Association of Diabetes and Body Mass Index with Levels of Prostate-Specific Antigen: Implications for Correction of Prostate-Specific Antigen Cutoff Values?

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Abstract

Background: **In a recent study, an inverse association between diabetes and prostate-specific antigen (PSA) levels was observed, and several studies reported lower PSA levels in groups with higher body mass index. However, all of the studies were conducted in populations with intensive PSA screening and the role of diabetes severity, duration, and therapy are yet to be explored.**

Methods: **Associations of diabetes duration and treatment, hemoglobin A1c, and BMI with PSA levels were assessed among 778 men ages 50 to 74 years, randomly chosen from the 2000 to 2002 baseline recruitment of a large population-based cohort study in Germany (prevalence of diabetes, 17%), using linear regression analyses.**

Results: **PSA values were significantly reduced in men with insulin treatment (−39%; P = 0.006) and oral diabetic medication (−24%; P = 0.030), and in men with elevated (6.1-6.9%) and highly (≥7%) elevated hemoglobin A1c values (−15%, P = 0.004 and −29%, P = 0.003, respectively). PSA reduction was not associated with duration of diabetes. Obesity was possibly associated with a reduction of PSA levels (−14%; P = 0.096).**

Conclusions: **Our study suggests that more severe forms of diabetes are associated with lower PSA levels and confirms the magnitude of reduction in PSA levels in diabetic men overall. The observed PSA reduction parallels reported risk reduction of prostate cancer among diabetic men.** (Cancer Epidemiol Biomarkers Prev 2009;18(5):1350–6)

Introduction

Measurement of prostate-specific antigen (PSA) is widely applied for early detection of prostate cancer. However, PSA levels seem to be influenced by a number of demographic, life-style, and health characteristics, which might deserve careful attention in the interpretation of test results. In a recent study from the United States, an inverse association between diabetes and PSA levels was observed (1), and several studies reported inverse associations between body mass index (BMI) and PSA levels (1-5), while others showed lower mean (6) or median (7, 8) PSA in higher BMI groups. However, the role of severity, duration, and therapy of diabetes are yet to be explored as more detailed data are still lacking. Furthermore, all of these studies were conducted in populations with intensive PSA screening, and might thus be affected by differential screening behavior of diabetic and overweight or obese men compared with the general population. This might lead to a reduction in mean PSA by the elimination of high PSA values (through exclusion of patients with a previous prostate cancer diagnosis) in the group with higher screening participation, which might be the case for diabetic men in the United States. Having diabetes was associated with a 9% increase in PSA screening after adjustment for other confounders (9). Thus, the association of diabetes and BMI with PSA levels require confirmation in populations with no or limited PSA screening. Additionally, the association of PSA change and prostate cancer risk change in diabetic and obese men needs to be addressed to evaluate whether there is a problem with current PSA screening modalities in these patient groups. To address these questions, we analyzed the association of diabetes and BMI with PSA levels in the baseline examination of a population-based cohort study, conducted in Germany in 2000 to 2002, i.e., before widespread use of PSA testing. Special attention was paid to the potential role of severity, duration and treatment of diabetes.

Materials and Methods

Study Design and Study Population. This study included male participants of a state-wide, population-based cohort study (ESTHER: epidemiological study on chances of prevention, early detection, and treatment optimization of chronic diseases in the elderly), conducted in Saarland, Germany. Between July 2000 and December 2002, 9,953 men and women, ages 50 to 74 y, were recruited by their general practitioner (~400 general practitioners participated) during a general health examination offered biennially to people ages

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35 y or older in Germany. Age and sex distribution are very similar to the population of Saarland in the respective age range, and furthermore, age-specific prevalence of diseases such as diabetes or hypertension were shown to be comparable with representative samples of the German population (10). This general health examination has the aim to identify common chronic diseases, in particular diabetes, cardiovascular diseases, or kidney diseases, at an early stage. The study was approved by the ethics committees of the University of Heidelberg and the medical board of the state of Saarland. Written informed consent was obtained from each participant. For the present analysis, 778 male participants of ESTHER with no prior history of cancer were randomly chosen from the baseline cohort. Men with newly diagnosed prostate cancer until the 2-y follow-up of the study (response rate at 2-y follow-up, 96%) were excluded.

Data Collection. In the general health examination, the general practitioner documents the patient's medical history and tests for common diseases by clinical and laboratory examinations (e.g., fasting blood glucose). As part of the ESTHER baseline examination, information on former and newly diagnosed diseases as well as the patient's current medication, height, and weight were documented in a standardized form by the general practitioner. Drugs were attributed to preparations available on the German market and linked to ''Gelbe Liste-Pharmindex'' (MediMeida) providing the active compounds and anatomic therapeutic chemical code. Additionally, all participants of ESTHER were asked to complete a standardized questionnaire containing detailed information on sociodemographic and life-style factors as well as on the medical history at the time of recruitment. Furthermore, EDTA plasma samples were taken by the physician and mailed to the study laboratory where the samples were frozen at −70°C until analysis.

Participants were regarded as diabetic patients if the general practitioner reported existing or newly diagnosed diabetes during the health examination or if intake of diabetic medication was reported by the physician. According to this definition, prevalence of diabetes was 17% in the male participants of the ESTHER study (n = 4,484 men). Duration of diabetes was calculable in those classified as diabetic patients by a physician if the respective participant reported age at first diagnosis of diabetes in his questionnaire (duration of diabetes calculated as current age − age at diagnosis of diabetes). In diabetic men who were newly diagnosed in the general health examination, the duration was defined as zero years. We could not distinguish between diabetes type 1 and 2, but expected the number of patients with diabetes type 1 as rather negligible, as there were only 2 participants who reported diagnosis of diabetes below age 30 y.

We used hemoglobin A1c (HbA1c) as an additional marker of glycemic control. This marker is indicative of glycemic control within the past 3 mo (11) and was shown to predict especially microvascular and neuropathic complications comparable with fasting plasma glucose or oral glucose tolerance test (12, 13). We defined HbA1c levels less or equal 6% as normal and 6.1% to 6.9% as high, thus using 6.1% as cutoff value, which was suggested by Bennett et al. (13) to identify diabetic patients. Furthermore, the category ''very high'' was defined for those requiring more intensive glycemic control (HbA1c, 7% and higher) to reduce the HbA1c value according to the standards defined by the American Diabetes Association (14).

To calculate the patient's BMI [weight (in kg)/height $(m)^2$], we used the variables height and weight from the patient's standardized questionnaire as there were less missing values for these two variables compared with the general practitioner's standardized form. To evaluate the data for height and weight given by the participants, we compared the data provided by the participant and the general practitioner. Most values were absolutely identical in the participants and general practitioners form (height, 74%; weight, 65%) or at least very close to the participants values (±3 cm in height, 95%; ±3 kg in weight, 93%), and we replaced the few missing values for height and weight in the patient's data by the general practitioners data where possible. BMI (in kg/m^2) was categorized as normal weight if BMI was <25, as overweight if 25≤ BMI <30, and as obese if BMI was ≥30.

Laboratory Analyses. PSA and HbA1c were measured in blood samples. PSA analyses were done using the test ''total PSA'' (Roche Diagnostics) on a Modular E-Modul of Roche Diagnostics. HbA1c analyses were done using high performance liquid chromatography on the Variant II system (Bio-Rad). All measurements were done in a central laboratory in blinded fashion and according to the manufacturer's instructions in a central laboratory. According to the study protocol, results of our measurements were not released to the study participants or their doctors, and had no influence on diagnosis of diabetes in the study.

Statistical Methods. PSA values were transformed into natural logarithm for analyses to approximate the normal distribution and were transformed back after analysis to present results in a clearer fashion. Thus, mean values of PSA are presented as geometric means in the tables but are referenced as ''mean PSA'' in the text to simplify matters. Linear regression analyses with the natural logarithm of PSA as the dependent variable were used to estimate and test for changes in PSA levels in the presence or absence of diabetes and overweight after adjustment for age. In the main analysis, age was included as a linear term and adjusted (geometric) mean levels are reported for an age of 51 y to ensure comparability with the PSA levels reported by Werny et al. (1). Alternative analysis with stratification of age by 5-y age groups (50-54, 55-59, 60-64, 65-69, 70-74) yielded very similar results and are therefore not shown separately. In additional analyses, estimates for the effect of diabetes indicators were adjusted for BMI (<25, 25-<30, ≥30), and estimates for the effect of BMI were adjusted for presence of diabetes (yes/no) to elucidate their independent effects on PSA levels. Additional analyses, in which BMI was controlled for as a continuous variable and analyses in which duration of diabetes rather than presence of diabetes was controlled for, yielded very similar results and therefore are not reported separately. As only few men reported to be born outside Germany or Central Europe, we did not introduce a variable for ethnicity/race. In the multivariate analyses, various interaction terms of the independent variables were also

evaluated (diabetes, BMI, age) but did not show statistical significance and thus were not included in the final models. All significance tests were two sided ($\alpha = 0.05$). SAS software version 9 was used for all calculations.

Results

Overall, 778 participants ages 50 to 74 years were included in the analyses. According to information of their general practitioner, 130 of 766 participants were classified as diabetic patients (due to missing values, no such classification was possible for 12 men). Men with diabetes were slightly older (65.8 years) than nondiabetic men (64.4 years), had a higher mean BMI (29.2 versus 27.4 kg/m^2), and were more often obese (40% versus 21%) compared with nondiabetic men (Table 1). In addition, mean HbA1c was higher in diabetic men.

In descriptive analyses with adjustment for age, mean PSA was 0.70 ng/mL in diabetic men and thus significantly lower (−17%) compared with nondiabetic men (Table 2). The reduction of PSA was of similar magnitude for diabetes duration 0 to 5, 6 to 10, and >10 years (−22% to −30%) compared with nondiabetic patients, although it was statistically significant only in the group with a diabetes diagnosis within the past 5 years. Mean PSA was significantly lower (−30%) in diabetic men using diabetic medication compared with nondiabetic men, whereas diabetic men using no medication had a mean PSA quite similar to nondiabetic men. When regarding diabetic medication in detail, insulin treatment was associated with a strong, significant decrease in mean PSA (−40%) compared with nondiabetic men, whereas the decrease for oral medication was weaker but still significant (−25%). The different oral medications showed a very similar reduction of PSA (biguanides, −22%; sulfonylureas, −16%; α-glucosidase inhibitors, −25%; data not shown).

Among men with high HbA1c (6.1-6.9%), there was a significant reduction (−16%) of mean PSA compared with those with a normal HbA1c (Table 2). Among men with very high HbA1c (≥7%), the reduction was much stronger (−30%) and also statistically significant. When analyzing men with diabetic medication and men without diabetes separately, the estimates for the PSA reduction according to Hba1c level were quite similar. A nonsignificant reduction in mean PSA compared with those with a BMI below 25 was shown for both men with a BMI between 25 and 30 (−4%) and men with BMI ≥30 kg/m^2 (−15%). All age groups above 60 years had significantly higher mean PSA compared with the age group 50 to 54 years and mean PSA increased with older age.

Because diabetes and BMI are strongly related, we additionally adjusted the various estimates for indicators of diabetes for BMI, whereas the estimates for BMI were adjusted for presence of diabetes to assess their independent effect (Table 2, *right hand columns*). Furthermore, various interaction terms of the diabetes-related variables, BMI, and age were created but not included in the final models because none of these terms was statistically significant.

Overall, additional adjustment for BMI had only very minor, mostly negligible effects on estimates of the association of the various indicators of diabetes with PSA. Vice versa, control for the presence of diabetes essentially left the estimated effect of BMI unchanged.

Table 1. Characteristics of study participants (classified as diabetic or not due to information of general practitioner)

Variable	Diabetics (n = 130)	Nondiabetics (n = 636)
Mean age (y)	65.8	64.4
Age distribution, n (%)		
50-54 y	6 (5%)	40 (6%)
55-59 y	10 (8%)	88 (14%)
60-64 y	30 (23%)	174 (27%)
65-69 y	41 (32%)	184 (29%)
70-74 y	43 (33%)	150 (24%)
Mean BMI (kg/m^2)*	29.2	27.4
BMI distribution, n (%)*		
<25 kg/m^2	21 (16%)	154 (24%)
25-<30 kg/m2	56 (43%)	348 (55%)
≥30 kg/m2	52 (40%)	134 (21%)
Median PSA (ng/mL)	1.0	1.3
Q1-Q3 PSA (ng/mL)†	0.7-1.8	0.7-2.3
Median HbA1c (%)*	6.6	5.6

*Missing values: 1 for BMI, 7 for HbA1c.
† Lower to upper quartile of PSA (ng/mL).

Discussion

In our study, men with diabetes medication, especially those using insulin, and also those with very high HbA1c levels had lower PSA levels than nondiabetic men, whereas diabetic men without medication tended to have similar PSA levels compared with nondiabetic men. These patterns, which persisted after control for BMI in addition to age, suggest that more severe forms of diabetes are independently associated with lower PSA levels. Additionally, our study confirmed the overall magnitude of PSA reduction in diabetic patients shown in another comparable study. Furthermore, we showed a trend toward lower PSA levels for obese men.

Compared with the United States National Health and Nutrition Examination Survey population, the geometric mean PSA was 5% and 15% higher in our study from Germany in the corresponding age ranges 50 to 59 and 60 to 69 years (1). This difference might reflect the different screening behavior in the United States and Germany. Although PSA screening is very common in the United States (15), this procedure is not recommended in Germany, and in 2000 to 2002, there was yet rather limited opportunistic (''gray'') PSA screening. Therefore, the PSA levels in our study are unlikely to be influenced by PSA screening or a different screening behavior between diabetic and nondiabetic men or between obese and normal-weight men.

The best comparison for our study to evaluate the influence of diabetes on PSA is the National Health and Nutrition Examination Survey study (1), which found for men with diabetes a similar decrease in mean PSA (−22%) as in our study (−17%), although their study was conducted in a population with intensive screening (American men). In a very recent study by Fukui et al. (16), a similar PSA reduction (−10 to −16%) was even shown in 50- to 79-year-old Japanese men with a

Table 2. Geometric mean of PSA according to different characteristics

		n	Geometric mean of PSA (ng/mL)*	Change in geometric mean (%)	95% CI for change in geometric mean		*P*	Change in geometric mean (%)	95% CI for change in geometric mean		*P*
					Lower limit	Upper limit			Lower limit	Upper limit	
Indicators of diabetes		Adjusted for age Total = 766						Additionally adjusted for BMI†			
Diabetic	No	636	0.84	Reference group				Reference group			
	Yes	130	0.70	−16.8%	−29.0%	−2.4%	0.024	−14.6%	−27.4%	0.5%	0.057
Duration of diabetes	0-5 y	34	0.59	−29.6%	−47.3%	−5.9%	0.018	−28.0%	−46.2%	−3.8%	0.027
	6-10 y	17	0.65	−22.4%	−48.3%	16.4%	0.220	−22.4%	−48.3%	16.4%	0.220
	>10 y	34	0.64	−24.0%	−43.2%	1.6%	0.063	−22.2%	−41.8%	4.2%	0.092
	No duration reported	45	0.88	3.9%	−19.4%	34.0%	0.769	9.7%	−15.5%	42.4%	0.486
Diabetes medication‡	No	59	0.86	2.6%	−18.0%	28.4%	0.821	6.1%	−15.4%	33.0%	0.610
	Yes	71	0.59	−30.1%	−43.1%	−14.1%	0.001	−28.7%	−42.1%	−12.1%	0.002
	Insulin	22	0.50	−40.4%	−58.3%	−15.0%	0.004	−39.5%	−57.7%	−13.6%	0.006
	Oral medication	51	0.63	−25.3%	−41.2%	−5.2%	0.017	−23.6%	−40.0%	−2.6%	0.030
HbA1c		Total = 771									
	Normal (<6.1%)	567	0.86	Reference group				Reference group			
	High (6.1-6.9%)	141	0.72	−15.7%	−27.9%	−1.4%	0.033	−14.9%	−27.3%	−0.5%	0.044
	Very high (≥7%)	63	0.60	−30.2%	−44.0%	−13.0%	0.001	−28.8%	−43.1%	−10.9%	0.003
BMI		Adjusted for age Total = 777						Additionally adjusted for presence of diabetes			
	<25	178	0.89	Reference group				Reference group			
	25-<30	408	0.85	−4.0%	−17.4%	11.4%	0.589	−3.5%	−16.9%	12.0%	0.637
	≥30	191	0.76	−14.6%	−28.2%	1.5%	0.074	−13.9%	−27.8%	2.7%	0.096
Age		Unadjusted Total = 778						Adjusted for presence of diabetes and BMI			
	50-54 y	47	0.86	Reference group				Reference group			
	55-59 y	102	1.03	20.8%	−10.1%	62.1%	0.209	15.5%	−14.1%	55.3%	0.340
	60-64 y	208	1.18	38.4%	5.6%	81.2%	0.018	37.5%	4.9%	80.2%	0.021
	65-69 y	227	1.37	60.6%	22.9%	110.0%	0.001	57.4%	20.4%	105.8%	0.001
	70-74 y	194	1.62	88.9%	43.9%	147.8%	0.000	88.7%	43.7%	147.8%	0.000

Abbreviations: CI, confidence interval.
*Adjusted to age, 51 y.
† All multivariate models included 765 persons, except for the model of HbA1c with 770 persons.
‡ Intake of more than one drug possible, 23 used biguanides, 33 sulfonylureas, 7 α-glucosidase inhibitors, 1 another oral drug.

considerably lower mean BMI (but similar mean Hba1c values as in the ESTHER study in both diabetic and nondiabetic men). In contrast to our results, in the National Health and Nutrition Examination Survey study, an inverse association of diabetes duration and PSA was found (1). However, duration of diabetes is a difficult to quantify parameter as ~50% of type 2 diabetic patients may be undiagnosed in the population (17), and known duration might be related to the degree of medical surveillance.

Our findings are consistent with the findings from the National Health and Nutrition Examination Survey study (1) regarding the particularly low PSA values among men using diabetes medication, which might be a proxy for severity of the disease. As our study was the first to investigate the diabetic medication in detail, we could further show the largest reduction for men using insulin, whereas oral diabetic medication was associated with a lower PSA reduction and whereas diabetic men with no medication tended to have similar PSA levels compared with nondiabetic men. The hypothesis that more severe forms of diabetes might be associated with a lower PSA level was further supported by the inverse association of HbA1c measurements with PSA levels in our study, a result that was also seen by Fowke et al. (18) in Caucasian men. In contrast, Fukui et al. (16) found no association between PSA levels and either Hba1c or medication in Japanese men. All in all, these results support the hypothesis of lower PSA levels with more severe forms of diabetes at least in Western populations.

With respect to interpretation of PSA levels among diabetic men, the important question arises if PSA reduction among diabetic men (−15%) agrees with reduction of prostate cancer risk. In the meta-analysis of Kasper et al. (19), an overall prostate cancer risk reduction of 16% was shown for diabetic patients. A comparable risk reduction was shown when regarding only aggressive prostate cancer (20, 21)—a very important finding with regard to the common overdiagnosis of prostate cancer (22). That is, if one assumed only a PSA reduction and no simultaneous prostate cancer risk reduction in diabetic men, one would expect a stage migration toward detection of later-stage prostate cancer and thus an increasing risk for advanced prostate cancer in diabetic men. But neither a stage migration (23) nor an increasing risk for advanced prostate cancer (20, 21) was shown yet. It is not clear to what extent a PSA reduction of 15% corresponds with a prostate cancer risk reduction of 16% and how much delay there is between change in PSA levels and changes in prostate cancer risk. However, as both PSA and prostate cancer risk tend to change in the same direction in diabetic patients, i.e., both are reduced, and two studies (24, 25) showed a prostate cancer risk reduction in diabetic men using insulin (−36% to −51%), which was comparable with our PSA reduction in these men (−40%), a recommendation to adjust PSA values for diabetes to improve prostate cancer detection does not seem to be warranted with current knowledge. Nevertheless, data that differentiate prostate cancer risk in diabetic men according to the severity of the disease are still rare and thus needed to assess the association of PSA and prostate cancer risk reduction.

Two important pathways might be involved in the association of diabetes and both PSA and prostate cancer. Lower testosterone levels in diabetic men (26) might be responsible for their reduced PSA levels, as PSA is regulated by androgens (27). Nevertheless, prostate cancer risk is not associated with serum testosterone levels at the same time (28). However, PSA cleaves insulin-like growth factor binding protein-3, which is the major binding protein for insulin-like growth factor-1 (27). This might lead to increased serum insulin-like growth factor-I, which is an important risk factor of prostate cancer (29). However, it is not clear whether the complex regulation of these mechanisms leads to a parallel reduction of PSA and prostate cancer in diabetic men or not.

Previous larger studies showed an inverse association between BMI and PSA (1-4), or lower PSA levels for men with BMI of $\geq$30 kg/m^2 (6). The results of our study suggested that a relevant reduction in PSA might be restricted to obese men (−14%), which in part might be attributable to the effect of hemodilution (30). The PSA reduction was comparable with the reduction found in previous studies: −9% to −19% (2, 3, 6, 8, 31). Likewise, the risk of localized prostate cancer was reduced in obese compared with normal-weight men (−8%, when assuming a BMI difference of 10 kg/m^2) according to the meta-analyses of MacInnis et al. (32). However, for aggressive prostate cancer, a risk increase of 25% has been reported (32). Such a large risk difference between localized and advanced prostate cancer was confirmed in three recent prospective cohort studies (33-35). Thus, the PSA reduction in obese men does not seem to reflect a risk reduction in advanced cancer (the clinically most relevant forms), and adjustment of PSA in obese men might help to identify some aggressive prostate cancer cases earlier. At the same time, such a correction could strongly increase overdiagnosis of prostate cancer, which is common in the general population (22), and therefore, the trade-off of such an adjustment is difficult to quantify. Nevertheless, it seems unlikely though that moderate decrease in PSA levels, such as the one found in our and previous studies, might be responsible for such a strong increase in aggressive prostate cancer, especially when considering that even in the United States, not all men undergo PSA screening.

Therefore, other factors might account for the risk increase of aggressive prostate cancer in obese men, such as elevated levels of leptin or insulin, which are associated with cell growth or lower levels of adiponectin, which might be an antiangiogenic factor (36). But as the effect of the other partly unknown risk factors is not quantifiable, the effect of a lower PSA threshold is difficult to evaluate. Thus, adverse effects by unnecessary treatment are likely to occur by lowering PSA values for obese men, whereas no evidence exists for a benefit yet.

As we have no confirmation by biopsy that our participants are free of prostate cancer, PSA values might be biased by unknown prostate cancer. But as we excluded all participants who reported prostate cancer at the 2-year follow-up of the study, we assume that the prevalence of clinically relevant prostate cancer is likely to have been small. We were not able to control for benign prostatic hyperplasia, which also might bias PSA values, if prevalence of benign prostatic hyperplasia was different in diabetic and nondiabetic men. However, a recent study did not find an association between diabetes and benign prostatic hyperplasia (37). A real strength of

our study is that definition of diabetes was based on medical diagnoses rather than self-report. To account for undiagnosed diabetes, we reanalyzed the data of the nondiabetic men, defining Hba1c values above 6% as incidence of diabetes. Men with potentially ''undiagnosed'' diabetes were shown to have similar PSA reduction as men with known diabetes. This confirms the overall reduction of PSA in diabetic men. As BMI cannot differentiate between peripheral and central fat, other measures, such as waist-to-hip ratio, waist-circumference, or proportion of body fat measured by bioelectrical impedance analysis might be more appropriate measurements to rule out residual confounding. However, pertinent data in combination with prostate cancer risk are very sparse. Furthermore, it has to be kept in mind that our cross-sectional study design does not allow causal inference on the relationship of diabetes and PSA values.

All in all, our study was the first to show that severity of diabetes seemed to be strongly associated with PSA levels. Furthermore, our study showed that the reduction of PSA in diabetic men was independent of obesity. The overall magnitude of PSA reduction that was shown for diabetic and obese men in other studies was confirmed in a population with low PSA screening activity. Nevertheless, an adjustment of PSA measurement for diabetes or obesity does not seem to be warranted with the current knowledge. The most compelling issue to be clarified first by the results from ongoing randomized controlled trials is whether PSA screening generally leads to reduction of prostate cancer mortality—the most important criterion for its use in potential screening (38). Further studies are needed to assess the association of both PSA change and prostate cancer risk change with regard to severity of diabetes—especially with regard to severe forms of diabetes where PSA reduction seemed to be rather large. Regarding obesity, more emphasis should be laid on the identification of the potential hormonal risk factors that lead to the increased risk of aggressive prostate cancer and the quantification of their effect.

Disclosure of Potential Conflicts of Interest

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