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Assessment of Thyroid Disorders and Autoimmunity in Patients with Rheumatic Diseases

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ABSTRACT

Objectives: The current study aims to find out the prevalence of thyroid dysfunctions in patients of rheumatoid arthritis.
Material and methods: A Observational Cross sectional study was conducted among 100 diagnosed rheumatoid arthritis patients attending the rheumatology OPD/Medicine OPD at Dr Babasaheb Ambedkar Hospital, Rohini, New Delhi. Blood samples were obtained from the patients who fulfilled the inclusion and exclusion criteria and blood was sent to the laboratory for the measurement of RF (rheumatoid factor), anti CCP (Anti cyclic citrullinated protein antibody), CRP (C reactive protein) and ESR (erythrocyte sedimentation rate).
Results: In our study, 81% of the patients had euthyroid. While 19% of the patients had thyroid dysfunctions. Among them, 12% had subclinical hypothyroidism, 3% had overt hypothyroidism ,2% had subclinical hyperthyroidism and 2 % had overt hyperthyroidism. Abnormal anti CCP was found in 43.2%, 100%, 100%, 100% and 66.7% among euthyroidism, overt hyperthyroidism, overt hypothyroidism, subclinical hyperthyroidism and subclinical hypothyroidism respectively. Abnormal ESR was found in 69.1%, 100%, 100%, 100% and 91.7% among euthyroidism, overt hyperthyroidism, overt hypothyroidism, subclinical hyperthyroidism and subclinical hypothyroidism respectively. Comparison of ESR and thyroid dysfunctions showed statistically significant result. Abnormal CRP was found in 49.4%, 100%, 100%, 50% and 58.3% among euthyroidism, overt hyperthyroidism, overt hypothyroidism, subclinical hyperthyroidism and subclinical hypothyroidism respectively.
Conclusion- The inflammatory markers were increased in reported in RA patients with thyroid dysfunction has been significantly higher than that of the RA patients with euthyroidism.

INTRODUCTION

Rheumatoid arthritis (RA) is the most common inflammatory arthritis affecting about 0.5-1% of general population. RA is a systemic autoimmune disorder characterised by symmetrical, inflammatory, deforming polyarthritis affecting small and large peripheral joints with associated systemic disturbance such as vasculitis and nodules. Rheumatoid arthritis (RA) is a chronic immune-mediated inflammatory disorder that mainly results in cartilage destruction as well as synovial joint inflammation, both the adaptive and innate immune responses involved in the progression of this disease. Considering that autoimmune elements may be common characteristics of thyroid autoimmunity and RA, it is likely that both disorders may coexist within some patients.[1]The worldwide prevalence of autoimmune thyroid disease (AITD) in RA varies considerably, ranging from 0.5% to 27%.[2,3] An association between RA and thyroid dysfunction with or without autoimmune origin has been reported in 6% to 33.8% of patients with RA.[4] Autoimmune thyroiditis, specifically Hashimoto's thyroiditis, is more prevalent in persons with autoimmune disorders including rheumatoid arthritis.[5]

Abnormal autoimmune response, genetic susceptibility, biological factors such as hormonal changes or viral infection and some environmental factors are known to trigger RA.[6] The synovial membrane is the primary target of the inflammatory process which lead to cartilage and bone destruction.[7] However, the corresponding systemic inflammation may result in disorders of multiple organ systems causing extra-articular manifestations.[8] The evolution of RA is highly variable. Some patients may have only a short-term process of oligoarticular involvement with minimum lesion, while others suffer a polyarticular disease evolving with progressive and continuous involvement of other organ systems.[9] Rheumatoid arthritis is commonly seen with thyroid hormone autoantibodies and thyroid dysfunction.[10] Joint symptoms can be a manifestation of hypothyroidism; physicians might consider whether it could be an early manifestation of RA.[11]

Thyroid diseases are, arguably, among the commonest endocrine disorders worldwide. India too, is no exception. According to a projection from various studies on thyroid disease, it has been estimated that about 42 million people in India suffer from

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thyroid diseases. Thyroid diseases are different from other diseases in terms of their ease of diagnosis, accessibility of medical treatment, and the relative visibility that even a small swelling of the thyroid offers to the treating physician. Early diagnosis and treatment remain the cornerstone of management.[12]
The prevalence of thyroid dysfunctions in New Delhi is around 14.4% according to a study conducted in GB PANT Hospital, New Delhi. This study was conducted on a total 7474 number of patients, out of which 13.2 % were hypothyroid and 1.2 % were hyperthyroid.[13]

The prevalence of hypothyroidism in India is 11%, compared with only 2% in the UK and 4·6% in the USA. Compared with coastal cities (eg, Mumbai, Goa, and Chennai), cities located in land (eg, Kolkata, Delhi, Ahmedabad, Bangalore, and Hyderabad) have a higher prevalence (11·7% vs 9·5%). According to Ambrish Mithal, chairman of the Medanta Division of Endocrinology and Diabetes (Gurgaon, India), the reason behind the higher mean thyroid stimulating hormone concentration in India compared with western countries is possibly linked to long-standing iodine deficiency in the country, which has only been partly corrected over the past 20 years. The highest prevalence of hypothyroidism (13·1%) is noted in people aged 46–54 years, with people aged 18–35 years being less affected (7·5%).[14] Subclinical hypothyroidism of moderate severity is associated with higher risk of heart failure and stroke in the younger population. Hypothyroidism has also been associated with nonalcoholic fatty liver disease, cancer mortality, arthritis, and kidney dysfunction but the causality in these situations is controversial.[15]

Autoimmune thyroid disease (AITD) is a term referred to who has thyroid dysfunction and an autoimmune response against this endocrine organ as its hallmark.[16] Thyroid autoimmunity, which is the most common immune-mediated disease, is frequently together with other organ as well as non-organ-specific autoimmune disorders. The term autoimmune hypothyroidism identifies situations with insufficient thyroid function caused by an autoimmune thyroid disease due to autoimmune destruction of the thyroid gland. In its initial stage, chronic autoimmune thyroiditis is characterized by the presence of hallmarks of thyroid autoimmunity and normal thyroid function.

Etiology and pathogenesis of chronic autoimmune thyroiditis and mechanisms leading to the hypothyroid phase remain elusive. However, some predisposing genetic factors and some triggering environmental factors have been identified. The role of antigen presenting cells, of T and B-cell response, and of effector mechanisms in the immunopathogenesis of chronic autoimmune hypothyroidism has been extensively investigated. Circulating thyroid autoantibodies are the hallmarks of autoimmune thyroid disease (AITD) and thyroid peroxidase antibodies is more sensitive than other antibodies in identifying thyroid autoimmunity.[17]

Thyroid disorder is associated with fatigue, anaemia, arthritis and myalgia, and also induces destructive arthropathy, mainly of the proximal interphalangeal joints which would normally be attributed to the inflammatory state of a patient with RA. Since autoimmune thyroiditis in rheumatoid arthritis is usually asymptomatic, any patient who is not responding to conventional treatment of RA or having altered levels of TSH should be evaluated for thyroid dysfunctions.[18]

Association between rheumatoid arthritis (RA) and thyroid disease has been an area of interest of researchers.[19]
Therefore, the current study aims to find out the prevalence of thyroid dysfunctions in patients of rheumatoid arthritis.

METHODS
This observational study was conducted at the rheumatology OPD/Medicine OPD at Tertiary Care Hospital. The study included patients of rheumatoid arthritis, aged >18 years, who fulfilled European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) - 2010 criteria for rheumatoid arthritis and was screened for: free T3 (free triidothyronine), free T4 (free thyroxine) and TSH (thyroid stimulating hormone).

Patients with history of Surgical removal of thyroid gland, Any malignancy or radiotherapy and damage to thyroid, Patients on drugs causing thyroid function disturbances (lithium, amiodarone, antithyroid drugs like carbimazole, methimazole, propylthiouracil; paraamino salicylic acid, interferon alpha, aminoglutethiamide, tyrosine kinase inhibitors like sunitinib, iodine containing contrast medias), with Pregnancy, Patients on oral contraceptives or Any serious underlying diseases were excluded.

Patients, already diagnosed as rheumatoid arthritis, attending Outpatient Department (OPD) of Rheumatology and Medicine at Dr Babasaheb Ambedkar Hospital, New Delhi were evaluated for a history of thyroid disease, use of thyroid drugs or supplementation. Blood samples were obtained from the patients who fulfilled the inclusion and exclusion criteria and blood was sent to the laboratory for the measurement of FT3(triiodothyronine), FT4 (thyroxine) and TSH (thyroid stimulating hormone), RF (rheumatoid factor), anti CCP (Anti cyclic citrullinated protein antibody), CRP (C reactive protein) and ESR (erythrocyte sedimentation rate).

Taking all aseptic precautions, about 3-5 ml of venous blood from median cubital vein was collected in clot activating

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vacutainer. The blood was collected after 10 to 12 hours of fasting.

In the laboratory, FT3 and FT4 levels were determined by competitive solid phase - enzyme linked immunosorbent assay (ELISA) method for the quantitative determination of these hormone levels in human serum using FT3 and FT4 ELISA kits respectively. TSH was determined by microplate based one step sandwich enzyme linked immonosorbent assay (ELISA) method. ESR was determined by modified westergen method.

RESULTS

Table 1: Age wise distribution of the study subjects:

Age – Group	**N (%)**
18-30	18
30-40	36
40-50	26
50-60	15
>60	5
Total	100 (18-70)
mean±SD	41.24±11.78

Mean age was 41.24 years. Maximum number of patients were found in 30-40 years age groups (36%) followed by 40-50 years age groups (26%) and 18-30 years age groups (18%).

Table 2: wise distribution of the study subjects:

Gender	N (%)
Male	22
Female	78
Total	100

Out of 100 subjects, 22 were male and 78 were female subjects.

Table 3: Gender wise distribution of the thyroid profiles of the study subjects:

			Gender		Total
			F	M	
Thyroid Dysfunctions	Euthyroid	N	61	20	81
		%	75.3%	24.7%	100.0%
	Overt hyperthyroidism	N	1	1	2
		%	50.0%	50.0%	100.0%
	Overt hypothyroidism	N	2	1	3
		%	66.7%	33.3%	100.0%
	Subclinical hyperthyroidism	N	2	0	2
		%	100.0%	0.0%	100.0%
	Subclinical hypothyroidism	N	12	0	12
		%	100.0%	0.0%	100.0%
Total		N	78	22	100
		%	78.0%	22.0%	100.0%

P value=0.24

Females were predominantly affected by different thyroid disorders as compared to males asshown in the table.

Table 4: RA factor wise distribution of the study

			RA factor		Total
			Abnormal	Normal	
Thyroid	Euthyroid	N	21	60	81
		%	25.9%	74.1%	100.0%
	Overt hyperthyroidism	N	1	1	2
		%	50.0%	50.0%	100.0%

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Dysfunc Tions	Overt hypothyroidism	N	3	0	3
		%	100.0%	0.0%	100.0%
	Subclinical hyperthyroidism	N	1	1	2
		%	50.0%	50.0%	100.0%
	Subclinical hypothyroidism	N	7	5	12
		%	58.3%	41.7%	100.0%
Total		N	33	67	100
		%	33.0%	67.0%	100.0%

P value=0.01 (S)

Abnormal RA factor was found in 25.9%, 50%, 100%, 50% and 58.3% among euthyroid, overt hyperthyroidism, overt hypothyroidism, subclinical hyperthyroidism and subclinical hypothyroidism respectively. Comparison of RA factor and thyroid dysfunctions showed statistically significant result.

Table 5: Normal RA factor wise distribution of the study

	N	Percentages
Euthyroid	21	63.6
Overt hyperthyroidism	1	3.03
Overt hypothyroidism	3	9.09
Subclinical hyperthyroidism	1	3.03
Subclinical hypothyroidism	7	21.21
Total	33	100

Normal RA factor was found in 63.6%, 3.03%, 9.09%, 3.03% and 21.21% among euthyroidism, overt hyperthyroidism, overt hypothyroidism, subclinical hyperthyroidism and subclinical hypothyroidism respectively.

Table 6: Anti CCP wise distribution of the study:

			Anti CCP		Total
			Abnormal	Normal	
Thyroid Dysfunct Ions	Euthyroid	N	35	46	81
		%	43.2%	56.8%	100.0%
	Overt hyperthyroidism	N	2	0	2
		%	100.0%	0.0%	100.0%
	Overt hypothyroidism	N	3	0	3
		%	100.0%	0.0%	100.0%
	Subclinical hyperthyroidism	N	2	0	2
		%	100.0%	0.0%	100.0%
	Subclinical hypothyroidism	N	8	4	12
		%	66.7%	33.3%	100.0%
Total		N	50	50	100
		%	50.0%	50.0%	100.0%

P value=0.04 (S)

Abnormal anti CCP was found in 43.2%, 100%, 100%, 100% and 66.7% among euthyroidism, overt hyperthyroidism, overt hypothyroidism, subclinical hyperthyroidism and subclinical hypothyroidism respectively. Comparison of Anti CCP and thyroid dysfunctions showed statistically significant result.

Table 7: ESR wise distribution of the study

			ESR		Total
			Abnormal	Normal	
Thyroid Dysfunct Ions	Euthyroid	N	56	25	81
		%	69.1%	30.9%	100.0%
	Overt hyperthyroidism	N	2	0	2
		%	100.0%	0.0%	100.0%
	Overt hypothyroidism	N	3	0	3
		%	100.0%	0.0%	100.0%
	Subclinical hyperthyroidism	N	2	0	2
		%	100.0%	0.0%	100.0%
	Subclinical hypothyroidism	N	11	1	12
		%	91.7%	8.3%	100.0%

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Total	N	74	26	100
	%	74.0%	26.0%	100.0%

P value=0.24

Abnormal ESR was found in 69.1%, 100%, 100%, 100% and 91.7% among euthyroidism, overt hyperthyroidism, overt hypothyroidism, subclinical hyperthyroidism and subclinical hypothyroidism respectively. Comparison of ESR and thyroid dysfunctions showedstatistically significant result.

Table 8 : CRP wise distribution of the study:

			CRP		Total
			Abnormal	Normal	
Thyroid Dysfunct Ions	Euthyroid	N	40	41	81
		%	49.4%	50.6%	100.0%
	Overt hyperthyroidism	N	2	0	2
		%	100.0%	0.0%	100.0%
	Overt hypothyroidism	N	3	0	3
		%	100.0%	0.0%	100.0%
	Subclinical hyperthyroidism	N	1	1	2
		%	50.0%	50.0%	100.0%
	Subclinical hypothyroidism	N	7	5	12
		%	58.3%	41.7%	100.0%
Total		N	53	47	100
		%	53.0%	47.0%	100.0%

P value=0.28

Abnormal CRP was found in 49.4%, 100%, 100%, 50% and 58.3% among euthyroidism, overt hyperthyroidism, overt hypothyroidism, subclinical hyperthyroidism and subclinical hypothyroidism respectively. Comparison of CRP and thyroid dysfunctions showedstatistically significant result.

DISCUSSION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder that affects many tissues and organs but principally affects the synovial joints. The relationship between RA and the thyroid gland have been studied extensively for a long time. Thyroid dysfunctions in RA patients are most often of autoimmune nature; they are accompanied by elevated thyroid autoantibody titers. The RA patients may present with hypothyroid or hyperthyroid manifestations. Due to overlapping symptoms, there may be an under recognition of thyroidal illness. Underlying thyroid problems may be missed if patients are not actively screened for thyroid dysfunction.In our study, 81% of the patients had euthyroid. While 19% of the patients had thyroid dysfunctions. Among them, 12% had subclinical hypothyroidism, 3% had overt hypothyroidism ,2% had subclinical hyperthyroidism and 2 % had overt hyperthyroidism.Out of 19 thyroid dysfunctional patients, 63.15% had subclinical hypothyroidism, 15.78% had overt hypothyroidism and 10.52% had subclinical hyperthyroidism and 10.52 % had overt hyperthyroidism. According to a study conducted by Unnikrishnan AG (2013)[20] *et al* to find out the prevalence of thyroid disorders in normal population in India which was conducted in Kerala, the prevalence of subclinical hypothyroidism was 9.4 %, the prevalence of overt hypothyroidism was 3.9% ,the prevalence of subclinical hyperthyroidism was 1.6 % and the prevalence of overt hyperthyroidism was 1.3 % .

According to a study by Kalra S (2011)[21] *et al* to find the prevalence of hypothyroidism in adults among normal population which was conducted across eight major cities (Delhi, Bangalore, Chennai, Goa, Mumbai, Hyderabad, Ahmedabad and Kolkata), the prevalence of hypothyroidism was 10.95 %. The sample size was 5376 in the study.According to a study by Velayutham K (2015)[22] *et al* to find the prevalence of thyroid dysfunctions among young females in south India population which was conducted in seven medical colleges across Tamilnadu, TSH value was elevated in 11 % of subjects. The sample size was 1292. They concluded that thyroid dysfunction was common in young women in south India and almost one out of eight young women had thyroid dyfunction.In our study, the prevalence of thyroid dysfunctions was in 19 % of RA patients. Nadeem M (2017) *et al*[23] in India found that 42% of the patients studied had thyroid dysfunctions. 37.9% of participants in Nadeem‟s study had subclinical hypothyroidism and only 3.6% had overt hypothyroidism. In India, one study by Joshi P (2017)[24] *et al* looking at the prevalence of hypothyroidism in RA demonstrated a prevalence of 38.4%. A study in China in 2019 observed a prevalence of 32.3% thyroid dysfunction of which there was a predominance of overt hypothyroidism at 26.2%.28 Elattar EA (2014)2 *et al* and Kumar VD and Arjuna R (2020)24 had found 24.4% patients had hypothyroidism. Przygodzka M and Filipowicz-Sosnowska A (2009)4 and Mosli HH and Attar SM (2014)[26] had demonstrated the prevalence of thyroid dysfunction as 29.3% in their study.

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The mean age of patients with RA in the present study group was 43.75 years. Most of the patients in the study group were between the ages of 18-70 years. In another study on 800 patients with rheumatoid arthritis by C´ardenas Rold´an J *et al*, the mean age (years) was 51.92 (±12.19).3 Porkodi *et al* studied 798 patients with rheumatoid arthritis. Mean age was 36.7 years (Range 25 – 50 years).[27]

In our study, there were 78 females and 22 males. Females were more affected than males. The ratio of males to females was 1:3.54. Rheumatoid arthritis is a disease affecting predominantly women in the ratio 3:1 according to Kumar VD and Arjuna R (2020)24 study. In a study done by Kvien TK *et al*, it was found that the prevalence of RA is higher in females than males, the incidence is 4-5 times higher below the age of 50, but above 60-70 years the female/male ratio is only about 2:1.45 Higher than normal ratio i.e. 9:1 has been reported by Mohammed F (7:1),[28] Kumar AVS *et al* (8:1)[29] study. Sowgandhi N *et al* was concluded that in South India, RA affects females predominantly.[30]

Hypothyroidism was the commonest thyroid abnormality seen 15% of subjects in our study. The reported prevalence rate of hypothyroidism varies from 8.88 to 21.67 % based on the place of study.[31] In our study the subclinical hypothyroidism (SCH) was seen in 12% cases, more common in females (100%) than males. SCH as the commonest thyroid abnormality has been reported in cross sectional studies from Cochin (9.4%)[32] and Delhi (19.3 %).[33] A multicentre (8 cities) study from India also reported prevalence rate of SCH to be 8.02 %. In the above studies the SCH was more common in females than males.[34] The prevalence rate of subclinical hypothyroidism decreased with age in our study. The prevalence of SCH is shown to increase with age in various other studies conducted.[31] In our study higher prevalence of SCH in lower age group particularly in age group of 20-45 years may be due to lesser number of subjects in this category as compared to ≥ 46 years.[33] In our study, the prevalence of overt hypothyroidism was 2 %. In Nadeem˝s study (2017), 3.6% had overt hypothyroidism.[23]

The high prevalence figures in Cochin, Kolkata have ascertained that thyroid disorders in India are not confined to the conventional iodine deficient sub-himalayan zone but extending to the plain fertile lands as well as areas reporting majority of population consuming iodized salt. A possible etiological role of cyanogenic foods acting as goitrogens,[35] industrial and agricultural contaminants acting as thyroid disruptors40 and deficiencies of micronutrients (iron, selenium and zinc)[36] which can interfere with thyroid function may be considered; in subjects consuming iodized salt. The prevalence rate of hypothyroidism was more in females than males, irrespective of age group of subjects.

Hyperthyroidism was the next common thyroid abnormality affecting 4% of subjects in our study. The prevalence rate of hyperthyroidism was more in females than males. The prevalence of overt hyperthyroidism was 2 % in our study. Earlier studies by Abraham R *et al* form Pondicherry and Menon UV *et al* from Cochin *et al* have reported prevalence of overt hyperthyroidism of 1.2 % and 1.3% respectively. In our study, two patients (2%) had subclinical hyperthyroidism. Elattar EA (2014)2 *et al* showed prevalence of 1.3% subclinical hyperthyroidism, which is similar to our results. Mosli HH and Attar SM (2014)[26] in a retrospective study showed a higher prevalence of Subclinical hyperthyroidism i.e. in 2.6%.54 Li Q (2013)[37] *et al* reported higher rate (6.2%) of subclinical hyperthyroidism. The subclinical hyperthyroidism was found in 2% subjects in the present study. The subclinical hyperthyroidism was common in age group of 40-50 and 50-60 years age. The prevalence rate was higher females than male subjects. Earlier studies have reported a prevalence rate of subclinical hyperthyroidism from 0.6-1.6 % which is similar to our study.[38]

In the study, there is an association between FT3, FT4, TSH levels, RF factor and anti CCP with thyroid dysfunction. RA patients expresses –high TSH titre while T3, T4 did not show any significant difference.[39] This is in harmony with Atzeni (2008)10 *et al* who detected significant elevation of TSH in RA patients when compared with control group. Thyroid function test should be included in clinical evaluation of RA patients[23].

Shiroky JB (1993)[40] *et al* in a cohort study of 119 RA patients, evaluating the association of thyroid dysfunction in RA, did not find any association between thyroid disorders and age, RF, and also ANA. While our results confirmed that there was association between presence of thyroid disorders in RA patients with IgM RF and anti-CCP. However, there was small difference between the present results and Shiroky *et al*'s results that might have been caused by methodological or laboratory analysis differences. A population-based, case-control study (1998 adult cases vs 2252 controls) by Bengtsson C (2014)[41] *et al* revealed that patients treated with thyroxin (hypothyroidism) were at double risk of both anti-CCP negative (odds ratio [OR] 2.1, 95% confidence interval [CI] 1.5–3.1) and anti-CCP positive (OR 1.9, 95% CI 1.4–2.6) RA. Cárdenas Roldán J (2012)3 *et al* found the prevalence of autoimmune thyroid disease equal to 9.8% in a cross-sectional study which evaluated 800 RA patients for concurrent autoimmune thyroid disease.

A case-control study in Egypt involving 200 participants found that high TSH levels were associated with higher Modified Health Assessment Questionnaire scores, P-value= 0.01. Similarly, high TSH was associated with high disease severity estimated using MDAS, P value=0.02. The varied results on associations between thyroid dysfunction and

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patient demographics, disease severity, and functional disability, delineate the need for more investigation to further explore these associations.[42]

In study by Przygodzka M, Filipowicz-Sosnowska A (2009)4 regarding prevalence of thyroid diseases and antithyroid antibodies in women with rheumatoid arthritis done among 100 patients with RA. Thyroid function and antithyroid antibodies were assessed. ATD was more prevalent (16%) in patients with RA than in the control group (9%). The difference was not statistically significant. Antithyroglobulin (anti-TG) and antithyroid peroxidase (anti-TPO) antibodies were present in similar percentage of patients with RA (12% and 15%, respectively) and in the control group (9% and 18%, respectively).

Conclusion- The inflammatory markers were increased in reported in RA patients with thyroid dysfunction has been significantly higher than that of the RA patients with euthyroidism.

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