ASSESSMENT OF THE EFFECT OF LONG-TERM GLUCOCORTICOID USE ON THE RISK OF TYPE 2 DIABETES MELLITUS IN PATIENTS WITH GOUT

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Abstract: The gout is the most common form of inflammatory arthritis, and in the United States alone it affects about 3.9% (9.2 million) of the country's population [1]. Despite the fact that the aetiology and pathogenesis of gout are well studied and there are effective drugs that allow you to fully control the disease, adherence to treatment remains unsatisfactory, and most patients do not receive adequate urate-reducing therapy [2-4]. One of the reasons for low adherence to therapy is the fear of the risk of exacerbation of gout arthritis, the likelihood of which increases when taking any urath-reducing drugs in the first months of therapy [5–7]. The appointment of preventive treatment can prevent repeated gout attacks. Such tactics of using anti-inflammatory drugs for an average of 6 months in parallel with the intake of urate-reducing therapy (UST) is proposed for practical use in patients with gout by most national and international recommendations [8][9]. The most widely used drugs for the prevention of attacks are colchicin, non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (GC) [10]. The latter are the least studied: studies on the long-term use of low doses of HA in patients with gout have not yet been conducted. While the use of a short course of GC to relieve acute attacks of gouty arthritis is considered safe and not inferior, and, according to some data exceeding NSAIDs in this regard [11-13], the data on long-term use of HA in gout are very limited and do not contain information on the safety of such therapy, including its impact on the risk of developing carbohydrate metabolism disorders in these patients [5][14].

GC began to be actively used in rheumatic diseases more than 70 years ago [15], and in diseases such as systemic lupus erythematosus, rheumatic polymyalgia and vasculitis, HC is one of the most commonly used classes of anti-inflammatory drugs and at the moment [16-19]. As a result of frequent use, the development of a number of undesirable phenomena when taking them is discussed, including an increase in the risk of developing type 2 diabetes mellitus (DM2) [19]. Since HAs reduce peripheral sensitivity to insulin, increase gluconeogenesis in the liver, causing insulin

resistance (IR) at the level of lipid metabolism and adipose tissue, as well as inhibit the production and secretion of insulin by the pancreas, they are a class of drugs with a potentially high risk of hyperglycaemia and DM2 [20-22]. Taking into account that, in general, the frequency of detection in patients with Gout 2 exceeds the population, reaching, according to some data, 29% [23][24], it can be assumed that an important role in this can be played by HA and research aimed at studying the effect of such therapy on the development of carbohydrate metabolism disorders is very important. In addition to these antibodies, in type I diabetes, other antibodies to pancreatic islet antigens are detected in the blood serum of patients: cytotoxic, to insulin, proinsulin and glutamate decarboxylase. In patients suffering from IDDM, organ-specific autoantibodies to thyroglobulin, thyroid peroxidase, gastric parietal cells, intrinsic Castle factor, adrenal cortex cells, antilymphocytotoxic, to tubulin, activin, immunoglobulins (IgG, Ab) and non-organ-specific autoantibodies are also detected in the blood serum : antinuclear, to smooth muscle fibers, fibroblasts, reticular and mitochondrial, and when treated with insulin - antibodies to exogenous insulin, glucagon, somatostatin, pancreatic polypeptide. All of these antibodies are currently considered as an epiphenomenon or as markers of IDDM. They are not involved in the mechanisms of β-cell destruction[26-31]. The following antigens were isolated in pure form from the islet and beta cells of the pancreas and identified: cytoplasmic, or ICA antigen; glutamate decarboxylase (GAD 65 and GAD 67); 38 kDa protein, secretory granule membranes; antigen 37/40 kDa, not related to GAD; carboxypeptidase H with mol. weighing 52 kDa; periphery with pier weighing 58 kDa; glucose transporter type II (GLUT-2), ICA 69 (Rgp-1); temperature shock protein (65 kDa); protein with mol. weighing 69 kDa with a cross-reaction to the ABBOS protein (a fragment of bovine albumin).A genetic predisposition to IDDM is associated (linked) with certain genes of the HLA system, whereas in NIDDM this connection is not observed. Inheritance of susceptibility to IDDM is a rather complex process, and several HLA genes are involved in the transmission of susceptibility or resistance to diabetes. Moreover, different alleles of the same gene are combined with different pathogenetic mechanisms and different haplotypes are associated with different susceptibility to IDDM. Predisposition to IDDM is combined with the following haplotypes: HLA-DR3, DQw2 (or DQBl*0201) and HLA-DR4, DQw8 (or DQB 1*0302). The clearest association of IDDM is observed with the genes of the DQAl*0501 - DQBl*0302 locus). Allele DQBl*0302 - in the 57th position of the P-chain of the DQ locus there is no aspartic acid (Asp); allele DQAl*0501 - in the 52nd position of the CC chain of the DQ locus there is an

arginine residue (Arg) [32-35]. However, there is still no consensus regarding the exclusive role of HLA genes in the predisposition to the development of diabetes mellitus. This is evidenced by numerous data that in different ethnic groups, predisposition to IDDM is combined with different haplotypes of HLA genes. For example, many authors indicate that the DR4 allele, combined with DQA 1*0301, is significantly positively associated with IDDM in many, but not all races. And in the Chinese population, this allele completely neutralizes the predisposition to diabetes. Another allele (DQB 1*0201) is positively combined in almost all populations, with the exception of the Japanese. This suggests that the predisposition to IDDM, combined with certain HLA genes, is complex[35-37].

Purpose: To assess the effect of long-term intake of low doses of HA on the risk of developing DM2 in patients with gout.

Materials and methods: 317 out of 444 patients with gout and lack of DM2 who participated in a prospective study to study the risk factors of DM2 were included. The sample did not include patients who used HC during the observation to stop an acute attack of arthritis, regardless of the method of their use (n=88), and who did not complete the study (n=39). The remaining patients were retrospectively divided into 2 groups: those who continuously took ≥180 days of prednisolone at a dose of 5-10 mg/day and did not use HC during the observation period. The planned visits were held at least once every 2 years. During the 1st visit, patients were prescribed or corrected for urate-reducing and preventive anti-inflammatory therapy, including low doses of HA. The primary end point is the development of DM2, the indicators of carbohydrate metabolism (levels of glycated haemoglobin (HbA1c), serum glucose level) were compared initially and at the end of the study.

Study results: 76 (24%) of 317 gout patients continuously took prednisolone at a dose of 5-10 mg/day for ≥180 days, 241 (76%) patients did not receive HC for the entire period of follow-up. The average dose of prednisolone in patients of the main group is 7.9±1.2 mg/day, the duration of administration is 206.3±20.4 days.

SD2 developed during the observation in 20% of the main group and in 22% of the comparison group (p=0.73). Patients who took HC were older than those who did not take HC (p=0.01), they were more likely to have chronic heart failure (p=0.04). There were no reliable differences between the groups for the other parameters to be compared. Patients receiving low doses of HA had a significant increase in the average level of HbA1c (p=0.002); an increase in the number of patients with glucose levels ≥6.1 mmol/l (p=0.004) by the end of the study relative to the initial level. The initial level of HbA1c in patients with developed DM2 was expected to be higher,

smokers were more common among them (p=0.01), they had a higher level of serum uric acid (p=0.001). The prevalence of other MD risk factors in those who developed and did not develop DM2 did not differ significantly.

Conclusion: Long-term intake of low doses of HA in patients with gout significantly does not increase the risk of developing DM2, but may have a negative effect on carbohydrate metabolism.

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