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ORIGINAL RESEARCH

Lower Serum IL-10 Linked to Oral Manifestations in Diabetes Patients

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Video Abstract

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Background: Diabetes mellitus (DM) is a chronic disease that remains a global health problem with increasing prevalence, particularly in Indonesia. The presence of oral manifestations in patients with DM is influenced by changes in immune system function. Interleukin-10 (IL-10) is an inflammatory marker implicated in DM. However, no studies have investigated the differences in IL-10 levels between non-DM and DM patients with and without oral manifestations.

Objective: This study aimed to compare the serum levels of IL-10 between non-DM and DM patients with and without oral manifestations at Dr. Hasan Sadikin Hospital Bandung.

Methodology: This observational study used a cross-sectional design. A total of 88 serum samples that met the inclusion criteria were selected, consisting of 37 (42%) samples from non-DM patients, 35 (39.8%) samples from DM patients with oral manifestations, and 16 (18.2%) samples from DM patients without oral manifestations. Serum levels of IL-10 were measured using an enzyme-linked immunosorbent assay (ELISA) kit.

Results: Among the 35 DM patients with oral manifestations, xerostomia was the most common (80%). The mean serum IL-10 level was 0.93 pg/mL in non-DM patients, 0.80 pg/mL in DM patients with oral manifestations, and 1.08 pg/mL in DM patients without oral manifestations. Statistical analysis using the Kruskal–Wallis test showed a p-value of 0.008 ($p \leq 0.05$), indicating a significant difference in serum levels of IL-10 between non-DM and DM patients with and without oral manifestations.

Conclusion: DM patients with oral manifestations had lower IL-10 serum levels compared to non-DM patients and DM patients without oral manifestations. These findings suggest that monitoring IL-10 levels could help identify diabetic patients at higher risk for oral complications.

Keywords: diabetes mellitus, interleukin-10, oral manifestation, serum

Introduction

According to the World Health Organization (WHO), diabetes mellitus (DM) is a group of metabolic disorders characterized by absolute or relative insulin deficiency and impaired insulin function.[1–3] The systemic nature of DM often leads to various complications, including those affecting oral health.[4] Oral manifestations such as gingivitis, periodontitis, xerostomia, caries, and oral candidiasis are prevalent among DM patients and can significantly impact their quality of life.[5,6]

IL-10 is an anti-inflammatory cytokine that plays a crucial role in modulating the immune response.[7] It regulates the immune response by inhibiting pro-inflammatory cytokines and promoting tissue repair.[8] IL-10 is produced in response to pro-inflammatory signals by all immune cells, including T cells, B cells, macrophages, and dendritic cells.[9] Given its role in controlling inflammation, IL-10 may influence the severity and development of diabetes-related complications, including oral manifestations.

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Recent studies have highlighted the role of inflammatory cytokines in DM and its complications; however, there is limited research specifically focusing on IL-10 levels in DM patients with oral manifestations. Previous studies have suggested that there is an association between IL-10 levels and the development of DM.[10] Yaghini et al[11] study found that IL-10 levels in type 2 DM patients were lower than in the control group (non-DM). Understanding the relationship between IL-10 levels and the presence of oral manifestations in DM patients could provide valuable insights into the underlying pathophysiology and aid in developing more effective management strategies.[12]

This study aimed to compare serum IL-10 levels in non-DM and DM patients, with and without oral manifestations, at the Dr. Hasan Sadikin Hospital in Bandung. By analyzing these differences, the present study aimed to clarify the potential role of this cytokine in the inflammatory processes associated with oral complications in diabetes. This study is important because it could provide new insights into the relationship between systemic inflammation, oral health, and diabetes, as well as how measuring IL-10 levels might help identify diabetic patients at higher risk for oral complications. These findings have the potential to lead to more effective therapeutic and preventive strategies for managing oral health in diabetic patients.

Material and Methods

Study Design and Data Collection

This observational study used a cross-sectional research design to compare serum IL-10 levels between non-DM and DM patients with and without oral manifestations. The study was conducted in accordance with the tenets of the Declaration of Helsinki. The oral condition, including oral hygiene and other oral manifestations, of DM patients and non-DM /healthy groups was assessed and diagnosed by dentists using standardized criteria. In this study, DM patients were patients who underwent routine control at the endocrine clinic of Dr. Hasan Sadikin Central General Hospital; they have HbA1c at a high level and with varying duration of DM.

Inclusion criteria were DM patients registered in July–September 2023, diagnosed by a physician in the Department of Internal Medicine, undergoing DM therapy, provided informed consent, aged ≥18 years, and able to read, write, and speak Indonesian. Patients with DM and other comorbidities were excluded. The samples were then categorized into three groups: Group 1 (serum from healthy individuals); Group 2 (serum from DM patients with oral manifestations); and Group 3 (serum from DM patients without oral manifestations). The ethical approval for the use of these samples was obtained by the Research Ethics Committee of Universitas Padjadjaran under registration number 722/UN6.KEP/EC/2023. Data from the clinical examination and IL-10 levels were analyzed at the Clinical Pathology Laboratory of Dr. Hasan Sadikin Hospital in Bandung, Indonesia, between January 2024 and February 2024. Blood samples were processed into serum and then used for this current research after receiving ethical approval from the Research Ethics Committee of Universitas Padjadjaran under registration number 1480/UN6.KEP/EC/2023.

Serum was collected and stored properly at temperatures below −80 °C. After thawing, the serum remained clear and colorless, and the volume was over 1 mL. The preparation process began with 3 mL of blood drawn into a vacutainer, which was left at room temperature for 30 minutes. It was then centrifuged at 3000 rpm for 15 minutes, and the serum was separated into two 500 µL aliquots. These aliquots were stored at −80 °C until needed. When preparing for testing, the serum was removed from the freezer and left at room temperature for 1–2 hours to thaw. It was then ready for analysis using the ELISA kit (Cloud-Clone Corp®, catalog number SEA056Hu).

The minimum detectable concentration of IL-10 is less than 2.8 pg/mL. This assay is highly sensitive, with the lower limit of detection (LLD) being the lowest concentration of IL-10 that can be reliably distinguished from zero. LLD was determined by adding two standard deviations to the average optical density of 20 zero standard replicates. The assay has excellent specificity for IL-10 detection with high precision. Intra-assay precision (Precision within an assay) was tested by running three samples with low, medium, and high IL-10 levels 20 times on the same plate, and inter-assay precision (Precision between assays) was tested by running the same samples on three separate plates, with 8 replicates on each plate. The coefficient of variation/CV (%) = SD/mean X 100. CV was less than 10% for intra-assay and less than 12% for inter-assay.

Data Analysis

The sample size for this study was calculated using G*Power software to ensure adequate power for detecting differences between the three groups with a one-way fixed effects ANOVA. Based on Cohen's guidelines, an effect size of 0.35 was chosen to detect moderate differences. The alpha level was set at 0.05, representing a 5% risk of Type I error (incorrectly rejecting the null hypothesis), and the desired power of 0.80 was selected to minimize the risk of Type II error, giving an 80% chance of detecting true effects.

Using these parameters, G*Power determined that a total sample size of 84 participants was required. The calculation included a non-centrality parameter (λ) of 10.29 and a critical F value of 3.1093, with 2 degrees of freedom for the numerator and 81 for the denominator. This sample size ensures the study is sufficiently powered to detect moderate effects, enhancing the reliability of the results.

The medians for each group were calculated based on individual data. The results are presented as the mean and standard error of the mean. Data were analyzed using SPSS for Windows, version 25.0, with a p-value ≤ 0.05 considered statistically significant. ELISA data were analyzed using the Kruskal–Wallis test, followed by the Bonferroni post-hoc test for further comparisons.

Ethical Considerations

The project was approved by the Universitas Padjadjaran Health Research Ethics Committee under registration numbers 1116/UN6.KEP/EC/2023 and 1480/UN6.KEP/EC/2023. The use of serum samples adhered to ethical and moral standards, in accordance with the 2011 National Guidelines for Health Ethics established by the National Commission on Health Research Ethics.

Result

A total of 88 serum samples that met the inclusion and exclusion criteria were collected, consisting of 37 samples from Group 1 (the healthy group), 35 samples from Group 2 (DM patients with oral manifestations), and 16 samples from Group 3 (DM patients without oral manifestations). Data on the general characteristics of each group, based on age, sex, and type of DM, are shown in Table 1.

Table 1 General Characteristics of Study Objects

Characteristics	Non-DM	DM		p-Value
		Oral Manifestation		
		With	Without	
	n=37	n=35	n=16	
Age (years)				
Median (IQR)	28 (23–35)	55 (45–60)	51 (35–63)	<0.001[a]*
Min–Max	20–44	18–76	19–70	
Age criteria, n (%)				<0.001[b]*
18–45	37 (100.0)	10 (28.6)	7 (43.8)	(χ^2=44.5; df=4)
46–65	0 (0.0)	22 (62.9)	6 (37.5)	
> 65	0 (0.0)	3 (8.6)	3 (18.8)	
Gender, n (%)				0.231[b]
Male	8 (21.6)	12 (34.3)	7 (43.8)	(χ^2=2.9; df=2)
Female	29 (78.4)	23 (65.7)	9 (56.3)	
Type of DM, n (%)				0.694[c]
Type 1		5 (14.3)	3 (18.8)	
Type 2		30 (85.7)	13 (81.3)	

Notes: Analysis using [a]Kruskall Wallis tests, [b]Chi Square, [c]Fisher-Exact, *significance.
Abbreviations: IQR, Inter Quartile Range; Min, minimum; Max, maximum; DM, diabetes mellitus.

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The non-DM group had a significantly lower mean age (29 ± 7 years) compared to the DM group with oral manifestations (51 ± 15 years) and the DM group without oral manifestations (48 ± 18 years). There was a significant difference in the mean age between the groups ($p < 0.001$). Age distribution showed that all non-DM groups were aged 18–45 years, whereas 28.6% of the DM group with oral manifestations and 43.8% of the DM group without oral manifestations were aged 18–45 years. This difference was statistically significant ($p < 0.001$).

The proportion of males was higher in the DM group without oral manifestations (43.8%) compared to the DM group with oral manifestations (34.3%) and the non-DM group (21.6%). However, this difference was not statistically significant ($p = 0.231$). In contrast, the proportion of women was higher in the non-DM group (78.4%) compared to the DM group with oral manifestations (65.7%) and the DM group without oral manifestations (56.3%). Most DM patients had type 2 diabetes, both in the group without oral manifestations (81.3%) and with oral manifestations (85.7%). There was no significant difference in the distribution of diabetes types between these two groups ($p = 0.694$).

Based on the medical records, Table 2 presents the clinical picture of the oral manifestations of DM patients. Out of 51 patients with DM, 35 had oral manifestations, with xerostomia being the most common, affecting 28 patients (80%). Table 3 shows the difference in serum IL-10 levels between non-DM and DM patients with and without oral manifestations.

The mean serum IL-10 level in the non-DM group was 0.93 ± 0.66 pg/mL. The DM group with oral manifestations had a mean serum IL-10 level of 0.80 ± 1.71 pg/mL, while the DM group without oral manifestations had a mean serum IL-10 level of 1.08 ± 0.74 pg/mL. Median serum IL-10 levels also showed a similar trend, with the highest median in the

Table 2 Distribution of Oral Manifestations in DM Patients

Oral Manifestations	Total	
	n	%
Xerostomia	28	80.0
Dental Caries	8	22.8
Exfoliative Cheilitis	8	22.8
Oral Ulceration	6	17.1
Gingivitis and/or Periodontitis	4	11.4
Oral Candidiasis	3	8.6
Oral lichen planus/ oral lichenoid reactions	1	2.9
Dysgeusia	1	2.9
Geographic tongue	1	2.9

Table 3 Differences in IL-10 Levels in Non-DM and DM Patients with and without Oral Manifestations

	Non-DM	DM		p-Value
		With Oral Manifestation	Without Oral Manifestation	
	n=37	n=35	n=16	
IL-10 levels				
Mean (SD)	0.93 ± 0.66	0.80 ± 1.71	1.08 ± 0.74	0.008*
Median (IQR)	0.66 (0.56–1.06)	0.54 (0.11–0.78)	0.82 (0.55–1.47)	
Min–Max	0.32–3.24	0.01–10.25	0.26–2.72	

Notes: Analysis using the Kruskal–Wallis test, *significance.
Abbreviations: SD, standard of deviation; IQR, interquartile range; Min, minimum; Max, maximum.

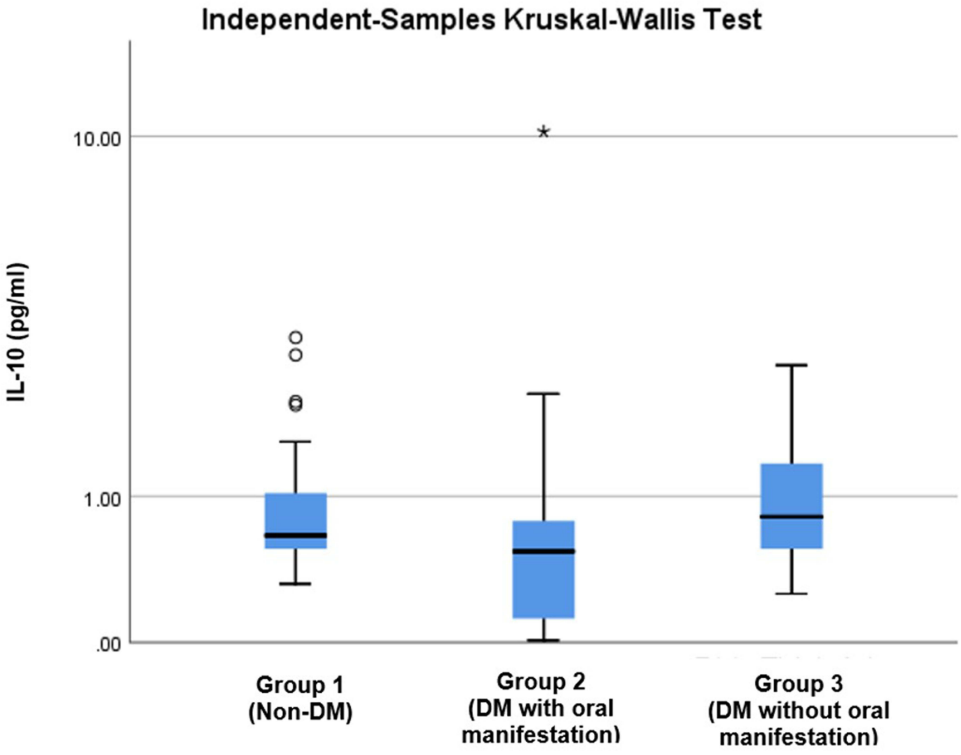

Figure 1 Boxplot of distribution differences of IL-10 levels in non-DM and DM patients with and without oral manifestations.
Notes: *outlier.

DM group without oral manifestations (0.82 pg/mL), followed by the non-DM group (0.66 pg/mL), and the lowest in the DM group with oral manifestations (0.54 pg/mL), as shown in Figure 1. Statistical analysis using the Kruskal–Wallis test showed that the differences in serum IL-10 levels between these groups were significant, with a p-value of 0.008.

A post-hoc test using the Bonferroni method was performed to further investigate these differences, and the results are shown in Table 4. The analysis revealed a significant difference in serum IL-10 levels (p = 0.026), indicating that Group 2 (DM with oral manifestations) had lower IL-10 levels than Group 1 (non-DM/healthy). There was also a significant difference (p = 0.028), indicating that Group 2 (DM with oral manifestations) had lower IL-10 levels than Group 3 (DM without oral manifestations). However, no significant difference was found between Groups 1 and 3 (p = 1.000), indicating that serum IL-10 levels in non-DM and DM patients without oral manifestations were similar.

Discussion

Systemic health and oral health are inextricably linked.[13] The relationship between oral health and DM is bidirectional, meaning that poor oral health can contribute to the development of diabetes, while uncontrolled diabetes can lead to poor oral health.[13,14] DM can cause various oral manifestations, including dental caries, xerostomia (dry mouth), burning

Table 4 Posthoc Test of Differences in IL-10 Levels in Non-DM and DM Patients with and without Oral Manifestations

Comparisons Between Groups	p-value
Group 1 vs group 2	0.026
Group 2 vs group 3	0.028
Group 1 vs group 3	1.000

Notes: Analysis using the Bonferroni test.

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mouth syndrome, dysgeusia, gingivitis, periodontitis, infections, oral candidiasis, impaired wound healing, and tooth loss.[4–6,12,13,15–17] Garcia et al also found that the greater the number of missing teeth, the worse the quality of life.[18] Additionally, poor oral health in people with DM may increase the risk of microvascular and macrovascular complications.[19]

The most common oral manifestation found in the DM group in this study was xerostomia, affecting 80% of patients. Xerostomia can lead to several issues, including glossitis, cervical caries, exfoliative cheilitis, dysgeusia, periodontal disease, and dysphagia.[6,20] According to Chavez et al,[21] individuals with uncontrolled diabetes may experience impaired salivary flow compared to those with controlled diabetes and non-diabetic subjects.[21] Ivanovski et al[22] studied 60 patients, including 30 people with DM and 30 healthy subjects, and found that 80% of people with DM had xerostomia.[22] These findings suggest that diabetes contributes to xerostomia, and there is a statistically significant relationship between xerostomia and blood glucose levels.[6]

Interleukin-10 is also known to be involved in DM pathogenesis.[12,23] IL-10 is a cytokine that plays an important role in regulating the complex multicellular interactions between pancreatic β-cells and immune cells in the development of diabetes.[23] Previous studies have suggested that there was an association between IL-10 levels and the development of DM.[10] Yaghini et al[11] found that serum IL-10 levels were lower in type 2 DM patients than in controls (non-DM). Decreased IL-10 levels indicate a failure of the immune system to suppress inflammation.[24]

Diabetes directly promotes inflammation and significantly alters the inflammatory response.[25] Hyperglycemic conditions are known to decrease the expression of anti-inflammatory cytokines such as IL-4, IL-10, and TGF-β1, while simultaneously increasing the levels of pro-inflammatory cytokines like IL-1β, IL-6, IL-8, IL-17, and TNF-α.[26] Elevated intracellular glucose levels lead to enhanced production of reactive oxygen species (ROS) within mitochondria.[27] ROS play a crucial role in modulating salivary gland function, inducing oxidative stress that results in salivary gland inflammation and dysfunction, contributing to xerostomia.[28] These changes in salivary gland cellular structure lead to a 20–40% reduction in saliva-secreting acinar cells, impairing cell function and reducing salivary secretion.[29] The consequences of xerostomia include glossitis, cervical caries, dry buccal mucosa, exfoliative cheilitis, dysgeusia, periodontal disease, and dysphagia.[6,20]

In this study, the mean serum IL-10 level in group 2 (DM patients with oral symptoms) was 0.80 pg/mL, which was lower than the mean serum IL-10 levels in groups 3 (1.08 pg/mL) and 1 (0.93 pg/mL). The result was in line with the research of Kassab et al,[30] who reported that the mean salivary IL-10 levels of DM patients with periodontitis (9 pg/mL) were lower than the healthy control group (14.7 pg/mL).[12,30] Research by Liu et al[31] found that gingival crevicular fluid IL-10 levels in the DM group with periodontal disease (4.40 pg/mL) were lower than those in the healthy control group (5.02 pg/mL).[31] Ikbal et al's research[32] revealed the same results, demonstrating that serum IL-10 levels were considerably lower in the DM group with periodontitis compared to the healthy control group.[12,32]

IL-10 is an anti-inflammatory cytokine that helps regulate the body's immune response by balancing pro-inflammatory and anti-inflammatory cytokines to defend against pathogens.[12,33,34] As an anti-inflammatory cytokine, IL-10 has various functions in different target cells.[35] In monocytes and macrophages, its primary target cell, IL-10, can inhibit the release of pro-inflammatory cytokines and antigen presentation while enhancing the phagocytosis process.[12,32,35]

Macrophages play an important role in all stages of wound healing, especially proliferation and remodeling.[27] During the acute phase of wound healing, macrophages transition from a predominantly pro-inflammatory (M1) state to an anti-inflammatory (M2) state.[27] Initially, M1 macrophages migrate to the wound site to eliminate pathogens, foreign debris, and dead cells.[27] M2 macrophages, stimulated by IL-10 and TGF-β, produce high levels of IL-16, MMP-9, IL-10, and TGF-β while secreting very low levels of IL-12.[27] M2 anti-inflammatory macrophages also secrete VEGF and TGF-β to promote cell proliferation and protein synthesis.[27] In chronic diabetic wounds, the healing process begins similarly to acute wounds but eventually slows down and halts.[27] These chronic wounds experience increased infiltration of inflammatory cells, leading to elevated levels of inflammatory cytokines such as IL-6, IL-1, and TNF-α and reduced levels of anti-inflammatory cytokines like IL-10.[27]

According to the results of Barry et al's research on the impact of type 2 DM on IL-10 function, high glucose interferes with the ability of IL-10 to inhibit inflammation.[12,34,36] IL-10 becomes less effective in inhibiting TNF-α secretion in whole blood cultures of type 2 DM patients.[12,34] IL-10 resistance, or hyporesponsiveness, was found in macrophages exposed to high

glucose.[34] High glucose interferes with the activation of the IL-10 signaling protein STAT3.[34] This hyporesponsiveness contributes to the chronic inflammation observed in patients with type 2 DM.[34]

There was a significant variation in serum IL-10 levels between non-DM and DM patients with or without oral manifestations. DM patients with oral manifestations had lower IL-10 levels than both non-DM and DM groups without oral manifestations.[12] This suggests that the oral manifestations in patients with DM may be associated with reduced IL-10 levels. The presence of oral manifestations in DM is influenced by altered immune function.[37] However, no significant difference in serum IL-10 levels was found between the non-DM and DM groups without oral manifestations, suggesting similar serum IL-10 levels in these two groups. This analysis highlights the importance of considering oral manifestations when evaluating IL-10 levels in DM patients.

Based on the link between low IL-10 levels and oral complications in diabetes, our findings suggest that IL-10 monitoring could be a useful marker for assessing oral health risk in diabetic patients. Routine measurement of IL-10 levels could help identify individuals at higher risk for oral issues like periodontal disease, xerostomia, or impaired wound healing, enabling early detection and personalized care. Incorporating IL-10 testing into diabetes management could improve the accuracy of oral health assessments and support more targeted prevention and treatment strategies for diabetes-related oral complications.

While the results of this study suggest an association between lower IL-10 levels and the presence of oral manifestations in diabetic patients, it is important to recognize that IL-10 may not be the sole factor contributing to these complications. Rather, lower IL-10 levels could be one of several contributing factors in the complex pathophysiology of oral manifestations in diabetes. Other factors, such as hyperglycemia, immune dysregulation, and oral hygiene, may also play significant roles. Future studies should aim to explore the interplay between IL-10 and these other factors to gain a more comprehensive understanding of the mechanisms underlying oral health issues in diabetes.

Research Limitation

This study has several limitations that should be acknowledged. Firstly, the cross-sectional research design captures data at a single point in time. Although useful for assessing prevalence and associations, it cannot establish causality or demonstrate changes in IL-10 levels over time in relation to the development of oral manifestations. Secondly, this study did not collect data on patient characteristics such as duration of diabetes, HbA1c levels, medications, or smoking status. Therefore, further research is needed to provide a more comprehensive understanding of the factors affecting diabetes-related oral complications.

Conclusion

Based on these results, it can be concluded that diabetes patients with oral manifestations have significantly lower serum IL-10 levels compared to non-diabetic individuals and diabetic patients without oral manifestations. These findings suggest that IL-10 may play a role in the development of oral manifestations in DM patients, offering insights into its involvement in diabetes-related complications.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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