Carotid Intima-Media Thickness and its Relations with the Complications in Type I Diabetic Children

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Abstract: Background: Diabetes mellitus is associated with a high risk of cardiovascular disease. Carotid intima-media thickness (CIMT) is increasingly used as a surrogate marker of atherosclerosis. Its use relies on its ability to predict future clinical cardiovascular endpoint. **The aim of this study:** was to evaluate the carotid intima-media thickness (CIMT) in patients with type I diabetes and to investigate its relations with diabetic microvascular complications (nephropathy and retinopathy). **Patients and Methods:** 50 children and adolescents with type I diabetes mellitus attending regularly the Outpatient Pediatric Clinic of National Institute of Diabetes and Endocrinology and from Al-Zahraa University Hospital aged from 6 to 18 years with Mean ± SD (13.4 ± 3.46) years, mean BMI was (19.16 ± 4.06 kg/m^2) and mean diabetic duration was (7.36 ± 2.57 years). And another 50 apparently healthy children and adolescents matched for age and sex as control group were included in this study. All patients and control groups were subjected to detailed history taking, throughout clinical examination and measuring of: fasting, postprandial glucose and glycated haemoglobin (HbA1C), lipid profile (TC, TG, HDLC and LDLC), kidney functions (urea, cratinine) urinary albumin,creatinine ratio, complete urineanalysis with culture and sensitivity, C-reactive protein, complete blood picture, liver functions (AST, ALT), fundus examination searching for retinopathy and assessment of carotid intima media thickness (CTMT) by high resolution B mode ultrasound for determining the presence of atherosclerosis. **Results:** Our results revealed significant increase in carotid intima media thickness (CIMT) in diabetic patients compared to normal controls (0.54 ± 0.08 mm) vs (0.41 ± 0.04 mm) respectively with *p*. value (0.0001). CIMT was significantly higher in diabetic patients with HbA1C ≥8% than in diabetic patients with HbA1C < 8% (0.55 ± 0.08 vs 0.40 ± 0.004) with *p* value (0.012). CIMT was significantly higher in diabetic patients with duration of disease ≥ 8 years than those with duration of disease < 8years. Mean ± SD was 0.58 ± 0.09 vs 0.53 ± 0.07 mm respectively with *p* value (0.02). CIMT was significantly higher in patients with nephropathy than patients without nephropathy (0.56 ± 0.09 vs 0.54 ± 0.08 mm). CIMT was significantly higher in diabetic patients with retinopathy than in patients without retinopathy (0.62 ± 0.09 vs 0.52 ± 0.07 mm) respectively; *p* value (0.0001). A statistically significant higher results were found in CIMT with the multiplicity of diabetic microvascular complications with (p value 0.008). Statistically significant increase in CRP level, serum total cholesterol, triglycerides, high density lipoproteins levels and A/C ratio in diabetic patients than control group with *p* value (0.001), (0.003), (0.0001), (0.0001) and (0.0001) respectively. Statistically significant positive correlations were found between carotid intima-media thickness and HbA1C ($p < 0.01$), triglycerides ($p < 0.05$), A/C ratio ($p < 0.01$), diabetic retinopathy ($p < 0.05$), duration of diabetes ($p < 0.05$) and the number of diabetic microvascular complications with $p < 0.05$. **Conclusions:** CIMT was positively correlated with diabetic microvascular complications (nephropathy and retinopathy), HBA1C, duration of diabetes, triglycerides and the multiplicity of the microvascular complications so we should consider the importance of these risk factors in development and progression of atherosclerosis.

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Key words: Carotid Intima-Media Thickness, atherosclerosis, Type 1 diabetes, microvascular

1.Introduction

Microvascular diabetes complications refer to diseases of the eyes (diabetic retinopathy), kidneys (diabetic nephropathy) and nerves (diabetic neuropathy). These diseases result from abnormalities in tiny blood vessels (capillaries) that supply every organ in the body [(1)].

There is a linear association between HbA1C and microvascular complications, including any mild and moderate retinopathy, chronic albuminuria and peripheral neuropathy without any clear consistent threshold effect across the different outcomes [(2)].

Carotid intima-media thickness (CIMT) is area of tissue starting at the luminal edge of the artery and ending at the boundary between the media and the adventitia. It is measured using B-mode ultrasound as the composite thickness of the intima and media [(3)].

Carotid intima-media thickness (CIMT) holds great promise for the non-invasive determination of the presence of atherosclerosis [(4)].

Carotid intima-media thickness is the early sign of atherosclerosis and thereby, also the sign of macrovascular diseases in diabetic patients [(5)].

The aim of the work was to evaluate the carotid intima-media thickness (CIMT) in patients with type I diabetes and to investigate its relations with diabetic microvascular complications (nephropathy and retinopathy).

2.Patients and Methods

This study is a case control comparative study that was conducted on 50 children and adolescents with type I diabetes aged 6 to 18 years. They were randomly selected from the outpatient pediatric clinic of the National Institute of Diabetes and Endocrinology and from Al-Zahraa University Hospital. Another 50 apparently healthy children and adolescents of comparable age and sex were the control group.

Inclusion criteria:

- Type I diabetes mellitus patients.
- Age from 6 to 18 years old.
- Duration of diabetes more than 4 years.

Exclusion criteria:

- Other types of diabetes mellitus.
- History or evidence of clinically relevant disease, that may affect the carotid intima-media thickness e.g. hypertension, obesity, familial hyper-lipidemia, hypothyroidism, positive family history of cardiac or renal diseases.

All patients and control group were subjected to the following: Full history taking and thorough clinical examination including anthropometric measures (weight, height and body mass index), BLP measurement and fundus examination.

Laboratory investigations: Including fasting and postprandial blood sugar, glyclated haemoglobin (HbA1C), complete blood picture, C-reactive protein (CRP), kidney functions (urea, creatinine), urine analysis and urinary Alb/creatinine ratio.

Liver functions (sGOT, sGOT) and lipid profile (cholesterol, triglycerides, LDL, HDL).

Ultrasonography (carotid ultrasound): A non-invasive method for measurement of the carotid intima-media thickness and was performed with a high resolution ultrasound scanner, using an "Acuson" machine and a "5-8 MHZ" probe with a high resolution B-mode system.

The technique, by which carotid IMT is determined, consists of two steps: the first step is the "scanning procedure" i.e. ultrasound scanning of the common carotid artery, with storage of pictures/ dynamic sequences and the second step is the "reading procedure" i.e. the following measurement of carotid IMT using a specialized software technique [(6)].

Statistical analysis:

Data was analyzed by SPSS (statistical package for social science version 15) and the results were tabulated by Harvard graphics packages version 4 that were used for representing the results graphically.

Quantitative variables from normal distribution were expressed as mean ± SD.

Qualitative variables were expressed as percentages and association measures available within cross tabs were used [(7)].

3.Results

The results of our study are represented in the following tables (1- 7) and figures (1-4).

Table (1): Comparison between diabetic and control groups regarding different clinical data

Variables	Diabetic		Control		t-value	*p*-value
	Range	Mean ±SD	Range	Mean ±SD		
Age in years	(7-18)	13.36 ± 3.46	(6-18)	13.04 ± 3.20	0.48	0.63(NS)
Weight(Kg)	(20.94-71.96)	43.45±13.36	(20.8-74.6)	43.97±13.06	0.19	0.84(NS)
Height(Cm)	(121-174)	149.36±13.4	(103.0-170.0)	145.1±15.11	1.49	0.14(NS)
BMI(Kg/m2)	(11-26.6)	19.16 ± 4.06	(15.3-30.0)	20.62 ± 4.21	1.77	0.08(NS)
SBP(mmHg)	(90-140)	109.6 ± 11.4	(90-130)	107.8 ± 9.3	0.86	0.39(NS)
DBP(mmHg)	(60-85)	69.3 ± 8.02	(60-80)	69.8 ± 7.42	0.32	0.75 (NS)

This table shows no statistically significant difference between diabetic and control group as regard age, body mass index, systolic and diastolic blood pressure.

Table (2): Comparison between diabetic and control groups as regard laboratory investigations of urea, creatinine, A/C ratio using T-test.

Variables	Diabetic		Control		t-value	*p*-value
	Range (Min-Max)	Mean ±SD	Range (Min-Max)	Mean ±SD		
Urea (mg/dl)	(13-62)	27.48 ± 8.83	(12-40)	24.84 ± 6.45	1.7	0.09 (NS)
Creatinine (mg/dl)	(0.4-6.0)	0.81 ± 0.18	(0.3-1.1)	0.66 ± 0.16	1.27	0.21 (NS)
A/C Ratio (mg/gm)	(5-139)	27.2 ± 22.7	(0.1-11.4)	3.04 ± 2.11	7.48	0.000 ***

This table shows statistically significant higher results in A/C ratio in diabetic than control group and non significant higher results as regard Urea and creatinine.

Table (3): Comparison between diabetic and control groups regarding CIMT

Variables	**Diabetic**		**Control**		**t-value**	***p* -value**
	Range	**Mean ±SD**	**Range**	**Mean ±SD**		
CIMT(mm)	(0.40-0.76)	0.54 ± 0.08	(0.35-0.51)	0.41± 0.04	10.08	0.000***

This table shows statistically significant increase in CIMT in diabetic than control group.

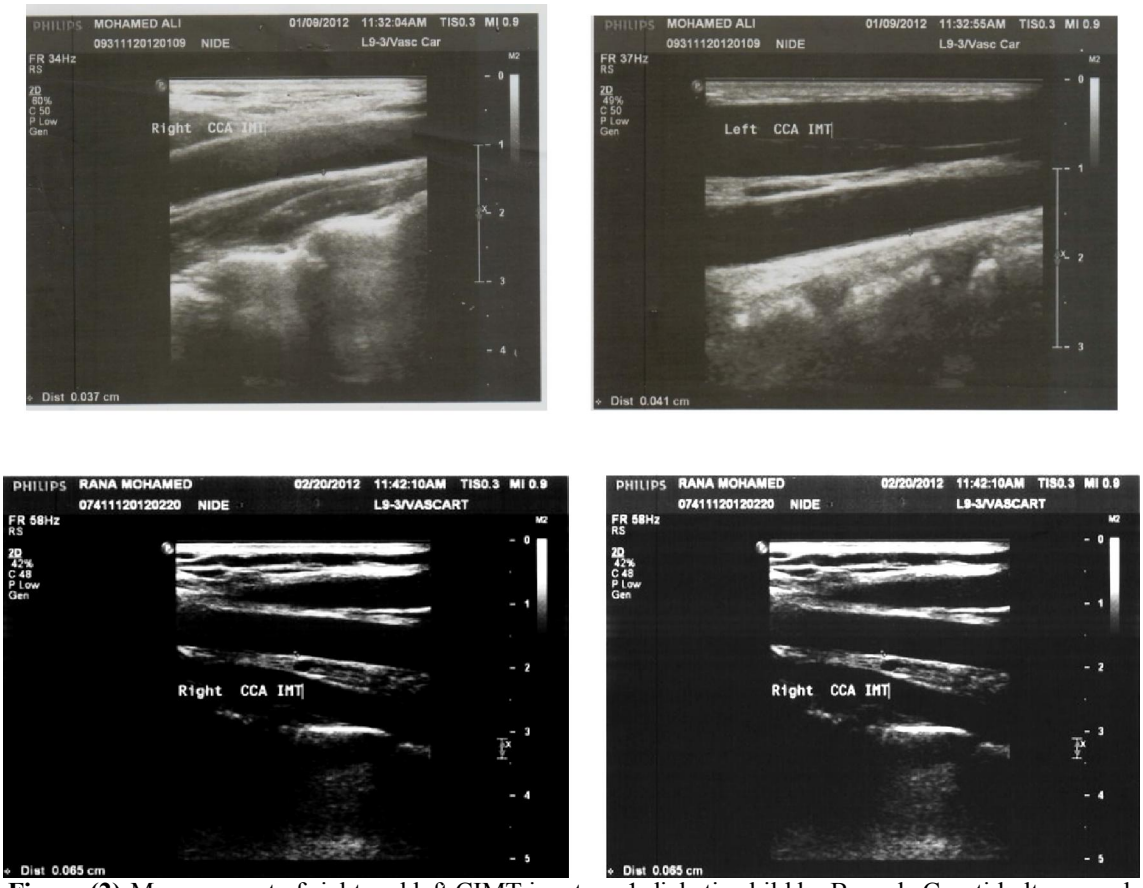

Figure (2): Measuerment of right and left CIMT in a type 1 diabetic child by B-mode Carotid ultra sound

Table (4): Frequency and percent of distribution of number of diabetic complication between males and females of diabetic group

Variable	Male		Female		Total	
Number of complications	**No.**	**%**	**No.**	**%**	**No.**	**%**
No complication(n=30)	14	58.4	16	61.5	30	60.0
1 Complication(n=12)(nephropathy or retinopathy)	5	20.8	7	26.9	12	24.0
2 Complications(n=8)(nephropathy and retinopathy)	5	20.8	3	11.6	8	16.0
Total	24	100.0	26	100.0	50	100.0

This table shows the number and percentage of diabetic complications among males and females in diabetic group.

Table (5): Correlation between CIMT with clinical and laboratory variables in diabetic and control groups

Clinical and Laboratory Variables	Diabetic(n=50)		Control(n=50)	
	R	*p* -value	R	*p*-value
Age in years	0.27	*p*> 0.05	0.27	*p* > 0.05
Kg/m2)(BMI	0.17	*p* > 0.05	0.18	*p* > 0.05
TC(mg/dl)	0.16	*p* > 0.05	0.14	*p* > 0.05
TG(mg/dl)	0.30	P < 0.05*	0.10	*p* > 0.05
HDLC(mg/dl)	-0.06	P > 0.05	0.02	*p* > 0.05
LDLC(mg/dl)	0.15	P > 0.05	0.17	*p* > 0.05
HbA1c %	0.39	P < 0.01**	-0.19	*p* > 0.05
A/C ratio(mg/gm)	0.43	P < 0.01**	0.18	*p* > 0.05
CRP(mg/L)	0.01	P > 0.05	0.04	*p* > 0.05
Diabetic retinopathy	0.49	*p* < 0.001***	--	--
Duration of Diabetic(years)	0.35	P < 0.05*	--	--
Total insulin dose, units /day	0.02	P > 0.05	--	--
Number of diabetic complications	0.35	*p* < 0.05*	--	--

This table shows statistically significant positive correlation between CIMT with duration of diabetes, HbA1c, A/C ratio, TG, diabetic retinopathy and number of complications in diabetic group. No statistically significant correlation was determined between CIMT with TC, HDLC, LDLC, BMI, CRP and total insulin dose in both diabetic and control group.

Table(6): Comparison of Mean ± SD CIMT in diabetic patients grouped by duration of diabetes (years)

Duration of DM	No.	%	Mean±SD	F value	*P* value
(Group1) 5-8 years	34	68.0	0.53±0.07	5.56	0.02
(Group2) ≥8years	16	32.0	0.58±0.09		

This table shows statistically significant increase in CIMT in group 2 (duration of diabetes ≥8years) than in group1 (duration of diabetes 5-8 years).

Table(7): Comparison of mean ± SD CIMT IN diabetic patients grouped by HbA1c%

HbA1c%	No.	%	Mean±SD	F value	*P* value
(Group1) <8%	2	4.0	0.40 ± 0.004	6.75	0.012*
(Group2) ≥8%	48	96.0	0.55 ± 0.08		

This table shows statistically significant increase in CIMT in group 2 (HbA1c% ≥8%) than in group 1 (HbA1c% <8%).

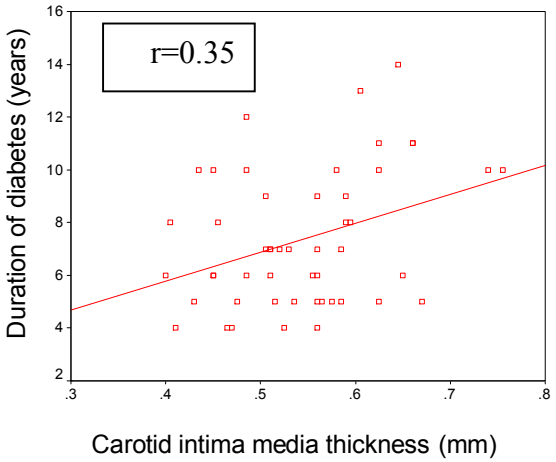

Figure (3): Correlation between carotid intima-media thickness (mm) and duration of Diabetic (years) in diabetic group.

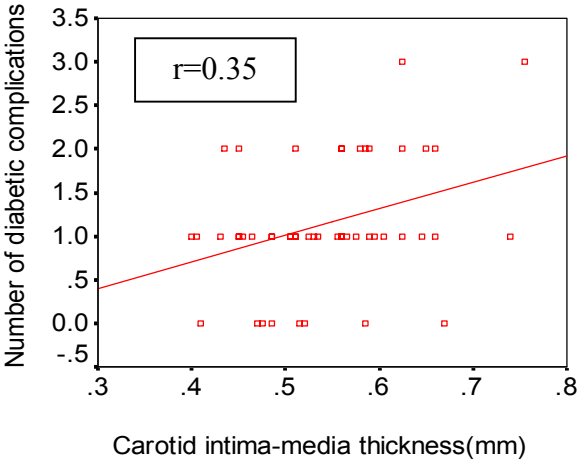

Figure (4): Correlation between carotid intima-media thickness (mm) and number of diabetic complications in diabetic group.

4.Discussion

Diabetes mellitus type I is an important risk for development of cardiovascular diseases. Patients with diabetes show a 2 to 10 fold risk for developing atherosclerotic lesions compared with normal population [8].

There is evidence indicating that endothelial damage precedes albuminuria in type I diabetes. Thus, it is more likely that the micro- and macrovascular damage seen in type I diabetes begins at the onset of the disease, probably via endothelial damage [9].

The most significant changes in early subclinical period of atherosclerotic disease are endothelial dysfunction and increase in intima-media thickness observed in all arterial beds [5].

The objective of our study was to evaluate the carotid intima-media thickness (CIMT) in patients with type I diabetes and to investigate its relations with diabetic microvascualr complications (nephropathy and retinopathy).

In the present study, we assessed HbA1C as a predictor for glycaemic control, A/C ratio as a marker of diabetic nephropathy, total cholesterol, triglycerides, C-reactive protein as a marker of endothelial damage, fundus examination to detect diabetic retinopathy and carotid intima media thickness (IMT) as a noninvasive marker of subclinical atherosclerosis.

The present study revealed that CIMT was significantly increased in children with type I diabetes (0.54 ± 0.08 mm) compared with control group (0.41 ± 0.04 mm) with *p* value (0.001).

Our results are in agreement with ***Brunk*** [10] who found that after adjustment for age, patient with type I diabetes had a significantly thicker CIMT, compared with controls (0.56 mm vs 0.50 mm respectively).

The same findings were showed in the study of ***Gül et al.*** [5].who reported that patients with type I diabetes had increased CIMT than control group (0.67 ± 0.11 mm vs 0.53 ± 0.07 mm respectively; $p < 0.001$).

As regard to the effect of the duration of the disease to CIMT, our results revealed that CIMT was significantly higher in patients with longer duration of diabetes lasting ≥ 8 years (n = (16) 32%) (0.58 ± 0.090) than in patients with duration of diabetes less than 8 years (n = (34) 68%) (0.53 ± 0.07) F-value (5.56) and *p*-value (0.02).

As regard to the correlation of CIMT with the duration of the disease, our results revealed that mean

± SD CIMT was positively correlated with the duration of the disease with r = 0.35 and $p < 0.05$.

Our results are in agreement with ***Jorvisalo et al.*** [11], ***Abdelghaffar et al.*** [12] and ***Gül et al.*** [5].as they reported that the mean ± SD of CIMT was positively correlated with duration of diabetes with (r = 0.32 and p value < 0.05), (r = 0.66, p value 0.0001) and (r = 0.46 and p value < 0.001) respectively).

Improved blood glucose obtained by intensive treatment is associated with delayed atherosclerosis development and less cardiovascular events [13].

As regard to the effect of HbA1C on CIMT, our results revealed that CIMT was significantly higher in diabetic patients with HbA1C ≥ 8% [N = (48) 96%] (0.55 ± 0.08) than patients with HbA1C < 8% [N = (2) 4%] (0.40 ± 0.004) with F-value 6.75 and p-value (0.012).

This is in agreement with ***Atwa and Shora***[14]. who found that carotid intima media thickness was significantly higher in diabetic children with poor diabetic control (0.57 ± 0.05 mm) than diabetic children with good control (0.45 ± 0.03 mm) with $p < 0.01$.

As regard to the correlation of CIMT with HbA1C%, our results revealed that mean ± SD CIMT was positively correlated with HbA1C% with r = 0.39 and $p < 0.001$.

In agreement with our study, a study done by ***Jarvisalo et al.*** [11] who revealed that endothelial dysfunction has proved to be positively correlated to the HbA1C level in diabetic children. Also, in a study done by ***Sibal et al.*** [3], CIMT was found to positively correlated with HbA1C (r = 0.40, p value 0.004).

About the prevalence of micro albuminuria (diabetic nephropathy), our results revealed that it was prevalent in 36.0% (18 cases) of all diabetic studied group (50 cases) which was prevalent in male diabetic group 41.7% (N = 10) from 24 male patients than female diabetic group 30.8% (N = 8) from 26 female patients.

In agreement with our result, a study of ***Sampaio et al.*** [15] who revealed that microalbuminuria was prevalent in 35.8% which is higher than the prevalence of diabetic retinopathy in 21% of 81 type I diabetic children.

The same as our study, ***Giordano et al.*** [16] reported that the probability of developing microalbuminuria was higher in males than in females.

About the prevalence of diabetic retinopathy, our results revealed that it was prevalent in 20.0% (10 cases) and it was prevalent in diabetic males 20.8% (N = 5) while in female diabetic group 19.2% (N = 5) were affected by diabetic retinopathy.

In this study, one diabetic microvascular complication (nephropathy or retinopathy) was prevalent in 24% (N = 12) of cases. While two complications (nephropathy and retinopathy) were prevalent in 16% (N = 8) of all diabetic studied group and when it is classified according to sex, one diabetic complication was prevalent in female diabetic group 26.9% (N = 7) than in male diabetic group 20.8% (N = 5), while in two complications it was prevalent in male diabetic group 20.8% (N =5) than in female diabetic group 11.6% (N = 3).

This is in agreement with the results of ***Hammes et al.*** [17] who reported that male sex is one of the recent risk factors for diabetic retinopathy (n = 1323 from total 1889) (p value 0.002) and disagreed with the results of ***Ammari*** [18] who reported that microvascular complications were prevalent in female group (29.5%) than in male group (10.3) and this may be attributed to the difference in the size of sample of the studied groups.

In our study, patients with microvascular complications had higher CIMT than those who did not have these complications (0.63 ± 0.08 vs 0.53 ± 0.07 mm) respectively with F-value 5.43 and p value 0.008.

In agreement with our results, a study of ***Gül et al.*** [5] found that patients with nephropathy and retinopathy had higher CIMT compared to the patients without complications (0.72 ± 0.13 vs 0.64 ± 0.09 mm) respectively with p value < 0.001, as the severity of nephropathy and retinopathy are increased, CIMT increased as well.

In our study, we demonstrated a higher increase in CIMT in patients with nephropathy (A/C ratio ≥ 30 mg/gm) than patients without nephropathy (A/C ratio < 30 mg/gm) (0.56 ± 0.09 vs 0.54 ± 0.08 mm) respectively with F value = 5.32 and p value 0.005.

This is in concordance with ***Abdelghaffar et al.*** [12] and ***Gül et al.*** [5] who found positive correlation between CIMT and urinary albumen excretion (mean ± SD 0.68 ± 0.09) vs (0.64 ± 0.09) in patients without nephropathy with p value 0.002 indicating that albumin excretion was associated with atherosclerosis.

As regard to the correlation of CIMT with the number of diabetic microvascular complications, our results revealed that CIMT was positively correlated with the multiplicity of diabetic microvascular complications with r = 0.35 and $p < 0.05$.

Our results are in agreement with ***Gül et al.*** [5] as they reported that the mean ± SD of CIMT was positively correlated with the number of diabetic microvascular complications with r = 0.37 and $p < 0.001$.

Conclusion

Carotid-intima media thickness (CIMT) was positively correlated to HbA1C, duration of diabetes, triglycerides; so we should consider the importance of these risk factors in development and progression of atherosclerosis.

CIMT was positively correlated with diabetic microvascular complications (nephropathy and retinopathy) and positively correlated with the

multiplicity of microvascular complications. Thus, when microvascular complications have developed, one should be alert to take precautions for atherosclerosis.

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