tunnel and the cubits to the shoulder. Currently, it is known that LJM may also affects lower limbs or joints of the cervical and thoracic-lumbar spine. These changes may be unnoticed by patients as they do not cause any pain.

Previous observations allow to state that the LJM syndrome occurs more often in diabetic patients than in non-diabetic subjects. It is a complication that occurs relatively early both in children and adolescents, as well as in adults with type 1 and 2 diabetes.[33-35]

Initially, studies on LJM were conducted mainly in patients with type 1 diabetes. This syndrome was diagnosed for the first time in juvenile patients in 1974 by A.L. Rosenbloom. Later investigations carried out by this author revealed that improved metabolic control in diabetes mellitus has a significant effect on the decrease of the LJM incidence.[36]

Lindsay et al. performed a retrospective analysis of the LJM incidence in patients with type 1 diabetes.[37] Authors revealed that a better diabetic treatment and improved metabolic control in diabetes mellitus distinctly decrease the LJM occurrence.

The first studies on the LJM incidence in Poland were conducted by Petrulewicz-Salamon.[35] They involved 51 patients with type 1 diabetes at ages of 11-57 (average: 26.6) and the diabetes duration from 1 to 34 years (average: 10.9 years). The LJM syndrome was diagnosed in 21 patients (41.18% of all the patients). The LJM syndrome was associated with other chronic complications (retinopathy, neuropathy, nephropathy and hypertension).

In particular, the group of patients with type 1 diabetes and LJM as the only chronic diabetic complication was very interesting. There were 8 patients (~30% of all subjects) aged 11-20 who had suffered from diabetes for 1-9 years. It may confirm the fact referred to in the subject literature that the LJM syndrome can foreshadow other chronic complications and its occurrence requires tightening of the metabolic balance criteria.

Currently, there are more and more cases where LJM is diagnosed in patients with type 2 diabetes. A comprehensive analysis of the incidence of musculoskeletal disorders of the hand in patients with type 2 diabetes has been carried out by Mustafa et al.[38]

Authors paid attention to the incidence of concomitant retinopathy and hypertension. Other scientists have focused on the association between diabetes mellitus and several pathologic conditions of the hand.[39] In the group of 200 diabetic patients, 30% of patients had neuropathy, 37.5% had nephropathy, and 44.5% had retinopathy. In the study population, 67% of patients were having one or more hand disorders. The most commonly recognized maladies are limited joint mobility, Dupuytren's disease, the trigger finger, and carpal tunnel syndrome. The incidence of these hand disorders has increased in the setting of diabetes.

The LJM syndrome is a diabetic complication that is linked to micro- and macroangiopathy. Correct metabolic control of glycaemia is very important in the LJM prophylaxis.[40,41]

Diagnosis of the LJM syndrome.

The basic test in the diagnosis of LJM is the assessment of the degree of the adherence of the palm to a flat surface. The correct result is when palms adhere to the surface with all of their surface area. Another preliminary test is the verification whether palms fit together in a 'prayer sign'. In both test fingers should be splayed. In the LJM syndrome palms do not fit together and do not adhere closely to the flat surface.[1,42,43]

The evaluation should include the thickening of tissues surrounding the joints. Inability to lift a skin fold,

especially on the dorsal side of the hand, indicates abnormality. The assessment of straightening of the carpus and cubit, of the flexion of the ankle, as well as the verification of the mobility of the cervical and thoracic-lumbar spine are necessary. The changes of joints are accompanied by skin lesions: thickening, tension and waxy appearance, predominantly on the dorsal side of palms and lower arms.

LJM is considered as the one of the complications in juvenile patients with type 1 diabetes that occur the earliest. In the subject literature, it is highlighted that the LJM syndrome may foreshadow other chronic complications, and thus it requires tightening of the metabolic balance criteria. The tests of fitting palms together ('prayer sign') and adhering hands to a flat surface, which are easy to perform, are useful in the assessment of the mobility of joints.

Screening tests are important, because the LJM syndrome does not cause pain, therefore its progression can be underplayed by both medical staff and the patient. An early diagnosis of LJM is an indication for physical rehabilitation to prevent the patient from becoming disabled.

The tendency to collapses in LJM patients constitutes a serious problem. Patients with LJMS had a moderate risk of falls compared with those without LJMS, which was of low risk. [44]

Joint disorders in diabetes mellitus

Joint disorders, both of the inflammatory and degenerative nature, have always been diagnosed in diabetic patients, but they have not been considered from the etiological perspective. In recent years there have been more and more studies devoted to the concomitance of diabetes and joint disorders and the possibility of establishing a cause and effect relationship.

The relationships between diabetes and joint lesions are differentiated. Autoimmune processes that lead to the destruction of beta cells and the progression of type 1 diabetes, are similar to the mechanisms of the synovial membrane annihilation in joints constituting a base for the rheumatoid joint inflammation. In both of these disorders, increased levels of inflammation markers are confirmed, such as C Reactive Protein (CRP), interleukin 6 (IL-6,) or the tumor necrosis factor - alpha (TNF-a).

In type 2 diabetes, degenerative processes of joints are observed.[45]

In OA (osteoarthritis, arthrosis deformans), like in type 2 diabetes, two risk factors play a significant role: obesity and age.[46]

Therefore, in the prevention of both disorders, the dietary treatment (to reduce the body mass), as well as physical activity are of fundamental importance. Diabetes mellitus is associated with a large variety of rheumatic manifestations.[47,48,49]

Conclusion

Diabetes mellitus accounts for a number of vascular complications, which impair patient survival. Musculoskeletal complications are also found, and, although assigned with lower importance than the vascular ones, they significantly compromise the patients' quality of life.

The musculoskeletal complications of diabetes can be manifested in different ways. They could be syndromes of the limited joint mobility, osteoporosis, diffuse idiopathic skeletal hyperostosis, neuropathies, or diabetic muscle infarction.

Most of these disorders can be diagnosed clinically, but some radiological examination may help, especially in the differential diagnosis. No specific treatment is available, and treatments used in the general population are also recommended for diabetic subjects. Infectious complications affecting the musculoskeletal system are common in diabetic patients. Many musculoskeletal manifestations are subclinical and correlated with the disease duration and its inadequate control. They should be recognized and treated properly, because their management improves the patients' quality of life.

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