

Backgrounds

Deficiency of thyroid hormones is accompanied by malfunction of metabolic processes followed by the development of changes with various stages of manifestation in all organs and systems, including sufficient changes in renal function. Nowadays, the issue of relation between thyroid functional state and kidneys has not been studied well and is a subject matter of numerous publications revealing various pathophysiological concepts. Changes in renal functions resulting from deficiency of thyroid hormones are characterized by decreased renal blood flow and glomerular filtration rate (GFR), abnormal concentrative function in distal canals and poor excretion of acid by kidneys. According to some authors, renal malfunction in patients with manifested hypothyroidism is caused by such nonimmune factors as high levels of total cholesterol, arterial hypertension, glomerular hypertension. Since the leading cause of the development of manifested hypothyroidism is chronic autoimmune thyroiditis (AIT), the influence of immune factors leading to renal dysfunction in patients with hypothyroidism is of great interest; however, this subject hasn't been studied to the fullest extent. Recently, the role of monocyte chemoattractant protein (MCP-1) in the development of nephropathies has been actively studied. It should be noted that increased glomerular expression of MCP-1 has been revealed in different nephropathies. Specifically, the latest investigations revealed that secretion of MCP-1 is raised in case of lupus-nephritis, various forms of glomerulonephritis and renal insufficiency. F. Chiarelli states that biosynthesis of MCP-1 in renal pathology is considerably high under the influence of proinflammatory interleukins, which in its turn causes monocyte infiltration of glomeruli. Investigation of MCP-1 in case of renal pathology proves its important role in inflammatory reactions and progress of renal malfunction, but scientific research base is limited. There are rare studies of MCP-1 concerning the evaluation of its clinical significance in patients with diabetes. As far as the influence of this mediator on the development of renal dysfunction in patients with primary hypothyroidism is concerned, such investigations are scarce in available literature and

data which they represent are quite contradictory. Thus, study of MCP-1 contents in patients with different causes of primary hypothyroidism, on one hand, will enrich current knowledge of the development of pathophysiological mechanisms of this disorder, and on the other hand, it has a scientific and practical significance as it will allow to manage the treatment plan and to make prognosis of the pathological process progress.

Taking into account everything mentioned above, **the aim** of the article was to determine the contents of MCP-1 in the urine of patients with primary hypothyroidism.

Materials and methods

The investigation involved 141 patients with manifested hypothyroidism, registered at the endocrinology dispensary of the disease in polyclinics of Ivano-Frankivsk, as well as in the endocrinology department in Ivano-Frankivsk regional clinical hospital. The average age of patients was 56 ± 8 ; and the duration of officially confirmed anamnesis of hypothyroidism was 2.8 (1.8; 4.9) years. The control group involved 20 people having none thyroid pathology, 9 men and 11 women among them. To achieve our goal, the presence and stage of manifestation of renal malfunction was evaluated, as well as the relation between found data and MCP-1 levels in patients with hypothyroidism in comparison to control group consisting of people without any thyroid pathology was estimated. Criteria of inclusion to the research were: previously confirmed diagnosis of hypothyroidism (primary or decompensated primary hypothyroidism) – with TSH level exceeding the uppermost margin of referent scale (4.0 mmol/L) and decreased levels of T_4 ($<10.3 \text{ pmol/l}$) and T_3 ($<2.3 \text{ pmol/l}$); patient's consent to participate in the experiment. Criteria of exclusion from the research were: disorders in cerebral circulation in anamnesis; ischemic cardiac disease (according to anamnesis and examination that included electrocardiogram, echocardiogram and revealed symptoms of circulatory insufficiency); arterial hypertension exceeding stage 1; chronic diseases of

cardiovascular system with developed circulatory insufficiency that exceeds functional class II according to NYHA classification; any chronic renal disorder in anamnesis; chronic liver diseases; oncological diseases; chronic diseases with allergic component in its genesis (bronchial asthma, etc.); autoimmune disorders (except AIT); acute inflammatory and/or aggravation of chronic inflammatory disorder; pregnancy; use of hypolipidemic preparations; mental disorders; other endocrine disorders. Complex laboratory and instrumental investigation of renal function included clinical, laboratory, and instrumental examination, as well as a special method – defining the level of monocyte chemoattractant protein-1 in urine. All patients underwent complex clinical examination, their body weight index (BWI) was measured, levels of urea, creatinine and total protein were defined. Kidney damage was confirmed on the basis of disorder of glomerular filtration, i.e. presence of albuminuria and index of GFR estimated by the formula CKD-EPI. Levels of thyroid hormones (free T₄ and free T₃) and TSH were determined at immunologic laboratory in the regional clinical hospital with the use of StatFax 303 analyzer and a set of DRG reagents (USA). Microalbuminuria was defined with the help of «Microalbumin» test strips («Cormay», Poland). MCP-1 concentration was estimated with the help of immunoenzymometric analysis by means of test system manufactured by Bender MedSystem (Austria). Ultrasonic scanning of the organs of genitourinary system was performed. To estimate renal vascular flow ultrasonic dopplerography of renal vessels was made; attention was paid to the vascular size and permeability, inner vascular changes and perivascular tissue condition. To evaluate the effect of autoimmune process in the thyroid gland as well as BWI on the stage of manifestation of renal malfunction and production of MCP-1, patients were grouped into: IA group which involved 35 patients with hypothyroidism resulting from AIT without obesity; IB group that included 35 patients suffering from AIT accompanied by hypothyroidism and obesity; IIA group that encompassed 34 patients with postoperative hypothyroidism without obesity; and IIB group involving patients with postoperative hypothyroidism accompanied by obesity, n=37.

Statistical analysis was made by means of variable-based statistical method. Analyzing the material, mean quantities (M), their standard errors (m) and confidence interval were estimated. Probability of differences was evaluated according to Student's t-criterion for dependent and independent sampling, in case of clustering nonparametric Mann-Whitney (U) and Wilkonson (W) criteria were used. Differences were considered statistically significant at $p < 0.05$. Dependence of indices was evaluated by means of estimation of correlation coefficient according to Spearman method. Statistical study of the material was made on the ground of variable-based and descriptive statistics by means of a standard set of statistical calculations Statistica 6.0, Foxbase, Exel 6.0 on the personal computer Pentium III.

Results

According to the findings of the research MCP-1 levels in the urine of patients with manifested hypothyroidism has proved to be significantly higher. Thus, considerably increased level of this mediator in comparison to control group has been revealed in patients with hypothyroidism resulting from AIT without obesity; it has reached 174.42 ± 4.21 pg/ml, while patients with hypothyroidism resulting from AIT accompanied by obesity have showed 190.36 ± 3.69 pg/ml. Significantly raised levels of chemokine has also been observed in the group of patients with postoperative hypothyroidism: 143.15 ± 2.25 pg/ml in patients without excessive weight and nearly 167.34 ± 3.85 pg/ml in obese patients with postoperative hypothyroidism. The mid-point of given index has exceeded the uppermost margin of referent interval for normal MCP-1 levels, which is 0-139 pg/ml. Increased levels of MCP-1 has proved the presence of active inflammatory response in the group of patients with manifested hypothyroidism and activation of monocyte sector of immunity, especially in patients with AIT. Moreover, significantly higher MCP-1 levels may be caused by such factors as hypertension, proteinuria and azotemia. Our research has revealed a direct mean stable correlation between MCP-1 levels and thyroid stimulating hormone in patients' blood serum, direct correlation between blood creatinine levels and albuminuria as well as reverse mean stable correlation between glomerular filtration

rate and MCP-1 concentration. Such relationships prove that the level of the latter reflects to some extent the functional state of kidney and may be applied additionally to conventional methods of patients' examination. Our findings prove the data according to which production of MCP-1 is increased in patients with noncompensated hypothyroidism. Generally, review of references has showed that data on the effects of MCP-1 in case of hypothyroidism are quite scarce and most works have rather experimental character. Thus, grounds have been given to include the examination of urinary excretion of MCP-1 to the complex of diagnostic procedures for patients with manifested hypothyroidism. It has been found that manifested hypothyroidism is characterized by chronic renal inflammation of low intensity, higher concentration of MCP-1 in urine being its marker. Quantitative measurements of monocyte chemoattractant protein-1 in urine is noninvasive indication that replacement therapy of manifested hypothyroidism is adequate.

Conclusions

Patients with manifested hypothyroidism have higher levels of monocyte chemoattractant protein-1. The relationship between hyperproduction of monocyte chemoattractant protein-1 and TSH levels, as well as renal malfunction with the highest level of manifestation in case of noncompensated hypothyroidism on the ground of autoimmune thyroiditis has been defined.