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Research Article

METABOLIC SYNDROME AS A HOMEOSTASIS MODIFICATION FACTOR

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A B S T R A C T

Various diseases, such as psoriasis and ischaemic heart disease, that are complicated by metabolic syndrome, were found to be accompanied by modification and aggravation of immune and metabolic disorders, particularly abnormal cytokine production, as well as monotonous changes in the responses of patients receiving conventional treatment and low efficacy of this treatment. In this study we have observed normalization of abnormal parameters by the use of intravenous low-level laser irradiation of autologous blood, as well as a crucial impact of the pathogenesis on the signal targets of various differentiated treatment modalities and the way they are affected by the immunomodulatory activity of laser irradiation alone.

INTRODUCTION

During the last years internists, endocrinologists, cardiologists, immunologists, and other medical specialists intensively studied the metabolic syndrome (MS), which includes the following: 1) abdominal obesity; 2) type 2 diabetes mellitus or impaired glucose tolerance; 3) arterial hypertension; 4) dyslipidaemia. The prevalence of this disorder is progressively increasing. When combined with various diseases, metabolic syndrome is associated with a probable homeostasis change that remains poorly understood (1, 2, 3, 4).

Changes in metabolic syndrome manifestations (significant increases in body mass index, leptin, glucose, insulin, and total cholesterol concentrations, imbalance between high- and low-density lipoproteins, stimulation of total oxidative capacity, presence of Stage 1 - 2 essential hypertension) were investigated depending on laboratory manifestations of immune disturbances and their treatment in patients with psoriasis (Ps) or ischaemic heart disease (IHD) receiving conventional or complex (combined with low-level laser therapy [LLLT]).

MATERIALS AND METHODS

The study population included 50 healthy individuals, 60 patients with Ps and 60 patients with MS complicated by Ps; 60 subjects with IHD and 60 patients suffering from MS complicated by IHD, who received treatment conventionally used for each of this condition (ConvTr) or a combination of this treatment with LLLT. The following parameters were assessed in study subjects before and after treatment: body mass index (BMI); carbohydrate metabolism parameters (glucose, insulin, glycated haemoglobin (Hb A1c), C-peptide (its concentration corresponds to the insulin level in the body and allows assessment of insulin secretion), homeostatic model assessment - insulin resistance index [HOMA-IR]); lipid metabolism parameters (total cholesterol (CH total), high- and low-density lipoproteins (HDL and LDL), oxidized LDL, atherogenic index of plasma [AIP]); antioxidant system parameters (plasma total oxidant status (PTOS), total oxidant capacity (TOC), superoxide dismutase [SOD]); cytokine profile (interleukins, gamma-interferon, tumour necrosis factor [IL-1, IL-1-beta, -4, -6, -8, gamma-INF, TNF]); and endocrine system adaptation factors **(**leptin (obesity hormone), ACTH, cortisol, growth hormone (GH), thyroglobulin (TG), and beta-endorphin).

Parametric and non-parametric tests were employed to analyze differences in laboratory test results from the normal level, from baseline, and from the post-conventional treatment level. To evaluate test variations, the study tests were grouped by method, using two versions of rank order analysis: by determining the rank of the difference between the obtained parameter value and the pre-determined level using the following scale: - significant (1, > 66 %), moderate (2, 33 % to 66 %), and minor (3, < 33 %) variations; and by ranking parameters in accordance with the absolute values of the diagnostic value coefficient, calculating the sum of the rating numbers of the parameters, meaning that the lower the sum the higher the difference.

The magnitude of changes in individual parameters was calculated using the Immune Disorder Formula (IDF):

$$\left(\frac{patient\text{-}value}{healthy\text{-}value} - 1\right) \times 100\%$$

changes in parameter values of up to 33 % indicate a minor degree (I) of the immune disorder, changes of 33 % to 66 % imply a significant disorder (II), and changes exceeding 66 % show a severe (III) immune disorder. Afterwards, conventional statistical methods were used to evaluate all investigated parameters and select values differing with statistical significance from the pre-determined level. The diagnostic value coefficient (Kj) and the formula:

$$Kj = \frac{2 \cdot (¢_1^2 + ¢_2^2)}{(M_2 - M_1)^2},$$

where δ_1 and δ_2 are the root-mean-square deviations, M_1 are the arithmetic mean values of the healthy individuals, M_2 are the arithmetic mean values of the main group patients, were then used to identify the key tests based on the following principle: the lower the absolute of the calculated Kj value the higher the magnitude of the difference from the pre-determined level.

These formulas were also used to derive the parameter shift formula (PSF), immunomodulation target formula (IMTF), and key IMTF tests independent of basic treatment [IMTFind] for changes from baseline and from the post-conventional treatment level (for all formulas and other above calculations – see 5, 6, 7).

OBTAINED RESULTS

The psoriasis plus metabolic syndrome combination

As presented in Table 1, reliable stimulation was universally observed in patients with Ps and Ps+MS, as compared with the reference data of healthy individuals, as shown by changes in body mass index, all carbohydrate metabolism parameters and four out five lipid metabolism indicators (with the exception of HDL); six pro- and anti-inflammatory cytokines; decreased PTOS, SOD, and beta-endorphin concentrations; increased TOC, leptin, cortisol, and TG; reduced ACTH and GH. In other words, patients with acute disease presented with impaired glucose tolerance, obesity with dyslipidaemia, excessive production of pro- and anti-inflammatory cytokines, and imbalances of antioxidant and endocrine adaptation factors.

Table 1 Changes in immunological laboratory test results in patients with psoriasis complicated by metabolic syndrome

Parameters	Control (reference interval) n=50	Ps without MS n=60 (+ or -)	Ps n=60 (+ or -)	Differences between Ps+MS and Ps (+ or -)
BMI, kg/m^2	23.84±0.14	+(27.46±0.13)	+(37.78±0.15)	+
Carbohydrate metabolism parameters				
Glucose, mmol/L	4.48±0.04	+ (5.55±0.07)	+(7.89±0.06)	+
Insulin, μIU/mL	6.37±0.13	+(8.54±0.09)	+(13.82±0.03)	+
Hb A1c %	4.55±0.09	+(5.69±0.09)	+(6.73±0.06)	+
C-peptide, ng/mL	1.82±0.03	+(2.61±0.09)	+(3.42±0.03)	+
HOMA-IR, units	1.28±0.04	+(2.12±0.0)	+(4.87±0.05)	+
Difference rank		1	1	1
Lipid metabolism parameters				
CH total, mmol/L	4.18±0.08	+(5.25±0.06)	+(6.74±0.06)	+
HDL cholesterol, mmol/L	1.5±0.03	-(1.22±0.02)	-(0.83±0.01)	-
LDL cholesterol, mmol/L	2.11±0.06	+(3.26±0.0)	+(4.68±0.02)	+
Oxidized LDL, ng/mL	62.16±1.26	+(106.32±1.69)	+(143.03±1.0)	+
AIP	1.79±0.04	+(3.36±0.05)	+(7.34±0.09)	+
Difference rank		1	1	1
Antioxidant system parameters				
PTOS, μmol/L	65.29±1.26	-(40.91±0.82)	-(25.57±0.49)	-
TOC, μmol/L	1.97±0.07	+(3.5±0.05)	+(4.98±0.04)	+
SOD, ng/mL	0.95±0.03	-(0.65±0.02)	-(0.33±0.0)	-
Difference rank		1	1	1
Cytokines				
IL-1, pg/mL	1.27±0.03	+(2.94±0.03)	+(4.51±0.01)	+
IL-4, pg/mL	1.77±0.05	+(4.77±0.07)	+(8.51±0.06)	+
IL-6, pg/mL	2.86±0.09	+(12.58±0.12)	+(18.17±0.09)	+
IL-8, pg/mL	3.68±0.09	+(11.81±0.37)	+(20.08±0.20)	+
INF-γ, pg/mL	15.8±0.29	+(61.3±1.58)	+(89.47±0.8)	+
TNF, pg/mL	4.67±0.13	+(18.4±0.33)	+(26.58±0.18)	Endocrine status parameters
Difference rank		1	1	1
Leptin, ng/mL	13.35±0.15	+(20.54±0.22)	+(26.84±0.13)	+
ACTH, pg/mL	15.7±0.15	-(11.04±0.15)	-(8.99±0.08)	-
Cortisol, μg/dL	0.79±0.02	+(1.12±0.01)	+(1.46±0.0)	+
GH, ng/mL	5.6±0.04	-(3.71±0.04)	-(2.90±0.03)	-
Beta-endorphin, μg/mL	5.6±0.04	-(3.71±0.04)	-(2.90±0.03)	-
TG, mmol/L	1.25±0.03	+(1.69±0.03)	+(2.69±0.02)	I
Difference rank		1	1	1
General differences		1	1	1

Legend: control – test results obtained in healthy individuals; differences from the reference values are shown as follows: - below normal, + stimulation at $P < 0.05$; Rank 1 – significant (> 66 %) deviations from the reference value

In patients with psoriasis complicated by metabolic syndrome, the overall profile of qualitative parameter variations was unchanged while quantitatively they were worse than in subjects with the underlying condition alone. In particular, direct comparison of the constituents of the immunological and metabolic status in study subjects revealed a statistically significant difference in patients with the combined disorder in all 26 parameters.

Parameters that were found to be stimulated in patients with Ps+MS included body mass index, five carbohydrate metabolism tests (glucose, insulin, glycated haemoglobin, C-peptide, insulin resistance index); lipid parameters (total cholesterol, oxidized LDL, LDL cholesterol, atherogenic index of plasma); antioxidant mechanisms (TOC); pro- and anti-inflammatory cytokines (IL-1, -4, -6, -8, TNF, INF-gamma); and endocrine parameters (leptin, cortisol, TG).The rating of differences between obtained grouped laboratory test results and the respective reference value in patients of both study groups (using the "significant", "moderate", and "minor" difference scale) yielded inconspicuous changes that were maximal in all cases.Application of the other rank order analysis version to the obtained Kj results revealed (see Table 2) that the "metabolic disorder" stimulated the parameters to a greater extent, specifically carbohydrate and lipid metabolism, TOC, and endocrine status, with a similar quantitative response in the cytokine system (19 and 19 ranks).

Table 2 Immunological laboratory test abnormalities in diseases of different origins using rank assessment in patients with metabolic syndrome

Disease	Grouped parameters					Rank sum
	Carbohydrate	Lipid	TOC	Cytokines	Endocrine	
Psoriasis	54/2	51/2	35/2	19/1	55/2	9/2
Psoriasis+ MS	43/1	42/1	31/1	19/1	30/1	5/1
IHD	43/2	17/2	46/2	61/2	82/2	10/2
IHD+ MS	28/1	16/1	34/1	58/1	76/1	5/1

Legend: numerator – sum of the ranks of the parameters, denominator – rank size, 1, 2 – maximal and minimal differences of the grouped parameters from the respective reference value.

Among all parameters investigated in patients with Ps and Ps+MS, the signal parameters, according to the IDFbas (baseline IDF), were cytokines: $IL1^{+}_{2}IL6^{+}_{3}TNF^{+}_{3}$ and $IL6^{+}_{3}TNF^{+}_{3}IL4^{+}_{3}$,,yet they had different variable data sets, order, and degree of changes in the key parameters of the formulas (Table 3).Comparison of results obtained with conventional or conventional plus LLLT treatment in the acute (10 - 12 days) and follow-up (3 months) periods revealed a manifestation of the modulatory effect of the non-pharmacological factor, i. e. a statistically significant suppression of originally increased laboratory test results and a stimulation of those laboratory values that had been decreased at baseline in study subjects.

We choose to explain the monotonous quantitative drift from normal of the laboratory status constituents observed in study subjects given one of the two treatment options during the two study periods by the presence of metabolic syndrome manifestations. These changes were, however, associated with a significant qualitative reaction described by the typical formulas detected by mathematical point-analysis (Table 3).

Table 3 Signal immunological laboratory test abnormalities and targets for different treatment modalities in patients with psoriasis complicated by metabolic syndrome

Immunological formulas	Psoriasis	Psoriasis + metabolic syndrome	
		Conventional treatment	Conventional treatment + LLLT
		10 - 12 days 3 months	10 - 12 days 3 months
IDFbas	$IL1^{+}_{2}$ $IL6^{+}_{3}$ $IL6^{+}_{3}$ TNF^{+}_{3} TNF^{+}_{3} $IL4^{+}_{3}$		
PSF		$SOD^{-}_{2}IL4^{+}_{3}HOMA\text{-}IR^{+}_{3}$	
IMTF		AIP^{-}_{1} $IL4^{-}_{1}$ HDL^{+}_{1} $ACTH^{-}_{1}$ LDL^{-}_{1} $HbIc^{-}_{1}$	$IL6^{-}_{2}$ $IL4^{-}_{2}$ $IL8^{-}_{2}$ $IL4^{+}_{2}$ $INF\text{-}\gamma^{+}_{2}$ $IL8^{+}_{2}$
IMTFind LLLT		10 - 12 days $IL4^{-}_{3}AIP^{-}_{2}IL1^{-}_{2}$	3 months $TG^{+}_{3}HDL^{+}_{3}LDL^{-}_{3}$
IDFfinal		TNF^{+}_{2} $IL4^{+}_{3}$ $INF\text{-}\gamma^{+}_{2}$ $IL6^{+}_{3}$ $IL6^{+}_{2}$ $IL8^{+}_{3}$	$CH\ total^{+}_{2}$ TOC^{-}_{1} $IL6^{+}_{3}$ $PTOS^{-}_{2}$ TG^{+}_{3} $ACTH^{-}_{1}$

Legend: see above. IDFfinal - final IDF (at discharge from hospital)

In particular, the IMTF for complex immunological therapy (ConvTr + LLLT) during the two study periods differed in all constituents: $IL6^{-}_{2}IL4^{-}_{2}IL8^{-}_{2}$ and $IL4^{+}_{2}INF\text{-}gamma^{+}_{2}IL8^{+}_{2}$. The additionally derived IMTFind LLLT independent of conventional treatment confirmed this conclusion: 10 - 12 days - $IL4^{-}_{3}AIP^{-}_{2}IL1^{-}_{2}$ and 3 months - $TG^{+}_{3}HDL^{+}_{3}LDL^{-}_{3}$.

Therefore, LLLT given early in the course of the disease primarily suppresses the anti-inflammatory IL4, atherogenic index of plasma, and IL1; later on, it has a different mechanism of action, stimulation of TG production and boosting HDL concentrations, while also decreasing the LDL content.

The ischaemic heart disease plus metabolic syndrome combination

The results showing the effects of metabolic syndrome on laboratory test results in patients with IHD are presented in Table 4 and indicate a different mechanism of this combined disorder.

In particular, the combination of IHD with MS resulted in stimulation of the carbohydrate, lipid, TOC, cytokine, and endocrine parameters in almost 100 % of cases, whereas seven tests remained normal in patients with IHD alone: glycated haemoglobin, C-peptide, HDL, SOD, leptin, ACTH, cortisol, and beta-endorphin. Direct comparison of results obtained in patients with IHD and in those with IHD + MS demonstrated statistically significant increases in indicators of various metabolic types in the latter group, specifically in glucose, insulin, Hb A1c, HOMA-IR, IL-1-beta, IL8, INF-gamma, and TG. The use of the two rank order analysis variants confirmed the aggravation of laboratory changes in IHD patients afflicted by metabolic syndrome. The deviations of the key IDF constituents ($CH\ total^{+}_{2}HOMAIR^{+}_{3}Glu^{+}_{2}$ and $TG^{+}_{2}CH\ total^{+}_{3}C\text{-}peptide^{+}_{3}$) from the normal level, as well as the PSF deviation from the IHD level ($HOMAIR^{+}_{3}IL1\beta^{+}_{3}TG^{+}_{3}$), were different for all constituents, as shown by Table 5, thus indicating that the mechanisms of the effects on laboratory test results differ between patients with the disease alone and those with the combination of the two conditions. Additional information was provided by analysis of the qualitative mechanisms underlying the mobile effects of the differentiated treatment (Table 5).

The key IMTF TrConv and TrConv + LLLT targets at work-up days 10 - 12 in this clinical model were found to be imbalance of antioxidant system factors - TOC, SOD, with decreased INF-gamma concentrations, and suppressed production of three cytokines: IL8, INF-gamma$^{-}_{3}$, and TNF$^{-}_{3.}$ At 3 months, the targets for the two treatment options included IL6$^{-}_{1}$TNF$^{-}_{1}$TOC$^{-}_{1}$ and- IL4$^{+}_{2}$INF-gamma$^{-}_{2}$IL8$^{-}_{2.}$ The attempt to identify the effect of LLLT proper, independently of conventional treatment (IMTFind), in patients with IHD + MS at different time points of the study revealed differences in two of the three components of the formulas IL4 $^{+}_{2}$IL6$^{-}_{2}$IL1β $^{-}_{2}$ andHOMA-IR$^{-}_{2}$ IL6$^{-}_{2}$ INF-gamma$^{-}_{2}$.

Assessment of the final IDF (at discharge from hospital), i. e. results of the key normalizing correction of the used treatment options for IHD + MS, demonstrated an absolutely different mechanism of the resulting immunological disorder. TrConv was followed by altered cytokine levels (IL8$^{+}_{3}$INF-gamma$^{+}_{3}$TNF$^{+}_{3}$) at 10 - 12 days and cytokine and TOC factor changes (INF-gamma$^{+}_{3}$IL8$^{+}_{3}$PTOS$^{-}_{2}$) at 3 months; whereas TrConv + LLLT was followed by changing concentrations of interferon, low-density lipoproteins, ACTH (INF-gamma$^{+}_{3}$LDL$^{+}_{3}$ACTH$^{+}_{2}$) and two cytokines, low-density lipoproteins (TNF$^{+}_{3}$LDL$^{+}_{3}$INF-gamma$^{+}_{3}$). A comparison of the formulas demonstrates a significant difference in the key composition, that of 100 % or 66 %.

Table 4 Immunological laboratory test abnormalities in patients with IHD complicated by metabolic syndrome

Parameters	Control (reference interval) n=50	IHD n=60 /tr	IHD + MS n=60/tr	Differences between IHD+MS and IHD
Carbohydrate metabolism parameters				
Glucose, mmol/L	1.87±0.19	2.63±0.57/+	3.39±0.6/+	+
Insulin, μIU/mL	6.29±0.19	9.51±0.1/+	15.51±0.2/+	+
Hb A1c %	4.4±0.1	5.3±0.4	7.1±0.9/+	+
C-peptide, ng/mL	1.87±0.19	2.63±0.77	3.39±0.6/+	
HOMA-IR, units	1.32±0.3	2.40±0.52/+	5.2±0.11/+	+
Difference rank		2	1	1
Lipid metabolism parameters				
CH total, mmol/L	4.02±0.7	5.61±0.87/+	6.72±0.6/+	
HDL cholesterol, mmol/L	1.47±0.38	1.1±0.18	0.87±0.2/-	
Oxidized LDL, ng/mL	57.5±0.7	101.6±0.3/+	137.5±0.42/+	
Difference rank		1	1	3
Antioxidant system parameters				
PTOS, μmol/L	58.8±0.12	41.6±0.16/+	26.8±0.17/+	
TOC, μmol/L	1.82±0.15	2.65±0.44/+	3.24±0.47/+	
SOD, ng/mL	0.86±0.14	0.58±0.31	0.35±0.25/+	
Difference rank		1	1	3
Cytokines				
IL-1-beta	1.15±0.22	2.82±0.11/+	5.02±1/+	+
IL-4, pg/mL	5.13±0.19	4.71±0.15/-	2.75±0.96/+	
IL-6, pg/mL	2.69±0.77	6.2±0.18/+	9.94±0.3/+	
IL-8, pg/mL	3.42±0.72	22.6±0.41/+	36.6±0.44/+	+
INF-gamma, pg/mL	16.2±0.24	69.8±0.11/+	101.2±0.17/+	+
TNF, pg/mL	3.99±0.8	13.53±0.4/+	24.5±0.8/+	
Difference rank		1	1	2
Endocrine status parameters				
Leptin, ng/mL	5.52±0.49	12.8±0.94	27.2±0.18/+	
ACTH, pg/mL	12.45±0.37	15.4±0.35	19.4±0.6/+	
Cortisol, μg/dL	13.08±0.4	16.76±0.51	23.4±0.59/+	
Beta-endorphin, μg/mL	4.98±0.15	4.23±0.14	3.26±0.17/+	
TG, mmol/L	1.19±0.17	1.61±0.1/+	2.7±0.12/+	+
Difference rank		3	1	3
General differences		2	1	2

Legend: IHD – ischaemic heart disease, 1, 2, 3 – significant (> 66 %), moderate (33 % to 66 %), minor (< 33 %) deviations from normal, see above for the other symbols.

Table 5 Effects of metabolic syndrome on signal immunological laboratory test abnormalities and targets for different treatment modalities in patients with IHD

Formulas	IHD	IHD + metabolic syndrome				
		IHD + metabolic syndrome	Conventional treatment		Conventional treatment + LLLT	
			10 - 12 days	3 months	10 - 12 days	3 months
IDFbas	CH total$^{+}_{2}$ HOMA-IR$^{+}_{3}$ Glu$^{+}_{2}$	TG$^{+}_{2}$ CH total$^{+}_{3}$ C-peptide $^{+}_{3}$				
PSF			HOMA-IR$^{+}_{3}$IL1 β$^{+}_{3}$ TG$^{+}_{3}$			
IMTF			TOC$^{-}_{1}$ SOD$^{+}_{1}$ INF-γ$^{-}_{1}$	IL6$_{1}^{-}$ TNF$^{-}_{1}$ TOC$^{-}_{1}$	IL8$^{-}_{3}$ INF-γ$^{-}_{3}$ TNF$^{-}_{3}$	IL4$^{+}_{2}$ INF-γ$^{-}_{2}$ IL8$^{-}_{2}$
IMTFind LLLT			10 - 12 days IL4$^{+}_{2}$IL6$^{-}_{2}$ IL1β $^{-}_{2}$		3 months HOMA-IR$^{-}_{2}$ IL6$^{-}_{2}$ INF-γ$^{-}_{2}$	
IDFfinal			IL8$^{+}_{3}$ INF-γ$^{+}_{3}$ TNF$^{+}_{3}$	INF-γ$^{+}_{3}$ IL8$^{+}_{3}$ PTOS$^{-}_{2}$	INF-γ$^{+}_{3}$ LDL$^{+}_{3}$ ACTH$^{+}_{2}$	TNF$^{+}_{3}$ LDL$^{+}_{3}$ INF-γ$^{+}_{3}$

Legend: see above.

Of considerable interest is the crucial impact that one of the treatment modalities, low-level laser therapy (LLLT), was found to exert on the combination of the "proper" targets in patients with different pathogenesis who were evaluated at different time points: these targets were $IL4^{+}{}_{3}AIP^{-}{}_{2}IL1^{-}{}_{2}$ and$TG^{+}{}_{3}HDL^{+}{}_{3}LDL^{-}{}_{3}$ at 10 - 12 days and at 3 months, respectively, for Ps + MS; and $IL4^{+}{}_{2}IL6^{-}{}_{2}IL1\beta^{-}{}_{2}$ and$HOMAIR^{-}{}_{2}IL6^{-}{}_{2}INF^{-}{}_{2}$ at 10 - 12 days and at 3 months, respectively, for IHD + MS. Basically, the identified different compositions of the key formulas casts doubt on the existence of fixed undoubted targets for LLLT.

Our analysis of the representation of laboratory parameters grouped by metabolism type in the diagnostically relevant, key constituents of the IDF, PSF, IMTF, and IMTFind formulas revealed that patients with psoriasis complicated by metabolic syndrome primarily had changes in the cytokine parameters (69.7 %), and smaller changes (21.2 %) in the lipid profile, while patients with IHD + MS mostly had cytokine abnormalities (66.7 %) along with changes in some other parameters: carbohydrate (23.0 %), lipid, and TOC (12.1 % and 12.1 %, respectively).

In conclusion, patients with diseases of different origin who presented with manifestations of metabolic syndrome were found to have: (1) a quantitative aggravation of changes in carbohydrate, lipid, and cytokine metabolism, endocrine and antioxidant factors (mostly stimulation), (2) a predominant variation of the production of pro- and anti-inflammatory cytokines, (3) qualitatively monotonous and quantitatively unreliable deviations of laboratory test results from the reference range as a result of conventional treatment, observed within the periods ranging from 10 days to 3 months, (4) augmentation by LLLT of the normalizing effects exhibited by conventionally used pharmacological therapy, (5) a decisive influence of the disease pathogenesis on the signal targets of the studied variants of complex differentiated treatment and of one non-pharmacological treatment factor alone.

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