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Smoking cessation increases serum adiponectin levels in an apparently healthy Greek population

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ABSTRACT

Background: Smoking has been associated with low serum levels of adiponectin, an adipocytokine with insulin-sensitizing, anti-inflammatory and anti-atherogenic properties. The objective of this study was to assess the early effect on adiponectin levels of smoking cessation supported by bupropion.
Methods: Apparently healthy smokers of both sexes with no additional cardiovascular risk factors were administered 150 mg sustained-release bupropion twice daily for 9 weeks. Quitters constituted the active group and non-quitters the control group. Sandwich enzyme-linked immunosorbent assays were employed for the measurement of serum adiponectin and cotinine, the latter used for validation of self-reported abstinence.
Results: Among the 106 participants (mean age 44.5 ± 11.3 years, 57 females, Brinkman index 512.2 ± 98.4, basal adiponectin 7.2 ± 1.5 mg/L), 45 (42.5%) had quitted smoking at week 9. Quitters' post-cessation adiponectin levels were significantly increased (mean difference with baseline 1.9 ± 0.8 mg/L, 95% CI 1.2, 2.3; $p < 0.001$), while non-quitters' adiponectin remained unaltered. A multiple regression model including female gender (standardized β coefficient = 0.480, $p = 0.002$), age (0.355, $p = 0.003$), body mass index (BMI) (−0.308, $p = 0.005$), waist circumference (−0.276, $p = 0.008$), smoking status (−0.255, $p = 0.010$), and cotinine levels (−0.233, $p = 0.021$) explained about two thirds of the variation in adiponectin levels (adjusted $R^2 = 0.656$).
Conclusions: Serum adiponectin levels appear to increase considerably within 2 months after smoking cessation. This finding may provide further insight into the mechanisms related to the detrimental effects of smoking and the benefits of quitting.

1. Introduction

Adiponectin is an adipocyte-derived protein, which has been the subject of immense interest since its discovery in the mid-1990s, because of its insulin-sensitizing, anti-inflammatory and anti-atherogenic properties [1]. Low serum levels of this cytokine are linked to obesity, type 2 diabetes, metabolic syndrome, hypertension and dyslipidemia [1], whereas hypoadiponectinemia is associated with greater risk of cardiovascular disease [1]. In this respect, raising adiponectin concentration is considered a promising therapeutic target for patients with metabolic and/or cardiovascular disorders.

Active smoking has been related to hypoadiponectinemia in apparently healthy individuals [2–8], and in patients with coronary artery disease [9–11]. Furthermore, acute experimental smoking has been shown to reduce adiponectin [3], whereas former smokers' adiponectin levels appear to range between those of current smokers and never smokers [3,6,8–10]. However, no data are available so far in regard to the short-term impact of smoking cessation on adiponectin. The objective of this study was to assess the early effect on adiponectin levels of smoking cessation supported by bupropion, a well-established pharmaceutical aid.

2. Methods

2.1. Selection criteria

Subjects were recruited at 'Hygeias Melathron' Infirmary, Athens, Greece. Eligibility criteria included age ≥18 years, smoking of ≥15 cigarettes/day for ≥5 years prior to study entry, and self-motivation for quitting. Exclusion criteria comprised the presence or a history of a seizures, severe head trauma, brain tumor, anorexia nervosa or bulimia, bipolar disorder or psychosis, pregnancy,

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lactation, alcohol dependence, use of psychotropic medications, smokeless tobacco or nicotine-replacement products, malignancy, established cardiovascular disease, hypertension, diabetes mellitus, obesity, and low-density lipoprotein cholesterol >4.1 mmol/L or use of hypolipidemic drugs.

2.2. Intervention and measurements

Bupropion administration lasted 9 weeks, while the target quitting date was set for the second week, usually day 8. Quitters constituted the active group and non-quitters the control group. All subjects received 150-mg tablets of sustained-release bupropion (*Zyban*, Glaxo Wellcome). One bupropion tablet was taken in the morning on the first 3 days, while one tablet in the morning and one in the evening were taken on days 4–63. The up-titration of bupropion dose to 150 mg twice daily after the first 3 days was chosen on the basis of the dosing schedule used in the largest trials assessing bupropion as anti-smoking drug, which had shown the dose of 150 mg twice daily to be the most effective [12]. Nicotine dependence was measured via the eight-item Fagerström Tolerance Questionnaire [13]. The Brinkman index (cigarettes smoked per day × years of smoking) was used to quantify the amount of smoking [14]. Fasting blood samples were obtained for determination of serum adiponectin, serum cotinine, glucose concentration, and lipid profile before study entry and at the end of week 9. Self-reported abstinence was confirmed by a serum cotinine level below 15 μg/L, a cut-off providing 96–97% sensitivity and 99–100% specificity for detecting tobacco use [15]. The study protocol was approved by the institutional ethical committee, and all participants provided written informed consent.

Laboratory analyses were performed at 'Attikon' and 'Hygeias Melathron' Hospitals. The serum concentration of adiponectin was measured by a commercially available sandwich enzyme-linked immunosorbent assay (ELISA, BioVendor Laboratory Medicine Inc.; Brno, Czech Republic) with detection limit 0.2 mg/L, and intra- and inter-assay coefficients of variation 6.4% and 7.3%, respectively. Serum cotinine was also measured via ELISA (Bio-Quant Inc.; San Diego, USA) with detection limit 0.5 μg/L, and intra- and inter-assay coefficients of variation 6.1% and 8.6%, respectively. Blood pressure and metabolic profile were determined by conventional methods.

2.3. Statistical analysis

A sample size of ≥33 subjects per group of quitters and non-quitters was calculated to be adequate for detecting half of a standard deviation (1.5 mg/L) of average basal adiponectin with a power 80% at a significance level of 5% via two-tailed tests. Analysis was performed using the Statistical Package for the Social Sciences software (SPSS Inc, Chicago, Illinois, release 10.0). Chi-square test or Fischer's exact test for categorical variables and Student's *t* test for continuous unpaired data were used for comparisons between quitters and non-quitters, and the respective ninety-five percent confidence intervals (95% CIs) were calculated. Intra-individual changes were assessed by Student's *t* test for continuous paired data. Correlations of adiponectin were evaluated by Pearson's coefficients, whereas a stepwise multiple regression model identified independent predictors of adiponectin levels.

3. Results

Among 110 enrolled subjects, adequate follow up data were available for 106 individuals. Four individuals were withdrawn from the study due to concomitant nicotine-replacement therapy (one subject used nicotine gums and three used patches). All participants were Greeks of Caucasian origin. Quitters did not differ from non-quitters in terms of baseline characteristics (Table 1). Moreover, smoking intensity prior to study entry was similar in quitters and non-quitters when participants were grouped according to the number of cigarettes smoked per day: 15–24 cigarettes/day were smoked by 20 out of 45 quitters (44.4%) and 29 out of 61 non-

Table 1
Participants' characteristics at baseline and at the end of study (HDL, high-density lipoprotein; LDL, low-density lipoprotein).

Participants' characteristics	Baseline			Week 9		
	Overall (*N* = 106)	Quitters (*N* = 45)	Non-quitters (*N* = 61)	Overall (*N* = 106)	Quitters (*N* = 45)	Non-quitters (*N* = 61)
Demographic data						
Age (years)‡	44.5 ± 11.3	46.0 ± 13.2	43.4 ± 12.1	–	–	–
Female sex (%)‡	57 (53.4)	25 (55.6)	32 (52.5)	–	–	–
Body mass index (kg/m^2)	26.7 ± 4.9	26.9 ± 4.2	26.6 ± 3.9	27.2 ± 4.7	27.5 ± 4.0	27.1 ± 3.7
Waist circumference (cm)	90.9 ± 13.1	91.4 ± 11.8	90.6 ± 12.3	91.9 ± 13.5	92.5 ± 12.1	91.5 ± 12.4
Alcohol consumption (units/week)	13.7 ± 3.8	13.4 ± 4.0	13.9 ± 3.6	14.6 ± 3.5	14.2 ± 2.4	14.9 ± 3.1
Smoking, adiponectin and cotinine						
Years of smoking‡	25.6 ± 11.1	26.8 ± 9.9	24.6 ± 10.5	–	–	–
Brinkman index‡	512.2 ± 98.4	517.3 ± 76.1	509.1 ± 86.3	–	–	–
Fagestrom score‡	7.4 ± 1.8	7.6 ± 1.5	7.3 ± 1.7	–	–	–
Previous attempts to quit‡	3.2 ± 3.1	3.4 ± 2.1	3.1 ± 2.2	–	–	–
Cigarettes/day	27.1 ± 10.6	28.0 ± 9.4	26.5 ± 9.8	8.6 ± 10.1*	0*, §	15.9 ± 10.5*
Menthol cigarettes (%)‡	13 (12.3)	5 (11.1)	8 (13.1)			
Serum cotinine (μg/L)	381.4 ± 191.1	385.5 ± 187.2	378.4 ± 195.4	123.2 ± 106.6*	3.8 ± 3.4*, §	211.2 ± 96.5*
Serum adiponectin (mg/L)	7.2 ± 1.5	7.3 ± 1.5	7.1 ± 1.4	8.1 ± 1.6*	9.2 ± 1.4*, §	7.2 ± 1.7
Metabolic profile						
Systolic blood pressure (mmHg)	133.5 ± 12.2	134.3 ± 11.4	132.8 ± 10.9	134.8 ± 12.8	135.3 ± 10.6	134.1 ± 10.5
Diastolic blood pressure (mmHg)	83.4 ± 8.7	83.0 ± 8.1	83.7 ± 7.2	83.9 ± 8.3	83.6 ± 7.1	84.1 ± 7.9
Total cholesterol (mmol/L)	5.3 ± 1.2	5.3 ± 1.0	5.3 ± 1.3	5.3 ± 1.1	5.2 ± 0.8	5.3 ± 1.3
LDL-cholesterol (mmol/L)	3.8 ± 0.4	3.7 ± 0.4	3.8 ± 0.3	3.7 ± 0.4	3.6 ± 0.5	3.7 ± 0.4
HDL-cholesterol (mmol/L)	1.1 ± 0.3	1.1 ± 0.2	1.1 ± 0.2	1.2 ± 0.3	1.2 ± 0.2	1.2 ± 0.2
Triglycerides (mmol/L)	1.0 ± 0.4	1.0 ± 0.3	0.9 ± 0.3	0.9 ± 0.4	0.9 ± 0.2	0.9 ± 0.3
Fasting glucose (mmol/L)	5.1 ± 0.4	5.2 ± 0.4	5.0 ± 0.4	5.1 ± 0.4	5.1 ± 0.3	5.0 ± 0.4

* $p < 0.001$ vs. baseline.

§ $p < 0.001$ vs. non-quitters.

‡ Assessment applicable only at baseline). Data are expressed as number of subjects (%) or mean value ± standard deviation. Differences not marked with one of the above symbols are non-significant.

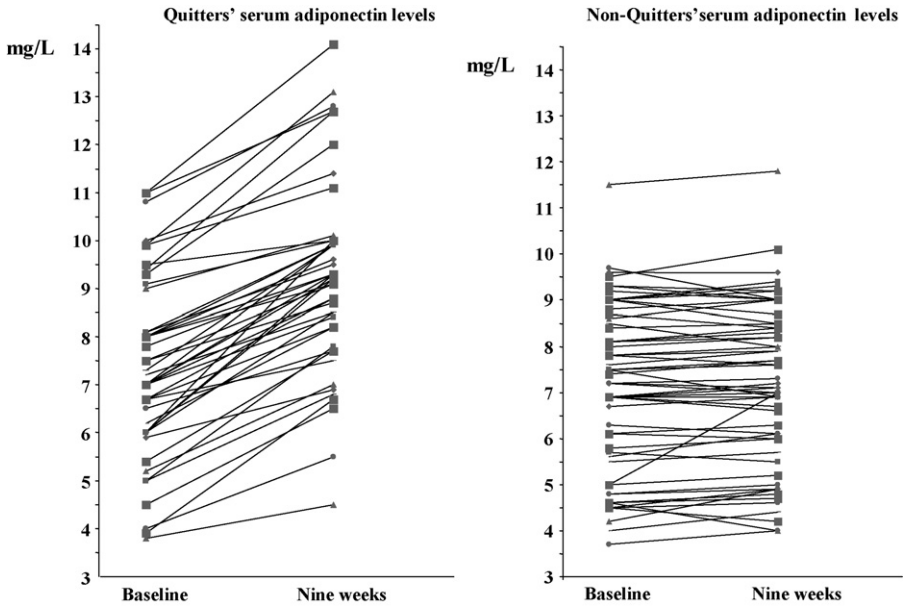

Fig. 1. (Panel A) Scatterplot of quitters' adiponectin levels at baseline and at week 9. (Panel B) Scatterplot of non-quitters' adiponectin levels at baseline and at week 9.

quitters (47.5%), whereas ≥25 cigarettes/day were smoked by 25 out of 45 quitters (55.6%) and 32 out of 61 non-quitters (52.5%; $p = 0.751$). Five individuals (3 quitters and 2 non-quitters) completed the study after discontinuing bupropion because of insomia (3 subjects), headache (1) and dry mouth (1) (overall compliance 101/106 [95.3%]; 42/45 [93.3%] in quitters vs. 59/61 [96.7%] in non-quitters, $p = 0.635$). The median interval between study entry and actual quitting time was 8 days (range 2–16 days). Accordingly, the iterative measurement of serum cotinine levels on day 63 was performed after a median interval of 55 days (range 47–61 days) from the onset of self-reported abstinence.

Quitters' adiponectin was increased at the end of study (mean change 1.9 ± 0.8 mg/L [95% CI 1.2, 2.3], $p < 0.001$), whereas non-quitters adiponectin did not change from baseline (mean difference 0.1 ± 0.4 mg/L [95% CI −0.2, 0.3], $p = 0.164$, Table 1; mean difference between quitters and non-quitters in adiponectin alterations 1.8 ± 0.6 mg/L [95% CI 1.3, 2.2], $p < 0.001$). Cotinine levels at week 9 were lower as compared to baseline in both quitters (difference -381.7 ± 184.4 μg/L [95% CI −437.1, −326.3], $p < 0.001$) and non-quitters (-167.2 ± 143.1 μg/L [95% CI −216.6, −117.7], $p < 0.001$, Table 1). Weight gain was non-significant in quitters (1.7 ± 1.0 kg [95% CI −1.6, 2.4], $p = 0.511$) as well as in non-quitters (1.5 ± 1.2 kg [95% CI −1.9, 2.5], $p = 0.598$; difference between the two groups 0.2 ± 0.2 kg [95% CI −1.1, 1.2], $p = 0.686$). Intra-individual adiponectin changes are illustrated in Fig. 1. Among the 61 non-quitters, 41 subjects (mean baseline cigarettes/day 25.1 ± 8.8, adiponectin 7.2 ± 1.6 mg/L, and cotinine 372.2 ± 170.4 μg/L) achieved a significant reduction in cigarettes smoked per day (mean difference -20.1 ± 6.7 [95% CI −22.2, −15.1], $p < 0.001$), which was compatible with a reduction in their cotinine levels (-230.6 ± 105.8 μg/L [95% CI −271.0, −119.6], $p < 0.001$). Although all these 41 non-quitters had higher adiponectin levels (average 7.5 ± 1.5 mg/L) at week 9 (Fig. 1, panel B), this trend did not reach statistical significance (difference 0.3 ± 0.3 mg/L [95% CI −0.2, 0.6], $p = 0.086$). The remaining 20 non-quitters (baseline cigarettes/day 29.6 ± 9.2, cotinine 390.1 ± 208.8 μg/L, and adiponectin 6.9 ± 1.8 mg/L) showed no significant change in cigarettes/day and cotinine (differences from baseline -1.5 ± 5.1 [95% CI −5.4, 3.7], $p = 0.344$ for cigarettes/day and -35.1 ± 21.9 μg/L [95% CI −49.3, 12.2], $p = 0.283$ for cotinine) and no alteration in adiponectin levels (difference from baseline -0.1 ± 0.3 mg/L [95% CI −0.4, 0.3], $p = 0.172$).

Table 2 demonstrates relationships between adiponectin and participants' characteristics in the overall population at week 9. There was a positive association between female gender, age and high-density lipoprotein (HDL) with adiponectin, while the latter exhibited a negative correlation with body mass index, waist circumference, smoking status, systolic and diastolic blood pressure, triglycerides, glucose, and cotinine. A multiple regression

Table 2
Linear relationships between adiponectin and participants' characteristics in the total population at week 9 (HDL, high-density lipoprotein; LDL, low-density lipoprotein).

Variable	Correlation coefficient r	p value
Gender (male = 0/female = 1)	0.681	<0.001
Age	0.545	<0.001
Body mass index	−0.522	<0.001
Waist circumference	−0.503	<0.001
Smoking (absent = 0, present = 1)	−0.441	0.002
Cotinine	−0.402	0.009
Alcohol consumption	0.139	0.061
Systolic blood pressure	−0.397	0.004
Diastolic blood pressure	−0.280	0.011
Total cholesterol	−0.092	0.133
LDL-cholesterol	−0.055	0.252
HDL-cholesterol	0.307	0.009
Triglycerides	−0.360	0.007
Glucose	−0.198	0.028

Table 3
Independent predictors of adiponectin levels in the total population at week 9 (HDL, high-density lipoprotein).

Variable	Standardized β coefficient	Standard error	p value
Female gender	0.480	0.019	0.002
Age	0.355	0.082	0.003
Body mass index	−0.308	0.011	0.005
Waist circumference	−0.276	0.036	0.008
Smoking	−0.265	0.042	0.010
Cotinine	−0.233	0.019	0.021
HDL-cholesterol	0.076	0.013	0.105
Systolic blood pressure	−0.042	0.021	0.119
Diastolic blood pressure	−0.013	0.006	0.285
Triglycerides	−0.006	0.008	0.441
Glucose	−0.002	0.005	0.625

model including female gender, age, body mass index, waist circumference, smoking, and cotinine concentration as independent predictors of adiponectin explained approximately two thirds of the variation in adiponectin levels (adjusted $R^2 = 0.656$; Table 3).

4. Discussion

This controlled study showed smoking quitters' adiponectin levels to increase significantly (approximately 25% in average) and early (8 weeks) after cessation supported by bupropion use. In fact, 95% CIs ruled out the possibility of an elevation in adiponectin concentration smaller than 15%, whereas the identification of smoking status and serum cotinine as independent predictors of adiponectin offers additional support to the view that the above difference corresponds to a true phenomenon. Notably, a remarkable reduction of daily smoked cigarettes resulted in a consistent – although non-significant – increase of adiponectin, the latter finding being accordant with the overall trend advocated by the present investigation. On the basis of the accumulating data that uphold the cardioprotective role of adiponectin, these data may provide further insight into the mechanisms related to the detrimental effects of smoking and the benefits of quitting.

The above observations are in line with the concept of the negative, dose-dependent [6] correlation between smoking and adiponectin, which has been recently suggested by several reports on Caucasian [2,5,11] and Asian [3,4,6–10] populations. Nevertheless, to our knowledge, the impact of quitting smoking on adiponectin concentration is addressed for the first time in the context of a prospective controlled trial. All the aforementioned investigations were cross-sectional surveys that reported on current, past and never smokers' adiponectin levels [2–10], thus lacking the potential to establish causality. Further, the only – as yet – relevant experimental study examined the inverse process, namely the acute suppressive effect of first-time smoking on never smokers' adiponectin concentration [3].

The positive associations of adiponectin in our study with female gender, age and HDL, and its negative correlations with BMI, waist circumference, triglycerides, glucose and blood pressure confirm numerous previous reports [1]. Adiponectin improves insulin sensitivity and lipid profile through stimulation of adenosine monophosphate-activated protein kinase in skeletal muscles and liver, leading to increased glucose uptake and fatty-acid oxidation, and reduced fatty-acid synthesis [1]. Insulin resistance related to low adiponectin concentration may, in turn, lower HDL concentration by stimulating the transcriptional activity of ApoA1, the major apolipoprotein of HDL, by decreasing VLDL production, and by enhancing the expression of lipoprotein lipase, thus leading to raised levels of triglyceride-rich lipoproteins, which can alter the formation and remodeling of HDL particles [1]. In clinical studies, hypoadiponectinemia has been associated with increased levels of inflammatory mediators, such as tumor necrosis factor-α, interleukin-6 and C-reactive protein, with activation of rennin–angiotensin system, and with endothelial dysfunction through impaired vasorelaxation [1]. In vitro, this adipocytokine hampers expression of adhesion molecules, vascular smooth muscle cell proliferation, and macrophage-to-foam cell transformation, while it inhibits neointimal thickening via reduction of plasminogen activator inhibitor type 1 [1]. In regard to gender, the difference in the number and the size of fat cells may account for the higher adiponectin levels in women, whereas the decline of both androgens and estrogens – which reduce adiponectin production – as well as the decreased adiponectin clearance in older individuals contribute to the age-related increase of adiponectin [16,17].

Despite the increased prevalence of insulin resistance in smokers [18], the reciprocal association of tobacco use with adiponectin has been consistently demonstrated independently of insulin sensitivity [2,5,8]. Although the above relationship between smoking and adiponectin has arisen after adjustment for conventional cardiovascular risk factors or disease [3–8,11], we excluded from our study individuals with such conditions in order to avoid potential confounding influences, which could escape the regulations of multiple regression analysis. Besides, unlike some of the previous relevant studies [3,4,8,10], we included female smokers, since the latter show higher adiponectin [16,17], different pattern of smoking-related sub-clinical inflammation [19], and different smoking cessation behavior [20] as compared to males.

Several biologically plausible explanations have been proposed for the relationship between smoking and adiponectin. Smoking provokes oxidative stress, which reduces adiponectin secretion and expression by inhibiting the function of phosphatidylinositol 3-kinase in adipocytes [3]. Nicotine itself induces lipolysis by activating local nicotinic cholinergic receptors in adipose tissue [3,21], and may suppress adiponectin gene expression by up-regulating post-ganglionic sympathetic nerves [22]. The consumption of circulating adiponectin in smokers represents another mechanism, inasmuch as this cytokine binds to collagens abundant in the vascular intima and accumulate in injured vascular walls [23]. Hence, via inverse pathways, smoking cessation can elevate adiponectin by reducing the tobacco-related detrimental effects and enhancing the partial regression of adiponectin-regulating factors towards the pre-smoking state. Further, an explanatory basis for the early increase of adiponectin may be derived through extrapolating on smoking cessation the immediate (12-h) decrease of adiponectin induced by the acute experimental exposure of never smokers to active smoking [3].

Certain concerns should be taken into account when considering interpretations and implications of the present results. Although quitters' cotinine levels were compatible with moderate exposure to environmental tobacco smoke [24], our study could not elucidate the influence of passive smoking on adiponectin concentration due to its design and the inherent limitations in the assessment of secondhand tobacco effects [15,24]. Moreover, there was a broad range in cotinine levels in our investigation as estimated by standard deviation (Table 1). This drawback, which has been consistently detected [24], may be attributed to various factors. First, the ratio of nicotine emission to respirable suspended particles emission varies among cigarettes; second, inter-individual differences in rates and patterns of nicotine and cotinine metabolism (coefficient of variation 22%) can produce outliers; and third, dietary nicotine exposure (e.g. from tomatoes, potatoes, cauliflower, and black tea) may confound low-level determinations of nicotine and cotinine in biologic fluids [15,24].

Although no data are available on any direct impact of bupropion on adiponectin, this seems quite unlikely, inasmuch as the compliance to study drug was comparably high among quitters and non-quitters. Nevertheless, such a possibility could not be excluded, since there was no placebo group in our study. On the other hand, a confounding effect of bupropion use in both groups could not be ruled out, because smoking cessation in our study – in line with previous investigations evaluating bupropion as anti-smoking drug [12] – was not associated with weight gain. In this respect, a considerable increase in weight – not unusual after non-pharmacologically supported smoking cessation [12] – might have decreased adiponectin levels, thus counterbalancing the beneficial effect of quitting. Likewise, the early post-cessation adiponectin change represents a surrogate finding, while the previous reports on ex-smokers' adiponectin values ranging between those of current smokers and never smokers suggest that even after cessation, the persistent – to some extent – smoking-related damage via endothelial dysfunction and low-grade inflammation may continue to influence adiponectin [25]. Thus, larger and durable cohort

studies are required to assess potential differences in cardiovascular outcomes between continuing smokers with respect to their adiponectin levels as well as the prognostic, log-term significance of the salutary effect of smoking cessation on adiponectin.

Conflicts of interest

There is no conflict of interest to disclose.

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