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Pathogenetic grounds for the development of insulin resistance in patients suffering from primary hypothyroidism

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Abstract
The main objective of the research was to study the levels of leptin, adiponectin, interleukin-6 (IL-6) and indices of insulin resistance in patients with primary hypothyroidism. The article reveals literary and personal data showing the role of leptin and adiponectin in the development of insulin resistance associated with obesity in patients with primary hypothyroidism. 112 patients, including 62 women and 50 men, suffering from primary hypothyroidism were examined. A positive correlative linear connection between HOMA IR and TSH levels has been established. Reasonably high levels of leptin and low levels of adiponectin have been detected in all patients under study with manifested hypothyroidism in comparison to control group. A positive correlation between IL-6 and leptin levels has been found, but the relation between IL-6 and adiponectin has proved to be negative, which confirms our suggestion that leptin, adiponectin and IL-6 participate in the development of insulin resistance in patients with primary hypothyroidism. Hyperleptinemia and hypoadiponectinemia may be considered the markers of hypothyroidism with elements of metabolic syndrome.

Keywords: hypothyroidism, insulin resistance, obesity, leptin, adiponectin, IL-6.

1. Introduction
Over recent years there has been noticed a pronounced tendency towards the increase in incidences of thyroid gland (TG) pathologies that are dominating in clinical endocrinology. The most widespread type of thyroid malfunction is primary hypothyroidism. People of old age-group have shown the highest prevalent rate of hypothyroidism, reaching 6-8%. According to epidemiologic survey, clinically manifested hypothyroidism makes up 2% and 0, 2% among women and men respectively [1]. Recent investigations have revealed the influence of thyroid gland (TG) hormones on insulin effect, the correlation between thyroid function and insulin resistance (IR), though these relations are rather complicated [1, 3, 5, 17]. Researches prove the fact that IR in case of obesity and hypothyroidism is associated with chronic inflammation and increased levels of adipocytokines. Adipocytokines are heterogeneous group of signal compounds secreted by the adipose tissue possessing various biological properties. Adipocytokines include leptin, tumour necrosis factor α (TNF- α), interleukin-6 (IL-6), transforming growth factor β (TGF- β), plasminogen activator inhibitor-1, angiotensinogen, adipsin (acylation stimulating protein), metallothionein as well as endocrine factors belonging to resistin and adiponectin family [2].
Nowadays, leptin is considered the most studied compound. According to references, it is a monomeric protein secreted almost exclusively by adipocytes. The major function of leptin is to provide a balance between fat storing, its usage and food consumption. Moreover, leptin possesses the capacity to stimulate directly neuroendocrine adaptation to fast partly altering reproductive and thyroid functions [2]. Majority of current researchers highlight the undeniable role of leptin in atherogenesis and, therefore, consider increase of leptin levels in plasma to be an independent risk factor of developing coronary diseases. It has been proved that increase of leptin levels causes the reduction of arterial walls elasticity. High level of leptin in patients diagnosed with atherosclerosis based on angiography is considered an adverse prognostic risk factor for developing cardiovascular complications irrespectively of lipid and C-reactive protein levels in blood plasma. Lately, there has been noticed an intensive study of pathogenetic effects of leptin, adiponectin and resistin in pathogenesis of metabolic syndrome and obesity, their influence on glucose and lipid metabolism, development of arterial hypertension (AH), abdominal obesity in patients resulting from hypofunction of the thyroid gland [4, 7].

It has been established, that with obesity adipocytes express higher levels of TNF- α, which, in its turn, stimulates the production of IL-6. IL-6 plays a special role in the development of various manifestations of hypothyroidism, takes an active part in differentiation of monocytes to macrophages, stimulates the expression genes of hepatocytes and macrophages, which are responsible for the synthesis of acute phase proteins, favours the enhancement of TNF-α synthesis by macrophages through lipopolysaccharides and induces proliferation of smooth muscle fibers in the vessels. Besides everything mentioned above, IL-6 in combination with TNF-α and IL-1 are the mediators of hypothalamic-pituitary-adrenal (HPA) system response to stress and inflammation. Pro-inflammatory cytokine stimulation of HPA activity and particularly IL-6 in obese people causes hypercholesterolemia, increase of IR, growth of glycaemia levels and body need in insulin [4, 12, 16].

In the meantime, solution of the problem concerning the intrinsic role of adipocytokines in the development of obesity-associated resistance to insulin is a complicated task due to a series of contradictions [1, 4, 5, 14].

Objective: of the investigation is to study levels of leptin, adiponectin, IL-6 and insulin resistance indices in patients diagnosed with primary hypothyroidism.

Materials and Methods: The research involved 112 patients (aged 56 ± 8), including 62 women and 50 men, suffering from primary hypothyroidism. Methods of the investigation included common physical examination, measuring waist circumference (WC) (cm) and body-weight index (BWI). WC was considered to be in norm if it did not exceed 88 cm in women and 102 cm in men. Fasting plasma glucose as well as postprandial blood glucose (2 hours after meal) were identified. Glucose levels in capillary blood were measured by means of AGKM-01 analyzer ("Kwerty-Med", Ukraine). The stage of IR was determined according to IR indices, HOMA-IR (Homeostasis Model Assessment Insulin Resistance) and Caro indices in particular. HOMA-IR index was identified according to the following formula: HOMA-IR = fasting plasma glucose (mmol/L) × fasting blood insulin (μU/L) / 22,5. Caro index was calculated by the following formula: glucose (mmol/L) / insulin (μU/L). Normally, HOMA-IR index does not exceed 2,77 but Caro index usually exceeds 0,33. Concentrations of endogenous insulin (EI), thyroid-stimulating hormone (TSH), IL-6, leptin and adiponectin were defined according to the method of enzyme immunoassay in the immunological laboratory of Ivano-Frankivsk regional clinical hospital by means of "Stat Fax - 303" automatic analyzer and a set of reagents, such as DRG (USA) reagent, used to determine the concentration of endogenous insulin (EI), Alkor Bio (Russia) reagent for TSH measuring, and Bender MedSystem (Austria) reagent for IL-6 identification.

All patients with primary hypothyroidism were divided into 4 groups. Group 1 involved 20 patients with subclinical hypothyroidism (SH) without obesity; Group 2 included 35 obese patients with SH; Group 3 encompassed 20 patients with manifested hypothyroidism without obesity and Group 4 involved the rest 37 obese patients with manifested hypothyroidism. The control group was represented by 12 healthy donors of the corresponding age.

For statistical analysis, both parametric and nonparametric methods were used, such as calculation of arithmetic mean (M), standard deviation (σ), mean error (τ) and study validity (p). Along with univariate statistics, Student's unpaired t-test was performed. The difference was considered significant at $p<0,05$. Correlation between received data was estimated according to Pearson correlation coefficient (r).

Results and Discussion: Out of 112 patients with hypothyroidism, 72 people were suffering from abdominal obesity. Their BWI was estimated at 32,63 ± 0,41 and 35,42 ± 0,48, while BWI of apparently healthy people made up 24.57 ± 0,24 kg/m^2. A pathogenetic component of the metabolic syndrome is IR, which develops on the base of abdominal obesity. Abdominal obesity is known to be associated rather with HOMA IR index than with BWI increase. Therefore, to determine "weight" component of metabolic syndrome WC was first measured. WC of patients with visceral obesity turned out to be typical of all participants of Group II and IV. Besides, the highest indices of WC were observed in patients with manifested hypothyroidism form Group IV. We have found out that in Group II women with SH measured 102,94 ± 2,32 cm in waist, and men – 114,36 ± 1,44 cm. At the same time WC of women and men with manifested hypothyroidism in Group IV was 122,84 ± 2,40 cm and 126,24 ± 2,65 cm respectively. Besides, we have discovered that EI levels in patients of all groups under study were considerably higher than those of control group ($p>0,05$). However, EI levels of patients with manifested hypothyroidism and obesity (Group IV) was high and 2,5-3,9 times exceeded that of the control group. Hence, EI levels increase as far as IR develops (see Table 1). Study of EI contents has revealed potential hyperinsulinemia: 46,25 ± 12,34 uIU/mL in obese patients with manifested hypothyroidism and 28,45 ± 2,29 uIU/mL in obese patients with SH in comparison to 11,85 ± 0,36 ($p<0,05$) in those from control group. HOMA IR index has appeared ambiguously higher in different groups. We have observed significant increase of HOMA IR index in obese patients with manifested hypothyroidism – 13,07 ± 6,22 and in obese patients with SH – 7,29 ± 0,80 in comparison to the findings received in control group ($p<0,05$). This index ranged within the boundaries of 3,46 ± 0,48 and 4,46 ± 0,92 in Group I and Group III respectively. HOMA IR indices of patients from Group II and Group IV have appeared 3 and 5,6 times respectively higher than those of healthy people have (see Table 1). Therefore, HOMA IR index raises in obese patients with manifested hypothyroidism. Analyzing the data of Caro index, we have established that in patients from Group I it does not differ greatly from the one in healthy people. Caro index turned out to be 1,7-2,7 times lower in patients from the rest groups than in healthy people ($p<0,05$).

Correlation analysis has shown the presence of positive correlation between HOMA IR indices and TSH levels in patients with hypothyroidism (r=0,572, p=0,001). Hence, increase of HOMA IR index in patients with hypothyroidism may indicate the presence of relation between hypothyroidism and disorder of tissue responsiveness to insulin.

Analyzing our findings, we have revealed that all patients of all groups had significantly lower adiponectin levels than the participants of the control group ($p<0,05$) (see Table 1). So, in comparison to the data of control group ($p<0,05$) adiponectin levels in patients of Group I were reduced by 27,6%, in Group II – by 47%, and in Group III and IV – by 41,2% and 61% respectively. Adiponectin levels turned out to be considerably lower in obese patients who had manifested hypothyroidism and reached 3,15 ± 0,15 μg/ml. Our findings coincide with the data of recent researches showing that with hypothyroidism

syndrome adiponectin levels are sufficiently lower.

Therefore, we have revealed the presence of interaction between the levels of adipocytokines and TSH that reflects the functional capability of the thyroid gland. Hence, a negative correlation between TSH and adiponectin levels in all patients with hypothyroidism has been established (r = -0,4742, p = 0,0318).

As it appears from the preliminary evidence, in our opinion, the interaction between the levels of adipocytokines and TSH does exist. We have performed a correlation analysis which proved a negative correlation between HOMA IR indices and adiponectin levels in all examined patients with hypothyroidism (r=-0,3682, p=0,002).

A strong negative correlation between HOMA IR indices and adiponectin levels has been revealed in the group of patients with both manifested hypothyroidism and obesity (r=-0,8763, p=0,042). Moreover, adiponectin in blood serum of patients under study correlated reversely to TSH levels (r=-0,456, p=0,022) and to WC (r=-0,3740, p=0,0021). Hence, adiponectin presence in blood serum negatively correlates to HOMA IR levels, to visceral obesity stage (WC) and to TSH levels.

Evaluating leptin levels we have found out that body weight gain by patients with hypothyroidism is accompanied by increase of leptin concentration in blood serum. Hence, leptin levels in patients with hypothyroidism have appeared two times higher in the group with BWI>24,9 kg/m2 than in the group with BWI<24,9 kg /m^2 (p<0,01) in contrast to control group with p<0,001. Patients of all groups under study have revealed a significant increase of leptin levels in comparison to control group (p<0,05) (see Table 1), although these levels have been lower in obese patients with manifested hypothyroidism and made up 32±4,2 μg/ml. Our findings coincide with the researches of the recent years suggesting that with hypothyroidism syndrome leptin levels rise.

Analysis of our investigation has shown that all patients under study had their IL-6 levels considerably higher in comparison to apparently healthy people (AHP) (p<0,05). So, IL-6 level was 2,1 times higher in patients from Group I; 2,6 times – in Groups II and III and 3,6 times – in Group IV (compare to p <0,05 in AHP) (see Table 1). We have established the interaction between the levels of pro-inflammatory cytokines and TSH. A positive correlation has been found between TSH levels and IL-6 (r=0,5842, p=0,00004). In our opinion, there is interaction between the intensity of inflammatory response and thyroid function. Besides, we have observed a positive correlation between IL-6 and leptin (r=0,5319, p=0,0003) and negative correlation to adiponectin levels (r=-0,5523, p=0,0001), which, we think, proves the influence of leptin, adiponectin and IL-6 on the development of insulin resistance in patients with primary hypothyroidism.

Table 1: Adipocytokines and IL-6 levels and IR indices in patients with manifested and subclinical hypothyroidism

Criterion	Apparently healthy people, n=12	Group I, patients with subclinical hypothyroidism without obesity, n=20	Group II, patients with subclinical hypothyroidism and obesity, n=35	Group III, patients with manifested hypothyroidism without obesity, n=20	Group IV, patients with manifested hypothyroidism and obesity, n=37
Leptin, ng/ml	5,4±1,56	8,1±1,5 *	20,8±2,3*	11,5±1,9*	32±4,2*
Adiponectin, μg/ml	8,19±0,27	6,93±0,12*	4,38±0,22*	4,81±0,32*	3,15±0,15*
IL-6, pg/ml	11,90±1,38	24,61±0, 93*	31,11±1, 44*	33,02±1, 54*	43,45±1, 77*
Fasting glycemia, mmol/L	4,14±0,07	4,46±0,02	5,77±0,33	4,32±0,21	5,87±0,10 *
BWI, kg/m^2	24.57±0,24	24,62±0,23 *	32,63±0,41 *	24,44±0,48	35,42±0,48 *
WC (cm) female	76,64±0,34	82,35±0,95	102,94±2,32 *	88,64±1,56	122,84±2,40 *
WC (cm) male	90,08±0,52	92,59±0,65	114,36±1,44 *	98,29±1,68 *	126,24±2,65 *
EI, uIU/mL	11,85±0,36	15,60±4,45 *	28,45±2,29 *	23,25±2,33 *	46,25±12,34 *
HOMA IR index	2,32±0,06	3,46±0,48 *	7,29±0,80 *	4,46±0,92 *	13,07±6,22 *
Caro index	0,35±0,01	0,28±0,03 *	0,20±0,03 *	0,18±0,01 *	0,13±0,01 *

Note: * - difference is significant with reference to the data of apparently healthy people (p <0,05)

Conclusions

1. Defining EI levels in blood, calculation of Caro and HOMA-IR indices are informative for the verification of IR in patients with primary hypothyroidism.
2. Hyperleptinemia, hypoadiponectinemia as well as raised IL-6 levels may be considered a marker of hypothyroidism with the elements of metabolic syndrome and can be an independent factor of IR development on the background of hypothyroidism.

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