Diabetes & its Complications

Microalbuminuria in Children and Adolescents with Type 1 Diabetes Mellitus: Prevalence and Predictive Factors

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ABSTRACT

Background: Microalbuminuria is usually the first microvascular complication of T1DM and several variables are believed to play a major role in its determination.

Objective: We aimed to identify microalbuminuria frequency, time after diagnosis and related risk factors.

Methods: Clinical reports and biochemical results of 201 children with T1DM, followed in our institution, were retrospectively analyzed.

Results: Seventeen patients (8.5%) presented microalbuminuria in a mean diabetes duration of 5.5 ± 3.8 years. Five children (29.4%) presented before 2 years of diabetes duration; 3 children between 2 to 5 years after the onset and 9 children (52.9%) 5 or more years afterwards. Logistic regression analysis revealed that longer diabetes duration (6.3 ± 3.7 years vs 3.5 ± 3.5 years), higher BMI (23.1 ± 4.9 vs 20.3 ± 4.1 Kg/m^2), total cholesterol (TC) (180.6 ± 57.5 mg/dL vs 159.1 ± 31.0 mg/dL), LDL (125.5 ± 36.3 mg/dL vs 110.9 ± 24.7 mg/dL), TG (133.3 ± 39.3 mg/dL vs 78.6 ± 38.4 mg/dL) and HbA1c (9.6 ± 1.9 vs $8.9 \pm 1.7\%$) were significantly associated with microalbuminuria. There were no statistical significant differences regarding gender, puberty and HDL-C.

Conclusions: In children, nephropathy can occur soon after T1DM onset. Besides poor metabolic control and longer diabetes duration, obesity and dyslipidemia seem to play a significant role. Our results indicate that yearly screening of microalbuminuria from T1DM onset and early treatment of dyslipidemia and obesity might be recommended / advisable.

Keywords

Type 1 diabetes mellitus, Children, Adolescent, Screening, Microalbuminuria.

Abbreviations

T1DM: Type 1 Diabetes Mellitus, ACR: Urinary albumin/creatinine ratio, BMI: Body Mass Index, HbA1c: Glycosylated Hemoglobin test, TC: Total cholesterol, HDL-C: High Density Lipoprotein cholesterol, LDL-C: Low Density Lipoprotein Cholesterol, TG: Triglyceride, vs: versus.

Introduction

Type 1 diabetes mellitus (T1DM) is increasing worldwide and is the most common chronic endocrine disease in children [1]. Achieving a good metabolic control during childhood and adolescence plays a key role in preventing future angiopathy and in improving patients' quality of life [2]. Prevention and management of micro vascular complications are an important part of diabetes care and essential

to decrease disease associated morbidity and mortality [3]. The prevalence of microvascular complications presents a remarkable variation in published studies [4-7] and numerous risk factors have been suggested.

According to the latest consensus report of the International Society for Pediatric and Adolescent Diabetes (ISPAD), it is recommended to screen annually for microvascular complications from age 10-years or at the onset of puberty if earlier and after two to five years' diabetes duration [8]. Screening is essential to prevent and diagnose diabetic microangiopathy and to start prompt treatment. Significant associations between the different microvascular complications of diabetes have been reported, suggesting common risk factors and/or pathogenic mechanisms [9]. Although clinically evident vascular complications are rarely seen in children and adolescents, they initiate during childhood and accelerate during puberty [10].

Several risk factors both modifiable (glycemic control, hypertension, dyslipidemia, diet and smoking) and non-modifiable (diabetes duration, puberty, genes, constitutional factors) have been related to the development of microvascular complications of T1DM [8-10]. As shown in DCCT study, poor glycemic control is related to the development of microangiopathy [11]; further data suggest a declining incidence of diabetic nephropathy with improved glycemic control [12].

However, glycemic control is not the only responsible for diabetic nephropathy risk, especially during puberty, when hormonal and metabolic changes together with lifestyle, environmental exposures and genetic factors could certainly play a crucial role [13]. Also, high blood pressure [14] and lipid abnormalities have been linked to the development and progression of vascular complications [15]. Chronic hyperglycemia, dyslipidemia and hypertension play a major role in diabetic angiopathy, through metabolic and structural derangements, namely accumulation of advanced glycation end products, increased production of reactive oxygen species, impaired vasodilatory response, smooth muscle cell dysfunction, overproduction of endothelial growth factors, chronic inflammation, hemodynamic dysregulation, impaired fibrinolytic ability and enhanced platelet aggregation [9,11,14,15].

It seems likely that these alterations are also related to obesity [16] and recent investigation propose that some peptides secreted by adipose tissue, namely adiponectin, may play a key role in kidney disease, as adiponectin levels in patients with type 2 diabetes mellitus are negatively correlated to early features of nephropathy [17]. By contrast, in type 1 diabetes mellitus this interplay nephropathyobesity is less clear. It is well recognized that genetic susceptibility plays a role in the pathogenesis of diabetic kidney disease, accounting for almost 40% of the cases [18], but the risk variables responsible for nephropathy in T1DM are still not fully established.

Diabetic nephropathy is the most common microvascular complication, affecting about 15-40% of T1DM, with a peak incidence 15-20 years after the disease onset [19,20]. Microalbuminuria is an early marker of structural renal disease [21], preceding the development of macroalbuminuria [22] and is related to cardiovascular disease [23].

In this study it is our aim to identify in a population of T1DM children and adolescents, the microalbuminuria frequency, time of occurrence and related risk factors. We also aimed to find if there is a relationship between nephropathy and obesity in our cohort of T1DM.

Patients and Methods
Study design and patients' characteristics
Retrospective study of T1DM patients followed in a tertiary pediatric diabetes center. The patients' clinical records were reviewed for data collection.

The inclusion criteria for patient selection were: positive T1DM antibodies at diagnosis, one year or more of T1DM duration, age less than 18 years and at least two medical appointments during the year 2013. Exclusion criteria were neonatal diabetes and microalbuminuria at the time of T1DM onset.

Patients were seen at diabetes clinic every 3 to 4 months; annually an extended laboratory evaluation is performed. All were on flexible intensive insulin therapy with multiple daily insulin doses.

Chronological age at the last clinical evaluation, age at diagnosis, diabetes duration, gender, weight, height, body mass index (BMI, Kg/m^2), systolic and diastolic values and laboratory exams, namely glycosylated hemoglobin (HbA1c), lipid profile and albumincreatinine ratio (ACR) values were recorded. In case of presence of microalbuminuria, date of diagnosis and treatment strategies were recorded.

Ethics
The study was approved by the Institution Ethics Committee.

Screening for microalbuminuria
Urinary albumin excretion was measured using the standard biochemical techniques of our hospital on the first void morning urine sample. Microalbuminuria was defined as ACR >30mg/g in at least two consecutive spot urine samples collected in the same year. An albumin level >300 mg/g creatinine in at least two consecutive samples collected in the same year defined macroalbuminuria. Transient microalbuminuria was defined as regression of microalbuminuria to normoalbuminuria in two consecutive spot urine samples collected in the same year, with no recurrence.

In our center, urinary albumin excretion is performed at least annually in all patients, regardless of age / pubertal stage.

Assessment of blood pressure
Systolic and diastolic blood pressures recorded during the study year were used in our model. Hypertension was defined as blood

pressure values > 95th percentile for gender, age and height on more than three occasions [8,24]. In patients with microalbuminuria, clinical records were investigated to determine the mean systolic and diastolic blood pressure in at least three consultations before microalbuminuria diagnosis and these values were used for statistical analysis.

Assessment of metabolic control
We considered the mean value of HbA1c achieved during the study year (DCA Vantage® Analyzer 2000) for assessment of metabolic control. For patients with microalbuminuria, we used the mean HbA1c value in the year before its onset.

Assessment of dyslipidemia
Dyslipidemia evaluation was performed according to the standard methods of the biochemistry laboratory. Total cholesterol (TC), triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) blood levels were evaluated. Low-density lipoprotein cholesterol (LDL-C) values were computed in accordance to the Friedewald formula. According to latest IASPD guidelines [8], LDL-C levels should be <2.6 mmol/L (100mg/dL) and there for we defined dyslipidemia as LDL-C ≥ 100 mg/dL.

For statistical analysis we used mean lipid values at two determinations before microalbuminuria diagnosis for patients with microalbuminuria and mean lipid values in the last year of follow up for those without microalbuminuria.

Assessment of BMI
At each consultation, height and weight were recorded. We considered the mean BMI in the last year of follow-up or in the year preceding microalbuminuria onset.

Assessment of smoking
We asked the patients whether they smoked or not.

Statistical analysis
Statistical analysis was performed with SPSS version 21.0 for Windows®. The results are presented as frequencies, means ± standard deviation (SD) and minimum and maximum values. Statistical significance was considered for a p value <0.05. Student t-test and chi-square tests were used for comparison of continuous and categorical variables, respectively and Fisher exact test when necessary. Binary logistic regression analysis (step by step regression model) was used to access the association between microalbuminuria and possible risk factors (gender, diabetes duration, age at diagnosis, hypertension, dyslipidemia, HbA1c and BMI at microalbuminuria diagnosis).

Results
The study group consisted of 201 T1DM patients: 102 girls (50.7%) and 99 boys (49.3%) with a mean age at the last clinical evaluation of 12.4 ± 3.9 years and a mean diabetes duration of 3.8 ± 3.6 years. The mean age at T1DM diagnosis was 8.1 ± 3.7 years: 147 subjects (73.1%) were diagnosed in pre-pubertal age (considered as age <10 years), 47 (23.4%) in the peri-pubertal age

(age between 10 to 15 years) and 7 (3.5%) in post-pubertal age (age >15 years). No patient presented HTA.

Mean HbA1c was 9.0 ± 1.8 %, dyslipidemia rate was 41.8%. Both BMI and dyslipidemia were not significantly higher in female patients when compared to male patients but neither diabetes duration nor HbA1c showed statistically significant differences between genders (Table 1).

Characteristics	Overall	Female	Male	p-value
n	201	102	99	-
Actual age (y)	12.4 ± 3.9	12.6 ± 3.8	12.2 ± 4.0	NS
Age at diagnosis (y)	8.1 ± 3.7	7.9 ± 3.5	8.3 ± 3.8	NS
< 10 years (n)	147	77	70	
10-15 years (n)	47	23	24	
>15 years (n)	7	2	5	
Diabetes duration (y)	3.8 ± 3.6	4.3 ± 3.6	3.4 ± 3.5	NS
BMI (Kg/m^2)	20.6 ± 4.3	21.4 ± 4.6	19.7 ± 3.7	0.004
HbA1c (%)	9.0 ± 1.8	9.0 ± 1.9	8.9 ± 1.7	NS
Dyslipidemia	84	50	34	0.045
TC (mg/dL)	161.2 ± 34.8	168.3 ± 40.3	153.4 ± 25.6	0.04
<170 (n)	116	54	62	
170-199 (n)	41	25	16	
>=200 (n)	18	13	5	
LDL-C (mg/dL)	112.4 ± 26.3	117.0 ± 28.0	107.3 ± 23.4	0.01
<100 (n)	92	42	50	
100-129 (n)	48	24	24	
>=130 (n)	36	26	10	
HDL-C (mg/dL)	53.2 ± 12.1	54.2 ± 13.7	52.2 ± 10.1	NS
<35 (n)	9	6	3	
35-44 (n)	35	15	20	
>=45 (n)	132	17	61	
TG (mg/dL)	83.9 ± 58.0	94.5 ± 74.0	72.2 ± 29.0	0.009
<100 (n)	138	67	71	
100-150 (n)	28	17	11	
>150 (n)	10	8	2	
Microalbuminuria				NS*
Yes	17	10	7	
No	184	89	84	

Table 1: Patients' Characteristics.

Seventeen patients (8.5%) met the study definition of microalbuminuria at a mean age of 11.1 ± 3.3 years and mean diabetes duration of 5.5 ± 3.8 years (Table 2). No patient had macroalbuminuria and 5 patients (2.5%) presented transient microalbuminuria.

At the time of this retrospective study, 12 children (70.6%) were treated with an angiotensin coverting enzyme inhibitor (ACEi) and none with angiotensin II receptor antagonist (ARA II).

When comparing the subgroup of patients with microalbuminuria with those without microalbuminuria, the former were older

(p=0.007), had longer diabetes duration (p=0.005), higher BMI (p=0.021) and higher HbA1c values (p=0.041), TC (p=0.032), LDL-C (p=0.043) and TG (p=0.006) as shown in Table 3.

Characteristics		Patients	p-value
Number		17	-
Gender	Female	10 (58.8%)	NS
	Male	7 (41.2%)	
Age at onset of T1DM (min; max) years		8.4 ± 3.7 (2.0 – 14.0)	NS
< 10 years		12 (70.6%)	
10-15 years		5 (29.4%)	
Age at onset of MA (min; max) years		11.1 ± 3.3 (6.4 – 14.5)	0.034
Female		10.5 ± 2.5 (min– max)	
Male		11.8 ± 3.0 (min– max)	
MA onset after T1DM diagnosis (min; max) y		5.5 ± 3.8 (0.75 – 14.0)	-
Δ DM1 (min; max) years		6.3 ± 3.7 (1.0 – 14.0)	-
MA present Δ DM1 < 2y		5 (29.4%)	-
MA present Δ DM1 2-5y		3 (17.7%)	-
MA present Δ DM1 ≥ 5y		9 (52.9%)	-

Table 2: Clinical Characteristics of the Patients with Microalbuminuria.

Data are expressed as absolute frequencies (numbers) and relative frequencies (%) or as means ± standard deviation (minimum - maximum).
Abbreviation: MA: Microalbuminuria; y: Years; T1DM: Diabetes Mellitus Type 1; Δ Duration; NS: Not Significant.

Characteristics		Microalbuminuria Present	Microalbuminuria Absent	p-value
n		17	184	-
Actual age (y)		15.2 ± 4.1	12.1 ± 3.7	0.007
Age at onset of diabetes (y)		8.4 ± 3.7	8.1 ± 3.7	NS
Diabetes duration (y)		6.3 ± 3.7	3.5 ± 3.5	0.005
Gender	Female (n)	10	89	NS
	Male (n)	7	84	
BMI (Kg/m²)		23.0 ± 4.9	20.3 ± 4.1	0.021
HbA1c (%) (min; max)		9.6 ± 1.9 (7.4 – 14.0)	8.9 ± 1.7 (4.8 – 14.0)	0.041
Dyslipidemia	Absent (n)	6	86	NS
	Present (n)	11	73	
TC (mg/dL) <170 (n) 170-199 (n) >=200 (n)		180.6 ± 57.5 7 6 4	159.1 ± 31.0 109 35 14	0.032
LDL-C (mg/dL) <100 (n) 100-129 (n) >=130 (n)		125.5 ± 36.3 6 7 4	110.9 ± 24.7 86 41 32	0.043
HDL-C (mg/dL) <35 (n) 35-44 (n) >=45 (n)		54.2 ± 14.8 1 4 12	53.1 ± 11.8 8 31 120	NS
TG (mg/dL) <100 (n) 100-150 (n) >150 (n)		133.3 ± 39.3 12 2 3	78.6 ± 38.4 126 26 7	0.006

Table 3: Clinical and laboratory differences between patients with / without microalbuminuria.

Data are expressed as absolute frequencies (numbers) and relative frequencies (%) or as means ± standard deviation (minimum, maximum).

Abbreviation: y: Years; HbA1c: Glycosylated Hemoglobin, NS: Not Significant; Min: Minimum; Max: Maximum; TC: Total Cholesterol; LDL-C: Low-density Lipoprotein Cholesterol; HDL-C: High Density Lipoprotein Cholesterol; TG: Triglyceride.

Female patients (10/17) developed microalbuminuria earlier than male patients and this difference was statistically significant (10.5 ± 2.5 versus 11.8 ± 3.0 years, p=0.034). No other statistically significant differences between females and males were found.

When comparing the patients developing microalbuminuria with T1DM onset before 10 years (n=12, 70.6%), with those with onset during puberty (10-15 years old; n=5, 29.4%), the time span to the detection of microalbuminuria was significantly longer: 6.1 ± 2.1 years versus 1.9 ± 1.0 years (p=0.04).

Five subjects (29.4%) presented microalbuminuria within the first 2 years of diabetes (3 of them with T1DM onset during puberty) and nine (52.9%) within the first 5 years of disease (5 of them with T1DM during puberty and the remaining 4 before puberty). The minimum observed time of diabetes duration to microalbuminuria was 0.75 years, in a 14-year-old boy; in this patient due to underachievement of metabolic goals with mean HbA1c=14.1%, the yearly biochemical evaluation was anticipated to 8 months after T1DM diagnosis. The maximum observed diabetes duration to microalbuminuria was 14 years.

In the logistic regression analysis, older age (OR=1.09, p=0.037, adjusted for diabetes duration), longer diabetes duration (OR=1.38, p=0.005), higher BMI (OR=1.13, p=0.026), higher HbA1c (OR=1.88, p=0.021), total cholesterol (OR=1.26, p=0.033), LDL (OR=1.44, p=0.042) and triglycerides (OR=1.63, p=0.006) were associated with microalbuminuria. There were no statistical significant differences regarding gender, puberty and HDL-C levels (Table 4).

Variable	OR	P Value	CI 95%
Actual age (y)	1.09*	0.037	[1.02; 1.17]
Age at diagnosis (y)	0.98	NS (0.77)	[0.85; 1.12]
Diabetes duration (y)	1.38	0.005	[1.11; 1.59]
Gender	1.34	NS (0.56)	[0.74; 1,11]
BMI (Kg/m²)	1.13	0.026	[1.04; 1.26]
TC (mg/dL)	1.26	0.033	[1.07; 1.44]
LDL-C (mg/dL)	1.44	0.042	[1.22; 1.63]
TG (mg/dL)	1.63	0.006	[1.31; 1.78]
HDL-C (mg/dL)	1.03	NS (0.72)	[0.95; 1.09]
HbA1c (%)	1.88	0.021	[1.45; 2.19]

Table 4: Logistic regression analysis of risk factors for microalbuminuria.

*adjusted for diabetes duration.
Abbreviation: y: Years; NS: Not Significant; CI: Confidence Interval; OR: Odds Ratio.

Discussion

The microalbuminuria prevalence found in our study (8,5%) is lower than reported in other studies in young people with T1DM [25,26]. The most recent data from the Oxford Regional Prospective Study (ORPS), a population-based inception cohort of children with T1DM, has shown a cumulative prevalence of microalbuminuria was 25.7% (95% confidence interval 21.3% to 30.1%) after 10 years of diabetes and 50.7% (40.5% to 60.9%) after 19 years of diabetes and 5182 patient years of follow-up [27], which is significantly higher than that reported in adulthood [28]. According to American Diabetes Association, about 20-30% of patients with T1DM will develop evidence of nephropathy during lifetime [29] and Alleyn CR et al. [30] reported that about 10% of adolescents with T1DM have microalbuminuria. We believe that the prevalence we found is due to the younger age of our cohort mostly before the end of puberty and with diabetes duration of 3.8 ± 3.6 years, much less than the 10 to 20 years of diabetes duration.

Our results indicate that higher HbA1c and longer diabetes duration are significant risk factors for microalbuminuria, in accordance to other reports [8,11,12].

Childhood and adolescence are transition phases with many physical and psychological issues representing barriers to optimal metabolic targets. Our data revealed a poor glycemic control in this cohort. In accordance to the literature, it was more evident in female patients, although we found no statistical significance. In the Hvidore study [31] metabolic control during adolescence was also disappointing. Neu et al. [32] reported an HbA1c at age 18 years of 7.7 ± 1.2 % and Sparud-Lundin et al. [33] have demonstrated mean HbA1c of 9.0% at age 18 years old for male patients and 9.4% for female patients.

In the T1D Exchange clinic Registry [34] microalbuminuria rate was 4.4% with a higher frequency also associated with female sex, as well as longer diabetes duration, higher HbA1c and older age (and among older participants especially those with HbA1c ≥ 9.5%).

In our series, we found a high prevalence of dyslipidemia and it did significantly increase the risk for microalbuminuria. According to the latest ISPAD guidelines [8], dietary changes and increased exercise should be instituted in all patients with LDL-C >100 mg/dL; if these measure fail to lower LDL-C <130 mg/dL statins should be considered in children aged > 10 years with one or more risk factors. The reason why no patients were under lipid lowering drugs is related to the fact that most patients are quiet young and long-term safety is not well established yet. Moreover, guidelines concerning lipid profile treatment are posterior to this study. Previous studies have suggested a positive association between nephropathy and dyslipidemia, but there is sparse data about the relationship between lipids and microalbuminuria. Recent reports suggest that increased total and LDL cholesterol [34,35] and lower HDL are associated with decreased glomerular filtration rate in normoalbuminuric T1 diabetic patients [36].

Our results indicate that obesity increases the risk for microalbuminuria in T1DM. This association is well established in type 2 diabetes mellitus [17] and recent data suggest that adipocytokines may play a key role in the pathophysiology of nephropathy in both type 2 and type 1 diabetes mellitus. Diabetic glomerulosclerosis remains the cause of nephropathy in T1DM but there are several individuals with progressive chronic kidney disease (decreasing glomerular filtration) despite normal urine albumin excretion or low-level microalbuminuria (albumin-to-creatinine ratio <100 mg/g) and these ones present interstitial or vascular changes in spite of glomerular ones. These alterations may be related to obesity and dyslipidemia [16].

During puberty, there is an increasing risk of microangiopathy. This is associated with insulin resistance [3] due to metabolic and hormonal changes of puberty that may contribute as independent risk factors [27,37,38]. Although detailed Tanner staging was unavailable in this study and puberty was considered according to chronological age, microalbuminuria tended to develop earlier in subjects with diabetes onset at ages 10-15 years old. This suggests that changes during the pubertal years might be important in the timing of the first appearance of microalbuminuria, as other authors have suggested [38].

Microalbuminuria was more frequent in female subjects and occurred earlier in life, in accordance with other reports [27,37]. Inversely, in adult T1DM cohorts, prevalence of microalbuminuria is greater in men [37]. The reason for the reversal in gender risk from childhood to adulthood to the onset of renal disease is unclear. Some data indicate that this might be explained by a renal damage caused by sex steroids [28]. Associations between hyperandrogenism, low-sex hormone binding globulin and abnormalities in the growth hormone insulin-like growth factor I axis in adolescent girls with microalbuminuria have been described [39]. Environmental factors, such as diet, lifestyle and smoking habits as well as genetic susceptibility can also contribute to the development of vascular complications [18,40]. None of our patients reported smoking, which might have been biased because of parents' presence during the consultations. Interestingly, we found one patient that developed microalbuminuria 0.75 years after T1DM diagnosis with no other cause to nephropathy, which might be due to diet or genetic susceptibility, associated to very poor metabolic control.

Limitations of Study

This is a retrospective study and so data used for analysis were collected from clinical reports made by different health care providers albeit of the same institution. It is not the ideal study design to analyze time of occurrence of microalbuminuria but we aimed to determine the prevalence of microvascular disease in our diabetic population in order to optimize diabetes care. We only assessed data regarding microalbuminuria and no other vascular complications of diabetes mellitus, as nephropathy is usually the first microvascular complication. For puberty assessment we used chronological age and defined 10 year-old in accordance to the threshold considered for nephropathy screening [8] instead of

Tanner stage. Another limitation of our study was being a single-centered study and therefore included a relatively small number of microalbuminuria cases and lack of stratification for ethnicity.

However, we believe that our results have provided important data on prevalence, predictive factors and screening of nephropathy in a young population of T1DM patients, as besides the well-described risk factors for microalbuminuria, we also found obesity and dyslipidemia to increase the risk of nephropathy.

Conclusions / Learning Points

- T1DM incidence is rising. Screening of microvascular complications plays a critical role in the management of T1DM, particularly in those with longer life-time expectancy, such as children and adolescents.
- Microalbuminuria is associated with poor glycemic control, obesity, dyslipidemia and longer diabetes duration.
- There is higher prevalence of microalbuminuria in female patients and it appears earlier in life. Adult cohorts report higher prevalence in males.
- According to our results, we recommend that microalbuminuria screening should be started after T1DM diagnosis if the subjects are diagnosed between ages 10-15 years old and 2 years after T1DM onset in those diagnosed in pre-pubertal ages.
- As vascular complications might be rare in childhood, it might be appropriate to decide on the screening time according to the individual patient (especially glycemic control, dyslipidemia and BMI) and age of diabetes-onset.

As the prognosis might be worse in subjects with T1DM diagnosis before 18 years old than in those with adult onset T1DM, there is a need to detect risk factors and diagnose microvascular complications as earlier as possible, as well as to consider prompt intervention strategies, in order to improve prognosis and reduce social, psychological and economic burdens.

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