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Research Article

Effect of Metformin on Parameters of Insulin Resistance in Patients with Primary Hypothyroidism

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Abstract
The research examined the frequency and nature of carbohydrate metabolism disorders in patients with primary hypothyroidism. In 25.8% of patients increased glycemic indexes responding to a prediabetes stage were found. In patients with thyroid hypofunction (TG) the presence of insulin resistance (IR) by defined HOMA IR and Caro indexes has been proved. The dependence of IR severity on heaviness of hypothyroidism and BMI has been determined.
Differentiated treatment of patients with primary hypothyroidism, obesity and initial carbohydrate metabolism disorders has demonstrated the priority of efficiency of combination therapy with appointed metformin and levothyroxine in comparison with the basic substitution therapy. Appointment of metformin for the treatment of the patients with proven IR contributed to the rapid compensation of hypothyroidism, normalization of carbohydrate metabolism indexes, and it is also preventing the possible development of metabolic syndrome.

Keywords
hypothyroidism, insulin resistance, obesity, metformin,thyroxin

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Problem statement and analysis of the latest research

In the contemporary medical science hypothyroidism, including subclinical one is regarded as one of the risk factors for cardiovascular diseases (CVD) [5, 6, 8, 9]. The prevalence of thyroid hypothyroidism among women is 4 to 21%, among men – 3 to 16

According to the latest researches, between hypothyroidism and risk factors of CVD there are metabolic relationships identified and traced through obesity, arterial hypertension (AHT), lipid and carbohydrate metabolism disorders [1, 3, 5, 11]. These factors are components of metabolic syndrome (MS), the main mechanism of the development of which is the IR [11].

New approaches to analyzing the IR syndrome in hypothyroidism are discussed. It has been established that thyroid hormones regulate the synthesis and activity of protein-glucose transporters (GLUT 1-5), affect the activity of tyrosine kinase, which is responsible for receptor sensitivity. Hypoxic changes in tissues in hypothyroidism stimulate process of lipid peroxidation (LPO) and the formation of free radicals, which contribute to the synthesis of vasoconstrictor substances, causing activation of the immune-inflammatory system, the synthesis of pro-inflammatory cytokines (tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) that lead to the receptor defect of immune-sensitive cells [2, 6, 8].

The analysis of effectiveness of the treatment of patients confirms the presence of IR clinical manifestations even in compensated hypothyroidism. Patients keep dyslipidemia, coronary heart disease (CHD), arterial hypertension and obesity. These changes do not always correlate significantly with the level of thyroid stimulating hormone (TSH) and tetraidothyronine (T4) [10, 11]. It has been found that patients with hypothyroidism are characterized by frequent carbohydrate metabolism disorders at the stage of prediabetes or diabetes [1, 3].

In the contemporary literature, the issue of impact of biguanides, metformin in particular as a modifier of thyrotropin-inhibitory effect of thyroxin [7], as well as a factor of improved sensitivity of the hypothalamic-pituitary-thyroid system and peripheral tissues to thyroxin (T4) is discussed, which leads to inhibition of processes of IR formation in this pathology. In the scientific literature there is much evidence of positive effects of metformin not related to its anti-hyperglycemic action [7].

Thus, the search for additional effects on pathogenic mechanisms of IR development at a hypothyroidism is an actual problem of clinical endocrinology.

Objective is to improve treatment of patients with primary hypothyroidism, obesity and initial carbohydrate metabolism disorders by the way of drug effects on insulin resistance.

1. Materials and methods of the research

At the initial stage of the research 120 patients with uncompensated primary hypothyroidism requiring replacement therapy have been examined. Before appointment of treatment, pa-

tients were divided into four groups, depending on the form of hypothyroidism and BMI:

- Group 1 – patients with apparent hypothyroidism with obesity (n = 45);
- Group 2 – patients with apparent hypothyroidism without obesity (n = 40);
- Group 3 – patients with subclinical hypothyroidism with obesity (n = 15);
- Group 4 – patients with subclinical hypothyroidism without obesity (n = 20).

In order to compare the studied parameters with options of norm 15 practically healthy individuals (PHI) were examined, donors selection of whom was carried out taking into account the data history, in the absence of clinical signs of hypothyroidism and obesity but under the normoglycemic condition.

Inclusion criteria for patients' participation in the study were: a diagnosis of apparent and subclinical hypothyroidism in combination with obesity or without excess body weight, absence of diabetes, the patient's consent.

An examination of the patients studied parameters of functional activity of the thyroid, carbohydrate metabolism, and IR indexes.

Capillary blood glucose level has been determined by a glucose oxidase method on the automatic analyzer AHKM-01 ("Kverti-Med", Ukraine). Indicators of glycosylated hemoglobin were studied by means of ion exchange chromatography with the help of an analyzer BIO-RAD D-10.

Determination of concentration of thyroid hormones (T3 (free), T4 (free), TSH, antibodies to thyroid peroxidase (AB to TPO), the immune-reactive insulin level (IRI) was measured by means of a method of enzyme-linked immunosorbent assay on an automated analyzer Stat fax + 303 (US).

An IR state was determined by IR indexes, HOMA-IR (Homeostasis Model Assessment Insulin Resistance) and Caro indexes in particular. HOMA IR index was calculated by the formula: HOMA-IR = fasting blood glucose (mmol/l) × fasting insulin blood (mcU/l) / 22.5. Caro index was determined by the formula: glucose (mmol/l) / insulin (mcU/l). Normally HOMA IR index does not exceed 2.77; the Caro index is higher 0.33.

Based on proven examination of IR state in patients with hypothyroidism, and taking into account the most expressive IR and frequent carbohydrate metabolism disorders in the group of patients with apparent hypothyroidism and obesity, the patients of this group participated (n = 45) at the stage of use of the studied medicine. Examined patients were divided into two groups:

- Group 1 – patients receiving basic therapy with levothyroxine (23 persons).
- Group 2 – patients receiving combination therapy with levothyroxine and metformin (22 persons).

Average individual dose of levothyroxine was 82.6 mcg/day. Metformin dose was 850 mg once a day.

Analysis of the received results was performed by the way of comparing the indexes of the examination of patients before treatment and 6 months later after the use of differential therapy.

Statistical analysis of the results was performed by means of the computer program Statistica-8 and a number of statistical functions of the program ≪Microsoft Excel≫. In order to represent the data we used the average arithmetic mean M and the average error of the arithmetic mean m, the number of a variant (n), the reliability of the difference of two average arithmetic means was determined by Student's t-test. The differences at $p<0.05$ are considered to be reliable.

To compare the reliability of the difference between the groups of the research on the emergence of clinical symptoms and physical changes the criterion χ^2 has been used.

2. Results of the study and their discussion

In the examined patients with hypothyroidism initial carbohydrate metabolism disorders such as fasting hyperglycemia and impaired glucose tolerance (IGT) were identified. In order to assess carbohydrate metabolism disorders we used criteria defined by the International Diabetes Association.

Fasting Hyperglycemia (FHG) was found in 15 individuals (12.5%) totally for all groups. In the group I – in 8 persons (17.8%), in the group II – 6 persons (15.0%), in the group III increased fasting blood sugar was found in 1 patient (6.7%), and in the group IV FHG was not revealed in patients (Table 1).

Impaired glucose tolerance (IGT) was found in 16 individuals (13.3%) of all patients. In the group I – in 8 patients (17.8%), in the group II – 5 persons (12.5%), in the group III – in 1 patient (6.7%), in the group IV – 2 persons (10.0%) (Table 1).

By and large, carbohydrate metabolism disorders at the stage of prediabetes were identified in 31 individuals, representing 25.8% of the patients, the vast majority of these changes were found in patients with apparent hypothyroidism (27 persons), representing 22.5% of all the patients. The overwhelming number of cases of carbohydrate metabolism disorders in patients of the group I proves dependence of dysglycemia on body mass index (BMI).

In order to assess IR HOMA IR index was determined, for calculation of which the EI blood level was examined. Significant hyperinsulinemia was found in all groups of patients compared to the PHI ($p<0.05$). In patients of the group I EI level was 39.68 ± 1.77 mc mU/ml, in patients of the group II – 30.90 ± 1.24 mc mU/ml, 28.33 ± 2.61 mc mU/ml in the group III, 25.81 ± 1.19 mc mU/ml in patients of the group IV. In PHI EI index is detected within 12.22 ± 0.32 mc mU/ml ($p<0.05$). In patients of group I EI level was the highest and excelled the PHI value by 3 times ($p<0.05$).

Table 1. Carbohydrate metabolism disorders in patients with hypothyroidism

Index	Total n=120		Group I n=45		Group II n=40		Group III n=15		Group IV n=20		p
	n	%	n	%	n	%	n	%	n	%	
FHG	15	12.5	8	17.8	6	15.0	1	6.7	0	0.0	>0.05
IGT	16	13.3	8	17.8	5	12.5	1	6.7	2	10.0	>0.05

Note.

% - in relation to all patients in each separate group;

d - reliability index of difference in relation to the indexes of the group I.

HOMA IR index in patients with hypothyroidism of all groups was increased in comparison with the PHI ($p<0.05$). In healthy persons the mentioned index was defined within 2.52 ± 0.05. In patients of the group I HOMA IR index was the highest 8.70 ± 0.41 and exceeded the PHI level almost by 3.5 times; in patients of the group II the index was 6.62 ± 0.35, in the group III – 5.83 ± 0.65, and in the group IV – 5.09 ± 0.29. Reliability difference of HOMA IR and EI indexes was found in groups II, III, IV in comparison with the group I ($p<0.05$) (Table 2).

In the patients with hypothyroidism of all groups Caro index was lowered by 1.5-2.0 times in comparison with the healthy, and it was significantly different from the PHI indexes ($p<0.05$). Reliability difference in Caro indexes was found in groups II, III and IV in comparison with the group I of patients ($p<0.05$) (Table 2).

Thus, when examining patients discovered increasing IR indexes proves the existence of pathogenetic factors that affect the state of the sensitivity of cells to insulin in hypothyroidism.

Results of comparison of the effectiveness of basic levothyroxine therapy for patients with hypothyroidism (group I) and combination therapy with metformin (group II) demonstrate positive dynamics by indexes, which were studied, in both groups.

The provided therapy supported correction of carbohydrate metabolism disorders in two groups of patients. However, after 6 months normoglycemia was achieved by 37.5% of the group I and 87.5% of the group II.

The positive dynamics was revealed in achieving thyroid compensation in both groups. However, during this period, the level of TSH only in patients of the group II has gained value close to the index of PHI ($p<0.05$). Besides, the TSH index in the group II after 3 months was significantly lower than in the group where patients received basic therapy with levothyroxine ($p<0.05$) (Table 3). A similar tendency was observed in the dynamics of changes of peripheral hormones.

It has been found that treatment of hypothyroidism in patients of both groups reduces the IR, a laboratory indicator of which is hyperinsulinemia. However, the received data show more effective impact of combination therapy of hypothyroidism with metformin. So in the group I EI level decreased by 34.7% and in the group II it decreased by 59.8%. In addition, EI levels in the group II after 6 months of treatment significantly lowered in comparison with the group I of the mentioned period ($p<0.05$) (Table 3).

The indicators of IR indexes are such as: HOMA IR and Caro after the provided therapy by two schemes show IR decrease in patients with thyroid hypofunction. However, only patients of the group II reached value of IR markers close to the PHI. HOMA IR and Caro indexes in patients of the group II with combination therapy of hypothyroidism with metformin were significantly different from the indexes of the group I ($p<0.05$) (Table 3).

When analyzing the correlation between TSH levels and IR indexes, it has been mentioned that even reaching compensation of hypothyroidism IR manifestations remain; HOMA IR and Caro indexes in both groups after treatment did not achieve the PHI value. But in the group II of patients IR indexes have changed more effectively than in the group I of patients ($p<0.05$). This indicates parallel, independent of compensation of hypothyroidism IR mechanisms, affecting which we prevent the development of metabolic syndrome components in the future.

3. Conclusions

1. Determination of carbohydrate metabolism indexes, HOMA IR and Caro indexes provides early diagnosis of IR state in patients with hypothyroidism.

2. The use of metformin in the combination therapy for patients with primary hypothyroidism and obesity and initial carbohydrate metabolism disorders has positive effect on the IR indexes, promotes the normalization of carbohydrate metabolism.

3. Appointment of metformin for the mentioned category of patients results in thyroid compensation for a shorter period of time in comparison with basic therapy.

4. The predominant pharmacological and therapeutic effects of the combination therapy on IR indexes and normalization of metabolic disorders could be the basis for appointment of metformin for patients with hypothyroidism, obesity and initial carbohydrate metabolism disorders.

Table 2. IR indexes in patients with primary hypothyroidism, (M±m)

Index	PHI n=15	Group I n=45	Group II n=40	Group III n=15	Group IV n=20
EI, mc mU/ml	12.22±0.32	39.68±1.77 *	30.90±1.24 */#	28.33±2.61 */#	25.81±1.19 */#
HOMA IR index	2.52±0.05	8.70±0.41 *	6.62±0.35 */#	5.83±0.65 */#	5.09±0.29 */#
Caro index	0.39±0.02	0.14±0.01 *	0.16±0.01 */#	0.19±0.02 */#	0.18±0.01 */#

Note.

* - difference is reliable in relation to the PHI indexes ($p<0.05$);

\# - the difference is reliable in relation to indexes of patients in group I ($p<0.05$).

Table 3. The dynamics of indexes of thyroid compensation and IR in patients with hypothyroidism on the background of combination therapy, (M±m)

Index	Periods of treatment	PHI	Group I n = 23	Group II n = 22
TSH, mc mU/ml	before	2.08±0.16	16.58±1.04 *	16.77±1.02 *
	in 3 months		8.34±0.53 */**	6.68±0.41 */**#
	in 6 months		5.28±0.36 */**	2.53±0.15**/#
EI, mc mU/ml	before	12.22±0.32	39.39±2.71*	39.96±2.29*
	In 6 months		25.74±1.91*/**	16.46±0.72*/**/#
HOMA IR index	before	2.52±0.05	8.76±0.56*	8.78±0.52*
	in 6 months		5.52±0.41*/**	3.50±0.16*/**/#
Caro index	before	0.39±0.02	0.14±0.01*	0.13±0.01*
	In 6 months		0.20±0.02*/**	0.0±0.02*/**/#

Note.

* - difference is reliable in relation to the PHI indexes ($p<0.05$);

\# - the difference is reliable in relation to indexes of patients in group I ($p<0.05$).

4. Prospects for further research

Prospects for further researches should be directed at studying the long-term effects of IR correction in patients with hypothyroidism, obesity and initial carbohydrate metabolism disorders with determination of the accurate dosage and continuance of metformin therapy.

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