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The Role of Triglyceride in Cardiovascular Disease in Asian Patients with Type 2 Diabetes - A Systematic Review

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■ Abstract

In Asian populations, diabetes mellitus is increasing and has become an important health problem in recent decades. Cardiovascular disease (CVD) is one of the most important complications and the most common cause of death in diabetic patients. Among the risk factors of CVD, elevated low-density lipoprotein cholesterol has been a major concern. Studies suggested that serum triglyceride may also play a role in predicting CVD in patients with type 2 diabetes mellitus, but the association is still debated. In this review, we summarized published studies focusing on the relationship between serum triglyceride and CVD disease in Asian diabetic patients. Ten studies conducted in six different Asian countries (three from Hong Kong, two from Taiwan, tow from Japan, one from Indonesia, one from South India, and one from South Korea) were summarized and discussed. CVD was subdivided into coronary heart disease, stroke, and peripheral arterial disease. Of the ten studies analyzed, one focused on CVD, five on coronary heart disease, three on stroke, three on peripheral arterial disease, and one on mortality from CVD. Studies from Hong Kong, Taiwan, and Japan suggested that triglyceride is a significant and independent risk factor for coronary heart disease, but not a significant risk factor for stroke (studies conducted in Japan and South Korea) or peripheral arterial disease (studies conducted in Taiwan, Indonesia, and South India). Although serum triglyceride may be a significant risk factor for coronary heart disease in Asian diabetic patients, clinical trials evaluating whether lowering triglycerides using fibrates can reduce the risk of coronary heart disease in these patients need to be initiated.

Keywords: Asian populations · cardiovascular disease · coronary heart disease · fibrates · triglyceride · type 2 diabetes

1. Introduction

Type 2 diabetes mellitus (T2DM) is now a global health problem with more than 60% of global diabetes appearing in the Asian population [1]. According to the prediction of the International Diabetes Federation, the number of T2DM cases in Western Pacific and Southeast Asia will increase to more than 179,000,000 by 2025 [1]. In Western countries, cardiovascular disease (CVD), including coronary heart disease (CHD), cerebral vascular disease, and other peripheral arterial disease (PAD), is a major complication and cause of mortality in patients with diabetes. In Taiwan, diabetic patients suffer from an overall 63% higher risk of mortality than the general population, and CVD remains the major cause of death in these patients [2]. The incidence of type 2 diabetes has been on the rise over the past decades in Taiwan. The optimal cutoff value for body mass index in the development of common chronic diseases including diabetes, hypertension, and dyslipidemia in Taiwan is approximately 23 kg/m^2. This is much lower than the currently recommended cutoff value of 30 kg/m^2 for obesity defined by the World Health Organization [3, 4].

Abbreviations:
ACCORD - Action to Control Cardiovascular Risk in Diabetes
Apo C-III - apolipoprotein C3
CHD - coronary heart disease
CI - confidence interval
CVD - cardiovascular disease
FIELD - Fenofibrate Intervention and Event Lowering in Diabetes
HDL-C - high-density lipoprotein cholesterol
LDL - low-density lipoprotein
LDL-C - low-density lipoprotein cholesterol
NCEP-ATP III - National Cholesterol Education Program Adult Treatment Panel III
PAD - peripheral artery disease
sd-LDL-C - small-dense low-density lipoprotein cholesterol
T2DM - type 2 diabetes mellitus
TG - triglyceride
TRL - triglyceride-rich lipoprotein
VLDL - very low-density lipoprotein

The prevalence of CVD in the Asian diabetes population was known to be lower than in Caucasians [5, 6]. In the early 1970s, renal failure and stroke were the leading causes of death in diabetic patients in China, Japan, and Pima India, compared with ischemic heart disease in Caucasian patients [6]. However, with continuing globalization, diet and lifestyle have changed rapidly in developing countries in Asia in recent decades [1]. In a report from the Asia Pacific Cohort Studies Collaboration, the relative effect of diabetes on the risks of CVD in Asian populations is about the same as for Caucasians [7]. In a recent questionnaire survey of 18,385 diabetics in Japan, the frequency of cause of death from CAD and cerebrovascular disease (10.2% and 9.8%, respectively) were similarly higher than from renal failure (6.8%) [8].

Dyslipidemia is a major risk factor for CVD [9]. In patients with T2DM, dyslipidemia is characterized by high serum triglyceride (TG), low high-density lipoprotein cholesterol (HDL-C), and increased small-dense low-density lipoprotein cholesterol (sd-LDL-C) [10]. Serum TG is considered a risk factor for CVD in the general population and in diabetic patients, especially for those with high non-HDL-C [11, 12]. Studies conducted in Taiwan have also suggested that triglyceride is associated with hypertension in patients with T2DM and may also be associated with the progression of albuminuria [13, 14]. Indeed, in the Asian population, hypertriglyceridemia may be more important than LDL-C as a risk factor for CVD in diabetic patients and non-diabetic patients [15-17]. In this article, we review the role of TG in CVD in patients with T2DM in Asian populations.

2. Literature search

We searched MEDLINE (Ovid) using the terms “diabetes mellitus” or “type2 diabetes” and other relevant keywords, including “cardiovascular disease”, “coronary heart disease”, “stroke”, “triglycerides”, and “triacylglycerol”. Separate queries were performed for the countries of the South-East Asian region and the Western Pacific region, as defined by the International Diabetes Federation (**Table 1**) [18, 19]. The South-East Asian region included Bangladesh, India, Maldives, Mauritius, Nepal, and Sri Lanka. The Western Pacific region included Australia, Cambodia, China, Fiji, Indonesia, Japan, Macao China, Malaysia, Mongolia, Nauru, New Zealand, Papua New Guinea, Philippines, Samoa, Singapore, South Korea, Taiwan, Thailand, Tonga, Vanuatu, and Vietnam. The queries were limited to English articles. The publication year was not limited. We excluded studies from Australia and New Zealand because these populations are largely Caucasian.

Publications on type 1 diabetes and studies simply comparing serum TG levels in controls and disease groups without multivariate analysis were also excluded. We abstracted the following information to a fixed protocol:

- Ethnicity
- Year of publication
- Name of the first author
- Recruitment period
- Follow-up duration
- Age
- Total case number
- Cardiovascular outcome
- Case number of cardiovascular outcome
- Average serum TG level in the disease group
- Hazard ratio
- Odds ratio or relative risk for total cholesterol, TG, HDL-C and LDL-C
- Variables adjusted in the modeling

3. Findings

We initially found 41 studies in fifteen different countries in the South-East Asian and Western Pacific regions. Among them, 14 studies were considered relevant to the topic. We further excluded 4 papers due to the lack of multivariate analysis [20-23]. As a result, a total of ten papers were included in the analysis, and the numbers of papers per country are shown in **Table 1** (three from Hong Kong, two from Japan, two from Taiwan, one from South India, one from Indonesia, and one from South Korea). The abstracted data from the 10 studies are listed in **Tables 2 and 3** according to the fixed protocol. In these ten studies, five focused on CHD, three on stroke, three on PAD, one on CVD, and one on CVD related mortality [15, 16, 24-31]. The findings on the association of TG and CVD are discussed as follows.

3.1 Triglyceride and coronary heart disease

In four studies, increased serum TG level was an independent risk factor for CHD (**Tables 2 and 3**). TG appeared to play a more important role in the development of CHD than LDL-C, HDL-C, or total cholesterol [15, 16, 24, 29], and was more obvious in female than male patients in two studies [24, 29]. The only study that did not indicate a role for TG in CHD was conducted in South India [30]. This study recruited only subjects who had diabetes for more than 25 years. Therefore, the study had limitations, and the findings cannot be generalized as applicable to the average diabetic patient.

3.2 Triglyceride and stroke

In three studies referring to stroke, none of the following were found to be significant risk factors: total cholesterol, HDL-C, or LDL-C. As for TG, the results were equivocal. In one study in Hong Kong, the relative risk (95% confidence interval, CI) was 1.43 (1.06-1.92) in males and was 1.35 (1.11-1.62) in females (**Table 2**) [29]. However, in studies from Japanese and South Koreans, TG was not a significant risk factor for stroke [15, 31].

3.3 Triglyceride and peripheral arterial disease

For PAD, the conclusions were consistent. In studies conducted in Taiwan, Indonesia, and South India, neither total cholesterol, HDL-C, LDL-C, nor TG were associated with PAD in multivariate regression models (**Tables 2 and 3**) [26, 27, 30].

3.4 Triglyceride and cardiovascular disease

In a recent study in Hong Kong, low HDL-C, and high LDL-C were significant predictors for CVD (including CHD and stroke), but TG was not a significant risk factor [25]. In contrast, another study from Hong Kong showed that increased levels of TG were the only significant predictor for cardiovascular mortality [28].

Table 1. Number of studies in different countries of the South-East Asian and the Western Pacific region (excluding Australia and New Zealand)

South-East Asia	Number of published papers	Western Pacific region	Number of published papers
Bangladesh	0	Cambodia	0
India	1	China	3
Maldives	0	Fiji	0
Mauritius	0	Indonesia	1
Nepal	0	Japan	2
Sri Lanka	0	Macao, China	0
		Malaysia	0
		Mongolia	0
		Nauru	0
		Papua new Guinea	0
		Philippines	0
		Samoa	0
		Singapore	0
		South Korea	1
		Taiwan	2
		Thailand	0
		Tonga	0
		Vannatu	0
		Vietnam	0

4. Discussion

4.1 Triglyceride and cardiovascular disease in a non-diabetic population

Unlike LDL-C, which is well-established as a major predictor for CVD in global populations, the independent relationship of TG on predicting CVD has long been controversial [11]. Although some studies do not favor hypertriglyceridemia as an independent risk factor for CVD, two recent meta-analysis studies have suggested that TG is independently associated with myocardial infection, CHD, CVD and CVD death [12, 32-34]. There is one meta-analysis study focusing on the Asia Pacific region. This study analyzed the results from 25 cohort studies in six countries including Japan, China, Taiwan, Thailand, South Korea, and Singapore. The results supported serum TG as a better predictor than total cholesterol, HDL-C, and LDL-C for CHD mortality and CVD mortality [35]. Another Japanese cohort study also showed an in-

Table 2. Findings from clinical studies on the association between triglyceride and cardiovascular disease in Chinese patients with diabetes

Parameter	**Chinese population (Hong Kong)**			**Chinese population (Taiwan)**	
Year	2003	2005	2010	2006	2007
Reference	Ko *et al.* [29]	Chan *et al.* [28]	Ting *et al.* [25]	Tseng *et al.* [16]	Tseng [27]
Recruitment period	1994-1998	1996	1996-2005	1995-1998	NA
Study design	Cross-sectional	Cohort (follow-up: 4.6 yr)	Cohort (follow-up: 4.9 yr)	Cross-sectional	Cross-sectional
Age	M: 56 (13)[1] F: 56 (13)[1]	M: 55 (13)[1] F: 53 (15)[1]	Non-CVD: 54 (21)[2] CVD: 64 (16)[2]	Non-CHD: 61 (12)[1] CHD: 66 (10)[1]	M: 62 (11)[1] F: 64 (10)[1]
Subjects (n)	M: 1370 F: 1963	M: 220 F: 297	M: 2094 F: 2427	M:542 F: 608	M: 268 F: 342
CV outcome	CHD and stroke	CVD mortality	CVD (CHD and stroke)	CHD	PAD
CV events (n)	CHD: 164 Stroke: 136	15	M: 196 F: 175	424	M: 23 F: 38
TG level in disease group (mg/dl)	175 (144)[1]	NA	124 (89)[2]	5.04 (0.57)[3]	NA
Findings from multivariable-adjusted regression					
Total choles-terol	CHD: NS Stroke: NS	NS	NA	NS	NS
TG	NS	RR: 2.96 (1.00-8.87)[4]	CHD: M: NS; F: RR=1.23 (1.02-1.49)[4] Stroke: M: RR=1.43 (1.06-1.92)[4] F: RR=1.35 (1.11-1.62)[4]	OR: 1.38 (1.04-1.83)[4]	NS
HDL-C	CHD: NS Stroke: NS	NS	HR: 0.59 (0.42-0.82)[4] per 1 mmol/l increase	NS	NS
LDL-C	CHD: NS Stroke: NS	NS	HR:1.36 (1.08-1.71)[4] (>3 mmol/l vs. <3 mmol/l)	NS	NS
Variables adjusted	Age, BMI, WHR, BP, fasting PG, HbA1c, lipid profile, albuminuria	Age, diabetes duration, and TG significant variables in stepwise regression. Other variables: gender, SBP, DBP, HbA1c, lipid profile, smoking, creatinine, albuminuria, previous macrovascular complication	Age, smoking, diabetes duration, HbA1c, urine albumin, use of statins, fibrates, gliclazide and rosiglitazone, years of enrolment	Age, sex, smoking, medication, BMI, FPG, HbA1c, SBP, DBP, TC, HDL-C, LDL-C	M: age, BMI, SBP significant variables. F: age, uric acid, insulin therapy significant variables in stepwise regression). Other variables: diabetes duration, TG, ApoB

Legend: [1] Mean (standard deviation). [2] median (interquartile range). [3] Ln(TG) shown as mean (SD). [4] 95% confidence interval. *Abbreviations*: BMI – body mass index, CHD – coronary heart disease, CVD – cardiovascular disease, DBP – diastolic blood pressure, F – female, FPG – fasting plasma glucose, HDL-C – high-density lipoprotein cholesterol, HR – hazard ratio, LDL-C – low-density lipoprotein cholesterol, M – male, NA – not available, NS – not significant, OR – odds ratio, PAD – peripheral arterial disease, RR – relative risk, SBP – systolic blood pressure, SD – standard deviation, TC – total cholesterol, TG – triglycerides. References [16, 25, 27-29].

Table 3. Findings from clinical studies on the association between triglyceride and cardiovascular disease in diabetic subjects from the Asian-Pacific region

Parameter	**Japanese**		**Indonesia**	**South India**	**South Korea**
Year	2011	2012	2010	1996	1989
Reference	Sone *et al.* [15]	Sone *et al.* [24]	Kuswardhani *et al.* [25]	Mohan *et al.* [30]	Kim *et al.* [31]
Recruitment period	1995-1996	1995-1996	NA	1992-1995	1983-1987
Study design	Cohort (follow-up: 7.8 yr)	Cohort (follow-up: 8 yr)	Cross-sectional	Cross-sectional	Cross-sectional
Age	M: 58 (7)[1] F: 59 (7)[1]	M: 58 (7)[1] F: 59 (7)[1]	Non-PAD: 65 (4)[1] PAD: 71 (6)[1]	NA (but all patients with diabetes duration >25 yr)	Stroke: 63(9)[1]
Subjects (n)	M: 940 F: 831	M: 940 F: 831	80	M:505 F: 221	416
CV outcome	CHD and stroke	CHD	PAD	CHD and PAD	Ischemic stroke
CV events (n)	CHD: 109 Stroke: 85	M: 70 F: 45	40	CHD: 238 PAD: 112	M: 114 F: 94
TG level in disease group (mg/dl)	124 (71)[1]	M:119.9 (81)[2] F: 129 (45)[2]	128 (59)[1]	NA	181 (89)[1]
Findings from multivariable-adjusted regression					
Total cholesterol	NA	M: HR=1.57 (1.25-1.99)[4] per 1 SD F: HR=1.58 (1.20-2.06)[4] per 1 SD	NS	CHD: NS PAD: NS	Log likelihood: -201.9
TG	CHD: HR = 1.54 (1.22-1.94)[4] per 1 SD Stroke: NS	M: HR=1.42 (1.08-1.85)[4] per 1 SD F: HR=1.72 (1.21-2.43)[4] per 1 SD	NS	CHD: NS PAD: NS	NS
HDL-C	CHD: NS Stroke: NS	M: HR=1.47 (1.09-1.98)[4] per 1 SD F: NS	NS	CHD: NS PAD: NS	NS
LDL-C	CHD: HR: 1.49 (1.25-1.78)[4] per 1 SD Stroke: NS	M: HR=1.59 (1.28-1.98)[4] per 1 SD F: HR=1.41 (1.06-1.86)[4] per 1 SD	NS	CHD: NS PAD: NS	NS
Variables adjusted	Gender, age, diabetes duration, BMI, SBP, HbA1c, LDL-C, HDL-C, TG, smoking, alcohol	Age, diabetes duration, BMI, SBP, HbA1c, smoking and alcohol intake	Age was the only significant variable in stepwise regression. Other variables: waist circumference, TG, lying DBP, homocystein	Fasting plasma glucose, postprandial plasma glucose, HbA1c, TC, LDL-C, HDL-C, TG, SBP, DBP, age, diabetes duration, BMI, serum creatinine	Previous ischemic stroke, hypertension, TC were significant variables in stepwise regression. Other variables: duration of diabetes, CHD, cardiac arrhythmia, TG, HDL-C

Legend: [1] Mean (standard deviation). [2] median (interquartile range). [3] Ln(TG) shown as mean (SD). [4] 95% confidence interval. *Abbreviations*: BMI – body mass index, CHD – coronary heart disease, CVD – cardiovascular disease, DBP – diastolic blood pressure, F – female, FPG – fasting plasma glucose, HDL-C – high-density lipoprotein cholesterol, HR – hazard ratio, LDL-C – low-density lipoprotein cholesterol, M – male, NA – not available, NS – not significant, OR – odds ratio, PAD – peripheral arterial disease, RR – relative risk, SBP – systolic blood pressure, SD – standard deviation, TC – total cholesterol, TG – triglycerides. References [16, 25, 27-29].

dependent relationship between hypertriglyceridemia and ischemic stroke and myocardial infarction [36]. In contrast to studies in Western populations, hypertriglyceridemia appeared to be more important than LDL-C for CVD in Asians.

4.2 Triglyceride and cardiovascular disease in diabetic patients

Hypertriglyceridemia, low HDL-C, and increased sd-LDL-C are typical presentations of dyslipidemia in patients with T2DM. The pathogenesis of hyperlipidemia is characterized by increased very low density lipoprotein (VLDL) production and defective removal of chylomicrons and its remnants [11]. In the United Kingdom Prospective Diabetes Study, LDL-C was the strongest predictor for CVD, and hypertriglyceridemia was not a predictor [37]. In contrast, in other case-control studies, the results were conflicting [9, 38, 39]. In one study, hypertriglyceridemia was an independent risk factor for CVD only in the high non-HDL-C group [12].

Since the pattern of dyslipidemia and its association with CVD may differ between diabetic and non-diabetic subjects, and studies conducted in Asian diabetic patients are rare, we reviewed the role of hypertriglyceridemia for CVD in diabetic patients in the South-East Asian and Western Pacific regions (excluding Australia and New Zealand). We found that the serum TG level is a major and independent risk factor for CHD in most studies except the one conducted in South India (Table 2). However, the results in the study from South India could not be applied to the general diabetic population because it recruited only patients who had diabetes for more than 25 years. In our review, serum LDL-C is not a predictor nor is it as good as TG for predicting CHD. The reason may be that the level of LDL-C cannot represent the amount of all real atherogenic lipoproteins in diabetic patients [40]. Besides, in studies from Japan and Hong Kong, the association between TG and CHD is stronger in female diabetics. The reason for such a gender difference has yet to be clarified. In patients with stroke, the role of TG is equivocal. Systolic blood pressure is a leading predictor of stroke in Western or Asian populations [15, 31, 41]. Thus, when compared with blood pressure, the influence of TG may be concealed.

PAD is common in diabetic patients [42-44]. In our review, hypertriglyceridemia was not an independent risk factor on PAD in multivariate analysis. However, the role of hypertriglyceridemia in the development of PAD remains controversial. In some case-control studies conducted in Asian, there were significant differences in the serum TG levels between disease and control groups [21, 22], although in another study conducted in Taiwanese diabetic patients, TG was not a significant risk factor for PAD, assessed by both univariate and multivariate analysis [43]. As a result, hypertriglyceridemia may not be a significant risk factor for PAD.

Two studies in Hong Kong focused on CVD events and CVD mortality, with contradictory results. In 2005, Chan *et al*. showed that hypertriglyceridemia is the only a predictor for cardiovascular mortality and the relative risk (95% CI) is 2.97 (1.00-8.77) (**Table 2**) [28]. In contrast, Ting *et al*. (2010) showed that low HDL-C and high LDL-C were risk factors for cardiovascular events, including ischemic heart disease and stroke, and that hypertriglyceridemia was not a significant predictor of CVD events and mortality (**Table 2**) [25]. However, in this study, CVD was not divide into subgroups. As we know, the prevalence of hemorrhagic stroke is higher in Asian populations and hypertension is a major risk factor leading to hemorrhagic stroke [45]. Therefore, the effect of TG may be attenuated in this population. Further exploration is needed to clarify the evolution of TG and LDL-C as risk factors for CVD in the Asian population.

4.3 Pathophysiology of triglyceride in cardiovascular disease

Currently, TG is considered a biomarker for CVD, although there is no strong evidence that TG can cause atherogenesis directly [46]. Hypertriglyceridemia is known to be associated with increased levels of prothrombotic factors, such as fibrinogen and plasminogen activator inhibitors, and is related to the size and density of the LDL particle [47, 48]. More importantly, hypertriglyceridemia is associated with some atherogenic remnant particles and apo C-III [46]. In addition to sd-LDL, triglyceride-rich lipoprotein (TRL), TRL remnant and apo C-III are also associated with atherosclerosis [11]. In subjects with insulin resistance, increased TG-rich VLDL and apo C-III formation from liver are observed, along with the excretion of TRL and a resulting decrease in its remnant. TRL remnant can pass through the endothelial cell and be taken up by macrophages, forming foam cells and leading to fatty streak formation. Furthermore, postprandial TRL has been shown to stimulate several proinflammatory genes, such as interleukin-6, intercellular adhesion molecule-1, etc. [49]. Apo C-III is a proinflammatory and proatherogenic protein. VLDL that have apo C-III can activate monocytes and endothelial cells to induce tumor necrosis factor-α, interleukin-1, nuclear factor-κB, etc. [50]. This may explain the findings that hypertriglyceridemia is a risk factor for CVD in diabetes.

4.4 Evidence of triglyceride control for preventing CVD in diabetes

According to the Adult Treatment Panel III of the National Cholesterol Education Program (NCEP ATP III), LDL-C is the primary target for dyslipidemia control in different cardiovascular risk categories. Although there is controversy in the practice of lowering TG for the prevention of CVD, NCEP ATP III recommends using non-HDL-C as a secondary treatment target for subjects having serum TG > 200 mg/dl [51]. Fibrates are useful for lowering hypertriglyceridemia. Currently, the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) and ACCORD (Action to Control Cardiovascular Risk in Diabetes) studies are both attempting to establish the role of TG lowering agents in primary prevention for CVD in diabetic patients [52, 53]. Both studies failed to demonstrate the lowering of CVD events by lowering TG. However, the subgroup analysis in the ACCORD study showed that fibrates were implicated in decreased CVD incidence in patients with TG ≥ 204 mg/dl and HDL-C ≤ 34 mg/dl [54].

In 2010, Jun *et al.* performed a meta-analysis including 18 trials, and reported a 10% relative risk reduction in major CVD events for subjects taking fibrates, especially in hypertriglyceridemia alone or in subjects with hypertriglyceridemia and low HDL-C [55]. The current consensus from the American Diabetes Association also favored the recommendation of the NCEP ATPIII to use non-HDL-C goals for patients with TG > 200 mg/dl [56]. In 2010, the Hong Kong Diabetes Registry reported a prospective study about fibrate use for preventing CHD. The hazard ratio was 0.34 with low significance [25]. Since hypertriglyceridemia is a major concern in Asian population, further explorations of the use of fibrates for lowering TG in Asian diabetic subjects are needed.

5. Limitations

There are several limitations in our review. First, the number of studies examining the relationship between TG and CVD in Asian populations is still small and studies from many countries such as Malaysia, Philippines, Thailand, Nepal, etc. are still lacking. Second, the authors in these studies used different statistical models adjusting for different sets of confounders; therefore comparisons are unreliable or inaccurate. The results may be influenced by choosing different confounders such as HDL-C, which is highly associated with TG [11]. Third, most studies did not take concomitant medical treatment such as statins or fibrates into consideration and could not demonstrate the influence of these lipid-lowering agents. Finally, many studies are cross-sectional, and the cause-effect relationship cannot be easily identified.

5. Conclusions

In Asian diabetic patients, the association between TG and CHD is strong, probably even stronger than LDL-C and CHD. For stroke and PAD, the role of hypertriglyceridemia is still controversial. Further studies with larger sample size and standard protocol are needed to clarify the role of TG in the development of CVD among Asian populations.

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