Original article

Siofor influence on the process of lipid peroxidation and antioxidant status at patients with metabolic syndrome

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Abstract: The *purpose* of the work is to research siofor influence (metformin) on the activity of the process of lipid peroxidation and antioxidant activity of blood serum at patients with metabolic syndrome. *Material and Methods* — 62 patients with metabolic syndrome at the age from 30 till 60 were examined and treated by siofor (1700 mg per day) during a year. The process of lipid peroxidation was studied due to the level of lipid hydroperoxide of blood serum. Antioxidant capacity was based on the antioxidant reaction in the blood serum with definite number of exogenic hydrogen dioxide (mkmole/l) with the method of enzyme-linked immunosorbent assay (ELISA). *Results* — Intensification of process of lipid peroxidation has been observed at patients with metabolic syndrome — the level of lipid hydroperoxide of blood serum has been 2.9 (1.9, 3.9) mkM (presented as median and interquartile range), antioxidant activity of blood serum has been decreased — 276.4 (239.0, 379.9) mkmole/l. In 12 months of siofor intake hydroperoxide level has been decreased till 1.1 (0.8, 1.9) mkM, but antioxidant activity has been increased and amounted 320.0 (278.9, 334.3) mkmole/l. *Conclusion* — Siofor has been proved to be a highly effective medicine for correction of process of lipid peroxidation and for improvement of antioxidant activity of blood serum at patients with metabolic syndrome.

Keywords: siofor intake, lipid peroxidation, antioxidant activity, metabolic syndrome

Introduction

Metabolic syndrome (MS) is a collective term; it unites a group of diseases and pathologic conditions of the same origin [1]. Metabolic syndrome is a common clinical implication; in the average every 5th adult person in developed countries has the syndrome [2]. Almost all components of the MS are independent risk factors of cardiovascular failures developing, and a complex of several components significantly increases the risk of their progress. MS is associated with a significant increase of an ischemic heart disease, especially among men after 45 years and women over 55 years old [3]. In the research performed by the scientific center there had been revealed that 62% of patients with MS had a I degree AH (arterial hypertension) and 30% – aII degree AH, this goes with a circadian BP rhythm defect and concentric hypertrophy of a left ventricle [4]. Patients with MS have a high risk of type 2 diabetes developing. According to World Health Organization (WHO) estimates the number of such patients in the world will go beyond 300 million people till 2025, and from 92% to 97% of all cases will include type 2 diabetes, which imparts the character of a pandemia to the disease [5].

The basic pathogenic component of the MS is an insulin resistance (IR) [6]. Nitrogen oxide provides a physiological smooth-muscle cell proliferation and reduces damaging effect of lipid peroxidation (LPO) on a vessel wall. But in an insulin resistance conditions a nitrogen oxide synthesis in a vessel wall is defected. As a result, an endothelial dysfunction is developed, which may

cause atherosclerotic lesions in vessels [7]. Besides, in a number of studies there was displayed that LPO in patients with MS effects on a structural-functional vessels condition and endothelium function, metabolism. Free radicals change apoprotein B structure, it causes producing oxidized low density lipoproteins which damage vessel endothelium [8]. This means that a high activity of a LPO processes in patients with MS leads to appearing and progressing of a cardiovascular pathology. IR causes compensatory hyperinsulinemia which increases the activity of a sympathetic nervous system and free radicals producing caused by catecholamines. To reduce IR Siofor (Metformin) medication was used. This medication is from the category of biguanides, stimulates tissue sensitization to insulin, and, probably, effects positively on LPO processes. In view of the foregoing the aim of the study is formed.

The research aimed to study an effect of Siofor (Metformin) on the activity of LPO process and antioxidant potency of a blood serum in patients with metabolic syndrome.

Material and Methods

The MS diagnostics is based on criteria suggested by experts of Russian Society of Cardiology (2009). The main criterion is waist circumference at females >80 cm and >94 cm at males. Additional features are following:

- arterial tension is ≥130/85 mmHg,
- increase of blood triglyceride level ≥1.7 mmol/l,

- decrease of high density lipoprotein cholesterol <1.0 mmol/l at males and <1.2 mmol/l at females,
- increase of low density lipoprotein cholesterol >3.0 mmol/l,
- fasting hyperglycemia (fasting glucose in blood plasma ≥6.1 mmol/l),
- impaired glucose tolerance (glucose in blood plasma in 2 hours after glucose loading in the range of ≥7.8 mmol/l and ≤11.1 mmol/l).

The presence of a central obesity and two additional criteria at a patient is the ground of a MS diagnostics.

Exclusionary for study were:
- age over 60 years old and younger than 30 years,
- active chronic diseases,
- hard uncontrolled arterial hypertension, active autoimmune diseases,
- blood system diseases,
- acute bacterial and virus infections for recent 3 months,
- malignant tumors,
- pregnancy,
- type 1 diabetes decompensation,
- hypothyroidism,
- thyrotoxicosis,
- taking glucocorticoids,
- surgical treatment earlier than 6 months ago.

At first we examined 70 persons with MS at the age from 30 to 60 years (49.00 (41.00, 54.00) years; data presented as median interquartile range) – 25 (62.5%) men and 15 (37.5%) women. 62 patients had not changed their principles of taking medications till the study finished (in 12 months) - 41 (66%) males and 21 (34%) females of 48 (39.0, 53.0) years. All of the patients agreed to be in for the research.

The control group included 70 persons matched with the patients without MS features in age (47.0 (40.0, 52.0) years) and sex (40 males — 57.1% and 30 females — 42.9%).

Examination report included anthropometric research (body height, body weight), waist circumference (WC) and hip circumference (HC), waist-to-hip-ratio (WHR), body mass index (BMI) and biochemical blood test performed after 12-hours fasting. Carbohydrate metabolism research included fasting glucose test, insulin level test in a blood serum using Insulin AccuBind Elisa kit by the EIA method, IR index (HOMA-IR) was calculated according to the formula:

$$glucose\ (mmol/l)\ x\ insulin\ (mcU/ml)\ /\ 22.5.$$

An increase of this parameter more than 2.77 displays the IR. Arterial hypertension was detected by office measuring of arterial tension using Korotkov's method, according to recommendations of Russian Society of Cardiology.

Lipid spectrum of the serum was estimated by total cholesterol level (TCL), triglycerids, high density lipoprotein cholesterol (HDLC), low density lipoprotein cholesterol (LDLC). Extra low density lipoprotein cholesterol (ELDLC) was calculated by the Friedwald's formula: $ELDLC=TCL–LDLC–HDLC$. Atherogenic index (AI) was calculated using the formula: $AI=TCL–HDLC/HDLC$. To study LPO process there was used Lipid Hydroperoxide (LPO) Assay Kit – hydroperoxide lipids level was tested in blood serum by EIA. Antioxidant system condition was evaluated by the EIA method using ImAnOx (Tas/Tac) Kit. Determining of an antioxidant capability is based on antioxidants response, which is in the sample with a certain amount of exogenic hydrogen dioxide (H_2O_2). Antioxidants in the sample eliminate some amount of hydrogen dioxide. The rest of H_2O_2 is determined by photometric method. Antioxidant activity: <280 mmol/l – low, 280–320 mmol/l – medium, >320 mmol/l – high.

Comparative characteristics of the patients with MS and the control group are presented in *Table* 1.

All of the patients were given a dietary guidance: feeding should be frequent, in small portions with no more than 1500 kcal per day; the last meal – 1.5 hours before bedtime. The base of the meals were low-glycemic complex carbohydrate, they should be 50-60% of nutrition value. Besides, the patients were instructed about keeping proper hours with dietary habits changing and regular physical exercises. The treatment using Siofor (Berlin-Chemie, Germany) was started from 500 mg/day during a week (to minimize gastro-intestinal tract side effects), then the doze was increased up to 1700 (850 mg twice a day) mg/day. The patients had been taking the medication for a year, with control after 3, 6, 9 and 12 months.

Statistical analysis of the results was performed by IBM using Statistica 7.0 (StatSoft, USA). Quantitative parameters were checked using Shapiro-Wilk test. The distribution number differs from normal parameters, so, the data are presented as Me (LQ, UQ), where: Me is mediana; LQ is low quartile; UQ is upper quartile. Group differences were estimated by Mann-Whitney non-parametric tests. The results were statistically significant at significance level of P<0.05.

Results

As we can see from the *Table* 2, there are statistically significant values in all studied parameters between the patients with MS and the control group, P<0.05.

Table 1. Comparative characteristics of the patients with metabolic syndrome and control group

Parameters	Control group (n=70)	Patients with metabolic syndrome (n=62)
BMI, kg/m^2	24.5 (21.3, 24.8)	35.0 (32.1, 41.3) *
Waist circumference, cm	88.0 (76.0, 92.0)	122.0 (113.0, 135.0) *
Hip circumference, cm	95.0 (93.0, 98.0)	113.5 (108.0, 134.5) *
SBP, mmHg	118.0 (110.0, 123.0)	151.0 (147.5, 155.0) *
DBP, mmHg	70.0 (65.0, 74.0)	95.0 (93.5, 99.5) *
Glucose, mmol/l	4.7 (4.5, 4.9)	5.9 (5.5, 6.2) *
Insulin, mcU/ml	10.13 (8.9, 11.6)	39.9 (31.9, 53.5) *
HOMA- IR	2.1 (1.8, 2.5)	9.4 (7.6, 13.5) *
Total cholesterol, mmol/l	4.5 (4.1, 4.8)	6.9 (6.3, 7.3) *
Triglycerides, mmol/l	1.33 (1.2, 1.5)	3.1 (2.2, 3.6) *
LDLC, mmol/l	2.3 (2.1, 2.4)	4.2 (3.8, 4.7) *
HDLC, mmol/l	1.6 (1.4, 1.7)	1.05 (1.0, 1.5) *
ELDLC, mmol/l	0.6 (0.6, 0.7)	1.4 (1.0, 1.7) *
Atherogenic index	1.8 (1.8, 1.9)	4.2 (3.5, 5.1) *

SBP, systolic blood pressure; DBP, diastolic blood pressure.

*P<0.05 by comparison of the research group and the control group.

Table 2. Comparative characteristics of the patients with metabolic syndrome and control group

Parameters	Control group (n=70)	Patients with metabolic syndrome (n=62)
Lipid hydroperoxides, µM	0.5 (0.5, 0.6)	2.9 (1.9, 3.9) *
Antioxidant activity, µM/l	304.5 (296.2, 311.7)	276.4 (239.0, 379.9) *

* P<0.05 by comparison of the research group and the control group.

Table 3. Dynamics of parameters of lipid peroxidation processes and antioxidant activity of blood serum at the patients with metabolic syndrome on the background of Siofor treatment

Observational period	Lipid hydroperoxides, µM	Antioxidant activity, мкМ/l
Before treatment	2.9 (1.9, 3.9)	276.4 (239.0, 379.9)
After 3 months	2.8 (1.9, 3.7)	279.0 (245.0, 375.6)
After 6 months	1.9 (1.5, 3.1) *	302.3 (254.1, 370.0) *
After 9 months	1.7 (1.3, 2.9) *	309.0 (247.5, 356.2) *
After 12 months	1.1 (0.8, 1.9) *	320.0 (278.9, 334.3) *

* $P<0.05$, statistical significance comparing with the parameters before treatment.

Performed tests displayed that LPO processes are intensified at the patients with MS – lipid hydrogen dioxide level almost 6 times higher then in the group of control. Antioxidant activity of blood serum of the patients with MS was reduced.

Analysis of the dynamics of these parameters on the background of Metformin taking displays its efficiency (*Table* 3), although statistically significant differences in the studied parameters appear only in 6 month of taking the medication.

It was found out that a hydrogen dioxide level had decreased almost 3 times during a year after medication taking – 1.1 (0.8, 1.9) µM. Antioxidant activity increases, and achieves physiological values after 6 months – 302.3 (254.1, 370.0) µM/l.

In our recent studies there was a strong correlative relationship between lipid hydroperoxides and BMI ($r=+0.77$, $P<0.05$) [9]. We divided all of the patients with MS into groups:
1) patients with BMI from 30.0 to 39.9 (I–II degree of obesity) – 32 patients (51,6 %);
2) patients with BMI from 40 and over (III and higher degree of obesity) – 30 patients (48,4 %).

In the 1st group BMI was 34.1 (32.3, 37.6), in the 2nd group – 41.3 (40.5, 43.6); index HOMA-IR 8.8 (7.1, 14.5) and 10.0 (8.9, 16.4) respectively, $P<0.05$. In the 1st group lipid hydroperoxides level in blood serum was 2.7 (2.2, 3.5) µM, in the 2nd one – 3.4 (2.9, 4.3) µM, $P<0.05$. Antioxidant activity in the 1st group was 343.2 (290.5, 363.7) µM/l, in the 2nd group – 263.1 (234.5, 290.4) µM/l, $P<0.05$.

Discussion

The results we got show that at the patients with MS LPO and antioxidant activity of blood serum disorders caused by IR evidence. MS in IR conditions is characterized by an increase of sympatho-adrenal system activity, which leads LPO processes activation. Whereas LPO which is caused by a complex reduction of antioxidant system and increased synthesis of free radicals at the patients with MS, is one of important reasons of IR support. So, there is a vicious circle. In this situation Siofor (Metformin) prescription is reasonable, because it reduces IR due to restoration of tissue sensitization to insulin by the growth of the amount of affinity receptors, through a stimulation of tyrosine kinase the activity of insulin receptors increases, expression and transposition of glucose transporters from intracellular store into cell membrane. All of these processes lead to an increase of glucose uptake by insulin target-organs: liver, skeletal muscles, fatty tissue. Besides, according to recent research data, the medication can trap free radicals or reduce their level by slowing down of intercellular forming of superoxide radicals (O_2^-), the major source of which is nitrogen oxides (NOX) acidification.

On the background of Metformin there was a significant reducing of lipid hydroperoxides and normalization of endogenic antioxidant background: after 12 months of Metformin taking hydroperoxides level decreased to 1.1 (0.8, 1.9) µM, and antioxidant activity increased to 320.0 (278.9, 334.3) µM/l. This is the ground to recommend Metformin as a medication for corrective treatment of LPO disorders and antioxidant status at MS.

Correlative analysis displayed that there is a strong direct connection between lipid hydroperoxides and BMI ($r=+0.77$, $P<0.05$). This may be explained as follows: in the recent studies we found out that IR is intensified when BMI increases [10]. The IR worsening leads to the LPO intensifying and increasing of lipid hydroperoxides.

It is an interesting fact about antioxidant activity of blood serum: it is higher at the patients with MS and I-II degree of obesity, and lower – at III and higher degree of obesity. This is evident that as the obesity is intensified LPO products are produced faster, and, in order to balance these changes, antioxidant activity increases, but on a certain stage it is wasted, adaptation failure and low antioxidant activity.

Conclusion

Siofor (Metformin) medication is effective in correcting of LPO processes and restoration of antioxidant activity in blood serum at the patients with metabolic syndrome.

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