Postprandial Lipidemia Is Normal in Non-obese Type 2 Diabetic Patients With Relatively Preserved Insulin Secretion

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To assess postprandial lipidemia in normotriglyceridaemic type 2 diabetic patients treated with diet only, 12 non-obese patients (8 males, hemoglobin A_{1c} [HbA_{1c}] 6.80 ± 0.67%) and 14 controls of similar age, body mass index (BMI), and fasting triglyceride (Tg) were given a test meal (58 g fat, 100,000 IU vitamin A). Fasting low-density lipoprotein (LDL) cholesterol (LDLc), high-density lipoprotein (HDL) cholesterol (HDLc), free fatty acids, and apolipoprotein B (apoB), and fasting and postprandial Tg, retinylpalmitate (RP), LDL size, glucose, and insulin were measured. The homeostasis assessment model (HOMA) index and lipoprotein (Lpl) and hepatic (HL) lipase activities were estimated. Patients showed lower fasting HDLc (1.12 ± 0.26 *v* 1.40 ± 0.28 mmol/L, *P* = .02) and a trend towards smaller LDL particles, which was significant 4 hours postprandially (25.86 ± 0.40 *v* 26.16 ± 0.30 nm, *P* = .04). The area under the curve of Tg (AUC-Tg) and RP, and Lpl were similar, but HL was higher in patients (156.63 ± 23.89 *v* 118 ± 43.27 U/L, *P* = .011). HL correlated inversely with LDL size and directly with the HOMA index. In conclusion, normotriglyceridemic type 2 diabetic patients with insulin resistance but relatively preserved insulin secretion show low fasting HDLc and increased HL, but normal postprandial lipidemia.

PATIENTS WITH TYPE 2 diabetes have an increased risk of developing cardiovascular events that is not completely explained by classical risk factors.[1] Diabetic dyslipidemia, which mainly comprises modest hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol (HDLc), and normal or slightly increased low-density lipoprotein (LDL) cholesterol (LDLc), has been proposed as an additional candidate to explain this high risk.[2] Other disorders that also have been considered to be components of diabetic dyslipidemia include hyperapolipoprotein B lipoproteinemia,[3] predominance of small dense LDL particles, and postprandial hyperlipidemia.[2] Not only has the latter proved to be associated with coronary heart disease in several cross-sectional studies,[4-6] but studying the postprandial state may also provide information on lipid metabolism and the other components of diabetic dyslipidemia which is not available in the fasting state.

Studies on postprandial lipidemia performed on diabetic subjects provide conflicting results. Fasting triglyceride (Tg) is closely related to and is the main determinant/consequence of postprandial lipidemia,[7] and many studies that show increased postprandial triglyceridemia in diabetic subjects also show higher fasting concentrations.[8-10] Nevertheless, when patients and control subjects are matched for age, body mass index (BMI), and fasting Tg concentrations, most studies show comparable areas under the curve (AUC) of Tg[8,11-13] and retinylpalmitate (RP),[10] but display minor abnormalities in diabetic patients.[11,13] On the other hand, data on postprandial LDL size is scant both in nondiabetic and in diabetic patients.

The aim of this study was to define postprandial lipidemia, including LDL size, and its relationship with other components of diabetic dyslipidemia in a specific group of normotriglyceridemic, type 2 diabetic patients, well-controlled with diet only.

MATERIALS AND METHODS

Patients

A total of 12, non-obese (BMI < 30 kg/m^2), normolipidemic (LDLc < 4.13 mmol/L and Tg < 2.25 mmol/L) type 2 diabetic patients with hemoglobin A_{1c} (HbA_{1c}) less than 8%, treated with diet only, were included in the study. Their main features are displayed in Table 1. Patients taking drugs or subject to conditions known to interfere with lipoprotein metabolism were excluded (established nephropathy, lipid-lowering drugs, steroids, nonselective beta-blockers, or high-dose diuretics). Postmenopausal women on replacement therapy were not excluded. None of the patients or controls was taking vitamin supplements.

A group of 14 nondiabetic normolipidemic, non-obese, control subjects of similar age, BMI, and fasting Tg was also included. Women with a history of gestational diabetes were excluded. Their main features are displayed in Table 1.

A history was taken, which included cardiovascular risk factors in the case of the control subjects, and also diabetes duration and complications in the patients. Physical examination, which included anthropometric parameters and blood pressure, was performed. A test meal was given, and laboratory determinations were made.

The protocol was approved by the local ethics committee and all of the subjects provided informed written consent before being included in the study.

Test Meal

After a 10- to 12-hour overnight fast, a peripheral intravenous catheter was inserted and a first blood sample was obtained in Vacutainer tubes (Beckton Dickinson, Plymouth, UK), containing EDTA or fluoride.

A test meal was given to be ingested in 20 minutes. It consisted of 600 mL of vanilla- or nut-flavored shake (NEPRO, Abbott Laboratories, Columbus, OH), and contained 1,200 kcal as fat (58 g), protein (42

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Table 1. Clinical Features of the Type 2 Diabetic Patients and Control Subjects

Characteristic	Type 2 Diabetic Patients	Nondiabetic Controls
No. (male/female)	12 (8/4)	14 (8/6)
Age (yr)	52.4 ± 10.4	54.0 ± 6.1
BMI (kg/m^2)	25.8 ± 2.6	24.3 ± 2.4
Men	26.9 ± 1.9†	24.8 ± 1.5
Women	23.5 ± 2.6	23.7 ± 3.3
Waist circumference (cm)	91.6 ± 3.0	85.8 ± 3.2
Men	96.9 ± 6.24	93.3 ± 9.5
Women	81.0 ± 8.8	75.9 ± 6.3
Waist/hip ratio	0.97 (0.78–1.00)	0.87 (0.76–1.00)
Diabetes duration (yr)	3.5 (2–13)	—
HbA_{1c} (%)	6.80 ± 0.67*	5.41 ± 0.34
Smoking	5	2
Hypertension	5	4
Menopause	1†	6
Hormone-replacement therapy	0	1
Retinopathy	0	—
Microalbuminuria	1	—
Polyneuropathy	0	—
Coronary heart disease	3	0
Cerebrovascular disease	1	0
Peripheral vascular disease	1	0

NOTE. Qualitative variables are expressed as number of subjects affected, and continuous variables are expressed as means ± SD (gaussian distribution) or as median (range) (non-gaussian distribution).

*$P < .0005$ and †$P < .05$ *v* controls.

g), and carbohydrate (134 g). A total of 100,000 U of vitamin A (Dif Vitamin A, Roche Farma, Madrid, Spain) were given with the meal in the form of a pill.

Patients were asked not to perform unusual exercise or drink alcohol the day before the test. Water was allowed, but no other beverages or food were permitted during the test. Walking, but no strenuous exercise or smoking, were allowed. Periodic blood samples were taken during the 8 hours following the meal. The tubes were covered with aluminium foil, and all handling was done away from direct light.

Laboratory Tests

Total Tg and cholesterol, LDL, HDL, and very-low-density lipoprotein (VLDL) cholesterol (VLDLc), apolipoprotein B (apoB), free fatty acids, LDL particle size, RP, HbA_{1c}, insulin, and glucose were determined in the fasting state. Insulin and glucose were also measured at 1, 2, 3, 4, 5, and 6 hours after the meal. RP, Tg, and LDL particle size were measured at 2, 3, 4, 5, 6, and 8 hours after the meal.

Total Tg and cholesterol and free fatty acids were measured from fresh plasma by automatic enzymatic methods. Net Tg was calculated, after measuring and substracting glycerol concentrations. LDLc and VLDLc were determined by beta-quantification, and HDLc by a homogeneous direct method. ApoB was measured by an immunoturbidimetric method calibrated against the World Health Organization (WHO)/International Federation Clinical Chemistry (IFCC) reference standard SP3-07. Glucose was measured in plasma by the glucose oxidase method, and samples were taken in tubes containing fluoride and kept at 4°C for no more than 2 hours before separation (all automated measurements from Roche Diagnostics, Basel; Switzerland). Insulin was determined by immunochemoluminiscence (Immulite 2000, Diagnostic Products Corp, Los Angeles, CA), with a lower detection limit of 14.3 pmol/L. HbA_{1c} was measured in an automatic DCA 2000 reader (Bayer, Elkhart, IN, reference no. 5035B; latex immunoagglutination inhibition; normal values, 4.3% to 5.7%), following the instructions provided by the manufacturer. The homeostasis assessment model (HOMA) was used to estimate insulin resistance.[14] RP was determined by HPLC, using retinyl acetate as an internal standard, following the method described by Ruotolo et al.[15] Total areas under the curves and incremental areas above baseline for Tg and RP were calculated by the trapezoid rule.[16]

LDL size was detemined by electrophoresis on gradient (2% to 16%) polyacrylamide gel, cast in the laboratory, according to the method described by Nichols et al, with modifications.[17] A volume of 10 μL of plasma samples was applied on lanes in a final concentration of 10% sucrose, stained with Sudan black (prepared in the laboratory using ethylene-glycol and 0.1% [wt/vol] Sudan black; Sigma, St Louis, MO). Electrophoresis was performed in a refrigerated cell for a prerun of 60 minutes at 120 V, followed by 30 minutes at 20 V, 30 minutes at 70 V, and 16 hours at 100 V. A pool containing sera with 4 LDL fractions whose diameter (22.9 ± 0.7, 24.5 ± 0.6, 26.2 ± 0.5, and 28.4 ± 0.9 nm) had been previously assessed by electron microscopy was used as control. The gels were scanned, and migration distances (from the top of the gel to the most prominent band) were measured. The predominant LDL particle diameter of each sample was calculated from a calibration line using the 4 standards of known diameter. LDL particle subclasses were classified as predominantly small LDL or phenotype B (diameter $\leq$ 25.5 nm) and non-small LDL (phenotype A, diameter $>$ 25.5 nm).[4] Both intra- and inter-gel imprecisions were below 1%.

Lipoprotein lipase (LpL) and HL activities were determined at baseline and 15 minutes after the intravenous administration of 100 IU/kg of sodium heparin. This test was performed on a different day, separated by at least 48 hours from the meal test. Blood was drawn into chilled lithium-heparin tubes kept on ice, and plasma was immediately separated and kept at −80°C until processing. LpL and HL activities against artificial substrates were measured in post-heparin plasma using a radiolabeled glycerol tri[9,10-(n)-^{3}H]oleate emulsion (Amersham Life Science, Bristol, UK).[18]

Statistical Analysis

Analysis was performed using SPSS 8.0 statistical package for Windows (SPSS, Chicago, IL). Quantitative data are expressed as mean and standard deviation (gaussian distribution) or as median and range (non-gaussian distribution), and qualitative data as percentages. Comparison between groups was performed using Student's *t* (gaussian distribution) and Mann-Whitney's *U* test (non-gaussian distribution) for quantitative data and chi-square test for qualitative variables. Comparisons within a group were made using Student's *t* test for paired data or Wilcoxon's test. Bivariate correlations were analyzed between continuous data (Pearson's *r* or Spearman's Rho depending on normality distribution). Multivariate analysis (including no more than 3 to 4 dependent variables at a time) was performed to ascertain the best independent markers and combination of markers of the AUC of Tg and RP. Partial correlations were used to correct for interference between variables with high colineality.

RESULTS

Fasting laboratory results in patients and control subjects are displayed in Table 2. Lower HDLc in the diabetic patients was the only lipidic component that was significantly different from the control group, and this difference remained significant after adjusting for gender and smoking. Postprandial glucose was, as expected, higher in patients than in controls, whereas no differences were found in postprandial insulin concentrations between the groups (Fig 1A and B). Postprandial Tg and RP curves are depicted in Fig 2A and B. The AUC of Tg (10.77

Table 2. Main Results Obtained in the Type 2 Diabetic Patients and Control Subjects

	Type 2 Diabetic Patients	Nondiabetic Controls
Fasting Tg (mmol/L)	0.92 ± 0.31	0.81 ± 0.20
Total cholesterol (mmol/L)	4.71 ± 0.85	4.99 ± 0.64
HDLc (mmol/L)	1.12 ± 0.26*	1.40 ± 0.28
LDLc (mmol/L)	3.25 ± 0.72	3.28 ± 0.60
VLDLc (mmol/L)	0.32 ± 0.17	0.30 ± 0.11
Apolipoprotein B (g/L)	0.95 ± 0.22	0.95 ± 0.13
Free fatty acids (mmol/L)	0.50 ± 0.16	0.42 ± 0.13
LDL size (nm)	25.90 ± 0.39	26.19 ± 0.38
HOMA index	4.90 (3.91-14.87)†	3.61 (3.02-10.86)
LpL (U/L)	106.41 ± 30.73	90.03 ± 24.99
HL (U/L)	156.63 ± 23.89*	118 ± 43.27

NOTE. Qualitative variables are expressed as number of subjects affected, and continuous variables are expressed as mean ± SD (gaussian distribution) or as median (range) (non-gaussian distribution).

*$P < .05$ and †$p < 0.0005$ vs controls.

[5.73 to 24.13] *v* 12.61 [6.57 to 22.77]) mmol/L × h, respectively), and peak Tg concentration (1.85 ± 0.64 *v* 1.94 ± 0.80 mmol/L) were not statistically different between patients and controls. The AUC of RP was also similar between the groups (2,291.25 [1,380.5 to 4,721] *v* 2,733.25 [1,795.5 to 7,717] μg/L × h, respectively). Although RP concentrations at baseline and 2 hours after the meal were higher in the diabetic patients (Fig 2B), their incremental AUCs for RP were similar. Postprandial LDL size in patients and controls are displayed in Fig 2C. No differences were found between postprandial and fasting LDL sizes within the diabetic group, but a small reduction of LDL size was found in the control group 2 hours after the meal (26.33 [25.34 to 26.7] *v* 26.23 [25.34 to 26.56], $P = .04$). Nevertheless, diabetic patients showed a trend towards smaller LDL size than control subjects, both at baseline ($P = .069$) and postprandially ($P = 0.13, 0.15, 0.041, 0.057, 0.19$, and 0.20, at 2, 3, 4, 5, 6, and 8 hours, respectively). No significant differences were found at baseline when women and men were compared separately (data not shown). No differences were found in LpL, whereas HL activity was higher in diabetic patients (Table 2).

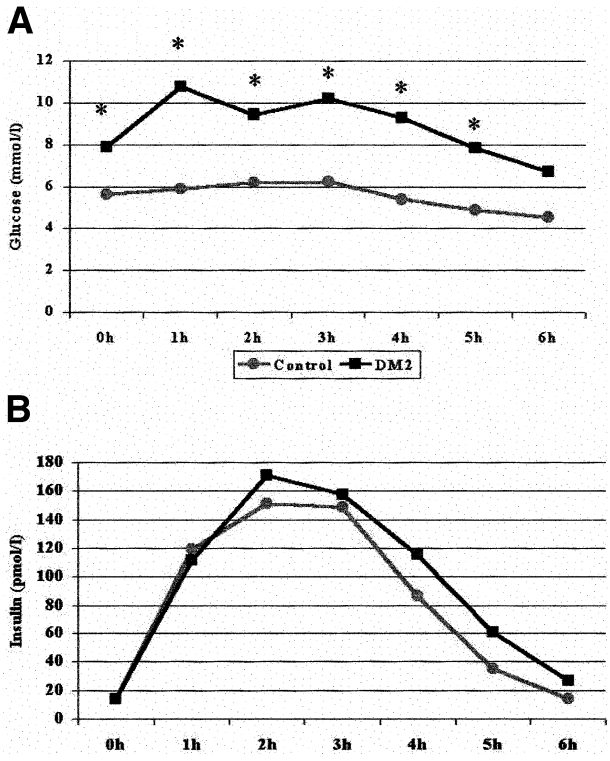

Fig 1. Postprandial (A) glucose and (B) insulin curves in the type 2 diabetic patients (■) and control subjects (●). *$P < .05$, patients *v* controls.

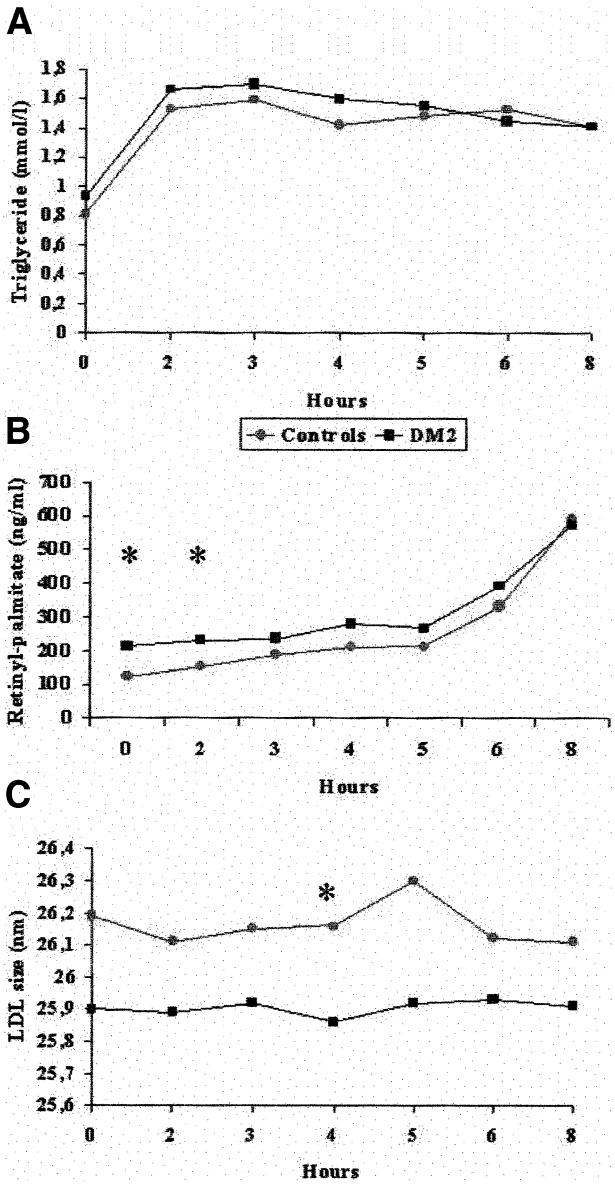

Fig 2. Postprandial (A) Tg, (B) RP, and (C) LDL size curves in the type 2 diabetic patients (■) and control subjects (●). *$P < .05$, patients *v* controls.

The AUC of Tg in diabetic patients was correlated with RP at 5 ($r = 0.657$, $P = .020$) and 8 hours ($r = 0.620$, $P = .020$) and all postprandial Tg concentrations. It was best correlated with Tg 4 hours after the meal ($R = 0.967$, $P < .0005$), whereas fasting Tg concentrations showed a somewhat weaker correlation ($r = 0.844$, $P < .0005$). In multivariate analysis, the combination of Tg and RP at 5 hours produced the best correlation with AUC of Tg ($r = 0.990$, $P < .0005$), and Tg at 5 hours remained correlated even after adjusting for RPat 5 hours ($r = 0.982$, $P < .005$). The AUC of RP was correlated with fasting free fatty acids ($R = 0.599$, $P = .040$) and RP ($R = 0.741$, $P = .006$) and with all postprandial RP concentrations between 2 and 6 hours after the meal, but most strongly with its concentrations at 3 and 4 hours postprandially ($R = 0.881$ and 0.916, respectively, $P < .0005$).

When all subjects (patients and controls) were included into the analysis, fasting LDL particle size correlated with LDLc/apoB ratio ($r = 0.512$, $P = .008$), but no correlation was found in the fasting or postprandial states between LDL size and Tg concentrations. HL activity was inversely correlated with LDL size at baseline ($r = -0.376$, $P = .058$), 2 ($r = -0.441$, $P = .024$), 3 ($r = -0.40$, $P = .043$), 4 ($r = -0.422$, $P = .032$), and 5 hours after the meal ($r = -0.473$, $P = .015$), and directly correlated with the HOMA index ($R = 0.455$, $P < .05$).

DISCUSSION

Differences Between Patients and Control Subjects

This specific group of normotriglyceridemic type 2 diabetic patients, with insulin resistance but with a relatively preserved insulin secretion, showed lower HDLc concentrations than the control group. However, their postprandial lipidemia, quantified as the AUC of plasma Tg and RP, is normal. This supports the idea that postprandial lipidemia, in diabetic as well as in nondiabetic subjects, is closely related to fasting Tg concentrations, either as a predictor or as a consequence of postprandial changes in Tg. Although HDLc concentrations have been described as predictors of postprandial lipidemia, nondiabetic subjects with isolated low HDLc have normal postprandial lipidemia, as do the type 2 diabetic patients included in the present study.[19] Although some previous studies performed in type 2 diabetes show increased postprandial lipidemia in these patients, groups are not always matched for interfering factors.[8-10] The patients included in the present study show very specific features, due to the selection criteria used to minimize the influence of associated variables. Non-obese patients with normal fasting triglyceridemia, well controlled without the need of oral agents or insulin, were selected. As a result, the study group comprises 12 “mildly” diabetic patients with insulin resistance, but relatively preserved insulin secretion, who displayed normal postprandial lipidemia. However, only whole plasma was assessed, and RP, but not apoB48, was measured. Even in the absence of gross postprandial whole plasma differences, minor changes are seen in diabetic patients in chylomicron remnant fractions,[11,13] which were not measured in this study. Although RP is not the ideal marker for the evaluation of chylomicrons and their remnants,[20] it is the most frequently used determination. On the other hand, compositional disorders have been described in type 2 diabetic patients both in LDL and HDL particles,[11,13] and a trend towards smaller LDL particles was seen in the diabetic patients included in the present study, despite the presence of more postmenopausal women in the control group. There are, to our knowledge, only 2 previous studies that assessed postprandial LDL size in diabetic patients. In disagreement with our results, one study displayed a postprandial shift in LDL size towards smaller denser particles 4 to 6 hours after a meal in normotriglyceridemic, normocholesterolemic type 2 diabetic patients, despite fasting features similar to those of control subjects.[11] The other study, in consonance with ours, showed a good correlation between both fasting and postprandial LDL size and HL activity, but, on the other hand, showed no differences in LDL size between normotriglyceridemic diabetic subjects and controls.[8] A more recent study, which assessed postprandial changes in nondiabetic women, both normo- and dyslipidemic, described a postprandial decrease in LDL size only among hypertriglyceridemic subjects.[21] LpL activity did not differ between the groups included in our study, in agreement with previous data,[7,8] but a higher HL activity in the diabetic subgroup, and its correlation with LDL size in the total of subjects, supports its influence on LDL size.[22] Furthermore, the correlation of HL with insulin resistance, which has also been described previously, especially in the presence of low HDLc,[23,24] might reflect a link between insulin resistance and the predominance of small dense LDL particles. Nevertheless, whether enrichment of LDL in Tg, despite similar fasting and postprandial Tg, stimulates HL, or whether enzymatic activity, per se, related to insulin resistance, causes a decrease in size in LDL particles in type 2 diabetes was not analyzed in our study and remains to be determined. However, the trend towards higher fasting Tg seen in the diabetic patients supports the former hypothesis.

Markers of Postprandial Lipidemia

Tg levels at 4 and 5 hours postprandially were the best predictors of the AUC-Tg. To our knowledge, this is the first study to assess postprandial markers of the AUC of Tg in order to avoid the performance of this cumbersome test in type 2 diabetic patients. The complexity of postprandial studies does not allow the inclusion of large samples of patients, which on the other hand limits the conclusions that can be drawn from them. Notwithstanding, the measurement of serum Tg 4 or 5 hours after a standard test meal would give reliable information about the postprandial state in these subjects, and would be less cumbersome than the performance of a complete meal test. Alternatively, capillary Tg measurements have been suggested, which allow more patients to be studied.[25]

No consistent correlations were found at any point between LDL size and triglyceridemia, probably because the subjects included were all normotriglyceridemic and most displayed an LDL phenotype A.[11] On the other hand, the LDLc/apoB ratio proved to be the best and most consistent predictor of LDL size. This ratio has previously been evaluated as a marker of LDL particle size, but the results from different studies conflict,

mainly depending on the accuracy of the method used for the determination of LDLc.[26-29] In the present study, where beta-quantification, which is the designated comparison method for the estimation of LDLc, was used, a fair correlation was found between LDLc/apoB ratio and LDL size.

In summary, normotriglyceridemic, non-obese subjects with "mild" type 2 diabetes (well controlled with diet alone, insulin resistant but with relatively preserved insulin secretion) show low HDLc concentrations and increased HL activity, but normal postprandial lipidemia. Thus, insulin resistance by itself does not seem to be sufficient to cause postprandial lipidemia, as long as insulin secretory capacity is preserved.

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