Hipotiroidide Otoimmünitenin NAMPT/Visfatin Düzeylerine Etkisi

The Effect of Autoimmunity on NAMPT/Visfatin in Patients with Hypothyroidism

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ÖZET

Amaç: NAMPT/visfatin inflamasyonu arttırır ve serum seviyeleri, otoimmün bozukluklar ve tiroid kanserleri gibi kronik düşük dereceli inflamasyonda etkilenir. Hipotiroidili kronik bir otoimmün tiroidit (KOT) olan Hashimoto Tiroiditi (HT) ve tiroid papiller karsinomunda (TPCa) NAMPT/visfatin düzeylerinin nasıl etkilendiğini göstermeyi amaçladık.

Gereç ve Yöntemler: Bu kesitsel bir vaka kontrol çalışmasıdır ve 2020 yılında yapılmıştır. Henüz tedavi görmemiş 193 HT hastası ve 29 TPCa hastası 150 sağlıklı kontrol ile karşılaştırılmıştır. Visfatin serum konsantrasyonu ELISA yöntemi ile ölçüldü,

Bulgular: En yüksek NAMPT/visfatin seviyeleri HT'de, en düşük ise kontrol grubunda görüldü. HT grubu en yüksek Anti-TPOAb seviyesine sahipti. TPCa ve kontroller, TPOAb ve Anti-Tiroglobulin Ab için negatifti. HT grubunun subklinik ve aşikar hipotiroidi alt grupları arasında; TSH, FreeT3, FreeT4 ve Tiroglobulin açısından anlamlı farklılıklar vardı (sırasıyla $p < 0{,}001$, $p = 0{,}037$, $p < 0{,}001$, $p = 0{,}001$). TPCa grubunun alt gruplarında; TSH ve FreeT4 açısından anlamlı farklılıklar vardı (sırasıyla $p < 0{,}001$, $p = 0{,}007$). Visfatin konsantrasyonları, FT3 ile önemli ölçüde korele idi ($r = 0.336$; $p = 0.034$).

Sonuçlar: Hipotiroidizmdeki visfatin seviyeleri, birlikte var olan KOT tarafından düzenlenir ve ayrıca TPCa'dan etkilenir ve FT3 ile koreledir.

Anahtar Kelimeler: Hashimoto Hastalığı, Hipotiroidizim, Nikotinamid Fosforiboziltransferaz, Otoimmün, Papiller, Tiroidit, Tiroid Kanseri

ABSTRACT

Background: NAMPT/visfatin increases inflammation and its serum levels are affected in chronic low-grade inflammation such as autoimmune disorders, and thyroid cancers.

Aim: We aimed showing how NAMPT/visfatin levels are affected in Hashimoto's Thyroiditis (HT), a chronic autoimmune thyroiditis (CAT) with hypothyroidism, and thyroid papillary carcinoma (TPCa).

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Materials and Methods: This is a cross-sectional case-control study and conducted in 2020**.** 193 HT patients not yet received treatment and 29 TPCa patients were compared with 150 healthy controls. Visfatin serum concentration was measured by ELISA method,

Results: The highest levels of NAMPT/visfatin were seen in the HT, and the lowest in the control group. HT group had the highest Anti-TPOAb level. TPCa and controls were negative for TPOAb and Anti-Tiroglobulin Ab. Between subclinical and overt hypothyroidism subgroups of HT group; there were significant differences regarding TSH, FreeT3, FreeT4, and Thyroglobulin ($p < 0.001$, $p = 0.037$, $p < 0.001$, $p = 0.001$, respectively). In subgroups of TPCa group; there were significant differences regarding TSH and FreeT4 ($p < 0.001$, $p = 0.007$, respectively). Visfatin concentrations were significantly correlated with FT3 ($r = 0.336$; $p = 0.034$).

Conclusions: Visfatin levels in hypothyroidism are regulated by co-existing CAT and are also affected in TPCa and correlates with FT3.

Key-words: Autoimmune, Hashimoto Disease, Hypothyroidism, Nicotinamide Phosphoribosyltransferase, Papillary, Thyroid Cancer, Thyroiditis

INTRODUCTION

Visfatin, originally identified as cytokine pre-B colony-enhancing factor (PBCEF), also known as nicotinamide phosphoribosyl transferase (NAMPT) [1]. NAMPT, an intracellular enzyme, is important for ATP synthesis. The main source of NAMPT / visfatin secreted by adipose tissue and leukocytes is still unclear [2, 3]. Elevated levels have been detected in obese and Type 2 Diabetes Mellitus (DM) patients and are involved in metabolic regulation [4, 5]. Both of the hypothyroidism and hyperthyroidism affect NAMPT / visfatin levels [6]. NAMPT /visfatin increases inflammation and has been found to be elevated in low degrees of inflammation such as sepsis, autoimmune disorders and atherosclerosis [7]. NAMPT / visfatin has apoptotic activity in many cancers, and its overproduction has recently been found in thyroid cancers. The grade of the tumor and lymph node invasion have been associated with NAMPT overproduction [8]. NAMPT / visfatin, a powerful stimulus of inflammation; increased in autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematous and has been associated with disease severity [9, 10]. Increased visfatin levels in other autoimmune diseases suggest that NAMPT / visfatin levels in hypothyroidism may be altered by co-existing chronic autoimmune thyroiditis (CAT). On top of that, recent studies have shown that visfatin is affected in autoimmune processes of thyroid diseases [11, 12].

There has been a steady increase in the incidence of autoimmune thyroid disease (ATD) recently. Causes of ATD are multifactorial, including environmental factors such as infection, diet, iodine and smoking, and genetic factors [13]. ATD etiology is mainly due to the development of autoimmunity against thyroid antigens. ATD is defined by the production of thyroid autoantibodies and lymphocytic infiltration of the thyroid [14]. The prevalence of Hashimoto's thyroiditis (HT), an ATD and determined by hypothyroidism, is estimated to be around 5% [15]. Thyroid peroxidase (TPO) and thyroglobulin (Tg) are the main autoantigens of HT [16].

Since visfatin levels are affected in autoimmune disorders especially ATD and overproduction of visfatin is observed in thyroid cancers. In this study, we compared and evaluated visfatin levels in three groups; HT patients who have not yet taken any treatment for their hypothyroidism, and thyroid papillary carcinoma (TPCa) patients who have been operated and under follow up and controls who have normal thyroid hormone levels with negative antithyroid antibodies.

MATERIALS and METHODS

Study Design and Patient Recruitment.

Our study is a cross-sectional case-control study. After taking approval of local Ethics Committee the research related to human use has been complied with all the relevant

national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee. We included patients applied to the internal medicine outpatient clinic and accepted joining the study and informed consent has been obtained from all individuals included in this study. 193 patients with autoimmune thyroiditis (HT)) and who have not yet received treatment (129 of them have subclinical hypothyroidism with TSH <10 mIU / L and 64 patients have overt hypothyroidism with TSH'ı ≥10 mIU/L), 29 TPCa patients (6 patients with subclinical hypothyroidism with TSH <10 mIU / L and 23 patients with overt hypothyroidism with TSH ≥10 mIU / L) and 150 healthy controls, matched with patient groups for age, gender and body mass index (BMI), with normal thyroid function and negative thyroid antibodies were included in the study. The diagnosis of HT was made by the presence of antibody positivity and / or typical ultrasound image. The patients who have other autoimmune diseases, diabetes mellitus, and an active infection, which were thought to alter their visfatin levels, were excluded from the study. Since it was previously proven that visfatin mRNA expression increases in thyroid malignancies and this correlates with tumor stage, we did not include those with any active neoplastic disease characteristics in our study.

Laboratory Analysis.

Fasting blood samples were collected for visfatin, TSH, free thyroxine (FT4), free triiodothyronine (FT3), thyroglobulin (TGAg), antitroperoxidase antibodies (TPOAb), antithyroglobulin antibodies (TgAb), glucose, insulin levels, and lipid profile. Visfatin serum concentration was measured with the ELISA Assay Kit from the Bioassay Technology Laboratory (419 Harborne Rd, Birmingham B15 3LB, UK). TSH, FT4, FT3, TGAb, TPOAb, TgAb and insülin were measured by using the electrochemiluminescence technique with Roche Diagnostics Cobas e 601 module of the Cobas 6000 (Roche, Basel, Switzerland) kits (normal reference ranges: TSH 0.27--5.6 μIU / mL; FT4 0.93--1.7 ng / dL; FT3 2--4.4 pg / mL, Tg 1.4-7.8 ng / mL, TPOAb <34 IU / mL and Anti-TgAb <115 IU / mL). Glucose, LDL, HDL, Triglyceride (TG) levels were evaluated with Roche Diagnostics Hitachi Cobas c501 analyzer photometrically and Roche Diagnostics (Roche, Basel, Switzerland) kits (normal reference ranges: Glucose 70--110 mg / dL; Insulin 2.6 -27 μIU / mL; LDL 62-164 mg / dL, HDL 45-65 mg / dL, TRIG 30-200 mg / dL). Estimation of insulin resistance was calculated by using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), which was calculated as the product of the fasting plasma insulin level multiplied by the fasting plasma glucose level [HOMA-IR = (fasting plasma insulin [U/mL] × fasting plasma glucose [mg/dL])/(22.5 × 18.182)] [17].

Statistics

Descriptive analyzes were made in order to give information about the general characteristics of the study groups. Data for continuous variables are as mean ± standard deviation; Data on categorical variables are given as n (%). While comparing the means of quantitative variables between groups, for parametric data, independent samples t test and One-Way Analysis of Variance are used, and for non-parametric data Mann Whitney U test or Kruskal Wallis test is used. Cross tables and chi-square tests are used to evaluate whether there is a relationship between qualitative variables. Pearson correlation coefficient is used for the relationship between quantitative variables. When p values were calculated less than 0.05, it was considered statistically significant. Ready-made statistics software was used in calculations (SPSS 22.0 Chicago, IL, USA).

RESULTS

The quantitative, clinical and laboratory data of the study and control groups are shown in Tables 1 and 2. TSH levels were <10 μIU / mL in 282 (76%) of all participants and ≥10 μIU / mL in 89 (24%). 80 of all participants (83.3%) had <2.5 and 16 (16.7%) had ≥2.5

HOMA-IR value. There was no significant difference in terms of age, BMI, glucose, insulin and HOMA-IR averages among HT, TPCa and controls (p: 0.070, p: 0.794, p: 0.271, p: 0.438 and p: 0.938, respectively). There was no significant difference among all three groups in terms of LDL and HDL (p: 0.336, p: 0.900), but TRIG showed a significant difference between them (p: 0.026). When all three groups are compared in terms of serum concentration levels of visfatin; the highest levels were seen in the HT group, then in the TPCa group, and the lowest levels in the control group. Visfatin serum concentration levels of HT group were significantly higher than controls (p <0.05). Visfatin serum concentration levels of patients with TPCa were significantly higher than controls (<0.05). There were statistically different levels of TSH, FT3, FT4, Thyroglobulin, Anti-TGab, Anti-TPOAb and LDL among the three groups (Table 2). The HT group had the highest Anti-TPOAb level. Papillary Carcinomia group and controls were negative for TPOAb and TgAb. Among the subclinical and overt hypothyroidism in the HT group; there were significant differences in terms of TSH, FreeT3, FreeT4, and Tg (p <0.001, p = 0.037, p <0.001, p = 0.001, respectively). In subclinical and overt hypothyroidism subgroups of the TPCa group; there were significant differences in terms of TSH and FreeT4 (p <0.001, p = 0.007, respectively) (Table 3). Visfatin serum concentrations were significantly associated with FT3 (r = 0.336; p = 0.034).

Table 1. Distribution of qualitative variables
Tablo 1. Kalitatif değişkenlerin dağılımı

Variables		n(%)
Groups	Hashimoto's Thyroiditis	193(51.9)
	Papillary Carcinoma	29(7.8)
	Controls	150(40.3)
Gender	Female	287(77.2)
	Male	85(22.8)
HOMA-IR	< 2.5	80(83.3)
	≥ 2.5	16 (16.7)
TSH (mIU/L)	< 10	282(76)
	≥10	89(24)

Table 2. Distribution of quantitative variables
Tablo 2. Kantitatif değişkenlerin dağılımı

	Groups			p
	Hashimoto's Thyroiditis	Papillary Carcinoma	Controls	
Age (Years)	46.22±15.98	42.34±16.14	42.84±12.41	0.070
BMI (kg/m^2)	23.4±1.21	23.14±0.99	23.32±1.54	0.794
Glucose (g/dl)	97.13±16.37	92.23±9.53	96.98±13.79	0.271
Insulin (µIU / ml)	8.22±1.78	8.01±0.42	8.74±1.41	0.438
HOMA-IR	2.03±0.71	1.94±0.31	2.05±0.51	0.938
TRIG (mg / dl)	161.66±104.63	122.81±35.64	135.13±114.77	0.336
LDL(mg / dl)	139.37±37.32 (a)	117.4±28.33 (ab)	120.82±46.43 (b)	0.026
HDL(mg / dl)	45.51±12.07	-	44.8±14.01	0.900
Visfatin (ng/ml)	20.54±19.39 (a)	20±16.33 (a)	16.42±7.69 (b)	0.047
TSH (mIU/L)	7.66[6.42-12] (a)	42.17[10.18-97.38] (b)	1.63[1.08-2.26] (c)	<0.001*
Free T3(pg / mL)	3.1±0.91	1.42±0.86	-	<0.001
Free T4 (ng / dL)	1.07[0.93-1.26] (a)	0.93[0.26-1.14] (ab)	1.01[0-1.31] (b)	<0.001*
Tg (ng / mL)	6.31[0.11-23.67]	0.04[0.04-0.16]	-	<0.001*
AntiTPO(IU / mL)	186.35[106.3-269.35] (a)	14.34[13.03-24.55] (b)	12.82[11.09-264] (b)	<0.001*
AntiTgAb(IU/ml)	104.76[26.38-537.35] (a)	14.39[10-25.15] (b)	10[10-10] (ab)	0.002*

*Data are presented as mean ± standard deviation or Median and interquartile difference. (abc): Common letter as a line denotes statistical insignificance. *: Kruskal Wallis test was used. One-Way Analysis of Variance was used for others.*

Table 3. Distribution of quantitative variables of TSH subgroups
Tablo 3. TSH subgruplarına ait kantitatif değişkenlerin dağılımı

	Hashimoto's Thyroiditis TSH_(mIU/L) subgorups		p	Papillary Carcinoma TSH_(mIU/L) subgroups		p
	< 10 (Occult)	≥10 (Overt)		< 10 (Occult)	≥10 (Overt)	
Age (Years)	44.92±16.73	48.77±14.17	0.114	48.5±18.71	40.74±15.46	0.303
BMI (kg/m^2)	23.38±1.19	23.43±1.28	0.858	22.58±1.13	23.37±0.88	0.182
Visfatin	20.8±19.5	20.02±19.32	0.792	14.26±2.96	21.5±18.06	0.342
Glucose (g/dl)	96.38±17.78	98.71±12.87	0.373	97.07±13.12	90.85±8.13	0.163
Insulin (µIU / ml)	8.32±1.68	8.07±1.93	0.552	8.2±0.42	7.82±0.39	0.317
LDL(mg / dl)	135.19±35.28	147.6±40.33	0.115	111.17±14.45	120.07±33.26	0.675
HDL(mg / dl)	47.38±11.38	39.3±13.27	0.155	-	-	-
TRIG (mg / dl)	133.42±71.17	209±132.57	0.001	99.7±.	126.67±37.41	-
HOMA-IR	2.12±0.82	1.9±0.5	0.215	2.14±0.33	1.74±0.13	0.119
Free T3(pg / mL)	3.42±0.85	2.58±0.81	0.037	1.69±1.21	1.35±0.78	0.497
TSH (mIU/L)	6.71[6-7.66]	16.07[12-30.09]	<0.001*	5.95[0.35-7.61]	86.61[22.22-107.3]	<0.001*
Free T4 (ng / dL)	1.16[1-1.33]	0.98[0.8-1.14]	<0.001*	1.3[1-2.35]	0.61[0.25-1.01]	0.007*
AntiTPO(IU/ mL)	182.9[79.42-262.6]	199.3[115.6-332.25]	0.718*	14.9[13.48-23.91]	13.78[12.65-24.89]	0.832*
AntiTgAb(IU/ml)	104.76[30.31-672.3]	212.12[21.84-402.4]	0.502*	15.95[10.44-22.75]	14.03[10-26.02]	0.894*
Tg (ng / mL)	7.04[2.04-42.35]	3.18[0.04-15.07]	0.168*	0.04[0.04-0.04]	0.04[0.04-0.27]	0.682*

*Data are presented as mean ± standard deviation or Median and interquartile difference. *: Mann Whitney U test was used. For Others, the Significance test of the Difference Between Two Means was used.*

DISCUSSION

In this study, in which we investigated whether visfatin levels in hypothyroid patients would be affected by coexisting autoimmune inflammation; we determined the highest visfatin serum concentration in HT group and then in patients with TPCa compared to controls (<0.05). While HT group had the highest level of TPOAb, TPCa and controls were negative for TPOAb and TgAb. Visfatin serum concentration was found to be significantly associated with FT3 (r = 0.336; p = 0.034). HT and TPCa groups were significantly different in FT3 (p <0.001).

In our literature review, we have seen that, to date, the serum concentration of visfatin in hypothyroidism has only been analyzed in a few studies. In the sudy of Caix`as et al. [6] hyperthyroid patients showed increased visfatin levels compared to controls (p = 0.061). After normalization of thyroid functions, visfatin levels were found to be further increased (p = 0.047). Hypothyroid patients, on the other hand, showed high visfatin levels (p = 0.049). After treatment, their visfatin levels increased further (p = 0.001) as well. As a result, they thought that Visfatin could play a role in the hormone stabilization process independently of anthropometric, inflammatory, or insulin resistance variables, due to a significant increase in both hyperthyroidism and hypothyroidism patients after treatment.

Ozkaya et al. [18] evaluated visfatin levels according to thyroid dysfunction in HT, Graves' disease and euthyroid healthy groups. They also evaluated the effect of treatment on plasma visfatin levels in 16 hypothyroid and 25 hyperthyroid patients. In patients with hyperthyroidism; they found significantly lower visfatin levels compared to the hypothyroid and control groups. Plasma visfatin levels decreased significantly in patients with hypothyroidism following treatment. Plasma visfatin levels increased significantly after antithyroid therapy in patients with hyperthyroidism. They noted that although the effect of thyroid dysfunction on adipocytokin production and release is still not fully understood, the results of their study showed that the effects of hyperthyroidism and hypothyroidism on various metabolic parameters may be partially mediated by visfatin.

The contradictory results of Caix`as [6] and Özkaya's [18] works may be attributed to the fact that hypothyroidism is not performed in homogeneous autoimmune patient groups, but in heterogeneous patient groups such as CAT, postpartum thyroiditis, radioiodine therapy or post-thyroidectomy thyroid dysfunction.

In our study; hypothyroidism was studied in homogeneous chronic autoimmune thyroiditis patients and thyroid antibody negative TPCa patients who were thyroidectomized and both groups were compared with healthy controls matched for age, gender, and BMI with normal thyroid function and negative thyroid antibodies.

Since Sawicka-Gutaj et al. [19] previously demonstrated that visfatin mRNA expression increases in thyroid malignancies and this correlates with tumor stage, we did not include those with any active neoplastic disease characteristics in our study.

Our study showed that Visfatin levels increased significantly in hypothyroidism seen in HT and Papillary Carcinomas compared to healthy controls, but could not say anything about the situation after recovery, as our study was cross-sectional.

Gutaj et al. [20] conducted a prospective case-control study with 118 subjects to investigate the effects of autoimmune inflammation associated with hypothyroidism on visfatin levels in patients with hypothyroidism. The highest visfatin serum concentration was in the autoimmune thyroiditis group, and healthy controls had higher visfatin levels than patients who underwent thyroidectomy for thyroid cancer. Simple linear regression analysis showed that visfatin was significantly associated with serum concentration, autoimmunity, and TPOAb, and the relationships were also confirmed in multivariate regression analyzes. The positive relationship between visfatin and TPOAb contributed to the view that TPOAb is the best serological marker of CAT.

Farghaly et al. [21] investigated the level of visfatin and its relationship with variables related to the disease in children and adolescents with autoimmune thyroiditis. In the overt or subclinical hypothyroidism cases studied; TSH, HOMA-IR, TPOAb, TgAb and visfatin were significantly higher and FT4 was lower than the control. While visfatin was positively correlated with BMI, HOMA-IR, TSH and TPOAb, it was negatively correlated with FT4. They observed a positive relationship between visfatin and TPOAb. TPOAb; They stated that TPOAb is considered as the best serological marker for CAT since it contributes to the destruction of the thyroid by cell cytotoxicity depending on the antibody and complement. The relationship between TPOAb and visfatin supported the hypotheses that visfatin may be involved in the pathogenesis of CAT, and it was stated that TPOAb contributes to the destruction of the thyroid with antibody and complement-mediated cell-cytotoxicity [22, 23].

Similarly, in the studies of Farghaly [21] and Özkaya [18], visfatin levels were significantly higher in the subclinical hypothyroid group compared to controls and were positively associated with TSH. This finding may contribute to the possibility that visfatin is involved in the pathogenesis of autoimmune thyroiditis.

Our study, like these studies, contributed to the possibility that visfatin may be involved in the pathogenesis of autoimmune thyroiditis. Our study supports the hypothesis that TPO-Ab is a marker of CAT; In the HT group, it was significantly higher than TPCa group and controls (p: <0.001), but there was no significant relationship between visfatin and TPOAb.

There are several conflicting findings regarding the effect of thyroid hormones on visfatin production. Özkaya et al. [18] found negative correlations between visfatin levels and free T3 ($r = -0.719$, $p < 0.001$) levels. However, Caix‘ as et al. [6] could not find any relationship between visfatin and free thyroid hormones. Gutaj et al. [20] linked visfatin levels in hypothyroidism to thyroid hormone level and the coexistence of autoimmunity. They stated that these two factors should be taken into account in order

to evaluate the visfatin level in patients with thyroid dysfunction. Han et al. [24] showed in their in vitro experiments that the nonlinear regulation of visfatin mRNA expression was affected by T3 in the 3T3-L1 cell culture model. The data show that thyroid dysfunction is associated with elevated visfatin levels, possibly because visfatin mRNA expression is due to an increase in visceral fat and T3 to a non-linear regulation in visfatin mRNA expression. Gutaj et al. [20] analyzed visfatin concentration in a wide spectrum of FT3 and FT4, as the groups differ significantly in terms of free thyroid hormones levels. Therefore, they proposed that the visfatin changes varied at different FT3 concentrations of the model.

In our study, we had the opportunity to evaluate visfatin concentration in a wide spectrum of TSH, FT3 and FT4. In our study, a significant positive relationship was found between Visfatin and FT3 in hypothyroid patients (p: 0.034), but no relationship was found with FT4.

We excluded individuals with these diseases to limit the possible effects of other known factors such as diabetes mellitus, other autoimmune processes, and infection; therefore, in our study, there was no significant difference in HOMA-IR levels between the groups (p = 0.938). There was no significant relationship between visfatin and HOMA-IR (r = 0.172, p = 0.093).

Visfatin levels in hypothyroidism can be regulated by co-existing CAT. Visfatin is a cytokine with broad immune and inflammatory activities such as stimulation of inflammatory cytokines, regulation of macrophage and lymphocyte proliferation. Cytokines in the pathogenesis of thyroid diseases play a role in both the immune system and by directly targeting thyroid follicular cells. They play a key role in the pathogenesis of autoimmune thyroiditis disease by taking part in the immune response and inflammatory phase, induction and effector. Visfatin supports the development of both T and B lymphocytes and induces leukocytes to produce pro-inflammatory cytokines like; IL-6, TNF-□ and IL-1b. However, the lack of immunological markers of autoimmune thyroiditis in our study is a limiting factor.

The main limitation of our study is its cross-sectional design, which limits our view of the effect of recovery after treatment on visfatin level.

In patients with CAT compared to controls, the highest visfatin serum concentration was observed in the HT group and then in patients with TPCa and controls respectively. While HT group had the highest level of TPOAb, TPCa and controls were found to be negative for TPOAb and TgAb. Visfatin serum concentration was significantly associated with FT3. HT and TPCa groups were significantly different from each other in terms of FT3. Visfatin levels in hypothyroidism are regulated by co-existing CAT.

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