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당뇨병 합병증 발생 이전의 위장관 증상

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Gastrointestinal Symptoms in Diabetes Occur Long before Diabetic Complications

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Background/Aims: Gastrointestinal (GI) manifestations are common in patients with diabetes complications, such as autonomic neuropathy. However, the prevalence of GI symptoms before the development of diabetes complications is unclear.
Methods: We conducted an interview survey of functional GI disorders among patients with diabetes visiting the endocrinology clinic of a general hospital using the Rome III criteria. The survey consisted of questions regarding functional dyspepsia, irritable bowel syndrome, and functional constipation, including functional defecation disorder.
Results: In total, 509 patients were included in the analysis. The patients were divided into three groups: prediabetes (n = 115), diabetes without neuropathy (n = 275), and diabetes with neuropathy (n = 119). With regard to GI symptoms, the prevalences of functional dyspepsia in the prediabetes, diabetes without neuropathy, and diabetes with neuropathy groups were 16.52%, 27.27%, and 23.53%, respectively; those of irritable bowel syndrome were 8.70%, 11.68%, and 16.81%, respectively, and those of functional constipation were 8.85%, 11.85%, and 15.25%, respectively. In the subgroup analysis, symptoms of postprandial distress syndrome (e.g., postprandial fullness and early satiety) were more prevalent than symptoms of epigastric pain. In the constipation group, symptoms of pelvic outlet obstruction (such as the sensation of anorectal obstruction or blockage and the need for manual maneuvers to facilitate defecation) were more prevalent than symptoms of slow-transit constipation.
Conclusions: The prevalence of functional GI disorders increases with diabetes severity. Diabetes-related GI symptoms appear long before the onset of diabetes complications. (Korean J Med 2024;99:210-218)

Keywords: Diabetes complications; Prediabetic state; Gastrointestinal diseases

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INTRODUCTION

The prevalence of diabetes mellitus has increased worldwide. More than 400 million people worldwide currently live with diabetes, and the number is expected to further increase in future [1]. This epidemic metabolic disease is associated with many complications, including macrovascular, microvascular, and nervous system types. Diabetic neuropathy, especially autonomic neuropathy, leads to gastrointestinal (GI) manifestations such as gastroparesis, diarrhea, and altered bowel habits [2].

Adults with longstanding type 1 and 2 diabetes develop significantly more GI symptoms relative to healthy adults without diabetes [3]. Gastroparesis, characterized by delayed gastric emptying, represents a large proportion of these GI tract disorders; diabetes is a major contributing factor [4]. Constipation, diarrhea, and abdominal distension are common disorders in the lower GI tract. A previous study showed that people with type 2 diabetes had a higher prevalence of constipation than people without diabetes [5]. Other research has shown that the prevalence of functional GI disorder symptoms is higher in people with diabetes than in community-based individuals [6,7].

However, there are few reports of GI symptoms in hyperglycemic patients before the development of diabetes mellitus, such as in the prediabetes state. Additionally, the relationships of abdominal symptoms with diabetic neuropathy in patients exhibiting diabetes and/or hyperglycemia have not been fully investigated. Therefore, we explored the prevalences of GI symptoms in patients with prediabetes, diabetes without neuropathy, and diabetes with neuropathy; we assessed the association of GI symptoms with diabetes severity using the Rome III criteria.

MATERIALS AND METHODS

Patients

We conducted a questionnaire interview study among patients who visited a diabetes clinic in a general hospital. The study was performed over 18 months to survey the prevalence of GI symptoms in patients with diabetes. Outpatients with prediabetes or diabetes mellitus were recruited and interviewed about their GI symptoms. To rule out organic causes, all patients with diabetes were confirmed to be free of organic diseases via gastroscopy and ultrasound within 2 years of the survey. Patients with prediabetes were generally healthy individuals who had undergone gastroscopy and ultrasound during their routine healthcare check-up. Tests for autonomic neuropathy included pulse wave velocity, heart rate variability, orthostatic hypotension tests, Valsalva maneuver tests, and neurometric assessments.

The exclusion criteria were refusal to participate in the interview or provision of an incomplete questionnaire, presence of severe systemic or mental illness, ongoing pregnancy, and a history of abdominal surgery (excluding appendectomy or hernia repair surgery). Written informed consent to participate was obtained from all patients before enrollment. This study protocol was approved by the institutional review board.

Functional GI disorder criteria

There are many subgroups of functional GI disorders in the Rome III classification. In this study, we investigated the prevalences of functional dyspepsia, irritable bowel syndrome (IBS), and functional constipation using the Rome III criteria. We also examined the prevalences of functional GI disorders in the presence of diabetes complications.

The Rome III criteria classify functional dyspepsia into two subtypes: epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS). We utilized this classification in the present study. IBS was categorized into three subtypes according to bowel habits: IBS with constipation, IBS with diarrhea, and IBS with mixed bowel habits or unclassified IBS.

We surveyed upper GI symptoms and bowel habit symptoms using a questionnaire. Regarding functional dyspepsia, we asked patients about upper GI symptoms (e.g., early satiety and postprandial fullness), in accordance with the Rome III consensus. The questionnaires for bowel symptoms adhered to the Rome III criteria for functional constipation.

Questionnaire

Patients were given a specific questionnaire to evaluate the

frequency and severity of functional dyspepsia symptoms. These symptoms included early satiety, postprandial fullness, epigastric pain, an epigastric burning sensation, epigastric bloating, and nausea. Severity was graded on a scale from 1 to 5 (1, absent; 2, mild; 3, moderate; 4, severe; 5, very severe). Symptom frequency was graded on a scale from 1 to 6 (1, never; 2, less than 1 day per month; 3, approximately 2 or 3 days per month; 4, at least 1 day per week; 5, at least several times per week; 6, almost every day).

In previous functional dyspepsia diagnostic questionnaires, including those based on the Rome III criteria, severity was not specifically addressed; therefore, we regarded the cut-off value as ≥ 3 [8,9]. However, we classified patients with functional dyspepsia into PDS and EPS subgroups, in accordance with the Rome III criteria. Patients were classified into the PDS subgroup if they experienced postprandial fullness and/or early satiety at least several times per week. The EPS subgroup comprised patients who reported epigastric pain at least once per week [10].

The questionnaire responses were used to divide the IBS group based on the Rome III criteria. The IBS disorder group was further categorized into three subgroups according to the bowel patterns at a specific time point [11,12]. The frequency of recurrent abdominal pain or discomfort was scored. The Bristol stool form scale was used to categorize stool types and divide the IBS subgroups.

Straining, lumpy or hard stools, an anorectal sensation of incomplete evacuation, an anorectal sensation of obstruction or blockage, the need for manual maneuvers to facilitate defecation, and fewer than three defecations per week were investigated using the questionnaire. If two of these were satisfied, the patients were assigned to the functional constipation group, in accordance with the Rome III criteria [12]. The prevalence of each symptom was also investigated.

Statistical analysis

Crosstabs were used to analyze prevalence. Multinomial logistic regression analysis was performed to assess the association of each Rome III subgroup with diabetic neuropathy after adjustments for age, sex, and HbA1c concentration. All results were considered statistically significant when p-values were < 0.05. SPSS version 18 software (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

Ethics statement

Written informed consent to participate was obtained from all patients before enrollment. This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital (approval no. 2020-07-047-001).

RESULTS

Baseline characteristics of the study population

In total, 720 patients who visited the endocrinology clinic because of an impaired fasting glucose status or diabetes mellitus were recruited and surveyed. Of these, 201 patients who did not complete the questionnaire and 10 patients who did not meet the inclusion criteria were excluded (Fig. 1). The remaining 509 patients were enrolled. Among these 509 patients, 115 (22.6%) had prediabetes, 275 (54.0%) had diabetes without neuropathy, and 119 (23.4%) had diabetes with neuropathy. Patients with prediabetes and patients who had diabetes without neuropathy were assigned to the no complication group; patients who had diabetes with neuropathy were assigned to the complication group. Among the enrolled patients, 311 (61.1%) were men, and the mean age was 53.9 ± 12.6 years (Table 1).

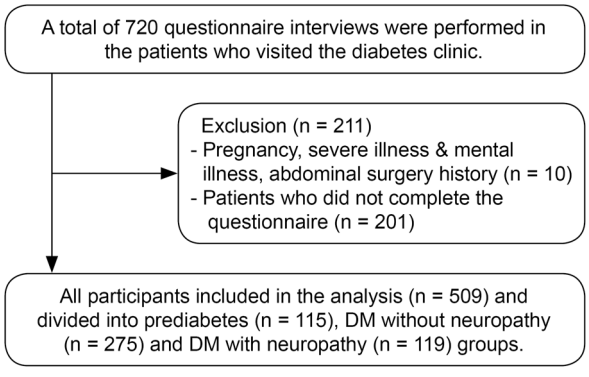

Figure 1. Summary of patient recruitment. DM, diabetes mellitus.

Table 1. Baseline characteristics of patients in this study

Variable	Total (n = 509)	Prediabetes (n = 115)	Diabetes without neuropathy (n = 275)	Diabetes with neuropathy (n = 119)	*p*-value
Male	311 (61.1)	86 (74.8)	161 (58.5)	64 (53.8)	0.002
Age, years	53.9 ± 12.6	48.5 ± 8.7	55.2 ± 12.4	56.1 ± 14.6	<0.001[a]
HbA1c	7.0 ± 1.7	6.1 ± 0.9	7.0 ± 1.5	8.0 ± 2.0	<0.001[a]

Values are presented as number (%) or mean ± standard deviation.
[a]Chi-squared test, analysis of variance.

Table 2. Prevalence of functional dyspepsia and subgroups based on Rome III criteria

Subgroup[a]	Prediabetes	Diabetes without neuropathy	Diabetes with neuropathy	Diabetes without neuropathy vs. prediabetes		Diabetes with neuropathy vs. prediabetes	
				Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Functional dyspepsia	19 (16.52)	75 (27.27)	28 (23.53)	1.895 (1.083-3.314)[b]	1.881 (1.032-3.428)[b]	1.555 (0.812-2.976)	1.533 (0.745-3.154)
EPS	13 (11.30)	38 (13.82)	12 (10.08)	1.258 (0.643-2.460)	1.301 (0.627-2.700)	0.880 (0.384-2.018)	0.923 (0.365-2.331)
PDS	7 (6.09)	55 (20.00)	26 (21.85)	3.857 (1.700-8.754)[b]	3.271 (1.380-7.753)[b]	4.313 (1.790-10.393)[b]	3.508 (1.355-9.082)[b]

Values are presented as number (%) unless otherwised indicated.
OR, odds ratio; CI, confidence interval; EPS, epigastric pain syndrome; PDS, postprandial distress syndrome.
[a]Model was adjusted for age and sex.
[b]$p < 0.05$.

Prevalence of functional GI disorders

The prevalence of functional dyspepsia in the prediabetes group was 16.52%, the prevalences of EPS and PDS in the prediabetes group were 11.30% and 6.09%, respectively. After adjustment for the confounding factors of age and sex, multinomial regression models were constructed. PDS was associated with the complication group (odds ratio [OR], 3.915; 95% confidence interval [CI], 1.591-9.633), but this association was not observed in the EPS group (OR, 0.911; 95% CI, 0.388-2.142) (Table 2).

The prevalences of gastric symptoms were also analyzed. The prevalences of postprandial fullness and early satiety in patients with prediabetes were 6.09% and 4.35%, respectively. After adjustment for the confounding factors of age and sex, multinomial regression models showed that postprandial fullness (OR, 2.135; 95% CI, 0.827-5.509) and early satiety (OR, 3.419; 95% CI, 1.197-9.762) were associated with the complication group. In the subgroup analysis, PDS symptoms such as postprandial fullness and early satiety were more prevalent than symptoms of epigastric pain (Table 3).

The prevalence of IBS in patients with prediabetes was 8.70% (OR, 2.478; 95% CI, 1.062-5.783). The diarrhea subtype (OR, 3.509; 95% CI, 0.655-18.805) and the mixed and unclassified subtype (OR, 2.113; 95% CI, 0.812-5.498) were also associated with neuropathy, but neither association was statistically significant ($p > 0.05$). Only one patient was assigned to the constipation subtype; therefore, the prevalence of this subtype could not be analyzed.

The prevalences of functional constipation in the prediabetes, diabetes without neuropathy, and diabetes with neuropathy groups were 8.85%, 11.85%, and 15.25%, respectively. Functional constipation was moderately associated with the complication group (OR, 1.513; 95% CI, 0.642-3.563), but the association was not statistically significant (Table 4). Similar to upper GI

Table 3. Prevalence of gastric symptoms

Symptom[a]	Prediabetes	Diabetes without neuropathy	Diabetes with neuropathy	Diabetes without neuropathy vs. prediabetes		Diabetes with neuropathy vs. prediabetes	
				Crude OR (95% CI)	Adjusted OR[b] (95% CI)	Crude OR (95% CI)	Adjusted OR[b] (95% CI)
Postprandial fullness	7 (6.09)	43 (15.64)	16 (13.45)	2.860 (1.246-6.563)[c]	2.359 (0.987-5.639)	2.397 (0.947-6.064)	1.872 (0.685-5.116)
Early satiation	5 (4.35)	39 (14.18)	19 (15.97)	3.636 (1.395-9.479)[c]	2.554 (0.927-7.037)	4.180 (1.505-11.613)[c]	2.712 (0.898-8.192)

Values are presented as number (%) unless otherwised indicated.
OR, odds ratio; CI, confidence interval.
[a]Model was adjusted for age and sex.
[b]OR was adjusted for age and sex.
[c]$p < 0.05$.

Table 4. Prevalence of irritable bowel syndrome and functional constipation

Characteristic[a]	Prediabetes	Diabetes without neuropathy	Diabetes with neuropathy	Diabetes without neuropathy vs. prediabetes		Diabetes with neuropathy vs. prediabetes	
				Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
IBS	10 (8.70)	32 (11.68)	20 (16.81)	1.388 (0.658-2.928)	1.683 (0.745-3.803)	2.121 (0.946-4.755)	2.563 (1.015-6.47)[b]
Constipation type	0 (0.00)	3 (1.09)	2 (1.68)	NA	NA	NA	NA
Diarrhea type	2 (1.74)	5 (1.82)	6 (5.04)	1.046 (0.200-5.473)	1.281 (0.223-7.376)	3.000 (0.593-15.182)	3.94 (0.646-24.02)
Mixed & unclassified type	8 (6.96)	26 (9.49)	14 (11.76)	1.402 (0.615-3.197)	1.716 (0.695-4.237)	1.783 (0.718-4.428)	2.12 (0.742-6.051)
Functional constipation	10 (8.85)	32 (11.85)	18 (15.25)	1.385 (0.656-2.922)	0.969 (0.422-2.228)	1.854 (0.816-4.212)	1.074 (0.414-2.789)

Values are presented as number (%) unless otherwised indicated.
OR, odds ratio; CI, confidence interval; IBS, irritable bowel syndrome; NA, not applicable.
[a]Model was adjusted for age and sex.
[b]$p < 0.05$.

symptoms, lower GI symptoms appeared to begin in the prediabetes state. However, upper GI tract symptoms, especially dyspepsia, tended to develop more frequently in the hyperglycemic state.

The prevalences of bowel symptoms are shown in Table 5. In the constipation group, symptoms of pelvic outlet obstruction such as the sensation of anorectal obstruction or blockage (OR, 5.613; 95% CI, 1.502-20.969) and the need for manual maneuvers to facilitate defecation (OR, 9.549; 95% CI, 1.068-85.411) were more prevalent than symptoms of slow-transit constipation. The prevalences of an anorectal sensation of incomplete evacuation, anorectal obstruction or blockage, and the need for manual maneuvers to facilitate defecation were generally higher than those of other constipation symptoms. However, these symptoms also failed to show pathologic significance, suggesting that they are associated with the hyperglycemic state (Table 5).

Table 5. Prevalence of bowel symptoms

Symptom[a]	Prediabetes	Diabetes Without neuropathy	Diabetes with neuropathy	Diabetes without neuropathy vs. prediabetes		Diabetes with neuropathy vs. prediabetes	
				Crude OR (95% CI)	Adjusted OR[b] (95% CI)	Crude OR (95% CI)	Adjusted OR[b] (95% CI)
Straining	8 (6.96)	25 (9.23)	15 (12.61)	1.359 (0.594-3.111)	0.962 (0.388-2.384)	1.929 (0.785-4.742)	1.212 (0.434-3.387)
Lumpy or hard stools	26 (22.61)	50 (18.18)	16 (13.56)	0.761 (0.446-1.297)	0.549 (0.302-0.998)[c]	0.537 (0.271-1.065)	0.326 (0.148-0.718)[c]
Sensation of anorectal incomplete evacuation	4 (3.48)	24 (8.89)	11 (9.24)	2.708 (0.918-7.989)	2.534 (0.810-7.925)	2.827 (0.873-9.151)	2.762 (0.774-9.856)
Sensation of anorectal obstruction/blockage	3 (2.63)	12 (4.44)	16 (13.45)	1.721 (0.476-6.218)	1.930 (0.467-7.978)	5.748 (1.627-20.302)[c]	5.847 (1.357-25.189)[c]
Manual maneuver to facilitate defecation	1 (0.87)	3 (1.11)	9 (7.56)	1.276 (0.131-12.400)	1.430 (0.102-20.045)	9.327 (1.162-74.854)	7.839 (0.584-105.241)
Fewer than three defecations per week	7 (6.14)	26 (9.49)	16 (13.45)	1.603 (0.675-3.805)	1.166 (0.454-2.996)	2.374 (0.938-6.009)	1.491 (0.516-4.309)

Values are presented as number (%) unless otherwised indicated.
OR, odds ratio; CI, confidence interval.
[a]Model was adjusted for age and sex.
[b]OR was adjusted for age and sex.
[c]$p < 0.05$.

DISCUSSION

This study showed that the prevalences of functional GI disorders and various GI symptoms tended to be elevated before complications occurred, consistent with our expectations. Although the values were not statistically significant, relatively higher ORs were observed for postprandial fullness and early satiety among upper GI symptoms, as well as for pelvic outlet symptoms among lower GI symptoms.

GI symptoms are often associated with abnormalities involving diabetic autonomic neuropathy, which affects the entire GI tract [13]. Various microenvironmental changes, especially hyperglycemia, affect the nervous system throughout the GI tract, leading to motor dysfunction and secretory dysfunction. These changes cause various symptoms, resulting in deterioration of the patient's quality of life [13].

GI symptoms in patients with diabetes are sometimes regarded as the result of abnormalities in the gut-brain axis [3]. Structural and functional changes in the central nervous system can affect the recognition and occurrence of symptoms, such as GI hypersensitivity and rectal sensitivity [14]. Hyperglycemia can impact motor function and sensory recognition in the GI tract, leading to increased proximal stomach compliance; delayed gastric emptying; and symptoms such as satiety, fullness, and nausea [15]. However, persistent hyperglycemia can alter the GI smooth muscle cellular phenotype to hypercontractile or hypocontractile through oxidative stress, which affects both neurons and muscle cells [16].

In our prevalence study, the main symptoms in patients with diabetes were nausea, vomiting, and bloating, consistent previous findings [17]. Delayed gastric emptying, a typical symptom of GI dysfunction, is closely related to reduction and loss of the interstitial cells of Cajal. It is also reportedly associated with immune cell infiltration [18].

Diabetes mellitus can affect colonic function, leading to commonly encountered symptoms such as constipation, diarrhea, abdominal distention, and abdominal pain [19]. Both IBS and diabetes are common conditions [20] with links to factors such as food, stress, and medication. Our study also showed an association with hyperglycemia, although the small number of patients

in the IBS with constipation group precluded analysis (Table 4).

Although colonic motility has not been extensively studied in patients with diabetes, the transition time is usually delayed in such patients [21]. In patients with diabetes mellitus, the colon may exhibit myenteric neuronal loss and evidence of increased oxidants [22]. Anorectal dysfunction in patients with diabetes includes impaired anal sphincter function and decreased rectal sensation of distension [21]. Similar to the upper GI tract, motor functions within the small intestine and colon are worse in the hyperglycemic state [23]. In our study, neither the diabetes without neuropathy group nor the diabetes with neuropathy group showed statistically significant differences in GI symptom prevalences compared with the prediabetes group. We hypothesize that the hyperglycemic state itself serves as a worsening factor in terms of GI symptoms, potentially leading to chronic functional GI disorders even before the development of diabetic autonomic neuropathy. Our findings suggest that further research regarding the usefulness of dietary and psychosocial interventions is valuable, beginning from the onset of hyperglycemia; there is also a need to investigate functional GI disorders and GI symptoms before the development of diabetic autonomic neuropathy.

This study had some limitations. We did not obtain data for comparison with a control group of individuals who had normal fasting glucose levels or individuals not exhibiting prediabetes. However, considering the timing of intervention in patients visiting the hospital, we believe that it will be insightful to compare findings between these control groups and individuals with prediabetes. GI symptoms may develop after the use of medications such as metformin or α-glucosidase inhibitors (e.g., peptide-1 receptor agonists) [24,25]. Therefore, if patients with diabetes develop GI symptoms, clinicians should investigate whether the symptoms are drug-related; if they are, medication may be necessary. In this study, we could not evaluate all medications that might have influenced GI symptoms. Therefore, it was not possible to determine whether GI symptoms were caused by specific diabetic drugs. However, patients who had recently changed their diabetic medication and reported GI symptoms were excluded from the analysis.

In conclusion, the significantly increased prevalence of GI symptoms suggests an association with the hyperglycemic state itself, rather than with autonomic neuropathy. We demonstrated that the prevalences of PDS symptoms and pelvic outlet symptoms were higher than those of abdominal pain, diarrhea, and slow bowel transit symptoms. Although GI symptoms can become more prominent as neuropathy develops, our data indicate that they can be detected long before complications arise. Therefore, the identification of GI symptoms during the prediabetic stage and implementation of appropriate interventions could be beneficial for patients who visit the hospital due to abnormal glucose levels.

요 약

목적: 자율신경계 합병증과 같은 당뇨 합병증을 갖고 있는 환자들에게 있어 위장관계 증상은 매우 흔한 편이다. 그러나 당뇨 합병증이 발병하기 전에 위장관계 증상의 유병률이 어떤지는 명확히 알려져 있지 않다.

방법: Rome III 기준에 의거해 내분비내과를 찾은 환자들에게 기능성 위장장애에 관한 증상 설문조사를 실시하였다. 조사 영역은 기능성 소화 불량과 과민성 대장증후군, 기능성 변비에 관련된 질문들로 구성하였다.

결과: 당뇨 전단계, 당뇨병성 신경병증을 가지고 있지 않은 당뇨병 환자들, 당뇨병성 신경병증을 가진 당뇨병 환자군에 있어서 기능성 위장장애의 유병률은 각각 기능성 소화 불량의 경우 16.52%, 27.27% 그리고 23.53%, 과민성 대장증후군의 경우 8.70%, 11.68% 그리고 16.81%, 기능성 변비의 경우 8.85%, 11.85% 그리고 15.25%로 확인되었다. 하위 분류 분석에서 식후 포만감과 조기 만복감과 같은 증상을 보이는 식후고통증후군의 유병률이 명치통증증후군보다 좀 더 높게 확인되었다. 기능성 변비에 관련된 하위 분류 분석에 있어 항문직장 폐쇄감이 있거나 배변을 돕기 위한 부가 처치가 필요한 경우와 같은 골반 출구 폐쇄 증상의 유병률이 서행성 변비 증상의 경우보다 더 높게 확인되었다.

결론: 기능성 위장장애의 유병률은 전반적으로 당뇨병이 더 심해짐에 따라 더욱 증가한다. 하지만 당뇨병과 연관된 위장관계 증상은 그 합병증이 발생하기 오래전부터 발생하게 된다. 따라서 이를 미리 확인하여 적절한 치료와 조치를 취할 필요가 있겠다.

중심 단어: 당뇨 합병증; 당뇨 전단계; 기능성 위장장애

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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