

ВОЗМОЖНОСТИ ПРИМЕНЕНИЯ МЕТФОРМИНА ДЛЯ КОРРЕКЦИИ ЭНДОТЕЛИАЛЬНОЙ ДИСФУНКЦИИ И АДАПТАЦИОННЫХ РЕЗЕРВОВ ОРГАНИЗМА У БОЛЬНЫХ МЕТАБОЛИЧЕСКИМ СИНДРОМОМ

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Цель. Изучение возможностей медикаментозной коррекции метформинем клинико-лабораторных показателей, эндотелиальной дисфункции и неспецифических адаптационных резервов организма у больных метаболическим синдромом (МС).

Материалы и методы. В трёхмесячной программе лечения приняли участие 53 больных МС, рандомизированных в две сопоставимые группы. Пациенты группы контроля соблюдали индивидуальную гипокалорийную диету и режим дозированных физических нагрузок. Больные исследуемой группы дополнительно к вышеизложенной программе модификации образа жизни принимали метформин. Всем участникам исследования двукратно оценивали антропометрические и клинико-лабораторные показатели, а также анализировали состав тела, состояние сосудистого эндотелия и неспецифические адаптационные резервы организма. Степень эндотелиальной дисфункции оценивали по уровню эндотелина-1 и показателям фотоплетизмографического исследования, неспецифические адаптационные резервы – методом анализа вариабельности сердечного ритма.

Результаты. Метформин в сочетании с диетотерапией и физическими нагрузками показал себя в качестве безопасного лекарственного препарата для коррекции компонентов МС и эндотелиальной дисфункции. У больных МС применение сочетания метформина, диетотерапии и дозированных физических нагрузок в сравнении с использованием только программы модификации образа жизни приводит к снижению индекса массы тела, окружности талии (у женщин) и массы общего жира. Внедрение метформина в программу комплексной терапии больных МС способствует более выраженной, нежели только изменение образа жизни, коррекции показателей углеводного обмена, снижению значений эндотелина-1 и индекса жесткости стенки аорты, усилению активности парасимпатического контура регуляции вегетативной нервной системы.

Заключение. Использование метформина в составе комплексной терапии метаболического синдрома в сравнении с программой модификации образа жизни способствует более значимому снижению клинико-лабораторных показателей, эндотелиальной дисфункции и улучшению неспецифических адаптационных резервов организма.

Ключевые слова: метаболический синдром; метформин; эндотелиальная дисфункция; эндотелин-1; вариабельность сердечного ритма.

POSSIBILITIES OF USE OF METFORMIN FOR CORRECTION OF ENDOTHELIAL DYSFUNCTION AND ADAPTATION RESERVES OF AN ORGANISM IN PATIENTS WITH METABOLIC SYNDROME

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Aim. To study possibilities of pharmaceutical correction of clinical laboratory parameters, of endothelial dysfunction and non-specific adaptation reserves in patients with metabolic syn-



drome (MS) through use of metformin.

Materials and Methods. The three-month program involved 53 patients with MS randomized to two comparable groups. Patients of the control group were kept on individual low-calorie diet and practiced graduated exercises. Patients of the studied group, besides the mentioned program of modification of the lifestyle, took metformin. In all participants, anthropometric and clinical laboratory parameters were twice evaluated, total body composition, condition of vascular endothelium and non-specific adaptation reserves of an organism were analyzed. The extent of endothelial dysfunction was evaluated by the level of endothelin-1 and by parameters of photoplethysmographic examination, non-specific adaptation reserves – by the method of analysis of the cardiac rhythm variability.

Results. Metformin in complex with dietary therapy and physical exercises proved to be a safe medical drug for correction of components of MS and of endothelial dysfunction. Use of metformin in patients with MS in combination with dietary therapy and graduated physical exercises as compared to use of the program of modification of the lifestyle alone, leads to reduction in the body mass, waist circumference (in women) and of the total fat mass. Introduction of metformin into the program of complex therapy of patients with MS, provides more evident correction of the parameters of carbohydrate metabolism, reduction of endothelin-1 and stiffness index of the aortic wall, enhancement of parasympathetic regulation, than modification of the lifestyle alone.

Conclusion. Use of metformin in the complex therapy of metabolic syndrome in comparison with the program of modification of the lifestyle, promotes a more significant reduction of the clinical laboratory parameters, of endothelial dysfunction and improves non-specific adaptation reserves of an organism.

Keywords: *metabolic syndrome; metformin; endothelial dysfunction; endothelin-1; cardiac rhythm variability.*

Metabolic syndrome (MS) is a cluster of traditional and common conditions – abdominal obesity, dyslipidemia, arterial hypertension and hyperglycemia – that increase risk of developing cardiovascular diseases [1,2,3]. These components of MS have a common pathogenesis – a cascade of metabolic and hormonal disorders launched by insulin resistance preceded by imbalance of the autonomic nervous system [4-6]. However, recently the increasing attention of scientific community is being given to the role of endothelial dysfunction (ED) in the pathogenesis of MS [6]. Numerous research works point to a tight connection between insulin resistance and reduction of the response of the vessel wall to vasodilating influences. Alterations of the vessel wall to a large extent are mediated by reduction of nitric oxide (NO) – the most potent relaxant of the vessel wall [7]. Besides,

in most cases dysfunction of the vascular lining is associated with the increased production of some vasoconstrictors, the most important being endothelin-1 (ET-1) [8]. Enhanced production of ET-1 is considered to be a marker of ED [9,10]. Hyperinsulinemia leads to expressed production of ET-1 by endotheliocytes that further increases vasoconstriction [9,11].

At present an important task is development of effective methods of influence on the condition of the vascular lining and of therapeutic strategies for arrest of progress of ED in patients with MS. A promising method of correction of ED and components of MS may be therapy with metformin in complex with dietary therapy and graduated physical exercises. Metformin, besides hypoglycemic effect, possesses a high cardioprotective potential through some pleiotropic

effects: it produces a positive influence on the endothelial lining of the vessels, and possesses hypolipidemic and antiatherogenic effects [12].

Aim – to study possibilities of dietary and pharmaceutical correction of clinical laboratory parameters, of ED and non-specific adaptation reserves of an organism of patients with MS.

Materials and Methods

The work was carried out in 2017-2018 on the base of RyazSMU and Municipal Clinical Hospital №11 (Ryazan) according to Good Clinical Practice and principles of Declaration of Helsinki. The protocol of the study was approved by Local Ethical Committee of RyazSMU (№3 of 2016 October 9).

The study involved 53 patients (10 men and 43 women) of 25-65 years of age with verified diagnosis of MS.

MS was diagnosed by the presence of the main criterion – visceral obesity ((waist circumference (WC) >94 cm in men and >80 cm in women)) and of two additional criteria – arterial hypertension (AH) (systolic arterial pressure (AP) ≥ 140 mmHg and/or diastolic AP ≥ 90 mm Hg), level of triglycerides (TG) ≥ 1.7 mmol/L, of high density lipoprotein cholesterol (HDL cholesterol) <1.0 mmol/L in men and <1.2 mmol/L, of low density lipoprotein cholesterol (LDL cholesterol) >3.0 mmol/L, fasting blood glucose ≥ 6.1 mmol/L or blood glucose in 2 hours after glucose load in the range ≥ 7.8 and ≤ 11.1 mmol/L [1].

All participants had stable parameters of lipid and carbohydrate profile and did not take hypolipidemic and hypoglycemic medical drugs in the preceding 6 months. Criteria of exclusion were renal and hepatic failure, congestion heart failure, respiratory failure, ischemic heart disease, diabetes mellitus, alcoholism, known intolerance to metformin, a possibility of use of radiocontrast substances, pregnancy or lactation.

Individuals included into the study were randomized to two groups – the studi-

ed group (n=28, 6 men and 22 women) and the control group (n=25, 4 men and 21 women). The patients included into the study had a sufficient level of compliance and adherence to treatment and signed a voluntary informed consent before inclusion into the program.

All participants received a low-calorie individual diet, were keeping the diary of nutrition and were doing graduated physical exercise for not less than 40 minutes a day. The patients of the group of study received metformin at a dose of 2000 mg/day in addition to dietary therapy and physical activity. The patients of the control group (n=25) only carried out the above measures for modification of the lifestyle. All the participants received pharmaceutical correction of AH according to the actual clinical recommendations. Duration of the observation was 3 months.

In randomization and in the course of treatment, the general examination was conducted with obligatory measurement of the arterial pressure by Korotkoff method and evaluation of anthropometric parameters ((body mass (BM), WC and body mass index (BMI) calculated by Quetelet formula). The data of clinical urine and clinical blood analyses, electrocardiogram, values of transaminases, of creatinine and lipid spectrum (TG, LDL cholesterol, HDL cholesterol) were evaluated twice. Condition of carbohydrate metabolism was evaluated by the results of oral glucose tolerance test (OGTT) and the level of glycosylated hemoglobin (HbA1c).

Total body composition was examined twice using the accepted method of Body impedance on ABC-01 Medass device (Russia) at the frequency of probe current 50 kHz. Within the frames of this work, mass of the total fatty tissue, skeletal-muscular mass, total fluid mass and lean mass were determined. Normal values of the given parameters were automatically calculated by the program individually for each patient.

Before the study and after its completion, the condition of vascular endothelium was evaluated by the level of ET-1 in the blood serum and according to the data of photoplethysmographic examination on the hardware-software complex AngioScan-01M (Russia).

ET-1 level in blood serum was determined by immunoenzymometric method using kits of Biomedica cat. № BI-20052 on the apparatus Labsystems MultiScan MS №35200 7588 after 12-hour fasting. The reference median value given in the instruction to the reagent was 0.26 fmol/mL. This work was conducted on the base of Central research laboratory of RyazSMU.

Evaluation of the automated contour analysis of pulse wave on the AngioScan-01M apparatus included measurement of:

- stiffness index (SI) – parameter reflecting the viscous-elastic properties of large resistance vessels (normal values 5-8 m/s);
- reflection index (RI) – parameter characterizing spasm of small peripheral arteries of muscular type (permissible values do not exceed 30%);
- calculated augmentation index (AIp75) – index of stiffness of the aortic wall. Its value depends on the stiffness of the aorta and noticeably increases with age.

Systemic non-specific mechanisms of adaptation were analyzed by a method of mathematical analysis of the cardiac rhythm using Varicard complex (Russia) in randomization and after completion of the observation. Parameters of the activity of the parasympathetic regulation – root mean square deviation of SDNN (normal values up to 40-80 ms) and RMSSD (permissible values 20-50 ms), and also parameters of the activity of sympathetic regulation – index of strain of regulatory systems IS (normal values 80-150 conv. un.) and index of centralization IC (permissible values 1.3-2.5 conv. un.) were evaluated.

Statistical processing of the obtained results was carried out using personal computer with the operation system Microsoft Windows 7, software Microsoft Excel 2016 and Statistica 6.0 (StatSoft Inc., USA). Nominal and categorical variables were presented as absolute and relative values [n (%)]. For comparison of relative parameters in two independent groups by quality characteristic, Pearson's χ^2 test was used, or Fisher's exact test in case of the lowest value of the expected characteristic <5. Normalcy of distribution of characteristics was determined using Shapiro-Wilk test. The distribution was considered normal at $p > 0.05$. Other than normal distribution of characteristics was presented as Me [Q25; Q75], where Me is median, and Q25 and Q75 are the values of the lower and upper quartiles, respectively. For comparison of the two groups of patients on the basis of quantitative characteristics Mann-Whitney test was used. The critical level of significance in verification of statistical hypotheses was taken to be $p < 0.05$.

Results and Discussion

At the beginning of the study all the patients were comparable in clinical and laboratory data, in parameters of the functional condition of the endothelium and variability of the cardiac rhythm (Table 1). It should be noted that patients were also divided to groups by the amount of the administered antihypertensive medical drugs [13]. This is associated with the peculiarity of some antihypertensive medical drugs to influence the condition of the endothelium.

In body impedance assessment, all patients at the moment of randomization were diagnosed with a significant increase in mass of the total fatty tissue relative to the individual norm. The values of lean mass, skeletal-muscular mass and total fluid mass were within the individual norm in all participants of the treatment program.

Table 1

**Clinico-Demographic Characteristics of Studied Patients with MS
at the Moment of Inclusion into Study**

Parameter	Studied Group	Control Group	p
n	28	25	-
Age, years; Me [Q25; Q75]	51.4±4	49.1±6	0.96 ¹
BM, kg; Me [Q25; Q75]	91 [77;100]	84 [77;102]	0.73 ¹
BMI, kg/m ² ; Me [Q25; Q75]	32.2 [29.1;34.7]	34 [29.7;38.3]	0.34 ¹
WC, cm; Me [Q25; Q75]	women	103 [95;110.5]	0.17 ¹
	men	102.5 [96;110]	0.11 ¹
Antihypertensive Therapy			
Enalapril, %	14.3	20	0.31 ²
Lisinopril, %	10.7	12.5	0.88 ²
Perindopril, %	17.9	24	0.58 ²
Losartan, %	7.1	4	0.62 ²
Valsartan, %	28.6	28	0.96 ²
Telmisartan, %	7.1	4	0.62 ²
Indapamide, %	28.6	28	0.96 ²
Hypothiazid, %	21.4	24	0.12 ²
Metoprolol, %	25	20	0.54 ²
Nebivolol, %	7.1	4	0.41 ²
Amlodipine, %	21.4	28	0.58 ²
Moxonidine, %	10.7	16	0.57 ²
Body Impedance Assessment			
Total fat mass, kg; Me [Q25; Q75]	34.2 [28.4;43.6]	40.9 [27.7;51]	0.28 ¹
Lean mass, kg; Me [Q25; Q75]	54.4 [47.4;58.4]	50.4 [46.9;58.2]	0.49 ¹
Skeletal-muscular mass, kg; Me [Q25; Q75]	23.7 [19.9;26.3]	20.8 [19.4;24.9]	0.31 ¹
Total fluid mass, kg; Me [Q25; Q75]	40.5 [34.9;42.8]	36.9 [34.4;41.5]	0.29 ¹
Carbohydrate and Lipid Metabolism			
Fasting glucose, mmol/L; Me [Q25; Q75]	5.9 [5.4;6.9]	5.7 [5.2;5.9]	0.08 ¹
OGTT, mmol/L; Me [Q25; Q75]	8 [7.7;9.8]	8.2 [7.1;8.8]	0.42 ¹
HbA1c, %; Me [Q25; Q75]	6.5 [5.9;6.8]	6.4 [6.2;6.8]	0.89 ¹
LDL cholesterol, mmol/L; Me [Q25; Q75]	4.2 [3.4;4.9]	3.9 [2.9;4.2]	0.17 ¹
HDL cholesterol, mmol/L; Me [Q25; Q75]	1.3 [1.1;1.5]	1.3 [1.2;1.5]	0.61 ¹
TG, mmol/L; Me [Q25; Q75]	1.9 [1.4;2.4]	1.7 [1.1;2.2]	0.23 ¹
Functional Condition of Endothelium			
ET-1, fmol/mL Me [Q25; Q75]	0.36 [0.2;0.61]	0.52 [0.28;1.12]	0.4 ¹
SI ³ , m/c; Me [Q25; Q75]	7.8 [7.2;8.2]	7.6 [7.3;7.9]	0.57 ¹
Alp75, %; Me [Q25; Q75]	14.2 [10.8; 21.5]	16.5 [7.4;24.6]	0.77 ¹
RI ⁴ , %; Me [Q25; Q75]	31.8 [28.6; 45.4]	33.6 [27.5;44.3]	0.74 ¹
Variability of Heart Rhythm			
SDNN ⁵ , ms; Me [Q25; Q75]	71 [30;163]	36 [24;121]	0.25 ¹
RMSSD ⁶ , ms; Me [Q25; Q75]	39 [16.5;127]	34 [18.5;111]	0.85 ¹
SI ⁷ , conv. un.; Me [Q25; Q75]	388 [146;668]	502 [178;804]	0.20 ¹
IC ⁸ , conv. un.; Me [Q25; Q75]	5.5 [2.1;8.1]	3.1 [1.03;5.1]	0.16 ¹

Note: ¹ statistical significance for Mann-Whitney test, ² statistical significance for Pearson/Fisher χ^2 test, ³ normal values 5-8 m/s, ⁴ normal values up to 30%, ⁵ normal values 55-65 ms; ⁶ normal values 20-50 ms; ⁷ normal values 80-150 conv. un.; ⁸ normal values 1.3-2.5 conv. un.

All patients completed the research program in full volume. In the course of treatment 79.2% (n=42) of participants showed a good tolerance of metformin, 20.8% (n=11) showed satisfactory tolerance. Satisfactory tolerance was considered to be unfavorable effects in the form of short-term diarrhea and/or nausea which disappeared within the first 4-5 days of intake of metformin. These phenomena were brief and mild, they disappeared spontaneously, did not ap-

pear when the dose of the preparation increased and were not accompanied by any significant deviations in the laboratory parameters. During the whole period of study no side effects and significant pathological alterations of general clinical parameters were recorded which could lead to cancellation of the drug.

Clinical characteristics of patients with MS after 3-month course of treatment is given in Table 2.

Table 2

Clinical Characteristics of Studied Patients with MS on Completion of Study

Parameter	Studied Group	Control Group	p	
n	28	25	-	
BM, kg; Me [Q25; Q75]	85 [74;93]	84 [76;99]	0.5 ¹	
BMI, kg/m ² ; Me [Q25; Q75]	30.5 [27.6;33]	33.7 [28.1;37.3]	0.004 ¹	
WC, cm; Me [Q25; Q75]	women	96 [84;99]	100.5 [93.5;109]	0.02 ¹
	men	109 [102;109]	100.5 [93.5;102]	0.9 ¹
Body Impedance Assessment				
Total fat mass, kg; Me [Q25; Q75]	30.5 [22.8;38.1]	39 [30.1;48.4]	0.04 ¹	
Lean mass, kg; Me [Q25; Q75]	54.2 [47.6;57.5]	50.6 [47.2;57.1]	0.47	
Skeletal-muscular mass, kg; Me [Q25; Q75]	23 [20.3;27.1]	21.2 [19;25.3]	0.26 ¹	
Total fluid mass, kg; Me [Q25; Q75]	40 [34.9;42.4]	37.1 [34.5;41.8]	0.36 ¹	
Carbohydrate and Lipid Metabolism				
Fasting glucose, mmol/L; Me [Q25; Q75]	5.5 [5;5.9]	5.5 [5.1;5.8]	0.83 ¹	
OGTT, mmol/L; Me [Q25; Q75]	6.9 [6.7;7.4]	7.8 [6.9;8.9]	0.03 ¹	
HbA1c, %; Me [Q25; Q75]	5.2 [5.1;5.6]	5.9 [5.5;6.1]	0.01 ¹	
LDL cholesterol, mmol/L; Me [Q25; Q75]	3.5 [3.2;4.2]	3.3 [2.7;3.8]	0.7 ¹	
HDL cholesterol, mmol/L; Me [Q25; Q75]	1.5 [1.2;1.7]	1.4 [1.2;1.7]	0.88 ¹	
TG, mmol/L; Me [Q25; Q75]	1.6 [1.1;1.8]	1.5 [1;2.1]	0.7 ¹	
Functional Condition of Endothelium				
ET-1, fmol/mL; Me [Q25; Q75]	0.21 [0.14;0.39]	0.42 [0.3;0.74]	0.02 ¹	
SI, m/c ; Me [Q25; Q75]	8.5 [7.1;7.8]	8.1 [7;7.6]	0.21 ¹	
Alp75, %; Me [Q25; Q75]	22 [6.9;17.5]	23.7 [4.6;21.8]	0.04 ¹	
RI, %; Me [Q25; Q75]	31.9 [27.8;43.5]	34.7 [26.4;38.1]	0.98 ¹	
Variability of Heart Rhythm				
SDNN, ms; Me [Q25; Q75]	170 [119;271]	116 [46;178]	0.03 ¹	
RMSSD, ms; Me [Q25; Q75]	156 [111;281]	125 [67.5;315]	0.3 ¹	
SI, conv. un.; Me [Q25; Q75]	297 [182;673]	428 [275;802]	0.2 ¹	
IC, conv. un.; Me [Q25; Q75]	2.4 [1.5;5.1]	2.1 [0.9;9.4]	0.16 ¹	

Note: ¹ – statistical significance for Mann-Whitney test

According to the data of Table 2, values of BM, BMI and WC decreased in both groups of patients which evidences the effectiveness of lifestyle modification for correc-

tion of MS. Here, in the course of the body impedance assessment it was found that BM in all patients decreased primarily due to loss of the total fatty tissue, while skeletal-

muscular mass, total fluid mass and lean mass showed almost no changes after the treatment course. However, patients of the studied group who received metformin, evidently showed a more significant reduction of BMI, WC in women, and of the total fat mass than patients of the control group. The identified positive effect of metformin in respect of reduction of fatty tissue agrees with the literature data. Thus, according to the results of earlier studies, metformin showed a sufficient anorexigenic effect aimed at reduction and stabilization of the body mass and reduction of deposition of visceral fatty tissue [14].

Resting on the results of Table 2, it is important to note a positive effect of metformin in respect of correction of disorders of carbohydrate metabolism in patients with MS. Thus, with intake of metformin, a statistically more reliable reduction of OGTT and HbA1c in comparison with control group was noted. These results evidence a sufficient hypoglycemic potential of metformin. A good tolerance to metformin shown in the given study permits to recommend it for inclusion into the complex correction of disorders of carbohydrate metabolism in patients with MS [15].

Analysis of the dynamics of the parameters of lipid metabolism with the underlying treatment shows reduction of LDL cholesterol, HDL cholesterol and TG (Table 2). However, no reliable difference was found between the numeric values of these parameters in the studied group and in the control group. Thus, according to the results of this study, a hypolipidemic effect of three-month intake of metformin in patients with MS was comparable with that of three-month application of the program of the lifestyle modification. However, data of the earlier studies show antiatherogenic potential of metformin [16]. The insufficient effectiveness of this drug in respect of correction of lipid metabolism may be attributed to a short observation period.

In the course of study a positive influence of metformin on the parameters of the

functional condition of the endothelium was shown. Correction of ED with metformin resulted in more significant reduction of ET-1 and Alp75 values than in the control group (Table 2). These results agree with literature data. In the earlier studies a positive effect of metformin on correction and maintenance of integrity of the endothelium was shown. In three-month course of treatment with metformin at a dose of 1000 mg/day, the values of endothelium-dependent dilatation of the brachial artery in patients with MS evidently improved [17]. In young women with polycystic ovarian syndrome, the values of ET-1 and parameters of endothelium-dependent dilatation of the brachial artery showed a statistically significant reduction after 6-month treatment with metformin at a dose of 1700 mg/day [18].

Patients of both groups showed a tendency to increase in the parameters of the parasympathetic regulation – SDNN and RMSSD (Table 2). Here, SDNN more significantly increased in the patients of the studied group than of the control group. The given results indicate a positive effect of metformin in terms of correction of non-specific adaptation mechanisms. Taking into account an unfavorable effect of hyperglycemia on non-specific adaptation reserves of an organism, it is possible to make a conclusion about connection of improvement of parameters of parasympathetic regulation with the hypoglycemic effect of metformin [6,15].

Thus, in patients with MS, besides a glycemic effect of metformin in complex therapy, a number of pleiotropic effects were found. With correction of MS with metformin, there were noted more positive than in the control group, changes of BM, of WC in women and of the total fat mass, and also more significant reduction of the endothelial dysfunction evaluated by ET-1 level and by parameters of photoplethysmographic study, and increase in the parameters of parasympathetic regulation.

Conclusion

According to the results of the given study, metformin in combination with dietary therapy and physical exercises showed itself to be a safe and effective medical drug for correction of components of metabolic syndrome, of endothelial dysfunction and non-specific reserves of an organism. Use of metformin in complex therapy for metabolic syndrome within 3 months is safe and clinically more effective than programs of modification of the lifestyle alone. A combination of metformin, dietary therapy and graduated physical loads within 3 months in patients with MS leads to a more reliably evident reduction of body mass, waist circumference in women, total fat mass (by the data of body impedance assessment), normalization

of the parameters of carbohydrate metabolism than use of measures for correction of the lifestyle alone.

Besides, a course of treatment with metformin in combination with measures for correction of the lifestyle within 3 months more significantly than in the control group, improves the values of endothelin-1 and index of the aortic wall stiffness (Alp75) evaluated by a photoplethysmographic method, and leads to enhancement of the activity of parasympathetic regulation.

Thus, taking into account safety and a number of pleiotropic effects of metformin, it is possible to use it as a means for correction of endothelial dysfunction and for reduction of the risk of developing cardiovascular diseases in patients with metabolic syndrome.

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