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# Assessment of Coagulation Profile among Subclinical Hypothyroid Patients Attending Immunoassay Lab, BPKIHS, Dharan

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## Abstract

A serum Thyroid-Stimulating Hormone (TSH) level above the upper limit of normal despite normal levels of serum free thyroxin is known as Subclinical Hypothyroidism (SCH). Various changes in the haemostatic profile have been described in patients with subclinical hypothyroidism. These changes could be encountered as complicating factors in various systemic disorders like cardiovascular disorders, endocrinal disorders. Objective of this study was to evaluate some haemostatic parameter among patients with subclinical hypothyroidism and compare them with healthy individuals and also compare the coagulation profile tests among the subclinical hypothyroid patients on medication and newly diagnosed hypothyroid patients. This study was conducted at immunoassay and hematology lab of BPKIHS from February to May 2017 which included 60 patients with subclinical hypothyroidism (31 of them were newly diagnosed subclinical hypothyroidism patients and 29 were subclinical hypothyroidism under the treatment) and 60 normal individuals as the control group. Platelet count, Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) were performed in patients and control samples. A questionnaire was used to obtain patient's information including as age, gender, duration of diseases, treatment, diet habitat and family history. The participants were orally interviewed after an informed verbal consent was taken. The result showed, in subclinical hypothyroidism the majority were females (90%), aged 46 years to 50 years, more than 50% had family history of the thyroid disease, with disease duration of up to one year in 55% of the cases. About 48% of the patients were under treatment while 52% were newly diagnosed subclinical hypothyroidism with high BMI (overweight 53% and obese 15%). PT value significantly decreased ($p<0.05$) in patients with subclinical hypothyroidism (14.24 ± 1.08) than in the control group (15.12 ± 0.97), INR value was also decreased significantly ($p<0.05$) in subclinical hypothyroidism patients (1.01 ± 0.82) than in the control group (1.08 ± 0.74). APTT value significantly increased ($p<0.05$) in patients with subclinical hypothyroidism (27.10 ± 3.10) than of control group (26.15 ± 1.57). No significant variation was observed in the PLT count among the study population. Platelet count, PT (INR), APTT were not significantly different ($p>0.05$) between newly diagnosed and under treatment subclinical hypothyroidism.

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## Abbreviations

PLT: Platelet Count; SCH: Subclinical Hypothyroidism; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; EDTA: Ethylene Diamine Tetra Acetic Acid; INR: International Normalize Ratio; TSH: Thyroid Stimulating Hormone; VWF: Von Willbrand Factor; LT4: Levothyroxine; t-PA: Tissue Plasminogen activator; SD: Stander Deviation; T3: Triiodothyronine; T4: Tetraiodothyronine; SPSS: Statistical Package for the Social Sciences, BPKIHS: B.P. Koirala Institute of Health Science

## Introduction

The thyroid gland is located in the front of neck just above trachea in the adult human which is butterfly in shape. The well developed thyroid gland in a human weighs approximately 15 gram to 20 gram and is connected by the isthmus which synthesizes and secretes $T_3$ and $T_4$ hormones and these hormones play an important role in the functioning of body [1]. Thyroid hormones are important mediators of many physiological and metabolic processes, including blood coagulation and their

abnormalities can adversely affect various steps in the coagulation process [2]. Hypothyroidism is defined as a low free $T_4$ level with normal or high TSH, which is one of the most common disorders of the thyroid gland, occurring 5% to 15% of women over the age of 65. Hypothyroidism can be categorized into primary, secondary, or tertiary disease, depending on the location of defect. Subclinical Hypothyroidism (SCH) is defined as a serum Thyroid-Stimulating Hormone (TSH) level above the upper limit of normal where levels of serum free thyroxin is normal. Typical symptoms are abnormal weight gain, tiredness, baldness, cold intolerance, and bradycardia. Hypothyroidism is treated with hormone replacement therapy, such as Levothyroxine ($LT_4$) is the treatment of choice [3].

The coagulation process is a complex series of enzymatic reaction involving the proteolytic activation of circulating coagulation factors (zymogens) and activity of co-factors (V,VII), leading to thrombin production which convert soluble plasma fibrinogen into insoluble fibrin. The fibrin traps platelet plug, forming a stable thrombus which prevents further blood loss from the damaged vessels [4]. Coagulation cascade has been classified into intrinsic and extrinsic pathways; both of these pathways converge on factor X activation.

**Extrinsic pathway:** It is called as the first step in plasma mediated hemostasis which is activated by tissue factor. Under normal physiological conditions, normal vascular endothelium minimizes contact between tissue factor and plasma procoagulants, but vascular exposed tissue factor which binds with factor VIIa and calcium to promote the conversion of factor X to Xa.

**Intrinsic pathway:** This pathway is parallel for thrombin activation by factor XII. It starts with factor XII, HMW kininogen, prekallekerin and factor XI, which results in activation of factor XI. Activated factor XI further activates factor IX, which then acts with its cofactor (factor VIII) to form tenase complex on a phospholipids surface to activate factor X [5].

Since the beginning of the past century the link between haemostatic system and thyroid disease has been known. The first clinical Association was described in 1913, when Kaliebe reported episodes of cerebral vein Thrombosis in a thyrotoxic patient. Both of thyroid dysfunction and autoimmunity may modify physiological processes of primary and secondary homeostasis which lead to bleeding or thrombosis. On the coagulation fibrinolytic system the influence of thyroid hormone is mainly mediated by the interaction between the hormone and its receptors. Various abnormalities have been described, ranging from subclinical laboratory abnormalities to major hemorrhages or fetal thromboembolic events. However, the relationship between thyroid hormones and the coagulation system is often ignored. Coagulation profile includes PT/INR, APTT, Platelets and fibrinogen. The APTT, PT and CT are common coagulation test that evaluate time necessary to clot *in vitro*, whereas the bleeding time is a test in which the interaction between platelets and the blood vessels wall is reflected *in vivo*. Therefore prolongation of these tests means a decreased haemostatic response and a bleeding tendency [6]. In hypothyroidism, the mechanism accounting for coagulation abnormalities are not well established. Most abnormalities have been assigned to decreased synthesis or activity of clotting factors, including Von Willi brand Factor (VWF) and factor VIII or to decreased response to adrenergic stimulation [7].

Erem, have been reported that the influence of subclinical hypothyroidism on hemostasis is controversial, having both hypercoagulable and hypocoaguable states. A hypercoagulable state might be a risk factor for thromboembolic disease in subclinical hypothyroidism. On the other hand, subclinical hyperthyroidism is associated with enhanced cardiovascular risk [8].

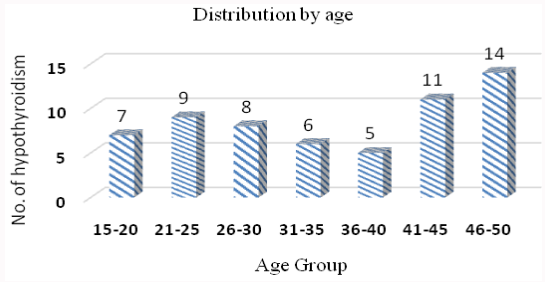


**Figure 1:** Distribution of subclinical hyperthyroidism patients according to age.

## Materials and Method

### Study design and area

A Cross-sectional comparative study was conducted in the Department of Pathology and the Department of Biochemistry, BPKIHS, Dharan, Nepal from February to May 2017. Convenient sampling technique was used. Sample size was 120, including study group (60 subclinical hypothyroid patients) and control group (60 healthy euthyroid individuals). Subjects who had normal thyroid functions assessed by Thyroid Function Tests (TFT) and no clinical signs and symptoms of hypothyroidism were considered as euthyroid controls. Their health status was assessed through questionnaires, which assessed their medical history and physical health status. Inclusion Criteria: Healthy (euthyroid) people of age 20 years to 50 years were taken as control, all clinical and subclinical hypothyroid patients were taken as subjects and Exclusion Criteria: Patients with diagnosed coagulation disorders such as hemophilia, thrombocytopenia etc, and Patients with diabetes, dyslipidemia, coronary or chronic liver diseases. Under any medication that alters coagulation profile tests. Anthropometric parameters, Thyroid Function Test (TFT) parameters, Coagulation Profile parameters were measured in this study.

### Procedures

Fully automated Chemiluminescent Immunoassay (CLIA) MAGLUMI 1000 was used to measure free Tri-iodothyronine (fT3), free Thyroxin (fT4) and Thyroid Stimulating Hormone (TSH) level.

**Sample collection method:** After informed consent from diagnosed case of subclinical hypothyroidism 5 ml of patient's blood samples for coagulation tests were drawn from ante-cubital vein and placed in one Vacutainer tube (Becton Dickinson) containing 3.2% buffered sodium citrate (volume of blood: volume of citrate =9:1) for estimation of PT and APTT. And another BD Vacutainer tube containing K2 EDTA anticoagulant was used for the estimation of platelets count.

**Anthropometric measurement: For height measurement:** Height was taken in centimeters using non stretchable measuring tape based on the principle of Stadiometer. For this the patient was asked to stand on a horizontal surface with legs straight, barefooted with heels together, shoulder relaxed with arms by their sides, heels, buttocks, shoulder blades and head in contact with a vertical wall. And finally head is positioned to look straight forward without lifting

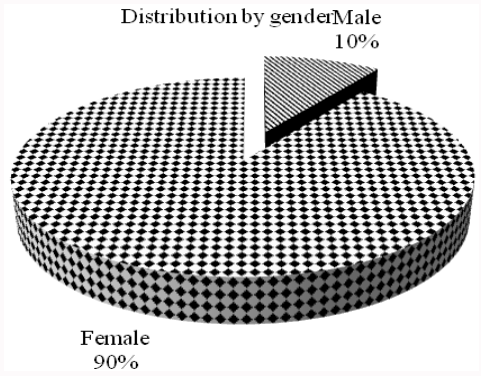


**Figure 2:** Distribution of subclinical hypothyroidism according to gender.

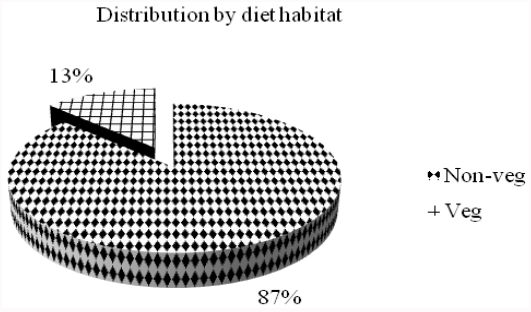


**Figure 3:** Distribution of subclinical hypothyroidism according to diet habitat.

the chin. A cardboard was placed on top of the head, perpendicular to the vertical wall and the height was recorded.

**For weight measurement:** Weight was taken using digital weighing scale. The scale was kept on a flat surface and the subject was requested to step on it in bare feet without holding on to anything. BMI was calculated as body weight (kg) divided by height squared ($m^2$).

Lab life D5 Supreme hematological auto analyzer was used to measure platelet count, LIQUIPLASTIN reagent was used for PT test and HEMOSTAT ($R_1$ AND $R_2$) reagent used for APTT test.

## Results

General characteristics of the studied patients:

### Anthropometric variables

The anthropometrical variables of the subject were statically significant ($p<0.05$) between the subclinical hypothyroidism (study group) and euthyroidism (control group).

### Demographic characteristics of subject

The demographic characteristics of 60 subclinical hypothyroid patients attended immunoassay lab BPKIHS, Dharan.

**Age:** The highest occurrence of subclinical hypothyroidism (23%) was found among those aged 46 years to 50 years and the least rate (8%) was found in those 36 years to 40 years old.

**Gender:** The studied patients characteristics represented female (90%) having highest frequency of subclinical hypothyroidism.

**Diet habitat:** Most of subjects (87%) in this study were non-veg.

**Family history:** More than half of the patients (58%) had family

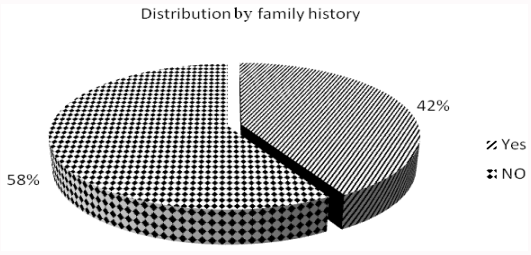


**Figure 4:** Distribution of subclinical hypothyroidism cases according to family history.

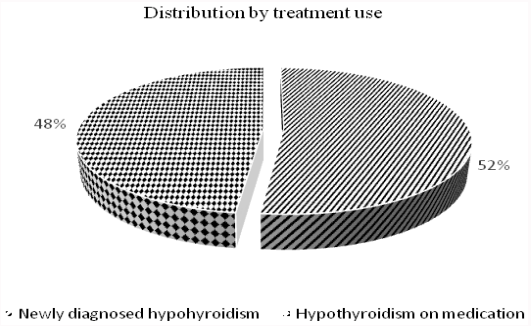


**Figure 5:** Distribution of subclinical hypothyroidism according to treatment use.

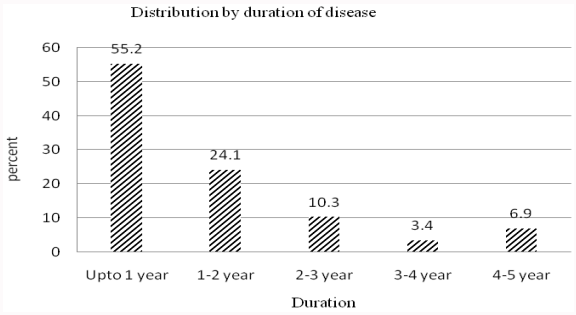


**Figure 6:** Distribution of subclinical hypothyroidism cases according to duration of disease.

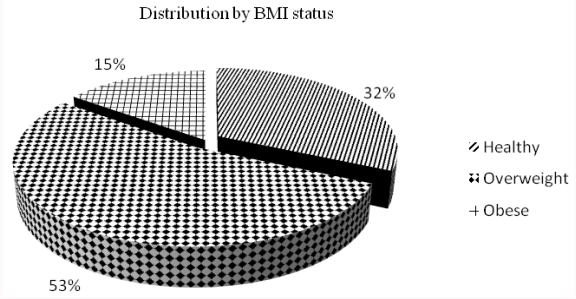


**Figure 7:** Distribution of subclinical hypothyroidism according to BMI status.

history of subclinical hypothyroidism.

**Treatment use:** About 48% of the patients were under the treatment while 52% were newly diagnosed subclinical hypothyroidism.

**Duration of disease:** Duration of the disease among the studied population was found more up to 1 year (55.2%) and 3.4% had disease duration of 3 years to 4 years.

**Table 1:** Comparison of anthropometric variables between subclinical hypothyroidism patients and euthyroidism control.

| Variables | Subclinical hypothyroidism (Mean ± SD) N=60 | Euthyroidism (Mean ± SD) N=60 | P value | Remarks |
|---|---|---|---|---|
| Age (Years) | 34.93 ± 11.18 | 28.58 ± 9.24 | 0.001 | S |
| Height (m) | 1.54 ± 0.73 | 1.55 ± 0.79 | 0.001 | S |
| Weight (Kg) | 61.57 ± 9.12 | 55.75 ± 9.24 | 0 | S |
| BMI (Kg/m²) | 25.75 ± 3.71 | 22.78 ± 3.18 | 0 | S |

**Table 2:** Means and Standard Deviations (SD) of the coagulation profiles in subclinical hypothyroidism patients in relation to the control group.

| Coagulation profiles | Subclinical Hypothyroidism (Mean ± SD) N=60 | Euthyroidism (Mean ± SD) N=60 | P value | Remarks |
|---|---|---|---|---|
| PLT | 247.11 ± 81.76 | 273.78 ± 92.77 | 0.098 | NS |
| PT | 14.24 ± 1.08 | 15.12 ± 0.97 | 0 | S |
| INR | 1.01 ± 0.82 | 1.08 ± 0.74 | 0 | S |
| APTT | 27.10 ± 3.10 | 26.15 ± 1.57 | 0.037 | S |

**Table 3:** Means and Standard Deviations (SD) of the coagulation profiles in newly diagnosed subclinical hypothyroidism patients in relation to subclinical hypothyroidism under treatment.

| Coagulation Profiles | Newly diagnosed Sub. Hypothyroidism (Mean ± SD) (n=31) | Sub. Hypothyroidism Under treatment (Mean ± SD) (n=29) | p-value | Remarks |
|---|---|---|---|---|
| PLT count | 246.54 ± 78.10 | 247.72 ± 86.90 | 0.95 | NS |
| PT | 14.16 ± 1.15 | 14.34 ± 1.01 | 0.51 | NS |
| INR | 1.008 ± 0.088 | 1.02 ± 0.76 | 0.48 | NS |
| APTT | 26.57 ± 2.60 | 27.59 ± 3.48 | 0.24 | NS |

**Body mass index (BMI) status:** Among the total of 60 subclinical hypothyroidism patients 53% were overweight, only 32% were healthy.

### Coagulation tests among the study population

Table 2 shows platelets count are decreased in patients with subclinical hypothyroidism compared to control group without statistical significance. In subclinical hypothyroidism patients PT values are significantly ($p \leq 0.05$) lower than that of the control group. INR values are significantly decreased ($p \leq 0.05$) in subclinical hypothyroidism patients compared to control group. Subclinical hypothyroidism patients exhibited significant ($p \leq 0.05$) increase in APTT values compared to the control group.

D. Coagulation test among the newly diagnosed subclinical hypothyroidism patients and subclinical hypothyroidism under treatment:

Table 3 indicates there is no significant variation between these two groups. As presented in this table, platelet count, PT, INR, APTT results were similar before and during treatment in subclinical hypothyroidism.

## Discussion

Haemostatic balances are maintained by many factors, hormones directly influence both primary and secondary hemostasis. A possible increased risk of myocardial infarction in patients with subclinical hypothyroidism suggested prothrombotic effect. In the past, other hypothesis has been postulated to explain coagulation abnormalities in thyroid patients such as endogenous arginine, vasopressin and adrenergic system imbalance, but these have never been proven [6].

Only few studies have been done to know the effect of coagulation parameters on subclinical hypothyroidism. Therefore, purpose of this study was to compare the coagulation profile among subclinical hypothyroidism and euthyroidism. This study hypothesized that platelet count; PT, INR and APTT alter in subclinical hypothyroidism patients. The study was conducted on 60 subclinical hypothyroid patients (study group) and 60 euthyroid patients (control group). Their anthropometric variables and coagulation parameter were measured.

### Anthropometric variables of studied patients

The present studies showed that subclinical hypothyroid patients were significantly older (34.93 ± 11.18) than the control group (28.58 ± 9.24). Some other studied have also found the prevalence of subclinical thyroid dysfunction to be increased greatly in the elderly [9]. BMI increased significantly ($p<0.05$) in subclinical hypothyroidism patients (25.75 ± 3.71) than of control group (22.78 ± 3.18) which was similarly reported by Hak AE et al. [10], who also revealed that subjects with SCH had higher BMI than euthyroid subjects [10]. This could be due to the TSH directly stimulating pre-adipocyte differentiation and resulting in adipogenesis [11].

### Demographic data of the study population

According to demographic data of this study population, it was clear that females (90%) are more prone to subclinical hypothyroidism than males (10%), the highest occurrence of subclinical hypothyroidism (23%) was found among those aged 46 years to 50 years. More than half of the patients (58%) had family history of subclinical hypothyroidism, 53% of subclinical patients were overweight. It seems that gender, age, family history of thyroid disorder, and BMI are risk factors for subclinical hypothyroidism.

### Coagulation test among the study population

In our study platelets count was numerically lower in hypothyroidism patients compared with the control group which was in consonance with the finding of Mustafa. Who reported a platelet count (259.13 ± 63.3) which is slightly lower in hypothyroidism than euthyroidism control group (270 ± 50.47) without statistical difference ($p>0.05$) [12]. Similarly Mohamed-Ali, found no significance difference of platelet count between subclinical hypothyroidism (209.2 ± 66.92) and control group (205.64 ± 60.21) [13]. Erem, also

reported no significance difference (p>0.05) of platelet count (254.05 ± 50.1) in control group and subclinical hypothyroidism patients (276.87 ± 69.19) [8]. Ford, Cantürk et al. [14], reported normal platelet count in subclinical hypothyroid patients which is fortified by the results of the current work [14,15]. This study postulated that platelet count is usually normal in hypothyroidism patients, in rare cases megakaryocytopoiesis may be severely inhibited in patients with hypothyroidism [16]. Our findings were contrary to that of Van et al. [17], who reported an unexplained increased platelet count in hypothyroidism [17]. False high count of platelet (pseudo thrombocytosis) may be due to severe microctytosis or fragmentation of erythrocytes. However there have been several controversial results in the literature to the findings of this work [18].

The present study showed decrease of PT (INR) of subclinical hypothyroid patients similar to findings of Mohamed-Ali, who found a significant reduction (p<0.05) in the values of PT (12.05 ± 1.15) in Sudanese patients with subclinical hypothyroidism than control group [13]. Our study was also consistent with the result obtained by Mustafa, who found PT value with hypothyroidism (10.20 ± 1.67) were significantly lower (p<0.05) than that of control group [12]. The decrease of PT in patients with subclinical hypothyroidism in our study was also similar to that reported by Muller et al. [19], which could be explained by the increase of factor VII activity (p<0.02) in subclinical hypothyroidism [19]. These results highlighted the presence of a hypercoagulable state rather than a bleeding tendency in patients with subclinical hypothyroidism, thus supporting the evidence of an increased risk of cardiovascular events in patients with this condition [16]. These findings disagree with that documented by Ford, who described low levels of plasma coagulation factor VII [15]. According to Cantürk et al. [14], higher values of PT (INR) (1.13 ± 0.41) and lower values of APTT (29.6 sec ± 3.4 sec) were found in women with subclinical hypothyroidism, this variation can be attributed to the severity of disease or inter-laboratory analytical variations [14].

Our study showed a significant increase in APTT (p<0.05) in subclinical hypothyroidism patients than that of control group while Mohamed-Ali, reported slight increase of APTT in subclinical hypothyroidism (32.75 ± 10.24) patients than that of control group (32.44 ± 2.97) without statistical difference [13], also Mustafa, found that hypothyroidism patient showed insignificant increases in APTT values (33.84 ± 3.28) to that of the control group (33.2 ± 2.86) [12]. Our finding was in consonance with finding of Gullu and Ford, which showed APTT in subclinical hypothyroidism patients increased significantly (p<0.01) than in control groups due to decrease of factor VIII and Von Willebrand factor activities [15,20]. This study speculated that either decreased protein synthesis or decreased response to adrenergic stimulation (enhanced VWF release from endothelial cells) are responsible to cause low level of VWF in hypothyroidism, interaction between thyroid hormones and β-adrenergic receptors could induce VWF release which is associated with prolonged APTT. In addition, all clotting factors are synthesized by liver except VWF [7].

This study found no significant difference (p>0.05) of platelet count, PT, INR and APTT between newly diagnosed subclinical hypothyroidism and under treatment subclinical hypothyroidism, these finding agree with Mohamed-Ali, who also reported no significant difference between clotting parameters (platelet count, PT and APTT) of patients under treatment or prior to treatment [13].

The data reported in the literature seem to indicate that disturbances of hemostasis are common phenomena in patients with thyroid diseases. In particular, with regard to the state of hypothyroidism, the more recent findings seem to indicate that its haemostatic profile depends on the degree of thyroid deficiency. Thus subclinical hypothyroidism is associated with a hypercoagulable state that, in association with the abnormalities of lipid profile observed in such patients, may account for the accelerated atherogenesis and the increased risk of coronary heart disease seen in subclinical hypothyroid patients [16].

## Conclusion

- Platelet count was not affected in subclinical hypothyroidism, these finding indicate there is no significant difference of platelet count between euthyroidism and subclinical hypothyroidism.
- PT (INR) is decreased significantly in subclinical hypothyroidism when compared to the control group which indicates that subclinical hypothyroidism is associated with little change in clotting parameter.
- APTT is significantly increased in subclinical hypothyroidism compared to control group.
- Platelet count, PT (INR) and APTT were not significantly affected by the treatment of subclinical hypothyroidism patients.
- This study concluded that subclinical hypothyroidism patients have significant abnormalities in some of the coagulation parameters.

## Ethical Clearance

Ethical Clearance was obtained from Departmental Research Unit (DRU), Department of Pathology, B.P. Koirala Institute of Health Science, Dharan, Nepal.

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