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Is smoking a risk factor for metabolic syndrome?

Czy palenie tytoniu jest czynnikiem ryzyka zespołu metabolicznego?

ABSTRACT

Background. We define metabolic syndrome as a non-random collective incidence of glucose metabolism disorders related to insulin resistance, central obesity, dyslipidemia, arterial hypertension and other factors which contribute to increased risk of ischemic heart disease and diabetes mellitus type 2. Smoking is one of the most significant risk factors for ischemic heart disease.

Objectives and methods. A prospective analysis of 125 patients (75 men and 50 women) with the average age of 57.3 years. A subset of smokers was composed of 59 patients; the average number of cigarettes smoked per day was 18 pieces. A subset of non-smokers was composed of 66 patients. We examined the presence of metabolic syndrome components according to the *International Diabetic Federation* criteria for the European population throughout the whole set of patients.

Results. Percentually higher incidence of metabolic syndrome occurred in the group of non-smokers. The incidence of metabolic syndrome in the group of smo-

kers was significantly influenced by their age. Arterial hypertension and impaired fasting glucose were the most frequent components of metabolic syndrome in the subset of smokers with metabolic syndrome. In the subset of non-smokers with metabolic syndrome arterial hypertension was the most frequently found component.

Conclusion. The results of the research did not show statistically significantly increased or decreased incidence of metabolic syndrome in case of smokers. We did not find any relation between the number of cigarettes smoked per day and metabolic syndrome development. (Diabet. Klin. 2014; 3, 4: 136–143)

Key words: metabolic syndrome, smoking, nicotine, obesity, cardiovascular risk

STRESZCZENIE

Wstęp. Zespół metaboliczny określa się jako współwystępowanie zaburzeń metabolizmu węglowodanów związanych z insulinoopornością, otyłością brzuszną, dyslipidemią, nadciśnieniem tętniczym i innymi czynnikami przyczyniającymi się do zwiększonego ryzyka choroby niedokrwiennej serca i cukrzycy typu 2. Jednym z najważniejszych czynników ryzyka choroby niedokrwiennej serca jest palenie tytoniu.

Cel badania i metody. Przeprowadzono prospektywną analizę 125 chorych (75 mężczyzn i 50 kobiet), których średnia wieku wynosiła 57,3 roku. Podgrupa osób palących obejmowała 59 chorych; średnia liczba wypalanych dziennie papierosów wynosiła 18 sztuk. Podgrupa osób niepalących składała się z 66 chorych.

Autorzy zbadali częstość występowania zespołu metabolicznego rozpoznawanego zgodnie z kryteriami International Diabetic Federation dla populacji europejskiej w całej badanej grupie pacjentów.

Wyniki. Większy odsetek osób z zespołem metabolicznym stwierdzono w grupie osób niepalących. Na częstość występowania zespołu metabolicznego w grupie osób palących istotnie wpływał wiek chorych. Nadciśnienie tętnicze i nieprawidłowa glikemia na czczo były najczęstszymi elementami składowymi zespołu metabolicznego w podgrupie osób palących z zespołem metabolicznym. W podgrupie osób niepalących z zespołem metabolicznym najczęściej stwierdzanym elementem zespołu metabolicznego było nadciśnienie tętnicze.

Wnioski. Wyniki badania nie wykazały statystycznie istotnego zwiększenia ani zmniejszenia częstości występowania zespołu metabolicznego w przypadku osób palących. Autorzy nie stwierdzili żadnych zależności między liczbą wypalanych dziennie papierosów a rozwojem zespołu metabolicznego. (Diabet. Klin. 2014; 3, 4: 136–143)

Słowa kluczowe: zespół metaboliczny, palenie tytoniu, nikotyna, otyłość, ryzyko sercowo-naczyniowe

Introduction, definition and diagnosis

The existence of several definitions led to problems with metabolic syndrome (MS) definition, especially in case of epidemiologic studies. In 2005 *International Diabetic Federation* (IDF) proposed a unification of this issue (for the clinical and laboratory personnel as well) [1]. The content of the definition is shown in Table 1. IDF has published other additional metabolic criteria for selected research purposes this year. These criteria are shown in Table 2. Metabolic syndrome is a predictor of ischemic heart disease (IHD). It predicts about 25% of new-onset ischemic heart disease [2]. A ten-year risk in case of men with metabolic syndrome is generally between 10–20%. Metabolic syndrome is a predictor of diabetes mellitus (DM) development. Almost half of the additional risk of DM was likely caused by the presence of metabolic syndrome [3]. Diabetes mellitus is a predictor of ischemic heart disease [4]. Every component of MS increases the cardiovascular risk. If more components are present, they multiply the risk. MS is associated with ca 3.5-fold increase in the relative risk of cardiovascular mortality [5, 6]. Smoking is one of the most influenceable risk factors for ischemic heart disease and also it is one of the most significant causes of death [7]. The main causes of death in case of smokers are, besides cardiovascular diseases, chronic obstructive pulmonary disease and lung cancer [8]. Passive smoking also increases the risk of coronary death by 22% in case of non-smokers. It decreases the level of HDL cholesterol by 0.1–0.15 mmol/L (by change in the activity of lecithin-cholesterol acyltransferase and increasing the risk of vasospasm); it negatively influences coronary flow and increases the prevalence of diabetes mellitus type 2 [9, 10]. In addition to this, smoking also increases the level of fibrinogen and thrombocyte aggregability. A smoker-diabetic is in higher risk of cardiovascular diseases than a non-smoker diabetic, and even in much higher risk in comparison to a non-diabetic non-smoker. The risk of cardiovascular system damage is increased and, similarly, the overall length of life is reduced by 12–15 years. During smoking, the levels of glycemia, insulin (hyperinsulinemia), and blood pressure (BP) are rapidly rising. Chronic smoking damages the artery endothelium and leads to insulin resistance. In case of smokers, hyperglycemia is mostly permanent and is responsible for the development of diabetic complications. Heavy metals in a cigarette — especially cadmium — also increase the incidence of diabetes mellitus. Observations had proven that the incidence of DM is significantly higher in smokers

Table 1. Metabolic syndrome (IDF, 2005) [43]

Central obesity (waist circumference)	European populations: in men > 94 cm, in women > 80 cm
	Asian and Chinese populations: in men > 90 cm, in women > 80 cm
	Japanese populations: in men > 90 cm, in women > 80 cm
Plus at least two of:	Triglycerides > 1.7 mM/L (150 mg/dL)
	HDL-cholesterol in men < 1.04 mM/l (40 mg/dL), in women < 1.29 mM/L (50 mg/dL)
	Blood pressure:
	systolic > 130 mm Hg or
	diastolic > 85 mm Hg or
	on antihypertensive therapy
	Fasting glycemia > 5.6 mmol/L (100 mg/dL) or pre-existing diabetes mellitus

Table 2. Additional metabolic criteria for research (IDF, 2005) [29, 44]

Abnormal fat distribution	Overall fat distribution (DXA)
	Central fat distribution (CT/ MRI)
	Biomarkers of fat tissue: leptin, adiponectin
	Fat content in liver (MRS)
Atherogenic dyslipidemia (additionally to triglycerides and low HDL-cholesterol)	ApoB (or non-HDL-cholesterol)
	Small dense LDL particles
Dysglycemia insulin resistance (additionally to increased fasting glycemia)	oGGT
	Fasting insulinemia/levels of proinsulin
	HOMA-IR
	IR by Bergman's minimal model
	Increase of free fatty acids (fasting and during oGTT)
	M value from clamp
Vascular dysregulation (additionally to blood pressure increase)	Measuring endothelium dysfunction
	Microalbuminuria
Proinflammatory state	Increase in CRP (SAA)
	Increase in inflammatory cytokines (TNF-α, IL-6)
	Decrease in adiponectin values

and the risk definitely increases with the number of cigarettes smoked per day and is highest for those, who smoke 20 or more cigarettes per day. Smoking causes increased cholesterol concentration in blood, which enhances the progression of atherosclerosis in diabetics; the level of fibrinogen and thrombocyte aggregability is also increased [11].

Methods

The examined set of patients was composed of 125 patients (75 men and 50 women) who were prospectively monitored for a 5 year period (2006–2011). We searched for the presence of metabolic syndrome components according to the IDF criteria for European population throughout the whole set. The set was composed of 59 smokers (47.2%) and 66 non-smokers (52.8%). The overall average age was 57.3 years, the average age of the smokers was 56.1 years, and in case of non-smokers it was 58.4 years. In the whole set there were 69 patients, who fulfilled the MS criteria, 33 men (44% of all men) and 36 women (72% of all women). The subset of smokers was composed of 59 patients; the average number of cigarettes smoked per day was 18 pieces (pcs). Only active smokers were classified for the subset of smokers. A subset of non-smokers was composed of 66 patients. Ex-smokers, who ceased smoking more than 20 years ago, were included in the subset of non-smokers as well. After processing the data, the groups of men and women were evaluated separately. We used Student's t-test. A null hypothesis used in this test was the claim that there are no statistically significant between-group differences in the mean values of

Table 3. Average waist circumference

	Average waist circumference [cm]	Average waist circumference [cm]
Male smokers	95.4	100.6
Female smokers	92.2	95.5

analyzed parameters. As the alternative hypothesis we used the claim that the mean of waist circumference in smokers is smaller than the mean of waist circumference in non-smokers. We determined the Pearson's correlation coefficient for finding out the correlation of the number of cigarettes smoked per day and the number of individual components of the MS. Further, we used the chi-square test for finding out the independence from age regarding MS incidence in smokers and non-smokers.

Results

The set contained 69 patients who fulfilled the IDF criteria for MS. Those were 33 men (44% of all men) and 36 women (72% of all women). In the subset of smokers there were 40.7% of patients, who fulfilled the criteria for MS, and in the subset of non-smokers there were 68.2% of such patients. Higher incidence of MS in the group of non-smokers is related to the smaller waist circumference in the group of smokers, as well as lower incidence of arterial hypertension (AH) in smokers (Tab. 3). The incidence of MS in smokers was statistically significantly dependent on their age, whilst the incidence of MS in non-smokers was not statistically significantly dependent on their age. Arterial hypertension and
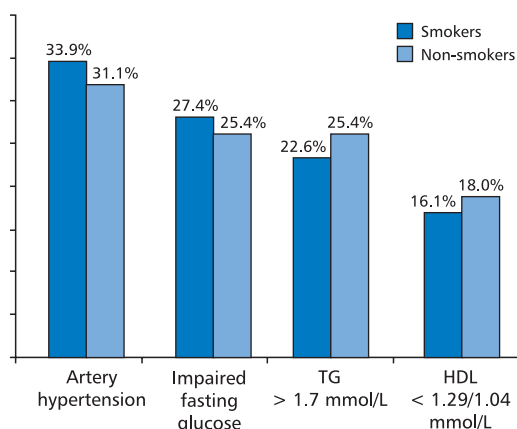
Figure 1. Frequency of the incidence of single components of metabolic syndrome (MS) in patients with MS

impaired fasting glucose of comparable incidence were the most frequent components of MS in the subset of smokers with MS. Arterial hypertension was most frequent component in the subset of non-smokers. In the whole set of patients (without respect to MS) impaired fasting glucose occurred most frequently in smokers, whilst abdominal obesity occurred most frequently in non-smokers. The distribution of the incidence of single MS components in smokers and non-smokers is shown in Figure 1. Average waist circumference in the examined set was 98 cm. Male smokers had 5.2 cm smaller average waist circumference than male non-smokers. In case of women the average difference in waist circumference was 3.3 cm. There were 65.6% of patients with AH in the examined set. In the subset of smokers it was 62.7% and in the subset of non-smokers it was 68.2%. Lower values of blood pressure (BP) are related to lower weight and are probably connected with vasodilatative effect of cotinine — the main metabolite of nicotine. We showed a statistically significant dependence between AH and age in the group of non-smokers, however, we did not prove this dependence in the group of non-smokers. 36% of men and 50% of women from the subset of smokers had lower values of HDL cholesterol. In case of non-smokers it was 42.3% of men and 20% of women. The levels of triglycerides (TG) were comparable in both the smoker and non-smoker groups. The average body mass index (BMI) value of the set was 29.5 kg/m^2. In case of all men the average value was 29.2 kg/m^2 and in case of all women it was 29.9 kg/m^2. The average BMI value in smokers (both men and women) was 29.7 kg/m^2 and the average value in non-smokers (both men and women) was 30.2 kg/m^2. We did not show any statistically significant difference between the BMI values in the groups of smokers and non-smokers. Further, we

examined the type of therapy in the group of patients already suffering from diabetes mellitus type 2. In the subset of smokers, 46.9% of patients were administered insulin, whilst in the subset of non-smokers it was only 23.5%. These results may be linked with increased progression of DM type 2 and the necessity of insulin therapy in smokers. Finally, we examined the strength of the relation between the number of cigarettes smoked per day and the number of single MS components in the group of smokers (p = 0.5799) and found no significant relation between the mentioned components in our set.

Discussion
Waist circumference

Projects IDEA and NEMESYS proved that there is lower prevalence of abdominal obesity in the population of smokers, similarly to our findings in our examined set of patients. Conversely, a study with randomly chosen 13,463 men of the age of 35 years and more, performed in China, did not confirm these data. Overall prevalence of central obesity was 35.9%. In contrast to non-smokers, only ex-smokers had statistically significantly higher prevalence of abdominal obesity [12]. Similarly to our observations on the set of patients, no relation between the number of cigarettes smoked and the waist circumference was found. The IDEA study proved that the waist circumference is an independent risk factor for cardiovascular (CV) diseases. Every increase in the waist circumference by 14 cm in men and by 14.9 cm in women increases the risk of CV disease by 21–40%. Thus, the waist circumference became the strongest predictor for CV diseases. The relation is even stronger in population of men. This relation was also observed in geographical areas with low prevalence of abdominal obesity (e.g. East Asia) [13–15]. A study by Dutch authors Lean et al. proved the waist circumference (greater than 94 cm in men and 80 cm in women) to be the strongest risk factor for CV diseases in comparison with BMI, levels of triglycerides and HDL cholesterol, values of blood pressure (BP) and lifestyle.

Diabetes mellitus type 2

It is generally known that smoking increases the level of fasting glucose, and we confirmed this association in our set off patients. Impaired fasting glucose with values higher than 5.6 mmol/L was present in 39 patients from the group of smokers, which is 66.1% of the group. This component of MS was the most frequent one in this group. Smoking is an independent risk factor for the development of diabetes mellitus

type 2. This is explained by several hypotheses. First of all, smoking is a risk factor for hyperinsulinemia. Smoking is also linked with chronic pancreatitis and pancreatic cancer development [17]. The risk for DM type 2 development is significantly higher in patients who smoke more than 20 cigarettes per day. According to the study of *American Journal of Epidemiology*, smoking 16–25 cigarettes per day triples the risk of DM type 2 compared to non-smokers. However, the highest risk of DM type 2 development is in ex-smokers. There is up to 70% higher risk of DM type 2 development during the first seven years after smoking cessation in comparison to non-smokers. The reason for this is probably a great weight gain [18]. It had been proven that passive tobacco exposures may lead to a so-called pancreatic "intoxication" and increased risk of DM type 2. Other hypotheses state that the passive smoking supports formation of pre-diabetic states, specifically the impaired glucose tolerance [19]. Smoking promotes the progression of DM type 2 complications. It also causes oxidative stress and transformation of the growth factor-β, which leads to changes in the glomerular basement membrane. In the population of American diabetics, the incidence of microalbuminuria and macroalbuminuria was significantly higher in case of smokers (53%) compared to non-smokers (20%) [3, 20, 21]. Smoking significantly affects the level of glycated hemoglobin (HbA$_{1c}$) [22]. Substances which cause increased levels of HbA$_{1c}$ in smoker-diabetics are still unknown. It is being discussed that the mentioned higher levels of HbA$_{1c}$ may be caused by nicotine as such, by direct impact on HbA$_{1c}$ levels and it can increase the HbA$_{1c}$ level up to 34%. Obviously, with increasing number of cigarettes smoked per day, the value of HbA$_{1c}$ is increasing as well. The use of nicotine patches, chewing gums etc. is still questionable. The advantages of not smoking whilst using these replacements may, however, overweight the risks related to these products, but always with emphasis on their short-term use [23].

Arterial hypertension

Arterial hypertension is a strong independent risk factor for cardiovascular mortality and morbidity. The risk of CV diseases triples in case of patients with AH, in comparison to those without AH, irrespective of age and sex. The risk of cardiovascular morbidity and mortality is also noticeably affected by smoking. Every 10 smoked cigarettes increase the mortality caused by CV diseases in men (18%) and in women (31%). Smoking increases the risk of CV diseases at any values of blood pressure. Influencing the BP by antihypertensive therapy did not bring satisfying results in terms of

lowering the risk of CV diseases. The risk of CV diseases was significantly lowered after other risk factors were influenced as well, including smoking. Hypertensive patients who smoke 20 cigarettes daily may lower the risk of CV diseases up to 35–40% after ceasing smoking. Transition to cigarettes with a filter brought no changes [2, 24]. According to the project *Prevalence of diabetes mellitus and metabolic syndrome in Slovakia*, arterial hypertension is one of the dominant components of MS and its incidence increases with age [25]. Throughout the whole set of patients, AH was the most frequent component of MS, and this proves the dominance of AH as the component of MS. Authors observed the prevalence of arterial hypertension and other risk factors of CV diseases including smoking in a study with 380 Brazilian men of the age of 19–35 years. The prevalence of hypertension in the observed group was 22% and the incidence of arterial hypertension was 68% higher in the ex-smokers compared to the non-smokers. The prevalence of arterial hypertension in case of smokers was 2 × lower than in case of ex-smokers, which was related to the weight gain after smoking cessation. With a weight loss of ca. 8 kg the systolic BP was lowered by 7–10 mm Hg and diastolic BP was lowered by 6–7 mm Hg [26]. Another available analysis proved that smoking is not linked with AH (considering both systolic and diastolic BP) [27, 28].

Atherogenic dyslipidemia and low values of HDL cholesterol

Similarly as in our set of patients, in the project *Prevalence of diabetes mellitus and metabolic syndrome in Slovakia*, the values of HDL cholesterol were also lower in the population of smokers; moreover, it was most frequently found in relatively young patients (age of 18–29 years). Authors explain this fact particularly by the highest prevalence of smoking in this age group [29]. In a study with 5,216 patients from North American states there were significantly lower values of HDL cholesterol in case of smokers in comparison to non-smokers (with no difference between men or women) and statistically significant relation between cigarettes smoked per day and the values of HDL cholesterol. The values of HDL cholesterol in case of men-smokers, who smoked more than 20 cigarettes per day, were in average 11% lower than in non-smokers. In case of women who smoked more than 20 cigarettes a day, it was up to 14% in average compared to non-smokers [30].

Metabolic syndrome

Prevalence of metabolic syndrome in Slovakia according the project *Prevalence of diabetes mellitus*

and metabolic syndrome in Slovakia, which used the NCEP/ATP III criteria, is 20.1%. There is significantly higher prevalence of MS in women than in men. The incidence progressively increases with increasing age and also in groups with low social status. The prevalence of MS according to this project is comparable to other European countries, and, similarly, higher prevalence of MS in women is found. The prevalence of MS in countries with low risk of CV diseases (e.g. Greece) is 24%. Despite comparable prevalence of MS in the mentioned countries, and the fact that its prevalence in Slovakia is even slightly lower, we experience one of the highest mortality rate due to CV diseases. This proves that MS is not the only cause of this phenomenon [29]. The prevalence of MS in Europe is, according to the authors Dellios et al. and the IDF criteria, 38% in men and 36% in women. Age increases the prevalence of MS in men by the age of 60 years. After reaching this age, the incidence due to age is stabilized. In case of women, the prevalence is rising up to the highest age group. The mortality due to CV diseases increased by 45% in men with MS and up to 73% in women with MS, in comparison to men and women without MS in the prospective study of the above mentioned authors. The study proved that the obese women with DM type 2 are in the highest risk of death due to CV diseases [31]. Smoking may be linked with higher risk of MS. This theory is supported by several scientific studies. According to the D.E.S.I.R. study, there is statistically significantly higher incidence of MS in male smokers in contrast to male non-smokers. In female smokers a higher incidence of MS had not been proved [32]. However, opposing evidence exist as well. It is appropriate to further examine the relation between metabolic syndrome and smoking mainly in the population of adult patients in the middle age, for whom there is high probability of MS development [33]. A study performed in Japan on 3,649 men of the age of 36–59 years evaluated the incidence of MS during 7 years and supplemented data about the ex-smokers, who had the highest weight in comparison to the smokers and non-smokers. The smokers in this study were divided by the number of cigarettes they smoked per day. The risk of MS development was significant in those, who smoked more than 21 cigarettes per day. Body weight was significantly higher in ex-smokers and they were in highest risk of MS development. For that reason, it is very important to support patients who want to cease smoking, mainly in physical activity and dietary habits, to prevent them from gaining weight [34]. The highest prevalence of MS in ex-smokers was also confirmed by a study performed in Saudi Arabia on 305 men and 359 women of the age of 25–70 years

during the period of 2006–2007. The ex-smokers were defined as non-smokers for the period of 1–2 years. The risk of MS development in ex-smokers in this study was 2 × higher in comparison to non-smokers (p = 0.009) [35]. The incidence of MS has increased in Asian countries during the last years. There is also higher prevalence of smoking opposed to Western countries, and this prevalence is still rising (predominantly in the population of young women). Several studies on Japanese population showed higher risk for CV diseases development in smokers, however, they did not prove a relation between MS and smoking. In another Japanese study of the authors Naoyuki Takashima et al. the relation between each component of MS and risk factors for CV diseases and death had been examined. The weightiest risk factors for CV diseases and deaths in this study were: smoking, ex-smoking, arterial hypertension, and impaired fasting glucose. The study also proved that a cumulation of individual risk factors increased the risk of death or CV disease without respect to obesity presence (assessed according to BMI) [36]. In American study on 2,273 individuals of the age of 12–19 years the prevalence of MS was examined. The examinees were divided into non-smokers without exposure to tobacco smoke, passive smokers and active smokers. In the population of adolescent youth, 5.6% of the participants fulfilled the criteria for MS. Throughout the examined set the incidence of MS substantially increased with exposure to tobacco. The incidence of MS in non-smokers without exposure to tobacco smoke was 1.2%, in passive smokers 5.6% and in active smokers up to 8.7%. Similar results were also recorded in excess weight and obesity assessment, where the weight had increased with exposure to tobacco [37].

Body mass index

In common practice, apart from BMI value calculation, it is essential to find out waist circumference in each patient, to determine the fat distribution on the body. Abdominal obesity significantly increases the risk of insulin resistance and the risk of DM type 2 development. An American study on 27,000 men and nearly 30,000 women assessed the relation between BMI and waist circumference. A very strong relation had been found between the waist circumference and the mortality due to CV diseases in patients with identical BMI values. This means that in patients with identical BMI value, the mortality due to CV diseases increases with increasing waist circumference. Conversely, in patients with identical waist circumference, mortality due to CV diseases was not increasing with higher values of BMI, moreover, in this group the mortality due to CV

diseases increased in cases of lower BMI values. The authors link this data with smoking, when patients have lower values of BMI, but simultaneously there is higher mortality due to CV diseases in this group [38]. A project of Swiss authors Chiolero et al. compared the BMI values of smokers and non-smokers. Physical activity and dietary habits were assessed as well. The prevalence of obesity was increasing with age and, naturally, higher incidence was related to lower physical activity. Men were more physically active, but had worse dietary habits than women. Nowadays, the relation between BMI and waist circumference is often being discussed. A frequently asked question is whether the BMI value is equally important risk factor for CV diseases as the waist circumference. The waist circumference has been repeatedly proven to be stronger risk factor for CV diseases than BMI [16].

Conclusion

Most components of the MS are known as the risk factors for atherosclerosis and ischemic heart disease since the announcement of Framingham study results. The original findings of the Framingham study were confirmed by numerous subsequent studies and they are still valid also with respect to other European recommendations [39]. Similarly high is the number of evidence based medicine studies on primary and secondary prevention that proved the reduction of cardiovascular consequences of atherosclerosis by risk factor intervention [40, 41]. Despite the results of our observation, as well as the other above mentioned studies (lower incidence of MS in the population of smokers), it is not possible to mark smoking as a protective factor regarding the proven adverse effects. Concerning smoking, it is essential to point out the most endangered group of patients, and those are the ex-smokers. The first 6 months after ceasing smoking are considered to be the most risky time period, since the weight gain (women are in higher risk than men) and the increased risk of weight gain may persist throughout 2 years from smoking cessation. Education is very important during this period; it is essential to mention lifestyle changes, dietary habits and, first of all, the necessity of physical exercise for at least 20 minutes each day.

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