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TUBULOINTERSTITIAL SYNDROME IN THE EARLY PERIOD OF ALLOXAN-INDUCED EXPERIMENTAL DIABETES

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Adequate assessment of the functional renal state, especially in the case of early diagnosis of its disorders, requires an analysis not only of the glomerular apparatus of the kidney, but also of the condition of tubulointerstitial tissue (TIT) known to be involved in the pathological process in the kidneys much earlier than glomerular apparatus, and, consequently, the relatively preserved glomerular structure, however, does not ensure the normal functioning of the nephron. Among the known markers of TIT damage, one of the most important elements that reflects its function is sodium metabolism. Disorders of tubular sodium transport, its retention in the body and accumulation in renal structures lead to changes in local hemodynamics in the kidneys, hydrophilicity of renal tissue, disturbance of the water-osmotic balance and, consequently, to the defeat of TIT and progressive decline of renal function.

Considering the importance of timely diagnosis of tubulo-interstitial syndrome, its character, severity of TIT lesions for prediction of renal impairment progression intensity in clinical and experimental studies, the objective of this research was to clarify the peculiarities of tubulointerstitialsyndrome (TIS) in the early period of alloxan-induced experimental diabetes mellitus (EDM) known to be accompanied by the pathology of the interstitium, tubular-interstitial dysfunction.

The experiments were carried out on 18 white non-linear mature male rats. Experimental modeling of DM was performed by the intraperitoneal administration of *Alloxan monohydrate* to 8 animals in a diabetogenic dose of 160 mg/kg. On the 11th day after the induction of experimental diabetes mellitus in white non-linear male rats the kidneys of diabetic and control animals were removed, dissected to renal cortex, medulla and papilla for further measurement of tissue sodium content and calculation of papillary-cortical, papillary-medullar and medullary-cortical osmotic concentration sodium gradients.

The results of the investigation demonstrated a decrease of sodium concentration in all layers of the diabetic kidney, mainly in the renal papilla. The sodium content in the renal cortex of experimental animals was decreased by 54,0% ($P<0,001$), in the renal medulla – by 13,7% ($P<0,01$) and in the renal papilla its concentration was found to be 2,3-times less than control level ($P<0,001$). This significant decrease of sodium content in the renal tissue in experimental animals was accompanied by a reliable decline of osmotic concentration sodium papillary-medullar gradient (by 49,7%, $P<0,001$), a 2-fold increase of medullary-cortical gradient ($P<0,001$) and practically unchanged papillary-cortical gradient (by 2,5%, $P>0,3$) as compared to the control indices.

The detected changes of papillary-cortical, papillary-medullar and medullary-cortical osmotic concentration sodium gradients are indicative of the inhibition of proximal tubular sodium reabsorption and, despite regulatory control of the renal countercurrent multiplication system and intensification of sodium reabsorption at the level of the ascending Henle loop, excretion of urine with high osmolarity and significant sodium loss from the body.

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EFFECT OF MYO-INOSITOL AND CHOLECALCIFEROL ON THYROID FUNCTION AND AUTOIMMUNITY IN PATIENTS WITH SUBCLINICAL HYPOTHYROIDISM

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In the absence of large randomized trials showing benefit from levothyroxine therapy, the rationale for treatment is based on the potential for decreasing the risk of adverse cardiovascular events and the possibility of preventing progression to overt hypothyroidism. Myo-inositol is the precursor of the synthesis of phosphoinositides, which are part of the phosphatidylinositol signal transduction pathway across the plasma membrane, via the second messenger 1,4,5-triphosphate

that modulates intracellular Ca^{2+} release. Therefore, it acts as a second messenger regulating the activities of several hormones, such as insulin, follicle-stimulating hormone, and thyroid-stimulating hormone (TSH).

The aim of the present study was to evaluate effect of cholecalciferol and myo-inositol on thyroid function and autoimmunity in patients with subclinical hypothyroidism.

68 patients with subclinical hypothyroidism (TSH between 4.5 and 8.0 mcIU/ml) were involved in this observational and retrospective study. They were meeting the inclusion criteria as follows: age range 20–65, elevated serum thyroid peroxidase antibodies (TPO Ab) and/or thyroglobulin antibodies (Tg Ab), and normal free thyroxine (fT_4) and free triiodothyronine (fT_3) levels. A complete thyroid assessment was evaluated in patients at baseline and after 3 months of treatment. Patients were divided into three groups: untreated (n=20), treated with cholecalciferol 4000 IU/day (n=25) and treated with myo-inositol 2000 mg/day (n=23) during 3 months. Ultrasound of the thyroid gland was performed to evaluate changes in thyroid echoic pattern during the study.

Compared to baseline, levels of TSH significantly declined (5.14±0.83, vs. 3.91±1.17, mcIU/ml, respectively; p=0.003), in patients treated with myo-inositol and in 39.1% of cases it reached the normal range. After the treatment, antithyroid autoantibodies levels decreased by 31% and 39%, respectively, in those treated with cholecalciferol and myo-inositol. There were significant decrements in both autoantibodies Tg Ab and TPO Ab serum levels after administration of mio-inositol: Tg Ab levels decreased from 438.9 ± 21.8 IU/ml to 261.4 ± 22.3 IU/ml after treatment ($p \leq 0.01$) and TPO Ab from 769.6 ± 41.9 IU/ml to 472.3 ± 37.8 IU/ml, pre- and post- mio-inositol treatment, respectively ($p \leq 0.002$). The serum fT_3 and fT_4 levels of patients were slightly but significantly higher at the end of 3-month period when compared with the values at baseline: fT_3 values were 2.63 ± 0.03 pg/ml at baseline and 2.71 ± 0.02 pg/ml posttreatment ($p \leq 0.05$) and fT_4 levels were 0.93 ± 0.02 ng/ml and 1.06 ± 0.02 ng/ml ($p \leq 0.05$) pre- and posttreatment, respectively. Analysis of thyroid ultrasonography showed an echoic pattern improvement in both treated groups compared to untreated patients, although this difference was not statistically significant.

Myo-inositol and cholecalciferol treatment are effective in patients with subclinical hypothyroidism. The results of the present study show an improvement of thyroid function in patients with subclinical hypothyroidism. Thus, myo-inositol treatment is effective in patients with subclinical hypothyroidism and its effect may be improved in combination with cholecalciferol through earlier achievement of TSH levels closer to physiological concentrations.

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THE ROLE OF PERFORIN/GRANZYME-INDUCED APOPTOSIS IN THE DEVELOPMENT OF COGNITIVE IMPAIRMENT IN DIABETES MELLITUS

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Diabetes mellitus is recognized as an independent factor of cognitive impairment. The risk of dementia in patients with type 2 diabetes increases almost twice. The results of epidemiological, visualization and autopsy studies showed the presence of both cerebrovascular and neurodegenerative mechanisms of brain lesions. Cell death of key substrates – neurons and endothelial cells lays in the basis of cerebral disorders. Granzyme B is a serine protease, which exerts both intracellular apoptotic and extracellular functions, leading to tissue injury and inflammation.

The purpose of the study was to find out role of the granzyme-induced mechanisms of programmed cell death in the development of cognitive impairment in patients with type 2 diabetes.

There were examined 70 type 2 diabetes patients and cognitive impairment and 26 sex, age and body mass index comparable non-diabetic subjects as control group. Patients were classified using neuropsychological assessment tests. The Mini-mental State Examination (MMSE) test, Montreal Cognitive Assessment (MoCA) test and the determination of cognitive-induced potentials