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Metabolic disorders induced by highly active antiretroviral therapy and their relationship with vascular remodeling of the brachial artery in a population of HIV-infected patients

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Abstract

Antiretroviral therapy has positively modified the natural history of HIV infection; but this treatment can induce metabolic abnormalities, including dyslipidemia, fat redistribution, high blood pressure, and insulin resistance. The metabolic syndrome, a clustering of the metabolic disorders, is frequently detected among HIV patients, especially those on antiretroviral treatment. All the arteries can modify their diameter in response to a chronic injury. This process, defined *vascular remodeling*, was demonstrated for the brachial artery. It is well known that the diameter of the brachial artery was correlated with the number of the elements of the metabolic syndrome and was associated with the severity of coronary artery disease. On this basis, we postulate that brachial arterial enlargement may be a process potentially correlated with the metabolic disorders induced by antiretroviral therapy. We tested this hypothesis in a large population of HIV-infected patients in which we measured brachial artery diameter, as an indicator of artery remodeling, by noninvasive, ultrasonographic technique. Our population consisted of 570 patients, with a mean age of 46.3 ± 7.1 years. All the patients were chronically treated with highly active antiretroviral therapy. Brachial artery diameter was correlated with insulin resistance, evaluated by the homeostasis model assessment of insulin resistance index ($r = 0.18$, $P < .0001$). There was a significant linear increase in brachial artery diameter as the number of components of the metabolic syndrome increased: brachial artery diameter for those with 0, 1, 2, 3, or + characteristics was 39.3 ± 7.2, 41.0 ± 6.8, 42.0 ± 7.3, and 43.8 ± 7.9 mm, respectively ($P < .001$ for trend). In multivariable logistic regression analysis, brachial artery diameter was independently correlated with the presence of metabolic syndrome. Our results are in line with the hypothesis that, among HIV-infected patients chronically treated with antiretroviral therapy, those with a larger brachial artery diameter are at high risk for metabolic disorders, including a more severe insulin resistance and the presence of metabolic syndrome.

1. Introduction

Combination highly active antiretroviral therapy (HAART) has positively modified the natural history of HIV infection, leading to a significant reduction in morbidity and mortality. However, long-term toxicity is recognized; and a variety of metabolic abnormalities, including dyslipidemia, fat redistribution, high blood pressure, and insulin resistance, has frequently been associated with this treatment [1-8]. The metabolic syndrome (MS), a clustering of the above-cited metabolic disorders, is frequently detected among HIV patients, especially those on HAART [9-11].

All the arteries can modify their diameter in response to a variety of stimuli, including hemodynamic changes or chronic injury. This process, defined *vascular remodeling*, was clearly demonstrated in patients with atherosclerosis [12-15].

The brachial artery, probably due to its favorable position, is one of the most studied artery in the body. It is well known that the diameter of the brachial artery was proportionally related with the number of the elements of the MS [16] and was associated with the severity of coronary artery disease [17]. On this basis, we postulate that brachial arterial

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enlargement may be a process potentially correlated with the metabolic disorders induced by HAART. We tested this hypothesis in a large population of HIV-infected patients in which we measured brachial artery diameter (BAD), as an indicator of arterial remodeling, by noninvasive, ultrasonographic technique.

2. Methods

2.1. Patients population

Consecutive HIV-infected patients undergoing HAART, evaluated for metabolic and cardiovascular risk at the Metabolic Clinic of Modena and Reggio Emilia University in Northern Italy, were enrolled after providing informed consent to participate in the study.

Physical examination variables measured at baseline included body weight, physical stature, waist circumference, and systolic and diastolic blood pressure. Participants provided questionnaire data concerning lifestyle practices and potential risk factors for cardiovascular disease. Patient history, 12-lead electrocardiogram, and echocardiogram were used to exclude past or present cardiac diseases. Age, sex, HIV disease status according to the 1993 Centers for Disease Control and Prevention classification of HIV disease, HIV duration, and type and duration of HAART were recorded.

We collected, in all patients, a venous blood sample to determine the concentrations of fasting glucose and fasting insulin. A homeostasis model assessment of insulin resistance index (HOMA-IR) was carried out to assess insulin resistance. It was calculated as follows: [fasting insulin (microunits per milliliter) × fasting glucose (millimoles per liter)]/22.5.

At baseline, moreover, each participant had fasting blood tests for levels of C-peptide, hemoglobin A_{1c}, liver-associated enzymes, creatinine, and blood urea nitrogen. Creatinine clearance was calculated using the Cockcroft-Gault equation based on creatinine, age, and weight. A complete fasting lipid and lipoprotein profile was also obtained in all patients. Metabolic syndrome was diagnosed according to the criteria of the National Cholesterol Education Program, Adult Treatment Panel III. Risk of cardiovascular events was quantified using Framingham equation.

CD4 lymphocyte cell count and HIV viral load were performed at entry into the study; the nadir of CD4 cell count was also recorded.

The exclusion criteria of the study were as follows: diabetes, history of angina, previous myocardial infarction, previous stroke or transient ischemic attack, and previous or current use of hormone replacement therapy. Patients HAART-naives or on drugs interruption as well as those with opportunistic infections within the previous 3 months were also excluded because of their possible impact on anthropometric and biochemical parameters.

At enrolment, all patients underwent a brachial artery ultrasonographic measurement using a 10-MHz linear array transducer (Logiq 3; General Electric, Greenville, SC). Study subjects were positioned in a comfortable supine position. After a 20-minute rest, the end-diastolic BAD above the antecubital fossa was recorded. Electronic calipers were used to measure BAD as the distance from the near (anterior) to the far (posterior) wall-lumen interfaces, coincident with the R wave on the electrocardiogram recorded simultaneously. Three measurements were averaged to calculate BAD.

All measurements were performed by the same technician with patients supine in a quiet, temperature-controlled environment. All patients were requested to refrain from smoking on the morning of the vascular measurements. Calcium-channel blockers and nitrates were withheld for at least 24 hours.

To evaluate the reproducibility of echographic measurements, 100 studies were reexamined by 2 different investigators (AN and AL). These examinations were selected at random, without knowledge of the patient's identity, clinical information, or previous evaluation results. The interobserver variability for BAD diameter was 0.1 ± 0.9 mm.

2.2. Statistical analysis

Descriptive statistics are given as means ± 1 SD or as frequency (percentage). Differences in baseline characteristics between groups were examined by analysis of variance and the χ^2 test, when appropriate. Pairwise correlation between BAD and HOMA-IR was assessed by Pearson correlation coefficients before and after adjustment for age, sex, and physical stature. The BAD values were compared across the ordered groups (number of components of MS: 0, 1, 2, 3, or +) using a nonparametric test for trend (Jonckheere-Terpstra test). Multivariable linear regression models were used to assess the association of BAD with MS. Multivariable logistic regression models were constructed using backward elimination to determine whether BAD was independently predictive of the presence, compared with the absence, of MS. Models were built from the following variables: age, sex, body mass index, total cholesterol, low-density lipoprotein cholesterol, lipoprotein (a) plasma levels, smoking history, Framingham risk score, HIV log of the viral load, CD4 cell count, CD4 nadir cell count, use of nucleoside reverse transcriptase inhibitor, use of nonnucleoside reverse transcriptase inhibitor, use of protease inhibitor (PI), duration of treatment with the above-cited drugs, duration of the HIV infection, and BAD. Variables were removed one at a time until all remaining variables were significant at P less than or equal to .10.

Statistical significance was determined at P less than .05.

3. Results

Our population consisted of 570 patients (356 [62.5%] men), with a mean age of 46.3 ± 7.1 years (range, 20-

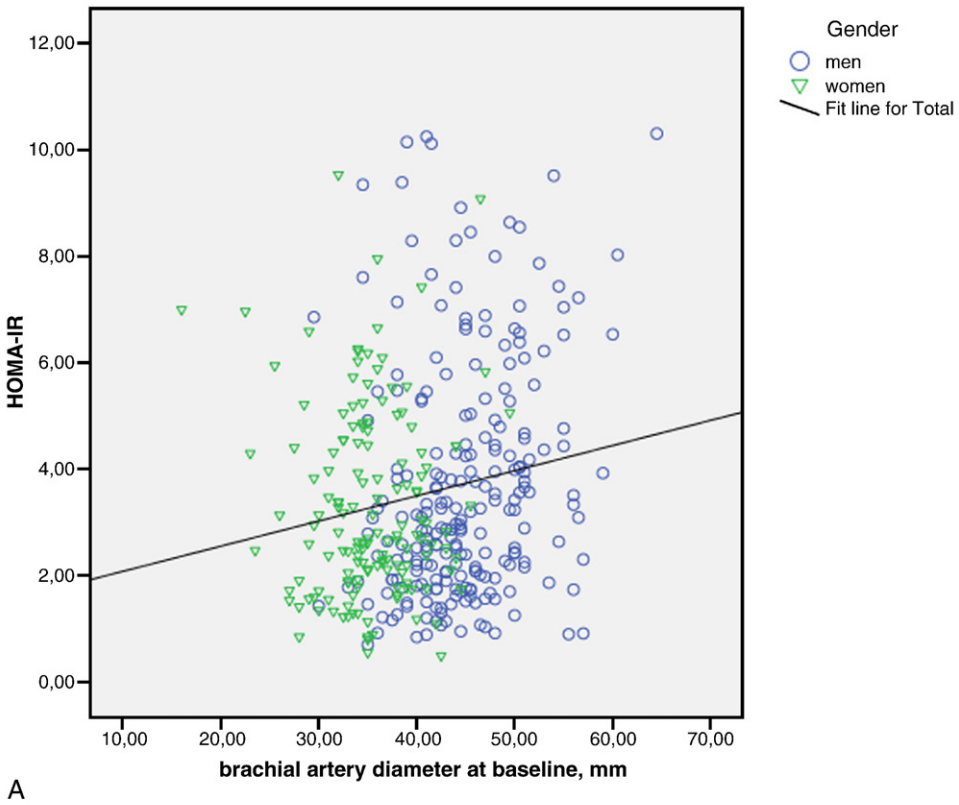
Table 1
Comparison between patients with vs patients without MS at baseline

	MS no (n = 466)	MS yes (n = 104)	*P*
Demographic characteristics			
Age (y)	45.7 ± 6.7	49.2 ± 8.2	.0001
Male sex	58.6% (n = 273)	79.8% (n = 83)	.0001
Anthropometric characteristics			
Body mass index, kg/m^2	22.8 ± 3.0	24.5 ± 4.2	.0001
Physical stature, cm	167.9 ± 8.9	169.1 ± 8.8	.238
Waist circumference, cm	82.6 ± 8.9	88.6 ± 10.4	.0001
Systolic blood pressure, mm Hg	115.3 ± 14.1	128.6 ± 14.2	.0001
Diastolic blood pressure, mm Hg	75.0 ± 13.4	86.5 ± 12.4	.0001
Hypertension	4.1% (n = 19)	7.6% (n = 8)	.1
Smoking history	40.0% (n = 177)	48.0% (n = 50)	.368
Fasting plasma levels			
Glucose, mg/dL	90.6 ± 10.9	115.2 ± 44.6	.0001
Insulin, U/L	3.54 ± 2.91	6.56 ± 4.95	.0001
C peptide, U/L	2.51 ± 2.83	3.58 ± 1.92	.0001
HbA_{1c}, %	5.2 ± 0.4	5.7 ± 0.9	.0001
Triglycerides, mg/dL	165.2 ± 113.8	280.4 ± 145.4	.0001
Total cholesterol, mg/dL	189.3 ± 44.9	182.9 ± 45.8	.2
HDL cholesterol, mg/dL	47.4 ± 15.2	34.1 ± 7.6	.0001
Apo A, mg/dL	143.5 ± 30.5	125.3 ± 17.7	.0001
LDL cholesterol, mg/dL	116.8 ± 35.2	106.6 ± 37.8	.013
Apo B, mg/dL	99.4 ± 25.7	105.0 ± 28.6	.07
Lipoprotein (a), mg/dL	23.3 ± 27.0	21.2 ± 28.2	.508
AST, U/L	46.0 ± 41.5	53.5 ± 52.1	.174
ALT, U/L	36.6 ± 27.9	38.9 ± 25.9	.430
Unconjugated bilirubin, mg/dL	1.27 ± 2.31	1.10 ± 1.25	.304
Conjugated bilirubin, mg/dL	0.37 ± 0.16	0.38 ± 0.18	.311
Homocysteine, U/L	10.2 ± 4.4	10.9 ± 3.4	.219
Creatinine, mg/dL	0.97 ± 0.28	1.00 ± 0.20	.118
BUN, mg/dL	33.4 ± 8.9	34.8 ± 10.7	.207
Brachial artery characteristic			
BAD, mm	40.9 ± 7.1	43.8 ± 7.9	.007
HIV infection characteristics			
Duration of HIV infection, mo	171.5 ± 61.0	176.8 ± 54.4	.386
CD4 nadir cell count, × 10^6 cells/L	172.9 ± 137.7	162.7 ± 121.6	.458
CD4 cell count, × 10^6 cells/L	531.1 ± 246.3	499.4 ± 270.7	.295
CD4 cell count, %	18.4 ± 12.6	16.3 ± 12.2	.135
Viral load, log copies/mL	2.21 ± 0.99	2.39 ± 1.09	.171
HIV disease category (C vs others)	25.5% (n = 119)	27.9% (n = 29)	.716
NRTI treatment	84.9% (n = 396)	88.4% (n = 92)	.003
NNRTI treatment	32.6% (n = 152)	30.7% (n = 32)	.865
PI treatment	43.3% (n = 202)	49.0% (n = 51)	.193
Duration of NRTI treatment, mo	120.4 ± 47.0	124.8 ± 51.6	.424
Duration of NNRTI treatment, mo	40.2 ± 31.9	42.2 ± 33.0	.608
Duration of PI treatment, mo	59.1 ± 34.8	69.7 ± 39.1	.019
Other parameters			
Creatinine clearance, mL/min	86.4 ± 23.4	89.5 ± 25.6	.263
HOMA-IR	3.54 ± 3.40	7.94 ± 9.94	.0001
Framingham risk score	4.3 ± 5.0	8.8 ± 7.1	.0001

Data shown are mean ± 1 SD or percentage (number). ALT indicates alanine aminotransferase; Apo, apolipoprotein; AST, aspartate aminotransferase; BUN, blood urea nitrogen; HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.

77 years). The mean duration of HIV infection was 172 ± 60 months. All the patients were chronically treated with HAART.

Metabolic syndrome was present in 104 of 570 patients (18.2% of the entire population). Comparison between patients with vs patients without MS is shown in Table 1.



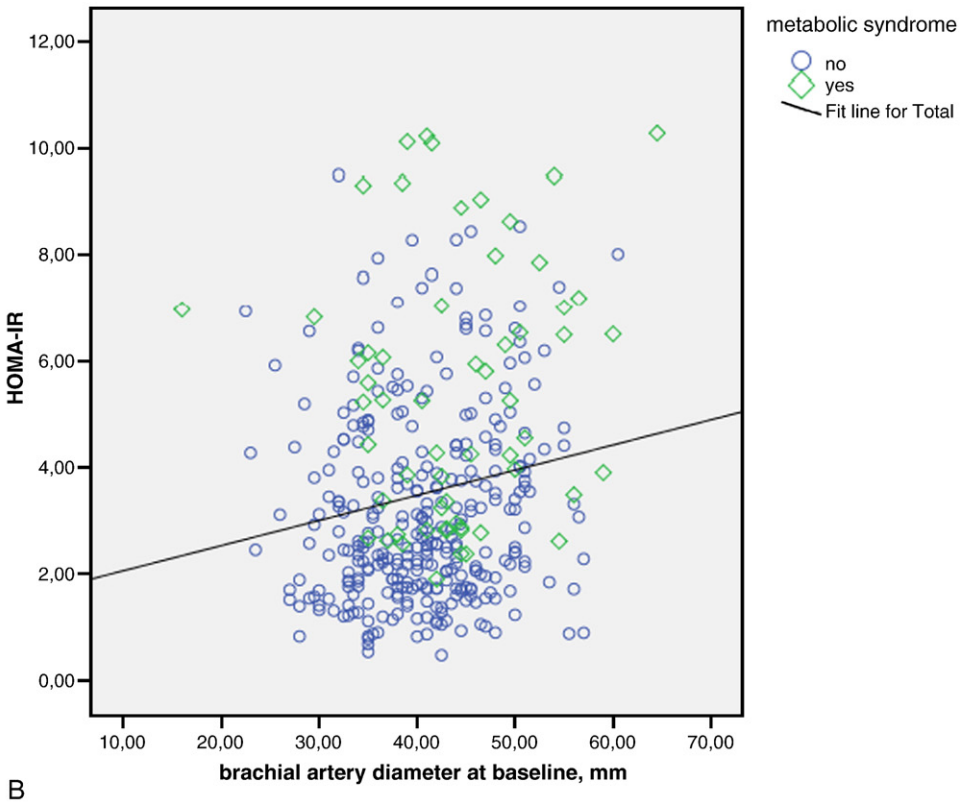


Fig. 1. Regression analysis between HOMA-IR and BAD ($r = 0.18$, $P < .0001$). The figure is divided into 2 sections: in A, sex is marked; in B, the presence of MS is highlighted.

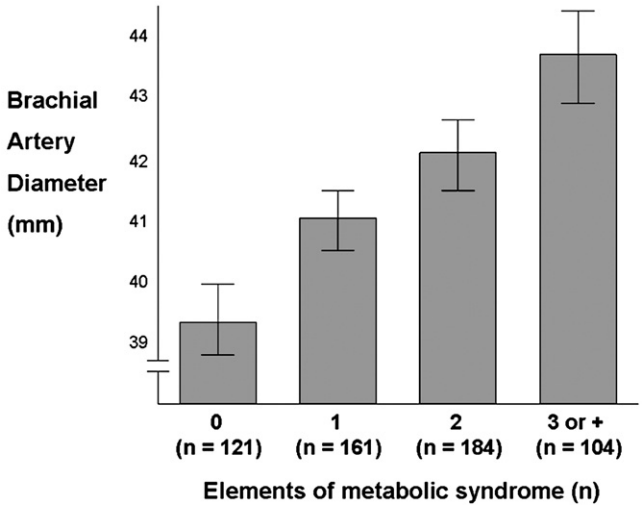


Fig. 2. Brachial artery diameter (mean values and SD) among 570 HIV-infected patients treated with HAART, according to the presence of 0, 1, 2, 3, or + components of MS.

In our population of HIV patients, BAD was positively correlated with HOMA-IR ($r = 0.18$, $P < .0001$, Fig. 1A and B); and this correlation persisted after adjustment for age, sex, and body mass index ($r = 0.13$, $P = .011$).

Regarding the exposure to antiretroviral drugs, our data demonstrated that BAD was significantly correlated with duration of PI treatment ($r = 0.11$, $P = .036$).

Fig. 2 displays the distribution of BAD in our HIV population, classified according to the total number of components of the MS. As shown, there was a strong linear increase in BAD as the number of components of the MS increased; BAD for those with 0, 1, 2, 3, or + characteristics of the MS was 39.3 ± 7.2, 41.0 ± 6.8, 42.0 ± 7.3, and 43.8 ± 7.9 mm, respectively ($P < .001$ for trend). In addition, BAD significantly correlated with all the elements of MS, as shown in Table 2.

Table 3 shows the linear regression equations that correlate BAD to the variables associated with the metabolic abnormalities commonly seen in HIV-infected patients treated with HAART.

In multivariable logistic regression analysis, BAD ($P < .001$) was a factor that was independently associated with the presence of MS (Table 4). Other significant associated parameters included age, male sex, and duration of PI treatment.

Table 2
Pearson correlation coefficients between BAD and the elements of MS

	WC	Glucose	TG	HDL-C	SBP	DBP
BAD	$r = 0.43$	$r = 0.12$	$r = 0.17$	$r = -0.24$	$r = 0.22$	$r = 0.21$
	$P < .0001$	$P = .012$	$P = .001$	$P < .0001$	$P < .0001$	$P < .0001$

DBP indicates diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides (fasting serum levels); WC, waist circumference.

Table 3
Linear regression equations that link BAD to the parameters correlated with the metabolism abnormalities commonly seen in HIV-infected patients treated with HAART

BAD =
39.1 + 0.59 ∗ HOMA-IR
14.15 + 0.32 ∗ WC
36.65 + 0.05 ∗ glucose
46.68 + (−0.12 ∗ HDL-C)
39.43 + 0.01 ∗ TG
40.29 + 0.02 ∗ months of PI exposure

Whereas the higher prevalence of men, who were characterized by greater BAD, in the group of HIV patients with MS could influence results, we also analyzed our data only in the female population, which consists of 193 women without MS and 21 with MS. In this last subgroup of HIV-infected women, BAD and HOMA-IR were significantly correlated ($r = 0.14$, $P = .01$). In addition, BAD was significantly higher in the group of women with MS with respect to others (42.8 ± 7.1 vs 39.2 ± 7.9 mm, $P < .01$).

4. Discussion

The main finding of the present study is that brachial artery enlargement was significantly correlated with the degree of insulin resistance in HIV-infected patients treated with HAART. In addition, BAD was associated with the presence of the components of MS.

Arterial remodeling is a result of the pathologic changes in the constituents of the arterial wall (produced by cardiovascular risk factors), which might produce arterial dilatation. In a study of 1272 subjects, increased carotid artery diameter was significantly related with risk factors and with subclinical carotid atherosclerosis [18]. In another study, the presence of a plaque in coronary arteries was associated with coronary artery enlargement [12]. Although arterial enlargement is considered to be a "local" compensatory mechanism to maintain lumen diameter in the face of an encroaching atherosclerotic plaque, the demonstration in the present study of an association between BAD and MS

Table 4
Parameters independently associated with the presence of MS using multivariable logistic regression analysis

Independent associated factors	β (SE)
Age (y)	0.196 (0.016)
	$P < .01$
Male sex	1.125 (0.197)
	$P < .01$
Duration of PI treatment (mo)	0.061 (0.023)
	$P = .011$
BAD (mm)	0.167 (0.011)
	$P < .001$

indicates that arterial dilatation may be a "systemic" process, correlated with a more severe metabolic profile. We postulate that all the arteries increase their internal diameter (not just those affected by atherosclerosis) when there is a metabolic disorder. The term *systemic* is used to define the opposite of local response.

In the Bruneck Study Group, Kiechl and Willeit [19] found carotid atherosclerosis to be related with arterial enlargement at both local and remote arterial sites; and in a study of women with chest pain undergoing coronary angiography, greater BAD was an independent predictor of coronary events [20]. In addition, a study of Mondy and coworkers [21] demonstrated that insulin resistance (measured by HOMA-IR) and BAD (noninvasively measured by ultrasound) were correlated; and both were independent predictors of endothelial dysfunction. This fact can explain the close relationship between an unfavorable metabolic profile and the risk of developing cardiovascular events [22-25]. Our study confirms only the significant association between insulin resistance, assessed by HOMA-IR, and BAD. In the study mentioned above, a significant correlation between insulin resistance and endothelial dysfunction was also shown, which we have not explored in the present study. In our article, we demonstrate that the patients with numerous elements of the MS have a brachial artery with a meaningfully greater diameter. Thus, our data are consistent with the concept that arterial enlargement is a systemic process occurring in insulin-resistant HIV-infected patients treated with HAART. Indeed, the relationship between BAD, insulin resistance, and the number of elements of the MS suggests that the severity of the metabolic abnormalities is able to stimulate arterial diameter enlargement, supporting a "dose-response" theory.

4.1. Limitations of the study

Our article has some limitations in that it is a nonrandomized, cross-sectional study in which multiple associations were explored. However, although the design of the study cannot establish causal links, the correlation between BAD and HOMA-IR is statistical significant and persists after adjustment for potential confounders.

4.2. Conclusions

Our results are in line with the hypothesis that, among HIV-infected patients chronically treated with HAART, those with a larger BAD are at high risk for metabolic disorders (a more severe insulin resistance and MS), independent of age, sex, and other cardiovascular risk factors. This independent predictive ability of BAD is of potential clinical impact because the measure of BAD is easy to perform, has a low interobserver variability, presents a well-studied very high reproducibility [26], and can be obtained in all clinical contexts.

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