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Influence of Thyroid hormones on serum Cystatin C

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Abstract: ***Background:*** *- Thyroid function tests which include TSH, free and total T3, T4, are the gold standard biochemical tests till date in the diagnosis of Thyroid disorders. But variations have been observed in the values due to the influence of different drugs and other associated conditions such as Heparin, Amiodarone, Phenylbutazone, Salicylates, etc. Another topic of debate is the reference range of TSH as it has feedback regulation with T3, T4 values. Cystatin C is a potent cysteine protease inhibitor involved in the catabolism of proteins. Serum concentration of Cystatin C is independent of age, body weight, gender and are not influenced by inflammatory, rheumatologic conditions and hepatic causes. The low molecular weight of Cystatin C in combination with its stable production rate makes it a novel markerfor assessing kidney function. Although cystatin C concentrations are not influenced by many pathophysiological conditions other than those affecting GFR, thyroid dysfunction has been demonstrated to have an impact on the serum concentrations of cystatin C.*
Methods: *- Hundred cases of thyroid disorder (50 hyperthyroid and 50 hypothyroid) on the basis of clinical diagnosis and thyroid function tests and 100 normal healthy individuals as controls were enrolled in the study. All the subjects were tested for serum Cystatin C and Thyroid profile. The biochemical parameters were compared using ANOVA and correlation between serum Cystatin C level and Thyroid hormones were established using Pearson correlation chart.*
Results: *- Mean ± SD serum Cystatin C level was significantly higher ($p<0.01$) among hyperthyroid group of cases (3.23±1.28) and significantly lower ($p<0.01$) in hypothyroid group (0.84±0.42) when compared to controls (1.22±0.65). A significant negative correlation was found between serum Cystatin C and TSH values ($r=0.25$) and positive correlation between serum Cystatin C and T3 ($r=0.53$), T4 ($r=0.60$) values.*
Conclusion: *- Thyroid hormones definitely influence the level of serum Cystatin C which is increased in hyperthyroidism and decreased in hypothyroidism. Serum level of Cystatin C may correctly give an idea about peripheral Thyroid hormone action and may be used in the diagnosis and follow up of Thyroid disorders. Cystatin C which is presently used as a superior tool for the kidney function tests may also be cautiously done in patients with a Thyroid disorder.*

Key words: *TSH, T3, T4, Cystatin C, GFR, ANOVA, Pearson correlation*

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I. Introduction

Thyroid disorders are the most common endocrine problems encountered in clinical and endocrinology laboratory.[1] The prevalence of these disorders in the lifetime is approximately (5–10) %.[2] It has been estimated that about 42 million people in India suffer from thyroid disorders.[3] Thyroid diseases are very often misdiagnosed, misunderstood, and frequently overlooked and they affect almost every aspect of health. Most of them remain undetected because the clinical assessment alone has less sensitivity and specificity and can suspect only up to 40% of symptomatic thyroid disorders. Only the biochemical tests can be used to confirm the diagnosis.[4]

Thyroid function tests which include TSH, free and total T3, T4 are the most used and gold standard biochemical tests till date, but different variation has been observed in the values due to the influence of different drugs and other associated conditions. An increase in serum free T4 concentrations has been reported after low molecular weight heparin, in specimens taken 2–6 hours after injection.[5] Amiodarone causes altered thyroid function tests, with rises in serum concentrations of T4 and a fall in T3. Phenylbutazone inhibits thyroid uptake of iodine and/or competes for protein-binding sites with thyroxine, and can thus interfere with the use of

thyroid function tests.[6] Through competitive binding to thyroid-binding globulin, salicylates in high concentrations can displace T4 and T3, thus interfering with the results of diagnostic thyroid function tests.[7] According to García-Mayor RV et al [8] current thyroid function tests may have limitations since they only measure the total or free T4 and/or T3 and TSH serum concentrations in peripheral blood and not the effect of T4 or T3 on different specific target tissues. TSH serum concentration is a good functional marker of the effect of thyroid hormones in the pituitary tissue but not an appropriate indicator of peripheral tissue euthyroidism.[9,10] Another topic of debate in this field is the reference values of TSH, with the suggestion that the upper reference limit should be reduced as the reference range is too high to include patients with thyroid antibodies that are destined for future hypothyroidism.[8] As a consequence, there is still great interest in new biomarkers that are more accurate, precise, also complement the existing diagnostic tools and may facilitate risk stratification in patients with thyroid diseases.

Cystatin C is a member of the Cystatin superfamily of potent cysteine protease inhibitors involved in the catabolism of proteins. [11-13]It is a non-glycosylated, 120 amino acid, single chain basic protein with a molecular mass of 13.36 K Da. The crystal structure of Cystatin C is characterized by a short and a long alpha helix which lies across a large anti-parallel, five stranded beta sheets. The structure has two disulfide bonds and around 50% of the molecules carry a hydroxylated proline. It forms dimers by exchanging subdomains. In the paired state, each half is made up of the long alpha helix and one beta strand of one partner, and four beta strands of the other partner.[14] Cystatin C is produced by all nucleated cells at a constant rate which can be detected in body fluids.[15,16] The structure of the CST3 gene located on the short arm of chromosome 20, which encodes Cystatin C, has been demonstrated to be of the housekeeping type, which is compatible with a stable production rate of Cystatin C by most cells.[17] Because of its small size, Cystatin C is freely filtered by the renal glomerulus but not secreted.[18,19] The low molecular weight of Cystatin C in combination with its stable production rate strongly indicates that the blood serum concentration of this protein is mainly determined by the glomerular filtration rate of the individual. Serum Cystatin C concentrations are independent of age, body weight and gender and are not influenced by inflammatory or rheumatologic conditions and hepatic cause or malignancy.[20-27]Even, the diurnal variation in Cystatin C level is insignificant and the concentration is stable in stored serum.[28-30] Cystatin C measurement in serum is neither interfered by icterus nor by hemolysis.[31]Hence, Cystatin C is considered as a novel marker for assessing glomerular filtration rate (GFR) according to many studies and claimed to be superior to serum creatinine.[32-36]

Although Cystatin C concentrations are not influenced by many pathophysiological conditions other than those affecting GFR, thyroid dysfunction have been demonstrated to have an impact on the serum concentrations of Cystatin C.[37-41] Although most of the studies reported that the changes of serum cystatin C level are directly proportional to the thyroid hormonal changes but some of the studies also report contradictory results. [41] It is with this view that the present study has been carried out to evaluate the serum concentration of Cystatin C among the patients with thyroid dysfunction and compared with normal healthy individual without any thyroid disorders to find out the influence of thyroid hormones on serum Cystatin C level.

II. Methods

The comparative study has been carried out in the Department of Biochemistry, Regional Institute of Medical Sciences (RIMS), Imphal in collaboration with department of Medicine, RIMS Imphal, Manipur, India after obtaining the approval from Institutional Ethical Committee, RIMS. The study population consist of patients of 18 years an above, diagnosed case of hyperthyroidism or hypothyroidism on the basis of clinical diagnosis and thyroid function tests either attending Endocrinology OPD or admitted in Medicine wards. A group of normal healthy individuals who are free of any systemic disease, are included in the control group. Patients with renal diseases are excluded from the study as it my influence serum Cystatin C level. Any patients with conditions which may affect one or more aspect of thyroid hormone metabolism like, Severe illness, Physical trauma, Psychological and Physiological stress, Malignancies, Haematopoietic disorders, Infection with human immunodeficiency virus (HIV), Glucocorticoids treatment, thyroid hormone supplement or anti thyroid treatment, Rheumatoid arthritis are excluded from the study. After screening by total T3 and T4 levels (Reference range of our lab T3 - 1.49 to 2.60 nmol/L, T4 - 4.4 to 11.6 μg/dl), a total number of 50 cases (T3 > 2.60 nmol/L, T4 >11.6 μg/dl) are included in hyperthyroid group and another 50 cases (T3 <1.49 nmol/L, T4 <4.4 μg/dl) are included in hypothyroid group. All the selected patients has been taken a voluntary consent before starting the study. A detailed history including the patient's name, age, sex, duration of disease, age of onset of disease, cause of disease, presence of diabetes, hypertension, use of prescribed drugs are taken. Personal history of smoking, consumption of alcohol, presence or absence of obesity and family history of diabetes or hypertension is recorded in the enclosed proforma. Systolic and diastolic blood pressure, weight, height and body mass index (BMI) are measured once at the beginning of the study.

After a proper informed consent 5ml of venous blood is collected in plain vials from the patients. Blood samples are allowed to stand for 30 minutes followed by 5 minutes centrifugation and the serum thus

separated is divided in two parts. One part is used to estimate the thyroid function tests including serum TSH, T3, T4 on the same day and another part is stored in -80^{0}C for future estimation of Cystatin C. No repeated freezing and thawing of the stored samples are done before the estimation. Serum Cystatin C is measured using Biovendor human Cystatin C ELISA kit as described by Pergande M and Jung K.[42]LabsystemsMultiskan model no. 352 Microplate reader manufactured by Thermo Scientific is used for sample analysis. Serum TSH, T3 & T4 is measured using Diagnostic Automation, inc.Chemiluminescence enzyme immunoassay (CLIA) TSH, T3 & T4 kit as described by Rongen HA et al.[43] VITROS ECiQ Immunodiagnostic system using micro well technology by Ortho Clinical Diagnostics, Jhonson and Jhonson Limited, manufactured in UK is used for sample analysis. The data entry and analysis are done using SPSS version 21 for Windows. Descriptive statistics like mean, standard deviation, frequency, percentage is used. Chi square test is used for categorical variables and independent sample t-test, ANOVA for continuous variables. Pearson correlation test is used for correlating biochemical markers. P value <0.05 is taken as significant.

III. Results

Table-I: Sex wise distribution of Cases and Controls

Sex	Cases		Controls	
	Number	Percentage (%)	Number	Percentage (%)
Male	16	16	17	17
Female	84	84	83	83
Total	100	100	100	100

Table–I show Sex-wise distribution of the cases and controls. Numbers of females are more in both the groups.

Table-II: Mean age ± SD of Cases and Controls according to Sex

Sex	Cases		Controls		p-value (T-test)
	Numbers	Mean ± SD (Years)	Numbers	Mean ± SD (Years)	
Male	16	41.56 ± 13.69	17	38.12 ± 12.93	0.46
Female	84	36.88 ± 11.90	83	35.93 ± 12.06	0.60
Total	100	37.63 ± 12.25	100	36.30 ± 12.17	0.44

Table–II show Mean age ± SD of cases and controls according to sex. The difference of Mean age (± SD) for males and females separately among Cases and controls is not found to be statistically significant. The difference of Mean age (± SD) for total population of cases and controls are also not statistically significant indicating both groups are of comparable age.

Table-III: Smoking and Alcohol status in Cases and Controls

Baseline Characteristics (n, %)		Cases		Controls	p-value (Chi-square)
		Hyperthyroid	Hypothyroid		
Smoking	Yes	7 (14)	6 (12)	16 (16)	0.80
	No	43 (86)	44 (88)	84 (84)	
Alcohol	Yes	6 (12)	4 (8)	13 (13)	0.65
	No	44 (88)	46 (92)	87 (87)	

Table III show the number of cases and controls according to smoking and alcohol intake status. The number of non-smokers and non-alcoholics are more in both case groups (n=87, 90) and controls (n=84, 87) compared to smokers and alcoholics but the difference is not statistically significant among case group and controls. (p=0.80, 0.65)

Table-IV: Other Baseline Characteristics in Cases and controls

Baseline Characteristics (Mean ± SD)	Cases		Controls	p-value (ANOVA)
	Hyperthyroid	Hypothyroid		
Duration of Disease (Years)	2.29±1.73	2.86 ± 2.69		0.21
BMI (Kg/m^2)	21.82±3.60	27.57±6.11	25.55±5.10	<0.01
Systolic BP (mmHg)	128.72±10.42	126.40±12.10	119.78±9.57	<0.01
Diastolic BP (mmHg)	80.52±4.77	77.04±7.10	79.56±5.74	0.09

Table IV show some other baseline characteristics in cases and controls. The mean duration of disease is more in hypothyroid group compared to hyperthyroid but it is not statistically significant. BMI is more in Hypothyroid group compared to hyperthyroid and controls ($p<0.01$). Systolic BP is more in case groups compared to controls. No significant difference is seen in diastolic BP.

Table-V: Biochemical parameters in Cases and Controls

Biochemical Parameters (Mean ± SD)	Cases		Controls	p-value ANOVA
	Hyperthyroid	Hypothyroid		
TSH (mIU/L)	0.13±0.15	31.62±35.05	2.00±1.05	<0.01
T3 (nmol/L)	4.27±2.35	1.06±0.29	1.76±0.42	<0.01
T4 (mmol/L)	216.16±55.93	52.71±19.84	106.45±23.03	<0.01
Cystatin C (mg/L)	3.23±1.28	0.84±0.42	1.22±0.65	<0.01

Figure-I: Bar Diagram showing level of Cystatin-C in Cases and controls

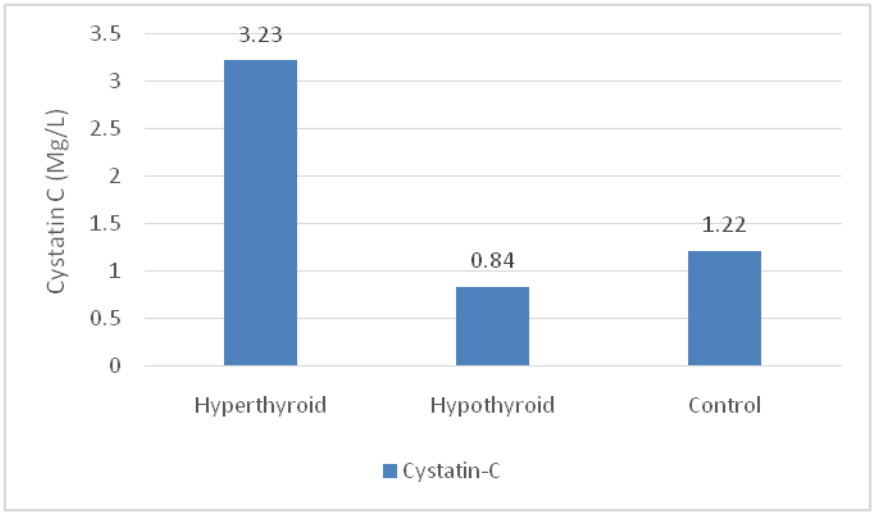
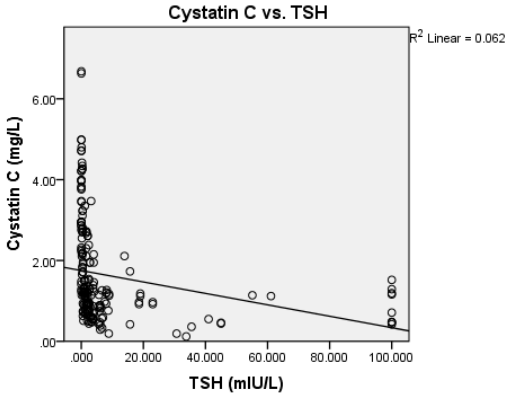


Table V and Figure I show the biochemical parameter in case groups and controls. Mean value of TSH is less in hyperthyroid (0.13 ± 0.15) and more in hypothyroid (31.62 ± 35.05) compared to controls (2.00 ± 1.05). Mean T3 and T4 values are more in hyperthyroid and less in hypothyroid compared to controls. The mean serum cystatin C level is more in hyperthyroid (3.23 ± 1.28) and less in hypothyroid (0.84 ± 0.42) compared to the controls (1.22 ± 0.65) but the difference is more marked in hyperthyroid with controls compared to hypothyroid. The differences in all the values among the case groups and controls are statistically significant ($p<0.01$).

Table VI: Correlation between Cystatin C and TSH, T3, T4 in all subjects

Parameters	Pearson Correlation	
	r-value	p-value
Cystatin C vs. TSH	- 0.25	<0.01
Cystatin C vs. T3	0.53	<0.01
Cystatin C vs. T4	0.60	<0.01

Figure II: Scatter plot showing the correlation between Cystatin C and other parameters



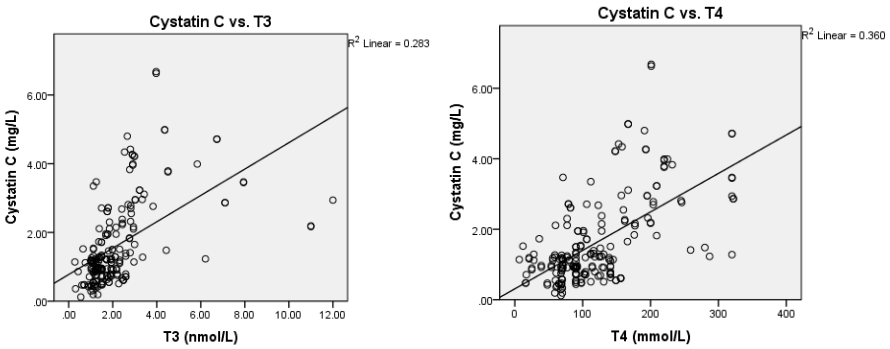


Table-VI and Figure II show Pearson correlation between the biomarkers among all the study population. The level of TSH is negatively correlated with serum cystatin C level (r=-0.25) which is statistically significant. ($p<0.01$). Serum T3 and T4 levels are positively correlated with serum cystatin C level. (r= 0.53, 0.60) which are also statistically significant ($p<0.01$) scatter plots for the correlation of cystatin C with TSH, T3 and T4 for total 200 subjects included in our study indicating the negative correlation between cystatin c and TSH; and the positive correlation of Cystatin C with T3 and T4

Table-VII: Effect of gender on Cystatin C level among case and controls

Sex*	Study Groups**					
	Hyperthyroid		Hypothyroid		Controls	
	Number	Mean ± SD	Number	Mean ± SD	Number	Mean ± SD
Male	10	3.27±1.16	6	0.77±0.46	17	1.38±0.74
Female	40	3.22±1.32	44	0.84±0.42	83	1.18±0.64

* p = 0.73, ** p < 0.01, (Univariate Analysis of Variance)

Table-VII show the difference of mean cystatin c level according to gender in different case groups and controls. The difference in mean cystatin C level of males among different groups and females among different groups are statistically significant ($p<0.01$) but the difference between males and females in individual groups are not statistically significant (p=0.73)

Table-VIII: Effect of smoking on Cystatin C level among case and controls

Smoking*	Study Groups**					
	Hyperthyroid		Hypothyroid		Controls	
	Number	Mean ± SD	Number	Mean ± SD	Number	Mean ± SD
Yes	7	2.20 ± 0.65	6	0.90 ± 0.39	16	1.37 ± 0.78
No	43	3.40 ± 1.28	44	0.83 ± 0.43	84	1.19 ± 0.63

* p = 0.07, ** p < 0.01, (Univariate Analysis of Variance)

Table VIII show the effect of smoking on serum cystatin C level among different case groups and controls. There is no statistically significant difference found in cystatin C level among smokers and non-smokers (p=0.07) but there is significant difference among the smokers in different groups and among the non-smokers also in different groups ($p<0.01$)

IV. Discussion

The pattern of change in serumCystatin C levels observed in our study i.e. elevated in hyperthyroidism (3.23 ± 1.28) and decreased in hypothyroidism (0.84 ± 0.42), may be due to various reasons. Thyroid hormones have significant effects on renal hemodynamics, renal handling of salt and water, and the active tubular transport processes for Na, K, and H resulting changes in kidney function.[44, 45] In healthy subjects, if the kidneys work effectively and GFR is within normal range, serum Cystatin C values should remain normal. Negative correlation was established between Cystatin C values and GFR – high Cystatin C values indicate low GFR and vice versa.[46]Stojanoski S et al [47] in their study suggests that the cellular production rate of Cystatin C has the dominant role of determination on its serum concentration. This suggestion is based upon the fact that despite the increase in GFR in hyperthyroid patients, Cystatin C values remain high, and vice versa. In hypothyroid patients low Cystatin C values can be observed even though the GFR is decreased. Den Hollander JG et al [38] in their study also concluded that thyroid hormones affect the production rate of Cystatin C, increasing it in hyperthyroidism and decreasing it in hypothyroidism. Schmid C et al [48] in their study showed that T3 increase Cystatin C production in Hep G2cells (kept in thyroid hormone-stripped medium, as assessed by RT-PCR of the

cells and a nephelometric immunoassay of the media) by about 30%.[49] Thyroid hormones increase cell metabolism; therefore, the demand for proteolysis control may also increase. T3 stimulation of Cystatin C production by several cells and spill over into the circulation may account for the dependency of Cystatin C serum levels on T3 in vivo rather than being dominated by renal catabolism and clearance (where Cystatin C production is considered constant).[48] A positive correlation was observed between serum concentrations of TGF-β1 and Cystatin C in patients with thyroid disorders.TGF-β1 has been reported to stimulate Cystatin C secretion from vascular smooth muscle cells and TGF-β1 treatment has been demonstrated to up-regulate Cystatin C transcript in murine embryo cells and 3T3-L1 fibroblasts. [50-54] The mechanisms for this may involve, at least in part, the elevation of serum TGF-β1 levels and the direct stimulatory effects of T3 and TGF-β1 on Cystatin C production in nucleated cells. [49]

In addition, the impact of thyroid dysfunction on Cystatin C is of special interest on the background of its recommended use as an earlier biomarker of acute kidney injury in emergency and intensive care medicine. [55, 56, 46]In the emergency department and especially in the intensive care unit, the prevalence of abnormal thyroid function tests is extremely high with more than 70% of the intensive care patients showing low total T3, and around 50% have low total T4. [57,58]Wang F et [59]al found that Cystatin C level was associated with FT4 in ICU patients. In our study, serum cystatin C level was negatively correlated with TSH (r=-0.25) and positively correlated with T3 (r= 0.53) and T4 (r=0.60) which were found to be statistically significant and in accordance with other previous studies, [40, 60, 61]The correlations found in our study may be little different than the previous reports, which is probably due to small sample size and different inclusion criteria. All hyperthyroid patients were included in our study irrespective of the cause of over production of thyroid hormones. Data of our study showed that majority of hyperthyroid patients included in our study were diagnosed as Grave's disease but we cannot state with confidence that this is the only thyroid dysfunction responsible for deranged Cystatin C levels because similar results were obtained in all other mixed cases of hyperthyroidism patients included in the study. Also, all cases of hypothyroidism showed decreased levels of Cystatin C. But the effect on serum Cystatin C concentration is more marked in patients with hyperthyroidism (3.23 ± 1.28) than hypothyroidism (0.84 ± 0.42) when compared to controls (1.22 ± 0.65). Large randomized controlled trials could provide more definitive evidence.

Serum Cystatin C concentrations were independent of gender in most previous studies. [62, 63, 31, 64, However, Pergande M et al [42] suggested that the serum levels of Cystatin C were lower in women than in men.No significant difference has been observed in the level of Cystatin C between males and females in our study (p=0.73). Since we have almost an equal and more number of females in both groups and the GFR is also not adjusted, the influence of gender on the level of Cystatin C cannot be elucidate properly.

Warfel AH et al [54] in their study showed a definitive influence of cigarette smoking on the level of Cystatin C but in this study, no significant effect of smoking is observed on the level of Cystatin C among thyroid disorder cases and controls (p=0.07). This may be due to the fact that maximum of the study population is female and non-smoker.

V. Conclusion

The findings of the study suggest that alterations in thyroid status can change serum Cystatin C concentration which is increased in hyperthyroidism and decreased in hypothyroidism. So, determination of serum cystatin C concentration may correctly give some idea about peripheral thyroid hormone action and diagnosis of thyroid disorders. The study does not provide any information on the mechanism underlying serum Cystatin C variations in patients with thyroid disorders but it is conceivable that thyroid hormone definitely affect the production rate of Cystatin C. This mechanism appears more likely than a modification of Cystatin C metabolic clearance rate. However, further scientific research in this field should be performed in order to determine up to which degree thyroid hormones affect the production rate of Cystatin C.

Cystatin C which is presently used as a superior tool for the kidney function tests may also be cautiously done in thyroid disorder patients and specially in critically ill or ICU patients where the thyroid hormones level are highly dysregulated. However, it should be considered that there is still little knowledge regarding the basic pathophysiology of correlation between Cystatin C and thyroid dysfunction. Considerably more work will need to be done to determine whether Cystatin C concentration is affected in all cases of thyroid dysfunction (especially in subclinical cases) and whether restoration of euthyroidism brings back serum Cystatin C level to normal. More information on the effects of treatment would help establishing a greater degree of accuracy on this matter.

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