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Pathogenetic aspects of renal dysfunction in patients with primary hypothyroidism

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Abstract
In order to investigate the peculiarities of renal function in patients with hypothyroidism, 152 people suffering from primary hypothyroidism were examined. Findings showed that patients with manifested hypothyroidism had renal malfunction marked by increased levels of creatinine and decreased rate of glomerular filtration (RGF), caused by such risk factors as hyperleptinemia, dyslipidemia, overweight and abdominal obesity. It was stated that higher indices of dyslipidemia were associated with highly manifested abdominal obesity defined by waist circumference (WC) ((96.58±1.70) and (98.73±3.35) cm), as well as with higher index of body weight (IBW).

Keywords: hypothyroidism, renal function, abdominal obesity, leptin, dyslipidemia.

1. Introduction
Hypothyroidism belongs to those diseases that contribute to the development of atherosclerosis, dyslipidemia, arterial hypertension (AH), abdominal obesity, endothelial dysfunction and cardio-vascular complications [3]. In recent years the rate of hypothyroidism in Ukraine has doubled. The incidence of manifested hypothyroidism of the whole population in the world has reached 2-3% of cases, while subclinical hypothyroidism (SH) in women of any age has made up approximately 10%, and in those aged over 60 the incidence has increased to 20%. Against the background of hypothyroidism renal function worsens secondarily involving heterogeneous mechanisms among which hemodynamic disorders such as negative inotropic effect on the heart, decrease in circulating blood volume, increase of general peripheral vascular resistance accompanied by renal vasoconstriction are predominant. Primary hypothyroidism is also related to abnormal glomerular filtration which is reversible with the use of hormone replacement therapy in nearly 55% of cases [4, 5]. On the other hand, even slight decrease of renal function is associated with high cardio-vascular risk that grows inversely to the rate of glomerular filtration (RGF). In case of hypothyroidism abnormal glomerular function (decreased rate of glomerular filtration) and slow rate of very low-density lipoprotein cholesterol (VLDL cholesterol) clearance contributes to the development of dyslipidemia [7, 8]. It has been recently revealed that hormone replacement therapy of subclinical hypothyroidism prevents the progress of renal failure and favors the enhancement of renal function [6]. Simultaneously, other scientists state that typical signs of both manifested and subclinical hypothyroidism are rather evident abdominal obesity associated with pro-atherogenic changes of lipid metabolism (increase of total cholesterol level and VLDL cholesterol) and generation of insulin resistance owing to hyperinsulinemia [7]. Recently much attention has been paid to the study of the role of adiponectins especially leptin in the regulation of metabolism in patients with low thyroid level. Higher leptin level is considered to be one of the prognostic risk factors of developing cardio-vascular complications [3]. However, some data have been found stating that leptin has harmful effect on the structure and function of the kidneys [13]. Thus, during the experiment it was demonstrated that introduction of recombinant leptin stimulates proliferation of the epithelium in glomeruli and increases expression of informational riziform TGF-β1 and its production. J. Chdek and co-authors [7] demonstrated that exogenous leptin injected during some weeks considerably increases production of I and IV types of collagen, causing the development of glomerulosclerosis and proteinuria even if the arterial pressure is normal. Besides, mediated effect of leptin on kidneys has been described.
The goal of the investigation is to study the correlation between leptin and renal malfunction in patients with primary hypothyroidism.

2. Materials and methods

Patients' clinical and functional biochemical examination was performed on the basis of the Department of endocrinology, dispensary department of endocrinology in Ivano-Frankivsk regional hospital.

152 patients suffering from primary hypothyroidism took part in the investigation. Criteria of choice were as follows: patients' age from 36 to 60 and presence of primary hypothyroidism or decompensated hypothyroidism. Presence of any acute or chronic renal disease or ischemic heart disease was the criteria of exclusion. The diagnosis was made on the basis of complaints, family history, typical clinical sign of manifested hypothyroidism and was confirmed by the results of hormonal analyses. Comparison group encompassed 22 persons who didn't have problems with their thyroid function and were of the same age and sex.

All patients underwent complex clinical examination, their waist circumference (WC)(cm), body weight index (BWI), levels of urea, creatinine and general protein were measured. Kidney damage was confirmed on the basis of abnormal penetration in the glomerulus, i.e. presence of albuminuria and indices of RGF, received according to CKD-EPI formulas. Thyroid level (T_4 and T_3) as well as thyroid stimulating hormone (TSH) were measured in the immunologic laboratory of the regional clinical hospital using analyzer StatFax 303 and the set of reagents DRG (USA). Complete cholesterol level and thyroglobulin were identified according to fermentation method using *Human* reagents, LDL cholesterol was measured with Diakon-DC reagents using Accept-200 analyzer. Very low-density lipoprotein cholesterol (VLDL cholesterol) in blood was measured according to the following mathematic formula: VLDL cholesterol= thyroglobulin/2,2 mmol/L, and low-density lipoprotein cholesterol (LDL cholesterol) using the formula: LDL cholesterol=complete cholesterol – (HDL cholesterol + thyroglobulin/2,2) mmol/L. Besides atherogenicity coefficient (AC) was calculated by the following formula: AC=(cholesterol - HDL cholesterol)/ HDL. Contents of leptin (norm being 3.7-11.1 ng/ml) was identified using "Diagnostics Biochem Canada Inc" set.

Compulsory instrumental examination included measuring blood pressure, ultrasound sonography of the abdominal cavity and Doppler sonography of the renal blood flow. Statistic analysis was carried out according to the variational statistic method. Analyzing the mean values (M), their standard estimated faulty proportion (m) and confidence interval were estimated. The possibility of difference was measured according to Student-t criterion for dependent and independent samples, in case of clustering distribution-free tests of Mann-Whitney (U), Wilkonson (W) were applied. Statistic difference was considered acceptable in case of $p<0,05$. Dependent samples were estimated by Spearman's method involving calculation of correlation coefficient. Statistic study of the material was made according to variational and descriptive statistics with the help of standard program of statistic calculations, such as Statistica 6.0, Foxbase, Exel 6.0 on Pentium III.

3. Results and discussion

Presence of metabolic, intercurrent and hemodynamic risk factors contributes to the development and progress of renal malfunction if thyroid hormonal deficiency is present. Among 152 examined patients, 47.4% didn't have problems with kidneys. Barrier malfunction was found in 52.6% of patients. Early stage of nephropathy (hyperfiltration without albuminuria) was found in 24% of patients. According to the classification of chronic renal disease, 20% of patients revealed stage 1.17% - stage 2 and 3% - stage 3.

It was discovered that in patients with hypothyroidism the frequency of albuminuria occurrence depends on the duration of a disease and varies from 16.7% to 5.6%. In case of hypothyroidism lasting five years the risk of albuminuria development is twice more than in patients suffering from the same disease during one year. Simultaneously, the duration of hypothyroidism persisting over five years triples the chance of albuminuria incidence in comparison to the patients suffering from hypothyroidism less than one year.

We have established a certain relation between the duration of the course of hypothyroidism and frequency of albuminuria occurrence. Thus, comparing frequency of albuminuria in patients suffering from hypothyroidism nearly one year and in those suffering from it from one to five years $p=0.04$, and comparing patients with hypothyroidism that started nearly one year ago and patients with the disease lasting for more than five years $p=0.025$.

Patients diagnosed with abnormal renal function were divided into four groups taking into account their body weight index (BWI), since this factor has a significant effect on changes in mentioned above parameters. Patients with hypothyroidism on the basis of Hashimoto thyroiditis with BWI< 24.9 kg/m² and BWI>25 kg/m² were included to IA and IB groups correspondingly. Group II A and II B encompassed patients with postoperative hypothyroidism (PH) with BWI< 24.9 kg/m² and BWI>25 kg/m² correspondingly.

The urea levels in blood serum in groups involving patients with Hashimoto disease statistically exceeded the data received in the control group ($p<0,001$); similar tendency was observed in the group of patients with PH. In this respect the median of this index exceeded the upper limit of the corresponding referent interval (8.3 mmol/L for urea). Having compared these groups the significant difference was not found.

Although the creatinine level in blood serum was within a normal range of referent interval (97 micromole/l in men and 80 micromole/l in women), statistically significant differences were found between the group of patients with Hashimoto thyroiditis and control group: 81.88±4.16 and 62.81±1.74 micromole/l ($p<0,001$); 85.79±0,16 and 62.81±1.74 micromole/l ($p<0,001$) in group II B. Similar changes were observed in the group of patients with PH as compared to control group: 83.16±5.86 and 62.81±1.74 micromole/l ($p<0,001$) in group II A; 84.91±4.85 in group II B. Moreover, three patients from the group with Hashimoto thyroiditis had their creatinine level exceeding 120 micromole/l, and two patients from the group with PH had it higher than 115 micromole/l. At the same time, calculating RGF by CKD-EPI formula considering sex and age, its value was found to be quite low (77.99±2.18) and essentially differed from the data received in the control group: 107.03±1.72 ml/min/1, 73m²; ($p<0,001$). Patients with PH and excessive body weight showed much lower RGF in comparison to control group ($p<0,001$).

Evaluating the leptin level it was noted that the bigger body weight patients with hypothyroidism had (as a result of both Hashimoto thyroiditis and PH), the higher concentration of leptin in blood serum was revealed. Thus, patients with hypothyroidism and Hashimoto thyroiditis had leptin level two times higher in the group with BWI > 24.9 kg/m² than in the group with BWI < 24.9 kg/m², and in the group of patients

with PH this level is three times higher. Hyperleptinemia is closely related to anthropometric indices and functional parameters of kidneys. The most distinct reverse contact was traced between leptin and RGF and direct contact – among waist circumference, thigh circumference, BWI and albumin secretion.

During ultrasound sonography of kidneys and ultrasound Doppler sonography of renal blood flow no pathology was revealed.

At the baseline a median of TSH was 8.6 mmol/L, which confirms the fact that nearly 20% of patients with hypothyroidism undergoing L T4 therapy had subclinical or even manifested hypothyroidism, i.e. they received inadequately low doses of L T4 for some reason. Having estimated lipidogram, most patients revealed dyslipidemia (79% according to thyroglobulin level and 76% according to high density lipoproteins (HDL) indices). Evaluation of the contents of total cholesterol (referent interval 3.63-5.2 mmol/L) showed its significant increase in all patients in comparison to healthy people. In both groups the median of this index exceeded the upper limit of a corresponding referent interval. Similar tendency was observed in groups of patients with hypothyroidism against the background of Hashimoto thyroiditis and PH while comparing low density lipoproteins (LDL): 2.95±0.46 and 2.82±0.21 mmol/L. Similar distribution of total cholesterol levels and LDL coincides with the data in literature describing frequent incidences of dyslipidemia in people suffering from primary hypothyroidism. Generally, increase in HDL cholesterol level was present both in groups with BWI < 24.9 kg/m^2 and BWI >25 kg/m^2. Analyzing findings of patients with hypothyroidism considering BWI, changes in lipid metabolism were found in groups of patients with excessive body weight suffering from both Hashimoto thyroiditis and PH. However, subgroup I B showed more significant data of dyslipidemia, associated with characteristic manifestation of abdominal obesity and waist circumference ((96.58±1.70) and (95,65±2,85), higher BWI (33.54±0.96) kg/m²) and (29,21±1,95) that corresponds to I stage obesity, as well as the highest leptin level. Correlation, that we established, confirms that hypothyroidism effects lipid metabolism, and increased BWI and hyperleptinemia aggravate the course of the disease.

4. Conclusion

According to our findings, patients with manifested hypothyroidism have revealed renal malfunction, predisposed by such risk factor as hyperlipidemia, hyperleptinemia, overweight and abdominal obesity. Examination of the thyroid gland is recommended for early diagnosis of patients with renal malfunction of unknown etiology, considering manifested hypothyroidism to be one of the possible causes.

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