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PATHOGENETIC PECULIARITIES OF DIABETES MELLITUS TYPE 2 AND PSORIASIS

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Abstract. *The article examines some aspects of the pathogenesis of diabetes mellitus (DM) and psoriasis. The author's analysis of literature data has made it possible to reveal a number of common features of these diseases. It is proved that psoriasis patients incur a much higher risk of developing DM type 2. Against a background of DM type 2 the course of psoriasis is, as a rule, more severe. Disruption of the liver enzyme function, breakdown of adaptive mechanisms and the autoimmune component are the common features of pathogenetic mechanisms in these diseases. In DM type 2, particularly at its initial stages, an abundant insulin secretion by pancreatic cells is observed. It is possible that hypersecretion of this hormone develops a higher expression of STAT3 with a resultant acceleration in keratinocyte proliferation. Taking into account that psoriasis is a dermatosis, characterized by an accelerated and distorted hyperproliferation of epidermal cells, it is possible to suppose that, against a background of coexistent DM type 2, the result of an abundant secretion of endogenous insulin is that this hormone acts as an activator of protein kinase C and STAT3. Further studies of separate links in the pathogenesis of these diseases can create necessary prerequisites for understanding mechanisms in the development of this pathology and result in the development of pathogenetically substantiated methods of treatment.*

Key words: *diabetes mellitus type 2, psoriasis, autoimmune processes, epidermal hyperproliferation.*

The study of diabetes mellitus (DM) is one of the most urgent problems in endocrinology. Experts of the World Health Organization define DM as a problem of all ages and all countries. At present, DM takes the third place among immediate causes of death after cardiovascular and oncological diseases [1]. According to literature data, up to 5 % of the world population suffer from DM. Every year the number of patients increases by 5-10 % [2, 3]. The frequent occurrence of DM, its chronic course, severe complications, early disability and high death rate present both a medical and social problem. Therefore in many countries the solution of problems, associated with this disease, is put on the state or federal level [1, 4].

In the opinion of the International Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (1997), DM is a group of metabolic disturbances, which are characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or a combination of both these factors [1]. DM is the syndrome of chronic hyperglycaemia, which develops as a result of the effects of genetic and exogenous factors, is caused by an absolute or relative insulin deficiency in the organism and characterized by disturbances in all kinds of metabolism, first of all the carbohydrate one [2].

Risk factors of the development of DM type 2 are as follows:

1. Abdominal obesity (male-type obesity).
2. Body overweight > 20 % versus the ideal one.
3. Fasting hyperglycaemia (elevation of blood glucose over 5.6 mM/l).
4. Disturbed glucose tolerance.
5. Dyslipidaemia – abnormal values of lipid metabolism:
   - triglycerides > 2.2 mM/l;
   - high-density lipoproteins < 0.8 mM/l.
6. Hereditary loading with DM in first degree relatives [1].

DM type 2 is inherited by one's both mother and father sides. The probability of the disease development is 80 %, if one of the parents is ill with DM type 2, and approaches 100 %, if both parents suffer from this disease [5].

DM may combine with metabolic syndrome, obesity and dyslipidaemia. Liver diseases are one of the most common pathologies in DM. Patients with DM type 2 reveal: disruption of the liver enzyme function, nonalcoholic fatty liver disease, liver cirrhosis, hepatocellular carcinoma, acute hepatic failure. Besides, DM types 1 and 2 may be associated with viral hepatitis [6].

A relative or absolute insulin deficiency in diabetes causes disturbances in the metabolism of glucose, fats and proteins. In DM type 2, chronic hyperglycaemia chiefly results from insulin resistance of target organs. Then it is followed by a progressing decrease of insulin excretion by the pancreas owing to the process of its exhaustion and aging. Diabetes results in involvement of the skin, kidneys, eyes,

cardiovascular and nervous systems [7]. The skin lesion in DM type 2 develops on the basis of disturbances in carbohydrate metabolism and an accumulation of relevant products of the changed metabolism. These processes, in combination with diabetic angiopathies, disorders of local] and general immunity, cause structural changes in the derma, epidermis, follicles and sweat glands [8]. It is not in rare cases that dermatological manifestations can serve as “signal signs” of the disease [9]. At present, more than 30 skin diseases are described, which precede DM type 2 or develop against its background [10, 11].

One of dermatoses, which accompany or precede the development of DM type 2, is psoriasis. During one study, whose purpose consisted in revealing relations between the general state of health and psoriasis, it was found out that female patients with psoriasis were by 63 % more predisposed to develop DM type 2 versus female patients without this dermatosis [12]. Researches, conducted in 2012 in the University of California, revealed that the risk of development of DM type 2 in patients with the moderate degree of psoriasis was 1.5 times higher than in the general population, and in patients with severe forms of psoriasis the above risk was 2 times higher [13].

DM and psoriasis have their common features. Like DM type 2, psoriasis is one of the most widespread, chronic, genetically conditioned diseases of the multifactorial nature. Approximately 2-3 % of the world population suffer from psoriasis, and its share in the total structure of skin diseases ranges within 3-15 %. According to the data of the International Federation of Psoriasis Associations, there are 125 million psoriasis patients in the world. In psoriasis, like in DM, stress is one of the causes, which provoke and aggravate the course of the disease.

At the present level of knowledge, psoriasis can be defined as genotypic dermatosis, transmitted by the dominant type with incomplete penetrance and irregular manifestations. The nature of this disease is multifactorial. Its pathogenic factors include changes in enzyme, lipid as well as, less commonly, protein and carbohydrate metabolisms, endocrine dysfunctions and functional abnormalities of the diencephalon in the form of adaptive disease, shifts in amino acid metabolism,

rather often combined with chronic tonsillitis, influenza and other infectious-allergic diseases (mainly of the strepto-staphylococcal and viral nature). The genetic apparatus of cells can be pathogenically influenced by filterable viruses with resultant violations in the control over biochemical processes. Patients with psoriasis revealed changes in the ratio of fractions of histone proteins, which take an important place in the regulation of proliferative activity and synthesis of DNA, the latter composing the major portion of chromatin [14].

Special genetic studies found out the multifactorial type of psoriasis inheritance with incomplete penetrance of genes. It has been shown that histocompatibility antigens B13 and B17 are found reliably more frequently in psoriasis patients only with skin manifestations, while B17, B27, B33 and B40 are typical for patients with skin manifestations in combination with arthritis. Besides the HLA system, another important genetic marker of psoriasis has been detected: coupling of the dominant forms of psoriasis with the distal part of chromosome 17. In psoriasis, both autosomal dominant inheritance (its probability is up to 50 %) and genetic predisposition to the appearance of the disease under effect of some factors are possible [14, 15]. The probability of this disease in a child is up to 25 %, if one of the parents suffers from psoriasis, and increases up to 75 % in case the disease has affected both parents [15].

As a rule, the course of psoriasis against a background of DM type 2 is more severe. Such forms are observed as exudative psoriasis, psoriatic erythroderma, arthropathic psoriasis, inverse psoriasis. Treatment of psoriasis patients with underlying DM is always difficult, because it is impossible to use photochemotherapy, systemic steroids, etc., in such cases [16]. DM type 2 and psoriasis are often accompanied with obesity, metabolic syndrome, dyslipidaemia, arterial hypertension, diseases of the cardiovascular system [16, 17, 18].

Prevalence of cardiovascular diseases was studied in 130,000 psoriasis patients. The study revealed that in the severe course of dermatosis arterial hypertension was in 20 % of cases (versus 11.9 % in the control group), diabetes mellitus in 7.1 % (versus 3.3 % in the control group), obesity in 20.7 % (versus

13.2 % in the control group), hyperlipidaemia in 6 % (versus 3.3 % in the control group) [19]. In psoriasis, liver pathology is rather often observed. Patients reveal phenomena of cytolysis, cholestasis, hepatocellular insufficiency as well as immune inflammations [20]. Hence liver pathology is one of the common pathogenetic mechanisms in the development of psoriasis and DM type 2 and requires correction with help of hepatoprotectors.

Those patients, who suffer from DM type 2, present complains about excessive dryness of their skin integuments and itching with different degrees of intensity. Also rather important for skin involvement is chronic hyperglycaemia. Disruption of the function and integrity of the epidermal barrier as result of the direct effect of factors of aggression on the epidermis may trigger the mechanism of hyperproliferation [21, 22, 23].

Data about the role of inflammation in the development of diseases are published with an increasing frequency in the recent time. Studies in DM and psoriasis are not exclusion. Autoimmune processes are typical for both diseases. An important part in the development of psoriasis is played by immune disorders: a higher activity of T helpers in case of a defect of T suppressors, an increased content of circulating immune complexes and higher titres of DNA autoantibodies. In psoriasis, cellular infiltrate chiefly consists of CD4+ T lymphocytes. All these data give grounds to regard psoriasis as an immunogenetic disease, where cytokines and growth factors determine the manifestation of inflammation and hyperproliferation caused by a disorder in the system of secondary messengers of cAMP/cGMP. Activated macrophages produce anti-inflammatory cytokines: tumour necrosis factor alpha (TNFα) and gamma (TNF-7), interleukins (IL-1a, IL-2, IL-6, IL-8). A key part is played by TNFα [14].

The role of cytokines in immunoregulation has been studied rather well. A relationship is found out between genetic polymorphism and mutations of cytokine receptors and components of their signal pathways on the one hand and diabetes on the other hand. Mechanisms of signal transduction of types 1 and 2 cytokine superfamilies have been studied. Studies of the signal pathways, switched on by these

receptors, have led to the discovery of the kinase signal transducer pathway (Signal Transducer and Activator of Transcription, STAT), which activates transcription. The STAT family includes seven DNA-binding proteins (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, STAT6). These proteins ensure a rapid transmission of a signal from the membrane to the nucleus for regulation of gene expression. Activated STAT factors participate in the regulation of different cell functions, including immune processes, proliferation, differentiation and apoptosis [24].

Interesting findings were obtained concerning a possible activation of STAT3 under the influence of insulin. The skin is not regarded as a classical tissue, which responds to insulin. Therefore insulin effects in the skin are usually explained by the ability of insulin to activate the heterogenous insulin-like growth factor receptor with a resultant induction of accelerated proliferation and differentiation of keratinocytes [25]. The conducted studies have made it possible to reveal that the transmission of the insulin signal and the stimulation of proliferation of keratinocytes are specifically mediated by protein kinase C (PKC). Insulin regulates phosphorylation, activation and nuclear translocation of STAT3 by specific activation of PKC [26, 27]. The fact that STAT3 knckout mice die at an early stage of their embryonic development demonstrates the vital necessity of this factor for the whole organism, whereas STAT1 knockout only reveals immunosuppression. It is important that biological effects of STAT1 and STAT3 are tissue-specific and can play exactly the opposite role in the proliferation and survival of cells [28].

In DM type 2, particularly at the initial stages of its development, an abundant insulin secretion by pancreatic cells is observed. It is possible that hypersecretion of this hormone develops a higher expression of STAT3 with a resultant acceleration in keratinocyte proliferation. Taking into account that psoriasis is a dermatosis, characterized by an accelerated and distorted hyperproliferation of epidermal cells, it is possible to suppose that, against a background of coexistent DM type 2, the result of an abundant secretion of endogenous insulin is that this hormone acts as an activator of PKC and STAT3 [29].

Our analysis of literature data has made it possible to reveal a number of common features, typical for DM and psoriasis. Further studies of separate links in the pathogenesis of these diseases can create necessary prerequisites for understanding mechanisms in the development of this pathology and result in the development of pathogenetically substantiated methods of treatment.

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Патогенетические особенности сахарного диабета 2 типа и псориаза

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Резюме. В статье рассмотрены некоторые вопросы патогенеза сахарного диабета и псориаза. Проведенный анализ литературных данных позволил выявить ряд общих черт, присущих этим заболеваниям. Доказано, что больные псориазом подвержены гораздо большему риску возникновения СД 2 типа. На фоне СД 2 типа псориаз, как правило, протекает более тяжело. Нарушение ферментообразующей функции печени, срыв адаптационных механизмов, аутоиммунный компонент являются общими чертами патогенетических механизмов при этих заболеваниях. При СД 2 типа, особенно на начальных этапах его развития, наблюдается избыточное выделение инсулина клетками

поджелудочной железы. Возможно, что в результате гиперсекреции этого гормона развивается повышенная экспрессия STAT3, что ведет к ускоренной пролиферации кератиноцитов. Учитывая, что псориаз является дерматозом, характеризующимся ускоренной извращенной гиперпролиферацией клеток эпидермиса, можно предположить, что на фоне сопутствующего СД 2 типа в результате избыточной секреции эндогенного инсулина этот гормон выступает активатором протеинкиназы С и STAT3. Дальнейшее изучение отдельных звеньев патогенеза этих заболеваний может стать предпосылкой для понимания механизмов возникновения этой патологии и привести к разработке патогенетически обусловленных методов лечения.

Ключевые слова: сахарный диабет 2 типа, псориаз, аутоиммунные процессы, гиперпролиферация эпидермиса.

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Патогенетичні особливості цукрового діабету 2 типу і псоріазу

Харьковский национальный медицинский университет, Украина

Резюме. У статті розглянуті деякі питання патогенезу цукрового діабету та псоріазу. Проведений аналіз літературних даних дозволив виявити ряд спільних рис притаманних цим захворюванням. Доведено, що хворі на псоріаз схильні до виникнення ЦД 2 типу. На тлі ЦД 2 типу псоріаз, як правило, протікає більш важко. Порушення ферментоутворюючої функції печінки, зрив адаптаційних механізмів, аутоімунний компонент є загальними рисами патогенетичних механізмів при цих захворюваннях. При ЦД 2 типу, особливо на початкових етапах його розвитку, спостерігається надлишкове виділення інсуліну клітинами підшлункової залози. Можливо, що в результаті гіперсекреції цього гормону розвивається підвищена експресія STAT3, що веде до прискореної проліферації кератиноцитів. Враховуючи, що псоріаз є дерматозом, що характеризується прискореною збоченою гіперпроліферацією клітин епідермісу, можна припустити, що на тлі супутнього ЦД 2 типу в результаті надмірної секреції ендогенного інсуліну цей гормон виступає активатором протеїнкінази С і STAT3. Подальше вивчення окремих ланок патогенезу цих захворювань може стати передумовою для розуміння механізмів виникнення цієї патології і привести до розробки патогенетично обумовлених методів лікування.

Ключові слова: цукровий діабет 2 типу, псоріаз, аутоімунні процеси, гіперпроліферація епідермісу.

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