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Fibronectin as a Nexus of Inflammation and Dysmetabolism in Type 2 Diabetes

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Abstract

Fibronectin (FN) is a major component of the extracellular matrix and is known to participate in essential biological activities such as wound healing, cell adhesion, and vascular remodeling. Several studies have suggested that FN might be involved in the metabolic disturbances and vascular complication commonly seen in type 2 diabetes mellitus (T2DM).

The purpose of this research was to investigate FN concentrations in Iraqi T2DM patients, examine their links to insulin resistance, and oxidative stress.

We conducted a study at Baghdad Medical City Hospital between January and June 2025. A total of 150 participants were enrolled and divided equally into three groups: patients with T2DM and complications, patients with T2DM but without complications, and healthy controls. For all participants, plasma FN, HOMA-IR, malondialdehyde (MDA), C-reactive protein (CRP), HbA1c, fasting glucose, and total cholesterol were assessed using validated ELISA kits together with routine biochemical techniques.

Our findings revealed that FN concentrations were substantially higher in patients with T2DM who had complications (662.6 ± 6.1 mg/dL) compared with those without complications (533.4 ± 6.2 mg/dL) and the control group (311.5 ± 6.2 mg/dL) ($p < 0.001$). Moreover, FN showed strong positive correlations with HOMA-IR ($r = 0.84$), CRP ($r = 0.88$), and MDA ($r = 0.85$), all of which were statistically significant ($p < 0.01$).

These observations highlight that FN is closely related to insulin resistance, oxidative stress, and inflammatory status in patients with T2DM. Its strong association with diabetic complications supports its potential value as a complementary biomarker to HbA1c. Our study adds new data from a Middle Eastern population, where few studies have examined FN in diabetes.

Keywords: Fibronectin, Type 2 diabetes mellites, Insulin resistance, Oxidative stress.

Introduction

Diabetes mellitus is a long-term problem with the pancreas that causes high blood sugar levels because the body doesn't make enough insulin, or it doesn't work properly. Type 2 diabetes occurs as a result of impaired pancreatic beta cell function and insulin resistance (1-3). The knowledge of the processes behind diabetes has evolved throughout the years. T2D accounts for over 90% of all cases of DM. Since several inflammatory molecules have a major role in the development and progression, it is now more evident that T2D and it's related to metabolic disorders (4-5).

Fibronectin is a versatile glycoprotein that participates in key biological processes such as tissue repair, cell adhesion, and maintenance of extracellular structure (6). It is found in two main isoforms: plasma FN, produced in the liver, and cellular FN, released by fibroblasts, endothelial cells, and macrophages (7). Glycation changes how FN looks and works. It cannot attach well to integrins anymore, which harms normal blood vessel function (8). One special form, FN-EDA, can activate TLR4. When this happens, inflammation increases, and insulin resistance can become more severe (9-10). CVD risk increases with rising blood sugar levels, even before reaching diabetic thresholds. Diabetes and hypertension (HT) are two of the most important cardiovascular risk factors (11). HT and type 2 diabetes are frequently coexisting diseases. Diabetes patients have a higher prevalence of hypertension, whereas hypertensive people are more likely to get diabetes. HT raises the probability of acquiring DM, while DM considerably increases the risk of future HT. Almost one-third of adults have HT. Approximately 75% of individuals with diabetes have hypertension (12).

Numerous epidemiological studies show that smoking cigarettes increases the incidence of type 2 diabetes. Additionally, the length of smoking was positively correlated with the incidence of type 2 diabetes. Chronic heavy smoking increases the risk of hyperglycemia, hyperinsulinemia, and hypertension (13-14).

There is a lack of data on FN in Middle Eastern patients with diabetes. Given that genetic background, lifestyle, and environmental exposures can vary across populations, region-specific studies are important. The purpose of this research was to investigate FN concentrations in Iraqi T2DM patients, examine their links to insulin resistance, oxidative stress, and inflammation, and evaluate the predictive power of FN for diabetic complications.

A point that makes our work valuable is the population we studied. Research on fibronectin in diabetes is still limited in Middle Eastern countries. People from different regions may show differences in biomarker levels because of genetic, environmental, or lifestyle factors.

MATERIALS AND METHODS

Study Design and Participants

Our study was carried out in the Department of Chemistry and Biochemistry at the College of Medicine, Al-Iraqia University in Baghdad. The work extended over six months, from January to June 2025.

The patients were recruited from the (medical city) hospital in Baghdad. The study enrolled a total of 150 people and divided them into three equal groups: patients with type 2 diabetes who already had complications, patients with diabetes but without any complications, and a control group made up of apparently healthy individuals.

To be part of the study, participants had to be between 40 and 70 years of age and have a confirmed diagnosis of type 2 diabetes according to the ADA guidelines.

Inclusion and Exclusion Criteria

This study only included patients who had been living with diabetes for at least five years. Anyone with type 1 diabetes, chronic liver or kidney disease, thyroid problems, cancer, or any acute infection was excluded. We also did not include individuals receiving long-term corticosteroids or antioxidant supplements, as well as pregnant or breastfeeding women.

Every participant was informed about the purpose and details of the research, and we obtained written consent before drawing any blood.

Ethical statement

The University of Iraq College of Medicine's Ethics Permission Committee at the Scientific Affairs Division provided ethical permission for this study in addition to the original approvals.

Sample collection

Blood samples were taken in the morning after the participants had fasted overnight for 10–12 hours. Around 5 mL of venous blood was collected under sterile conditions. A part of the sample was placed in EDTA tubes for HbA1c testing, while the rest was placed in plain tubes. After centrifugation at 3000 rpm for 10 minutes, serum was separated and stored at −20 °C until the tests were performed.

Biochemical Measurement

Fibronectin levels were measured with a commercial ELISA kit from MyBioSource (USA). Fasting plasma glucose was analysed by the glucose oxidase–peroxidase method, and HbA1c was measured using HPLC on the D-10 system from Bio-Rad. Serum insulin was determined with an ELISA kit from DRG Instruments (Germany), and the HOMA-IR index was calculated in the usual way by multiplying fasting insulin by fasting glucose and dividing by 405. Malondialdehyde (MDA) was estimated using the TBARS method, high-sensitivity CRP was measured with an ELISA kit (Thermo Fisher Scientific, USA), and total cholesterol was determined using a colorimetric enzymatic method (Spinreact, Spain). To ensure accuracy, all tests were done twice, and variability within and between runs was kept below 10%.

Statistical analysis

Programs used: IBM SPSS version 30, Graph Pad Prism version 10.4.1
Statistical tests: mean, standard error of mean, independent t-test, ANOVA table (Duncan test) for categorical parameters.
While frequency and percentage, and Pearson’s chi square test was used to calculate the probability of nominal data such as sex, smoking status, complications.
Pearson’s correlation was used to calculate the correlations among the studied parameters.

Results

Table (1) shows the demographic characteristics of the patients with complications, patients without complications, and healthy individuals, respectively. each group consists of 50 participants. The average age was close between the groups suffering from complications and those without complications, about (58.66 ± 1.46, 58.50 ± 1.46), while the average age of healthy people was relatively lower, about (55.64 ± 1.34). Thus, we conclude that age has no statistical value or effect on the study. Regarding sex, Females showed a slight significant ((58.0%) when compared to male in the group diabetic with complications (42.0%), but in contrast to the group diabetic without complications, male showed a clear increase (62.0%) and female (38.0%), and the control group was almost equal between males and females, (52.0%), (48.0%) respectively. Given that they varied between smokers and non-smokers, the values in the three groups were quite close (52–54%) and (46–48%) respectively. The study draw the conclusion that smoking had no bearing on the study.

The results showed that comorbidities in diabetes with complications were approximately (42.0%) CVD and (30.0%) Hypertension, and the number of those who did not suffer from comorbidities was about) 28.0% (patinas without complications were approximately (42.0%) CVD and (30.0%) Hypertension, and the number of those who did not suffer from comorbidities was about) 28.0% (CVD and Hypertension were equal (30.0%), and (40.%) of them had no other comorbidities. There were no comorbidities in the healthy group.

Table 1: Bibliography of the study

Demographical data		Diabetic with complications	Diabetic without complications	Healthy control
Age mean ± SE (Years)		58.66 ± 1.46 ^{A}	58.50 ± 1.46 ^{A}	55.64 ± 1.34 ^{A}
Sex No. (%)	Males	21 (42.0)	31 (62.0)	26 (52.0)
	Females	29 (58.0)	19 (38.0)	24 (48.0)
	Total	50 (100.0)	50 (100.0)	50 (100.0)
Smoking status No. (%)	Smokers	27 (54.0)	26 (52.0)	27 (54.0)
	Non-smokers	23 (46.0)	24 (48.0)	23 (46.0)
Comorbidities No. (%)	CVD	21 (42.0)	15 (30.0)	0 (0.0)
	Hypertension	15 (30.0)	15 (30.0)	0 (0.0)
	None	14 (28.0)	20 (40.0)	50 (100.0)

Table (2) The three groups showed notable differences in biomarkers (fibronectin, HOMA-IR, MDA, CRP, fasting glucose, HbA1c, and total cholesterol): 662.57 ± 6.07, 6.46 ± 0.08, 6.02 ± 0.08, 15.41 ± 0.27, 273.08 ± 7.05, 10.04 ± 0.13, 268.95 ± 2.33, respectively, being considerably higher significance in diabetic with complications than diabetic without complications 533.36 ± 6.20,4.51 ± 0.08, 3.96 ± 0.07, 8.72 ± 0.27, 153.19 ± 2.43, 7.46 ± 0.08, 209.53 ± 2.54 respectively.

In general, the result raised in diabetic patients when comparing to healthy controls 311.53 ± 6.19, 1.74 ± 0.06, 1.71 ± 0.06, 2.64 ± 0.13, 84.42 ± 1.22, 5.12 ± 0.04, 162.26 ± 3.49 respectively.

Table 2: Biomarkers result

Parameters	Mean ± SE		
	Diabetic with complications	Diabetic without complications	Healthy control
Fibronectin level (mg/dL)	662.57 ± 6.07^{A}	533.36 ± 6.20^{B}	311.53 ± 6.19^{C}
HOMA-IR	6.46 ± 0.08^{A}	4.51 ± 0.08^{B}	1.74 ± 0.06^{C}
MDA (nmol/L)	6.02 ± 0.08^{A}	3.96 ± 0.07^{B}	1.71 ± 0.06^{C}
CRP (mg/L)	15.41 ± 0.27^{A}	8.72 ± 0.27^{B}	2.64 ± 0.13^{C}
Fasting glucose (mg/dL)	273.08 ± 7.05^{A}	153.19 ± 2.43^{B}	84.42 ± 1.22^{C}
HbA1c (%)	10.04 ± 0.13^{A}	7.46 ± 0.08^{B}	5.12 ± 0.04^{C}
Total cholesterol (mg/dL)	268.95 ± 2.33^{A}	209.53 ± 2.54^{B}	162.26 ± 3.49^{C}
Duncan's test: similar letters show that there are no appreciable variations across groups.			

Table 3 demonstrates the smoking effect on three groups: diabetic with complications, diabetic without complications, and healthy controls, while the probability shows the significance in the same group between smoking and non-smoking. We often see that diabetics with complications have higher values than diabetics without complications and healthy people.

Smoking and non-smoking didn't have any significance, but the results show some exceptions in: HOMA-IR group 2 probability (0.016) while group 1 and group 3 (0.576), (0.484) respectively. CRP group 1 shows a slight increase (0.022) from group 2 (0.019) and group 3 (0.710).
The diabetic with complications, diabetic without complications, and healthy control in Table 4 were subdivided into three groups: CVD, hypertension, and none. The result shows a high significance in group comorbidities without comorbidities (675.56 ± 9.83 mg/dL), followed by those with hypertension (658.74 ± 10.67 mg/dL) and CVD (655.69 ± 10.36 mg/dL) when compared with group 2 were diabetic without comorbidities.

Fibronectin levels show a high significance (551.15 ± 9.55 mg/dL) from hypertension (521.58 ± 12.32 mg/dL) and CVD (521.42 ± 9.04 mg/dL). HOMA-IR and MDA levels show a higher significance value in diabetic groups than healthy controls, with no changes in the subgroups of the initial group. CRP levels were highest value observed in patients without comorbidities (15.93 ± 0.45 mg/L) in group 1.

Fasting glucose and HbA1c levels in patients without comorbidities had higher levels (291.38 ± 10.35 mg/dL and 10.22 ± 0.24%, respectively), and total cholesterol had no significant differences among comorbidity subgroups.

Table 3: Effect the smoking on parameters

Parameters		Mean ± SE		
		Diabetic with complications	Diabetic without complications	Healthy control
Fibronectin level (mg/dL)	Smokers	664.48 ± 7.45^{A}	531.85 ± 9.42^{B}	311.86 ± 9.37^{C}
	Non-smokers	659.45 ± 10.03^{A}	534.99 ± 8.11^{B}	311.16 ± 7.98^{C}
	Probability	0.687	0.801	0.955
HOMA-IR	Smokers	6.49 ± 0.11^{A}	4.69 ± 0.12^{B}	1.79 ± 0.08^{C}
	Non-smokers	6.41 ± 0.13^{A}	4.32 ± 0.10^{B}	1.68 ± 0.09^{C}
	Probability	0.576	**0.016**	0.484
MDA (nmol/L)	Smokers	5.97 ± 0.11^{A}	3.94 ± 0.09^{B}	1.75 ± 0.08^{C}
	Non-smokers	6.09 ± 0.13^{A}	3.97 ± 0.11^{B}	1.65 ± 0.1^{C}
	Probability	0.415	0.857	0.499
CRP (mg/L)	Smokers	14.93 ± 0.35^{A}	9.23 ± 0.38^{B}	2.56 ± 0.17^{C}
	Non-smokers	15.97 ± 0.38^{A}	8.17 ± 0.35^{B}	2.73 ± 0.19^{C}
	Probability	**0.022**	**0.019**	0.710
Fasting glucose (mg/dL)	Smokers	268.20 ± 9.11^{A}	156.74 ± 3.31^{B}	83.02 ± 1.71^{C}
	Non-smokers	278.80 ± 11.09^{A}	149.34 ± 3.46^{B}	86.07 ± 1.71^{C}
	Probability	0.229	0.339	0.728
HbA1c (%)	Smokers	10.0 ± 0.20^{A}	7.40 ± 0.11^{B}	5.07 ± 0.05^{C}
	Non-smokers	10.09 ± 0.15^{A}	7.52 ± 0.11^{B}	5.18 ± 0.07^{C}
	Probability	0.627	0.527	0.564
Total cholesterol (mg/dL)	Smokers	270.97 ± 3.60^{A}	210.33 ± 3.66^{B}	162.27 ± 4.58^{C}
	Non-smokers	266.59 ± 2.77^{A}	208.67 ± 3.57^{B}	162.26 ± 5.48^{C}
	Probability	0.446	0.773	0.998
Duncan's test: similar letters show that there are no appreciable variations across groups				

The diabetic with complications, diabetic without complications, and healthy control in Table 4 were subdivided into three groups: CVD, hypertension, and none. The result shows a high significance in group comorbidities without comorbidities (675.56 ± 9.83 mg/dL), followed by those with hypertension (658.74 ± 10.67 mg/dL) and CVD (655.69 ± 10.36 mg/dL) when compared with group 2 were diabetic without comorbidities.

Fibronectin levels show a high significance (551.15 ± 9.55 mg/dL) from hypertension (521.58 ± 12.32 mg/dL) and CVD (521.42 ± 9.04 mg/dL). HOMA-IR and MDA levels show a higher significance value in diabetic groups than healthy controls, with no changes in the subgroups of the initial group. CRP levels were highest value observed in patients without comorbidities (15.93 ± 0.45 mg/L) in group 1.

Fasting glucose and HbA1c levels in patients without comorbidities had higher levels (291.38 ± 10.35 mg/dL and 10.22 ± 0.24%, respectively), and total cholesterol had no significant differences among comorbidity subgroups.

Table 4: Effect of biomedical parameters on comorbidities

Parameters		Mean ± SE		
		Diabetic with complications	Diabetic without complications	Healthy control
Fibronectin level (mg/dL)	CVD	$655.69 \pm 10.36^{A}_{b}$	$521.42 \pm 9.04^{B}_{b}$	-
	Hypertension	$658.74 \pm 10.67^{A}_{b}$	$521.58 \pm 12.32^{B}_{b}$	-
	None	$675.56 \pm 9.83^{A}_{a}$	$551.15 \pm 9.55^{B}_{a}$	311.53 ± 6.19^{C}
HOMA-IR	CVD	$6.47 \pm 0.11^{A}_{a}$	$4.34 \pm 0.16^{B}_{a}$	-
	Hypertension	$6.56 \pm 0.18^{A}_{a}$	$4.73 \pm 0.15^{B}_{a}$	-
	None	$6.32 \pm 0.16^{A}_{a}$	$4.48 \pm 0.56^{B}_{a}$	1.74 ± 0.06^{C}
MDA (nmol/L)	CVD	$6.0 \pm 0.15^{A}_{a}$	$3.88 \pm 0.13^{A}_{a}$	-
	Hypertension	$6.05 \pm 0.14^{A}_{a}$	$4.05 \pm 0.14^{A}_{a}$	-
	None	$6.03 \pm 0.13^{A}_{a}$	$3.94 \pm 0.11^{B}_{a}$	1.71 ± 0.06^{C}
CRP (mg/L)	CVD	$14.89 \pm 0.46^{A}_{a}$	$8.61 \pm 0.51^{A}_{a}$	-
	Hypertension	$15.66 \pm 0.42^{A}_{a}$	$9.24 \pm 0.54^{A}_{a}$	-
	None	$15.93 \pm 0.45^{A}_{a}$	$8.42 \pm 0.39^{B}_{a}$	2.63 ± 0.13^{C}
Fasting glucose (mg/dL)	CVD	$259.76 \pm 11.87^{A}_{b}$	$150.93 \pm 4.25^{B}_{a}$	-
	Hypertension	$274.65 \pm 12.87^{A}_{ab}$	$153.30 \pm 4.50^{B}_{a}$	-
	None	$291.38 \pm 10.35^{A}_{a}$	$154.81 \pm 4.06^{B}_{a}$	84.42 ± 1.22^{C}
HbA1c (%)	CVD	$10.14 \pm 0.19^{A}_{ab}$	$7.38 \pm 0.16^{B}_{a}$	-
	Hypertension	$9.73 \pm 0.23^{A}_{b}$	$7.59 \pm 0.14^{B}_{a}$	-
	None	$10.22 \pm 0.24^{A}_{a}$	$7.42 \pm 0.12^{B}_{a}$	5.12 ± 0.04^{C}
Total cholesterol (mg/dL)	CVD	$269.57 \pm 3.13^{A}_{a}$	$212.15 \pm 5.20^{A}_{a}$	-
	Hypertension	$266.30 \pm 3.91^{A}_{a}$	$204.68 \pm 3.89^{A}_{a}$	-
	None	$270.87 \pm 5.63^{A}_{a}$	$211.21 \pm 4.09^{A}_{a}$	162.26 ± 3.49^{A}
Duncan's test: Similar capital letters above the line indicate no significant differences between the groups (horizontal comparison), while small letters below the line indicate no significant differences between the subgroups of the multiples (vertical comparison).				

Table 5 shows obvious the correlation coefficient between biomarker parameters in patient groups. levels of fibronectin showed a high correlation with another biomarker, HOMA_IR, MDA, CRP, fasting glucose, HbA1c, and total cholesterol: 0.844, 0.853, 0.875, 0.851, 0.817, and 0.851,0.817,0.752, respectively. Also, all parameters increased when HOMA_IR evaluated, MDA, CRP, Fasting Glucose, HbA1c, and Total Cholesterol: 0.879, 0.861, 0.806, 0.878, and 0.808, respectively.

From this table, variables are significantly related to each other.

Table 5: Correlations between biomarker parameters

	Fibronectin	HOMA_IR	MDA	CRP	Fasting Glucose	HbA1c	Total Cholesterol
Fibronectin	1	0.844**	0.853**	0.875**	0.851**	0.817**	0.752**
HOMA_IR		1	0.879**	0.861**	0.806**	0.878**	0.808**
MDA			1	0.844**	0.858**	0.864**	0.787**
CRP				1	0.835**	0.824**	0.752**
Fasting Glucose					1	0.817**	0.716**
HbA1c						1	0.793**
Total Cholesterol							1
**. Correlation is significant at the 0.01 level (2-tailed).							

Discussion

Our study shows clear and consistent differences between groups of patients: higher fibronectin (FN) levels in type 2 diabetes mellitus (T2DM) patients, especially those with complications, compared to healthy controls. Alongside that, HOMA-IR, MDA, CRP, HbA1c, and total cholesterol were also elevated in the same pattern—worse in complicated cases, moderate in uncomplicated diabetes, and lowest in healthy individuals.

It is long known that chronic high blood sugar drives FN overexpression. In experimental diabetes, FN accumulates in tissues such as the kidney, heart, retina, and colon (15). That tissue buildup reflects structural damage, and it aligns with our finding that circulating FN is higher in patients with complications. Fibronectin may act not just as a bystander, but as a signal of ongoing vascular injury (16).

Moreover, glycation alters FN structure, affecting how it binds integrins like α5β1 and disrupting signaling pathways such as Ang-1/Tie-2, which are essential for endothelial cell function (17). This mechanistic disruption likely links high FN levels with impaired vascular integrity seen in diabetic complications.

The findings showed strong positive correlations between FN and HOMA-IR, CRP, and MDA. HOMA-IR reflects insulin resistance. That connection is important because some isoforms of FN, especially FN-EDA, can activate Toll-like receptor 4 (TLR4) and promote insulin resistance directly (18). So, FN might not just mirror disease severity—it could worsen it.

CRP is a general marker of inflammation, produced by the liver in response to inflammatory cytokines (19). Many T2DM patients with complications had high CRP and high FN. These two markers appear linked: chronic inflammation likely stimulates FN expression, and FN may contribute further to local inflammatory processes in vascular tissue (20).

MDA reflects oxidative stress—the damage caused by reactive oxygen species when antioxidant systems fail. In T2DM, oxidative pathways are overactive; they damage proteins, lipids, and DNA, and they promote both inflammation and vascular injury (21). The association between FN and MDA in our data suggests that when stress is higher, FN tends to be elevated as well.

Comparing diabetic groups: with vs. without complications

One key finding: diabetic patients with complications consistently had higher FN, HOMA-IR, CRP, and MDA than diabetics without complications—even when age or duration of disease were similar. This suggests FN may reflect disease severity. In other words, FN may help distinguish stable diabetes from diabetes complicated by vascular issues.

That distinction matters clinically. Many patients with acceptable HbA1c still go on to develop nephropathy or retinopathy because glycemic control alone doesn't tell the full story (22). FN, together with markers like CRP or MDA, may help point to patients at higher risk—those whose disease is progressing quietly despite acceptable glycemic levels (23).

The researcher studied a Middle Eastern (Iraq) population, where data on fibronectin in diabetes are scarce. Most FN research comes from Europe or East Asia. Yet genetic, lifestyle, dietary, and environmental factors differ across regions—and these differences may affect baseline biomarker levels and their clinical meaning. Our data fills a gap: they show how FN behaves in a regional context and support the idea that FN may be a useful marker in diverse populations.

Although this study cannot show cause and effect because of its cross-sectional design, the results suggest that fibronectin could be a useful extra marker along with HbA1c. Using markers of endothelial injury together with standard glucose measures might give doctors a better way to see which patients are at higher risk and to manage them earlier.

So, what do these results mean for practice? HbA1c remains essential—it reflects long-term glucose control—but doesn't inform about oxidative stress or vascular remodeling. Adding FN to the assessment toolbox could give clinicians a broader view of patient risk:

- Patients with elevated FN—even with moderate HbA1c—might need closer monitoring.

Fibronectin could be useful for making earlier decisions about preventing vascular problems.

Checking FN levels regularly might also show how patients respond to treatments aimed at reducing inflammation or oxidative stress (24-25).

Conclusions:

This study showed that fibronectin levels were higher in people with type 2 diabetes, especially those who already had complications. We also found that fibronectin was linked with insulin resistance, oxidative stress, and inflammation. These results suggest that fibronectin might be a useful marker in addition to HbA1c when evaluating diabetic patients.

Our findings are important because there are very few studies on fibronectin in diabetic patients from the Middle East. By adding this information, we help to fill a gap in knowledge for this region.

Even though our study cannot prove cause and effect, it shows clear associations. More research that follows patients over time is needed. If future studies confirm these results, fibronectin could become part of a group of tests to better predict complications and guide care for people with diabetes.

Conflict of Interest: None

Funding: Nil

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