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## Influence of certain components of metabolic syndrome on renal function in hypothyroidism (literature review)

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**Abstract.** *The article deals with the influence of certain components of the metabolic syndrome, such as arterial hypertension, obesity and dyslipidemia, on renal function in hypothyroidism, causal relationship between these components and hypothyroidism and renal dysfunction. It has been shown that arterial hypertension, abdominal obesity, hyperleptinemia and dyslipidemia are independent risk factors for renal dysfunction in hypothyroidism.*

**Keywords:** *hypothyroidism; arterial hypertension; obesity; leptin; dyslipidemia; chronic kidney disease; review*

International research proves that diabetes mellitus, arterial hypertension (AH), obesity and dyslipidemia, i.e. major components of metabolic syndrome (MS), constitute an independent risk factor not only for the development of cardiovascular diseases, but also of chronic kidney disease (CKD) [1–3].

Negative influence of MS components on the functional state of kidneys is manifested at various stages: from the development of albuminuria — to progressive decrease of glomerular filtration rate (GFR), including administration of dialysis and kidney transplantation [4]. At the same time, manifestations of CKD, in addition to albuminuria and decrease in GFR, include AH and dyslipidemia, which significantly impairs the prognosis of such patients.

CKD is treated as a disease characterized by prolonged (at least three months) structural and/or functional renal changes according to clinical, laboratory, instrumental and morphological investigations, which give grounds for eliminating the acute nature of the pathological process in kidneys [5, 6].

CKD is identified as a risk factor for cardiovascular events; for example — the risk of cardiovascular mortality is 6 times higher with albuminuria threshold exceeding 300 mg/day and 5 times higher if GFR decreases to less than 70 ml/min. Therefore, experts recommend to consider CKD an independent factor of cardiovascular complications and cardiac death [7].

Stages of CKD are determined according to the level of GFR, rather than that of creatinine, since blood cre-

atinine begins to increase when GFR is half less than its normal value, i.e. hypercreatinemia is observed in case when more than 50 % of nephrons are inactive [6]. Very high concentrations of creatinine in combination with low GFR are independently associated with mortality from all causes, while an isolated reduction of GFR is associated with death caused by cardiovascular disease [5]. In order to calculate GFR, Cockcroft-Gault formula and MDRD (Modification of Diet in Renal Disease) are commonly used; they are easy to apply and validate according to standard methods for GFR evaluation. Common disadvantage of the mentioned above formulas is their inaccuracy in normal or slightly lowered GFR values. CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration), a newly developed formula, which provides more accurate results, even with preserved kidney function, has been developed [5, 8].

Cystatin C measurement as a confirmatory test for the diagnosis of CKD in adult patients with reduced GFR, measured by the level of creatinine, is recommended by the work group KDIGO CKD [8, 9]. Cystatin C is a non-glycosylated protein inhibiting cysteine proteinases [10, 11]. It is formed in the body at a constant rate, is freely filtered through the glomerular membrane, and then it is completely reabsorbed by proximal tubules without further secretion [12]. Cystatin is less dependent on age, sex, race, muscle mass, drug therapy, physical activity, and diet as compared to creatinine. These enumerated properties have made it almost an ideal candidate for assessing kidney function. Trials on humans and ani-

mals have proved that, as a rule, cystatin C levels have a tendency opposite to those of serum creatinine [13, 14]. With hypothyroidism, reduction of cystatin C level due to its lower production and further decrease in the intensity of cellular metabolism, is observed. However, there is an assumption that thyroid hormones directly affect the synthesis of cystatin C, although the exact mechanism of this action is still unknown. Thus, presented facts about the variability of this marker indicate that cystatin C cannot be used for the evaluation of GFR in patients with thyroid diseases [15, 16].

No doubt that AH plays a leading role in the development of CKD of any genesis. Moreover, there is no fundamental difference whether AH is a separate disease, associated with the pathology of the kidneys, or is the result of nephropathy [17].

Hypertension accompanying hypothyroidism develops primarily as a result of increased peripheral vascular resistance, which is a compensatory response to the decreased total diameter of the vasculature due to a decreased cardiac output, circulating blood volume, as well as the result of mucoid edema of small vessels and reduced arterial elasticity. N.B. Zelinska [18] indicates such peculiarity of hypertension accompanying hypothyroidism as growth of diastolic blood pressure and pulmonary arterial pressure, which occurs in case of mild and moderate severity of the disease, and increase of systolic blood pressure is observed only with AH development to hypothyroidism or in patients over the age of 50. Since the highest prevalence of AH and hypothyroidism has been observed in the age group over 50, the problem of combining AH and hypothyroidism, especially in patients of older age groups, is of paramount importance nowadays.

Although most researchers consider hypertension a disease which develops regardless of the presence of hypothyroidism, all of them confirm a positive effect of substitution therapy with thyroid hormonal preparations on the level of blood pressure (BP) [19, 20]. However, there are studies that show persisting hypertension in 50 % of patients and lack of normalization of hemodynamic disorders, even after achieving a euthyroid condition. This is due to the disorder of elastic properties of the aorta and large arteries with the development of rigidity in case of hypothyroidism.

A number of authors describe significantly higher values of systolic BP, diastolic BP, pulse BP in patients with hypothyroidism with obesity than in non-obese patients. Authors [18, 21] correlate such increase of blood pressure in patients with hypothyroidism and obesity with their inherent insulin resistance and hyperinsulinism. These changes increase the peripheral vascular resistance with further growing risk of disorders associated with insulin resistance.

In addition, prolonged increase of BP causes hypertensive changes in intrarenal arteries, their sclerosis and gyalinosis, which leads to ischemia of glomeruli and nephroangiosclerosis. But even before the manifestation of first morphological signs of renal vascular damage, high BP causes growth of intraglomerular transcapsillary pressure and leads to intraglomerular hypertension,

which contributes to the development of glomerulosclerosis [22].

Numerous clinical studies show that accelerated CKD progression is influenced by AH. MDRD (Modified Diet and Renal Disease) research has stated that patients, who have managed to achieve appropriate low blood pressure values, have lower rate of glomerular filtration (especially patients with high proteinuria levels). BP is considered an important determinant of renal damage progression, both in early and late stages of CKD.

Obesity is one of the main problems of modern society [23–26]. Epidemics of obesity spreads in parallel with the increase of incidences of CKD [21, 27–31].

Hypothyroidism is traditionally referred to a condition associated with an increase in body weight. Up to 54 % of patients with primary hypothyroidism report gain of body weight. In this case, primary hypothyroidism is found in 11.8 % of patients with morbid obesity, and increase of TSH levels to the subclinical level is observed in 7.7 %. The cohort study of Norwegian Nord-Trandelag (15 020 euthyroid patients monitored for 10.5 years) demonstrated a relationship between thyroid condition, body weight, and body mass index (BMI). It has been revealed that increase of TSH by 1 mIU/l in women is accompanied by body weight gain by 0.9 kg, and BMI increase by 0.3 kg/m<sup>2</sup>, while in men — by 0.8 kg and 0.2 kg/m<sup>2</sup>, respectively.

A number of studies have proved that expression of the thyroid receptor  $\alpha$  and  $\alpha 1$  is increased in the subcutaneous fatty tissue in comparison to visceral one in obese patients, and expression of TSH receptor in the subcutaneous fatty tissue correlates with BMI [32, 33].

Recent studies indicate that excessive body weight and obesity are independent predictors of CKD development and end-stage of renal diseases (ESRD) [25, 26, 31]. Particular attention is drawn to cardio-renal syndrome, which is frequently manifested by involvement of kidneys in the pathological process at the background of primary heart and circulatory diseases and is one of the causes of chronic renal failure [31].

The effects of excessive body weight on the functional state of kidneys are treated ambiguously nowadays. Most researchers point to a positive correlation between BMI and renal filtration capacity.

Negative effect of obesity on the structure of the kidneys is explained by the influence of hyperleptinemia, hyperinsulinemia, activation of local adipocyte renin-angiotensin-aldosterone system and hemodynamic factors (fat tissue compression, inadequacy of nephron number to body size, constriction of the efferent arterioles, hyper- and hypofiltration, intraglomerular hypertension). Studies show a cause-effect relationship between these mechanisms of damage and renal dysfunction [26]. Prolonged intraglomerular hypertension contributes to disorders of architectonics and basal membrane permeability, which ultimately leads to glomerulosclerosis and tubulointerstitial fibrosis [31].

The role of adipose tissue hormone — leptin, concentration of which significantly increases with obesity due to the development of leptin resistance [26], remains rather interesting. In case of leptin resistance, peroxide

oxidation of free fatty acids is activated, which can stimulate the development of lipotoxic disorders: development of insulin resistance, endothelial dysfunction or oxidative stress [31]. In case of visceral obesity and leptin resistance this hormone is able to cause calcification of vessels, accumulation of cholesterol by the vascular wall cells, increased sympathetic tone [32]. According to some researchers, the content of thyroid hormones and TSH do not affect the synthesis and secretion of adipose tissue hormone (leptin) in any way [34]. Other studies reveal that there is a positive correlation between leptin levels and TSH in obese patients, which reflects a positive correlation between TSH and BMI [35]. However, a number of studies highlight that serum leptin content in patients with hypothyroidism increases, even after correction of BMI values [32]. Physiologically, leptin regulates energy homeostasis, informing the central nervous system about the stores of adipose tissue, affects neuroendocrine and behavioral responses to overeating; and TSH, in its turn, stimulates the secretion of leptin in the adipose tissue; and increase of leptin induces secretion of thyroliberin [32].

Leptin plays an important role in the development of renal pathophysiological processes. In kidneys, leptin receptors are found in the tubular epithelial cells. These receptors are responsible for diuresis and natriuresis, without changes in blood pressure and  $K^+$  excretion [31]. In the culture of endothelial cells of rats with body weight within norm, prolonged infusion of recombinant leptin of mice stimulated increase of the mRNA-transforming growth factor  $\beta 1$ , its secretion and synthesis of type IV collagen, which was accompanied by the development of focal glomerulosclerosis and proteinuria. There is evidence that with hyperleptinemia glomerular endothelial cell damage by oxygen radicals and peroxides is increased due to activation of oxidative stress [36].

It has been proved that the condition of even “minimal thyroid insufficiency” greatly contributes to the development of hyperlipidemia, ischemic heart disease [38, 39]. It has been noted that with hypothyroidism, dyslipidemia is observed twice often in comparison to patients with euthyroidism [39].

Mechanisms of dyslipidemia development in case of hypothyroidism include a number of biochemical changes: decreased activity of cholesterol-ether-transport protein and hepatic lipase, which provide about 30 % of reverse transport of cholesterol; disorders of HDL structure; decreased number and sensitivity of LDL receptors in the liver, as well as impaired renal glomerular function (decreased GFR) and slower LDL clearance [40]. Administration of hormonal replacement therapy optimizes lipid-lowering effect of statins, but is not an alternative to lipid-lowering therapy [41]. Findings of experimental and clinical studies provide an opportunity to positively assert the significance of dyslipidemia not only in the development of atherosclerotic lesions of renal vessels, but also glomerulosclerosis [42]. Accumulation of lipid by cells or “lipotoxicity” is a well-known phenomenon that plays an important role in the process of atherosclerosis [22]. “Lipotoxicity” is associated with the damage to internal organs, including renal diseases. Autopsy data

indicate a direct relationship between sclerosis of the glomerular renal apparatus and processes of atherosclerosis [43, 44]. Although some scholars believe that lipid metabolic disorders trigger kidney disease, still the overwhelming majority of scientists consider dyslipidemia a condition that only contributes to the progression of renal pathology.

In terms of CKD and associated dyslipidemia, the rate of deterioration of renal function is twice higher than in individuals with CKD and normal lipidogram parameters [6]. Negative effects of dyslipidemia on renal glomeruli are conditioned by endothelial and mesangial cell dysfunction, direct cytotoxicity, vascular wall proliferation, cytokine release, growth factors, inflammatory mediators, etc. [22].

Thus, components of MS are independent risk factors for the development of renal dysfunction in hypothyroidism. Therefore, patients with impaired renal function of non-inflammatory genesis and abdominal obesity are recommended a comprehensive examination for the diagnosis of hypothyroidism (ultrasound examination of the thyroid gland and determination of TSH level) and administration of adequate treatment. At the same time, high levels of TSH can be considered a predictor of GFR decrease.

**Conflicts of interests.** Author declares the absence of any conflicts of interests that might be construed to influence the results or interpretation of their manuscript.

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### Вплив окремих компонентів метаболічного синдрому на функцію нирок при гіпотиреозі (огляд літератури)

**Резюме.** У статті висвітлено вплив окремих компонентів метаболічного синдрому: артеріальної гіпертензії, ожиріння й дисліпідемії на функцію нирок при гіпотиреозі, причинно-наслідковий зв'язок між вказаними компонентами й гіпотиреозом та нирковою дисфункцією. Показано, що артеріальна гіпертензія, абдомінальне

ожиріння, гіперлептинемія, дисліпідемія є незалежними факторами ризику розвитку порушення функції нирок при гіпотиреозі.

**Ключові слова:** гіпотиреоз; артеріальна гіпертензія; ожиріння; лептин; дисліпідемія; хронічна хвороба нирок; огляд

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### Влияние отдельных компонентов метаболического синдрома на функцию почек при гипотиреозе (обзор литературы)

**Резюме.** В статье освещено влияние отдельных компонентов метаболического синдрома: артериальной гипертензии, ожирения и дислипидемии на функцию почек при гипотиреозе, причинно-следственная связь между указанными компонентами и гипотиреозом и почечной дисфункцией. Показано, что артериальная гипертензия,

абдоминальное ожирение, гиперлептинемия, дислипидемия являются независимыми факторами риска развития нарушения функции почек при гипотиреозе.

**Ключевые слова:** гипотиреоз; артериальная гипертензия; ожирение; лептин; дислипидемия; хроническая болезнь почек; обзор