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Blood Cortisol Level in Patients with Metabolic Syndrome and Its Correlation with Parameters of Lipid and Carbohydrate Metabolisms

Liliya Nadolnik[1*], Vyacheslav Polubok[1] and Kirill Gonchar[2]

[1]Institute of Biochemistry of Biologically Active Compounds, National Academy of Sciences of Belarus, Grodno, Belarus.
[2]Grodno State Medical University, Grodno, Belarus.

Authors' contributions

This work was carried out in collaboration among all authors. Author LN designed the study, wrote the protocol, managed literature searches and wrote the first draft of the manuscript. Author VP performed biochemical analyzes and statistical analysis and Author KG performed patient examinations and blood sampling. All authors read and approved the final manuscript.

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ABSTRACT

Background and Objective: Disturbance in adrenocortical mechanisms of regulation can play a significant role in the development of metabolic syndrome (MS).
The goal of the work was to study the correlations between the glucocorticoid status of patients with metabolic syndrome and the severity of disturbances in carbohydrate and lipid metabolisms.
Materials and Methods: Our studies carried out on two groups of patients, healthy subjects (n=28) and patients with MS characterized by obesity, insulin resistance, type 2 diabetes and hypertension (n=20), provide evidence for close relationships between the level of blood cortisol and the extent of MS severity. The concentration of cortisol, glucose, triglycerols, total cholesterol, HDL and LDL was determined in blood samples.
Results: Patients with MS and low blood cortisol level showed less pronounced disturbances in lipid metabolism: The concentration of triglycerols was decreased by 30.2%, whereas that of LDL was reduced by 16.3% compared to patients with MS and normal cortisol level. The level of cortisol

**Corresponding author: E-mail: lnadolnik@tut.by;*

was correlated to the level of total cholesterol (r_s= –0.3601, p=0.046). These relationships were more pronounced in patients with MS: their LDL levels highly significantly correlated to the cholesterol/cortisol ratio (r_s=0.7062, p=0.01). In contrast to the higher blood glucose concentrations (>7.1 mmol/l), the low levels (<5.0) in patients with MS (and not in healthy subjects) were related to the risk of increase in morning blood cortisol concentrations in fasting patients.

Conclusion: The results obtained show that the correlations between glucocorticoids and cholesterol can play a significant role in the mechanisms of MS development, which is most probably related to dysregulation of the pituitary-adrenal system in the development of MS.

Keywords: Cortisol; cholesterol; triglycerols; glucose; metabolic syndrome.

1. INTRODUCTION

Glucocorticoid hormones play an important role in regulation of carbohydrate and lipid metabolisms. They are necessary for the development of adaptation of the organism to stress. There is a close relationship between glucocorticoid status and control of blood glucose level. Glucocorticoids (GCs) directly increase production of endogenous glucose, activating numerous genes participating in carbohydrate metabolism in the liver, which leads to enhancement of gluconeogenesis [1], and also inhibit production and secretion of insulin from pancreatic β-cells [2]. GCs can induce dysfunction of β-cells, increase insulin resistance in other systems and decrease peripheral absorption of glucose in muscles and adipose tissue [3-6]. Chronically raised levels of GCs change distribution of fat in the organism and aggravate visceral obesity [7,8], as well as play a significant role in the development of metabolic syndrome [9]. Nevertheless, patients with obesity generally show either normal or subnormal concentrations of blood cortisol [10,11]. Insight into the role of adrenocortical mechanisms in the development of MS is important in working out of methods for its prevention and treatment.

The goal of the work was to study the correlations between the glucocorticoid status of patients with metabolic syndrome and the severity of disturbances in carbohydrate and lipid metabolisms.

2. MATERIALS AND METHODS

This research was carried out at the Institute of Biochemistry of Biologically Active Compounds of the National Academy of Sciences of Belarus in collaboration with scientists from Grodno State Medical University. The study incorporated 48 patients who were subdivided into 2 groups: the first group included apparently healthy subjects (n=28) and the second one consisted of patients with signs of metabolic syndrome (MS) (n=20). All the subjects examined were patients of one doctor who consulted and treated them for 3 to 5 years. Men and women (1:1.4) aged 35 to 65 years took part in this study.

All the subjects examined were questioned and measurements were taken of their weight, waist circumference and arterial pressure. All the patients of the MS group were diagnosed with type 2 diabetes, obesity and hypertension. They we appropriately treated for diabetes, dyslipidemia and hypertension. The group of healthy subjects included random patients who had no disorders in carbohydrate and lipid metabolisms without manifestations of hypertension. The patients of this group were age- and sex- matched to Group 2 patients.

2.1 Eligibility Criteria

1) Men and women aged 35-65 years with established diagnosis of type 2 diabetes mellitus. 2) Obesity with BMI of 35 kg/m^2 and more. 3) Arterial hypertension of the first or second extents of disease. 4) Patients treated with stable doses of hypoglycemic, antihypertensive and hypolipidemic drugs not less than 6 months before inclusion in the study.

2.2 The Withdrawal Criteria were the Following

1) Uncompensated hypothyroidism, endogenous hypercorticoidism. 2) Chronic cardiac insufficiency of the third and forth extents, uncontrolled arterial hypertension, myocardial infarction or stroke occurring during the last 6 months. 3) Liver failure, chronic kidney disease of 3B-5 extent. 4) Acute infectious diseases, exacerbation of chronic diseases. 5) Type 1 diabetes mellitus (diabetic ketoacidosis and pancreatitis in past medical history).

2.3 Collection of Samples

Blood samples (5 ml) were obtained from the cubital vein from patients admitted to clinical hospital No1 in Grodno after fasting overnight. Serum was obtained by centrifugation of the samples at 1500 rpm for 20 min and stored at –80°C.

2.4 Biochemical Assay

The concentrations of blood serum triglycerols (TG), total cholesterol (TC), high density lipoproteins (HDL) and low density lipoproteins (LDL) were determined enzymatically according to the manufacturer instruction using the following commercial kits: Triglycerides (010.057.01-001), Cholesterol (010.055.01-001), HDL (010.058.02-002) and LDL (010.059.02-002) (Arvit Medical, Belarus). Glucose concentrations were measured by a glucose oxidase method using the Glucose IM-7.100272/1805 kits (Analiz X, Belarus). All the spectrophotometric measurements were carried out by a Cary 100 Scan spectrophotometer (Varian). The blood serum cortisol levels were determined by the ELISA assay using the ELISA-Cortisol, 03.001.01-004 commercial kits (AnalizMed, Belarus). To access the assay results, a multimode microplate reader was used (Fluostar Omega, Germany).

2.5 Statistical Analysis

Data were expressed as mean ± standard deviation (Mean±SD). The groups were compared by Kruskal-Wallis one-way analysis of variance in the package of the statistical software Statistica 12.0 (Statsoft, USA). The Mann-Whitney rank test was used to assess the significance of differences in independent variables between the 2 groups. For finding correlations between the parameters studied, we used Spearman rank correlation coefficient STATISTICA 12.0 (StatSoft, USA). Graph Pad Prism software 5 (Graph Pad Software, USA) was applied for regression analysis. The level of significance was set at $p < 0.05$ for all the data.

3. RESULTS

3.1 Parameters of Carbohydrate and Lipid Metabolisms and Cortisol Level in Healthy Patients and Patients with MS

Table 1 show data on the levels of glucose and cortisol as well as parameters of lipid metabolism in healthy patients and patients with MS. The groups of patients considerably differed in all the parameters studied. The fasting blood glucose concentrations were increased by 91.2% (8.49±0.82 mmol/l) in patients with MS and corresponded to normal values in healthy subjects (4.44±0.08 mmol/l). Considerable changes were found in lipid metabolism: the level of TG under MS was raised by 139.53%, the concentration of TC was increased by 20% (p_{1-2}=0.01) and that of HDL was decreased by 14.65%. The concentrations of cortisol did not differ in blood serum of patients with MS (456.74±41.24 nmol/l) and healthy subjects (469.29±27.03 nmol/l).

3.2 Analysis of Parameters of Carbohydrate and Lipid Metabolisms in Healthy Patients and Patients with MS in Relation to Blood Cortisol Level

The analysis of blood cortisol level in the total pool of findings showed cases with high and low values of this parameter both in Group 1 and Group 2 (Table 2). The number of patients with normal cortisol values amounted to 60% in the MS group and 68% in the group of healthy

Table 1. Concentrations of glucose, triglycerols, total cholesterol, HDL, LDL, and cortisol in blood of healthy subjects and patients with metabolic syndrome

Parameter	Healthy patients, (Mean ± SD)	Metabolic syndrome, (Mean ± SD)	P value
	Group 1, n=28	Group 2, n=20	
Glucose, mmol/l	4.44±0.08	8.49±0.82	<0.001
Triglycerols, mmol/l	0.86±0.05	2.06 ±0.21	<0.001
Total cholesterol, mmol /l	5.31±0.12	6.42±0.26	<0.01
HDL, mmol /l	1.91±0.07	1.63±0.10	0.042
LDL, mmol /l	1.82±0.07	2.95±0.31	0.43
Cortisol, nmol/l	469.29±27.03	456.74±41.24	0.289

patients. Increased cortisol levels were found in 8 patients: 4 patients were in the healthy group and 4 patients – in the MS group. Low cortisol levels were detected in 5 patients from the group of healthy subjects (232.60±21.69 nmol/l) and 4 patients from the MS group (229.35±21.89 nmol/l). Independently of the blood cortisol level, the control groups (Groups 1c, 3c, 5c) had normal levels of blood glucose and normal parameters of lipid metabolism.

In the groups with normal cortisol levels (Groups 1c and 2c), the concentrations of glucose, triglycerols, HDL and LDL in MS patients exceeded the values in healthy individuals ($p<0.05$). The groups with high (Groups 3c and 4c) and low (Groups 5c and 6c) cortisol values did not show significant differences between the parameters in healthy patients and MS patients. But the MS patients having high cortisol values demonstrated the lowest blood glucose concentrations (7.57±1.84 mmol/l). MS patients with low cortisol (Group 6c) had less significant impairments in lipid metabolism. The TG and LDL concentrations in this group (Group 6c) were lowered (TG levels were decreased by 30.2%, whereas LDL concentrations – by 16.3%) compared to Group 2c patients. Patients from Group 4 with high cortisol values had TG levels increased by 148.2% (p_{1-4} =0.02) in comparison with Group 1c.

The TC/cortisol coefficient had the highest values in groups with low cortisol levels (Groups 5c and 6c), but no significant differences were revealed between the groups of healthy subjects and patients with MS. Only in group 2c, with normal cortisol values, the TS/cortisol coefficient in MS patients 1.34-fold exceeded the values in healthy individuals.

3.3 Cortisol Level in Patients with Normal and Increased Concentrations of Blood Glucose

The Fig. 1 shows data on the cortisol levels in patients with MS and healthy subjects in relation to the blood glucose concentration. The correlation analysis did not reveal relationships between the concentrations of blood cortisol and glucose in the groups of patients examined. The healthy subjects did not show differences in cortisol levels at glucose concentrations of less than 5.0 mmol and 5.1-5.5 mmol/l.

In patients with MS, whose glucose levels were lower than 5.0 mmol/l, blood cortisol concentration amounted to 664.91±115.14 nmol/l, which is above the accepted normal values. And at glucose concentrations from 5.1 to 5.5. mmol/l, the concentration of cortisol was 289.14±96.06 nmol/l (p=0.07).

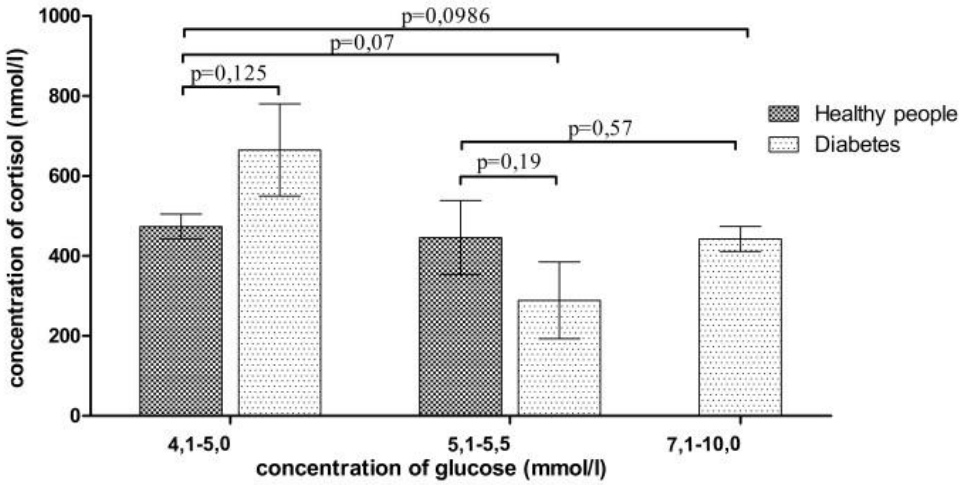

Fig. 1. Cortisol concentration in blood serum of patients with metabolic syndrome and healthy subjects in relation to glucose level

In the first group, patients with blood glucose levels of 4.1-5.0 mmol/l were examined, while in the second and the third groups subjects with 5.1-5.5-mmol/l and 7.1-10.0-mmol concentrations, respectively, were studied

It should be taken into consideration that in patients with MS, the levels of blood glucose depended on the dose of hypoglycemic drugs taken. As our findings show, a significant decrease of glucose level (<5.0 mmol/l) can be a cause for elevated cortisol concentrations in patients with MS. The optimum normalization of glucose concentration (5.1-5.5) was characterized by normal blood cortisol levels. This has a rather beneficial effect, taking into consideration the above data on the improvement in lipid metabolism under conditions of low cortisol concentrations.

Even when fasting blood glucose was decreased down to 7.1-10.0 mmol, the concentrations of blood cortisol were 442.32±31.18 nmol/l and this corresponded to the normal value.

3.4 Characteristics of Correlation Relationships of the Parameters Studied in Groups with Normal Cortisol Level

The correlation analysis of the total pool of the parameters of the two groups examined (healthy subjects and patients with diabetes, n=31) with normal cortisol levels revealed some interesting correlations. The levels of glucose significantly correlated to the levels of TG (r_s=0.7357, p<0.001), HDL (r_s= –0.5186, p=0.003), and LDL (r_s=0.4789, p=0.006) and less significantly – to the concentrations of TC (r_s=0.3396, p=0.061). The correlations found agree with the results obtained by other authors and confirm that the development of dyslipidemia is a cause for the development of hyperglycemia. The levels of cortisol negatively correlated to the levels of TC (r_s= –0.3601, p=0.046) and less significantly – to the concentrations of TG (r_s= –0.3030, p=0.097). It can be suggested that the high TC and TG values can be a cause for the decreased blood cortisol levels. In the control group (Group 1, n=19), glucose correlated only to the TG levels (r_s=0.4419, p=0.058) and the levels of TG- with the HDL concentrations (r_s= –0.5053, p=0.027). The MS group (Group 2, n=12) showed correlations between the levels of glucose and HDL (r_s= –0.6713, p=0.017) and between TC and TG (r_s=0.6339, p=0.027). Moreover, in this group, the concentrations of LDL highly significantly correlated to the cholesterol/cortisol ratio (r_s=0.7063, p=0.01), which counts in favor of the correlation between cortisol and the disturbances in lipid metabolism in patients with MS. The correlation between cortisol and TC was more pronounced in patients with MS compared to the control group, which confirms the correlation between HDL and the cholesterol/cortisol ratio only in patients with MS.

Fig. 2 shows regression analysis results. The correlation between TC and cortisol was characterized by inverse linear relationship. The application of the determination coefficient (R^2=0.2193, n=31) for the pooled group of data (healthy subjects and patients with MS) showed a rather weak correlation between the levels of TC and cortisol (Fig. 2A). The value for the determination coefficient (R^2=0.3253, n=12) provides evidence for MS patients having a more significant correlation between these parameters.

This can be due to the disturbances in regulatory mechanisms observed during MS development since the group of healthy subjects (Group 1c) did not demonstrate a significant correlation between the levels of TC and cortisol (R^2= 0.0118, p=0.658, n=19). The pattern of the correlation between the levels of TC and cortisol can be used as a prognostic indicator of MS development in patients with elevated TC values.

4. DISCUSSION

The metabolic syndrome is a complicated combination of diseases characterized by impaired functions of different regulatory systems [12-15]. This is a disorder of lipid metabolism which is related to dysregulation of the mechanisms of body mass control and development of obesity, hyperglycemia, insulin resistance and type 2 diabetes and is manifested by glycotoxicity and impaired glucose tolerance.

The results listed in Table 1 confirm that the group of patients with MS had significant impairments in carbohydrate and lipid metabolisms. Moreover, the eligibility criteria for the MS group of patients (obesity, BMI>35 kg/m^2, type 2 diabetes and arterial hypertension of the first and second extents) substantiate the correctness of this group formation.

Our research is related to a rather specific question: the role of cortisol in patients with MS. Nevertheless it is quite significant, with consideration for the key role of glucose, fatty acids and amino acids in distribution of energy and redistribution of fat in the body [16].

The correlation analysis did not find relationships between the concentrations of blood cortisol and glucose in the groups of patients studied.

Table 2. Parameters of carbohydrate and lipid metabolisms in patients with metabolic syndrome in relation to blood serum cortisol levels (normal, high, low)

Parameter	Normal level of cortisol (Mean ± SD)		High level of cortisol (Mean ± SD)		Low level of cortisol (Mean ± SD)	
	Healthy patients n=19	Metabolic syndrome n=12	Healthy patients n=4	Metabolic syndrome n=4	Healthy patients n=5	Metabolic syndrome n=4
	Group 1c	Group 2c	Group 3c	Group 4c	Group 5c	Group 6c
Cortisol, nmol/l	531.58±10.83	496.88±16.37	1318.43±110.01 p_{2-3}=0.06	1207±154.49 p_{2-4}=0.07	232.60±21.69 p_{1-5}=0.02 p_{3-5}<0.001 p_{4-5}<0.001	229.35±21.89 p_{1-6}=0.06 p_{3-6}<0.001 p_{4-6}=0.001
Glucose, mmol/l	4.46±0.09	8.81±1.11 p_{1-2}<0.001	4.32±0.14 p_{2-3}=0.06	7.57±1.84	4.46±0.30 p_{2-5}=0.07	8.43±2.06 p_{1-6}=0.06
Triglycerols, mmol/l	0.85±0.07	2.22±0.31 p_{1-2}<0.001	0.83±0.10	2.11±0.51 p_{1-4}=0.02	0.96±0.06	1.55±0.28
Total cholesterol, mmol/l	5.24±0.16	6.48±0.37 p_{1-2}=0.08	5.23±0.49	6.18±0.48	5.62±0.14	6.50±0.59
Total cholesterol/ cortisol	9.95±0.37	13.34±1.07	4.05±0.48 p_{2-3}=0.02	5.23±0.37 p_{2-4}=0.06	25.00±2.34 p_{1-5}=0.02 p_{3-5}<0.001 p_{4-5}<0.001	29.24±4.38 p_{1-6}=0.03 p_{3-6}<0.001 p_{4-6}=0.001
HDL, mmol/l	1.93±0.09	1.64±0.10	2.03±0.11	1.67±0.26	1.76±0.13	1.59±0.37
LDL, mmol/l	1.82±0.09	3.19±0.49 p_{1-2}=0.06	1.76±0.27	2.50±0.38	1.83±0.07	2.67±0.20

Note: the table shows the values p <0.05 and 0.01 <p <0.05; p_{3-5} – statistical significance between the indicators of groups 3c and 5c; also for other groups

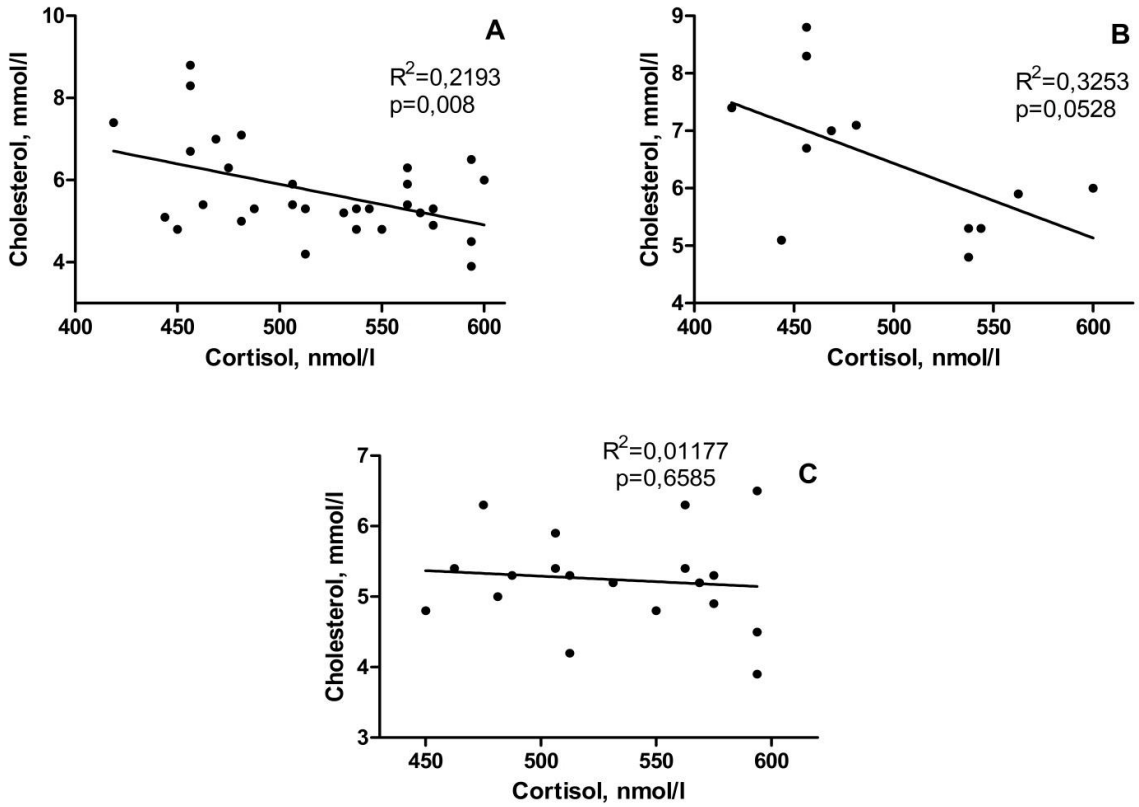

Fig. 2. Plot of regression between cholesterol and cortisol levels

A, linear cholesterol/cortisol regression curve of pooled data of healthy subjects and MS patients (n=31, p=0.008). B, linear cholesterol/cortisol regression curve of patients with MS (n=12, p=0.053). C, linear cholesterol/cortisol regression curve data of healthy subjects (n=19, p=0.658)
(R^2– determination coefficient, p – correlation significance level)

Nevertheless normal blood cortisol concentrations were detected at the concentrations of glucose of 5.1-5.5 mmol/l. Decreasing of glucose concentration down to the values lower than 5.0 mmol/l in treatment of hyperglycemia was connected with the risk for elevation of cortisol concentrations in morning blood compared to the higher values (>7.0 mmol/l). This can suggest the development of hypercorticoidism and, probably, more significant disorders of carbohydrate and lipid metabolisms.

Healthy individuals and patients with MS (Table 1) did not exhibit differences in cortisol levels ($p>0.05$). But the number of patients with normal cortisol concentrations in the MS group was 60% opposed to 68% in the control group. We believe that this difference can rise in increasing the sample. We can explain the absence of dissimilarities in the blood cortisol levels in healthy patients and patients with obesity by the elevated intracellular cortisol concentration in adipose tissue [17,18].

These studies found that less significant disorders in lipid metabolism (a lower TG level) occurred at low cortisol concentrations in patients with MS. This can probably agree with the well-known data on cortisol synthesis by adipocytes, which is related to increased expression of 11β-hydroxysteroid dehydrogenase (11-HSD) in obesity [19].

The negative correlation of cortisol to the levels of TC and TG in patients with normal cortisol concentrations suggests that high TC and TG values can be a cause for the decreased blood cortisol concentration. As the regression analysis data indicate, the cholesterol/cortisol correlation was enhanced in the MS group ($R^2=0.3253$) and weakened in the control group. Only in the MS group the level of LDL highly significantly correlated to the cholesterol/cortisol coefficient ($r_s=0.7063$, $p=0.01$), which emphasized the relationship between cortisol and impaired cholesterol metabolism in MS patients.

Cholesterol is a precursor of cortisol synthesis in the adrenal glands. Moreover, the cholesterol and cortisol metabolisms are interrelated through the nuclear liver LXR receptor activated by oxysterol [20]. LXR is a regulator of tissue cholesterol, lipids and glucose, including the adrenal glands where it protects cells from toxic concentrations of cholesterol. LXRs are also considered as regulators of adrenal steroidogenesis and HPA axis feedback [21]. It has been found that increased LXR expression in adrenal cells inhibits the expression of a variety of steroidogenic genes and reduces the production of steroid hormones [22]. The decreased expression of 11-beta hydroxysteroid dehydrogenase 1 observed in pituitary cells after LXR activation suggests weakening of the negative glucocorticoid feedback [22]. A regulatory role of oxysterol- binding protein (ORP2), which inhibits cortisol synthesis and increases adrenal cholesterol level, has been established [23]. At the same time, ORP2 is necessary for expression of LXR target- genes, including ABCA1 and the LDL receptor [23]. It can be suggested that the decreased cortisol level in the setting of improving lipid metabolism in patients with MS can be related to increased LXR expression. The negative correlation between the levels of TC and cortisol reflects regulatory effects of LXR and ORP2, but the regulation of this relationship is probably of a more complicated character. Nevertheless, the results obtained can indicate that the relationships between the glucocorticoids and cholesterol can play a definite role in the mechanisms of MS development.

5. CONCLUSION

The results obtained confirm a close correlation between the level of cortisol and the severity of metabolic disorders in patients with MS. Improvement in lipid metabolism was found in patients with MS having low cortisol values. A negative correlation between the cortisol level and the cholesterol concentration was observed at normal blood cortisol concentrations and it was more significant in patients with MS. Only the MS patients, and not the healthy subjects, showed a positive correlation between the TC/cortisol ratio and the LDL level.

The positive correlations of glucose to the levels of TG, HDL, LDL and TC confirmed the close regulatory interactions of these parameters. These interactions were disturbed in the development of MS since this group only demonstrated a relationship between glucose and HDL. MS patients with high cortisol concentrations had the lowest blood glucose values. A decrease in glucose levels in treatment of type 2 diabetes down to the values lower 5.0 mmol/l was related to the risk of increasing cortisol concentrations in morning blood in contrast to the higher values (> 7.0 mmol/l). The data obtained confirm the importance of optimum blood glucose values in choosing methods for treatment and follow-up.

The correlations found reflected disturbed regulatory effects of GCs and provide evidence for contribution of adrenocortical dysregulation to the development of MS. Considering the significant role of GCs in the development of obesity and insulin resistance the disturbance in regulatory mechanisms in developing MS is of interest for further studies on elucidation of the contribution of mechanisms related to the system of LXR regulation. Methods for prevention of chronic stress-induced hypercorticoidism and treatment of this disease using GCs can also be interesting.

6. RECOMMENDATIONS

This study has certain limitations which are related to a small sample of patients examined. Further studies involving a greater number of participants are needed.

CONSENT AND ETHICAL APPROVAL

All the patients signed the informed consent to participate in the study. The design and plan of the research was approved by the Committee on Biomedical Ethics of Grodno State Medical University.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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