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Research Article

Correlation of Autoimmune Thyroid Disease with Subclinical Hypothyroidism in Primarily Infertile Female Population

Tabassum Mansuri, Bhanu Pratap Singh Shekhawat, Akash Dave, Richa Chaturvedi, Sadiq Khalifa, Chitra Nair, Malvika Chaudhari and Pushpa Robin*

Department of Biochemistry, Faculty of Science, The M.S. University of Baroda, Vadodara, Gujarat, India

***Corresponding Author:** Pushpa Robin, Department of Biochemistry, Faculty of Science, The M.S. University of Baroda, Vadodara, Gujarat, India.

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Abstract

Infertility is a serious health concern affecting 15% of couples of reproductive ages worldwide and female infertility has been recognized as a global public health issue by WHO. Reports on the prevalence of infertility in women with chronic endocrine disorders are abundant but 'subclinical' aberrations in hormone levels affecting fertility are difficult to discern and hence often go undiagnosed, subclinical hypothyroidism (SCH) being the case in point. SCH acts as a silent perpetrator of infertility and by and large goes unnoticed owing to asymptomatic condition. Autoimmune thyroid disease (AITD) is one of the most common etiological factors responsible for hypothyroidism. A correlation between the prevalence of SCH and AITD in population, if any, will help in counseling of infertile females. This study was undertaken to estimate the prevalence of SCH in infertile females and to find out the prevalence and involvement of AITD amongst them so as to help in making decisions to decide course of treatment.

Keywords: *TSH; Subclinical Hypothyroidism; Infertility; Prevalence; Autoimmune Thyroid Disease; Correlation*

Abbreviations

SCH: Subclinical Hypothyroidism; TSH: Thyroid Stimulating Hormone; fT_3 and fT_4: Free Thyroid Hormone Level; AITD: Autoimmune Thyroid Disease; ET: Euthyroid; IF: Infertile Female; Ab: Antibody

Introduction

Female infertility occurs in about 37% of all infertile couples. A continuous interaction with multiple endocrine organs is responsible for successful reproduction. An aberration in any of the endocrine pathway can result in infertility and this makes the diagnosis of infertility a difficult exercise for the physician. Thyroid disorders, both hyperthyroidism and hypothyroidism, can influence the functionality of the ovaries. Reproduction can be jeopardized by alterations in the hypothalamus-pituitary-thyroid axis, a direct effect or autoimmunity affecting thyroid hormone levels. Overt Hypothyroidism affecting fertility is easy to diagnose and treat but diagnosing subclinical hypothyroidism (SCH) (elevated TSH and normal thyroid hormone levels) and deciding how to treat it is tricky. Studies have reported the association of overt hypothyroidism with infertility, miscarriage, and adverse pregnancy outcomes in female populations [1,2]. Subclinical hy-

pothyroidism (SCH) on the other hand is a milder form of hypothyroidism and is defined as an elevated TSH concentration in conjunction with normal free thyroxine (fT_4) levels. Subclinical hypothyroidism is a condition in which a slightly raised thyroid stimulating hormone (TSH) signal exists which could represent an early, mild thyroid failure. Subclinical hypothyroidism state suggests possible dysfunction of the thyroid which may increase the risk of infertility and problems with pregnancy. SCH is a common diagnosis among women of reproductive age and as such it can affect women planning conception and pregnant women [3]. SCH acts as a silent perpetrator of infertility as by and large goes unnoticed owing to asymptomatic condition. TSH is considered as a sensitive indicator of the thyroid status and thus of SCH. In euthyroid condition which indicates normal thyroid hormones levels, serum TSH level ranges from 0.3 - 4.0 µIU/mL and is finely regulated within an individual. Some authors have proposed restricting the upper normality limit of serum TSH to 2.5 mU/l. The burden of SCH in normal population is from 5 to 7% but prevalence in infertile women could range from 11 - 27% in different populations indicating a considerable burden of SCH as a silent precipitator of female infertility [2,4,5]. In India, it has been estimated that about 42 million people suffer from thyroid diseases, and hypothyroidism is the most common endocrine abnormality, seen in infertile population. The prevalence of SCH is reported to be high in various studies with prevalence of SCH reported to be as high as 15 - 25% with a greater propensity in females (81% in females to 18% in males) [6,7].

Autoimmune thyroid disease (AITD) is one of the most common etiological factors amongst the causes for the thyroid destruction resulting into overt and subclinical hypothyroidism [8]. The prevalence of AITD is higher in women than in men with the prevalence of 5 to 20% and thyroid dysfunction is more frequent in women who have thyroid autoimmunity [9,10]. The American Society for Reproductive Medicine states the routine measurement of TSH and anti TPO-abs in infertile women with TSH levels are ≥ 2.5 mIU/L [11,12]. Studies have shown the prevalence of AITD in different populations concluding significantly increased incidence of AITD in women with infertility [9]. The 2017 American Thyroid Association (ATA) pregnancy guidelines have confirmed adverse effects of subclinical hypothyroidism and thyroid peroxidase antibody (TPO Ab) positivity on obstetrical outcomes and pregnancy complications, including infertility [13].

Though the potential consequences of SCH can lead to infertility standardized treatment to correct this are uncommon and well designed clinical trials addressing various unnoticed issues regarding thyroid dysfunction and fertility are still needed from different populations. Assisted reproductive treatment (ART) for infertile female targets hyper-stimulation of ovaries and this may result in further strain on thyroid gland in SCH compromised patients, potentially resulting in permanent hypothyroidism. Since thyroid functions exert effect over fertility with various mechanisms, evaluation of thyroid functions during both pregnancy and treatment of infertility as well as in treating relevant pathologies become important. Treating "subclinical" thyroid dysfunction can reverse menstrual abnormalities and thus improve fertility. As thyroid status has been shown to vary with population, understanding it for every group is important to draw a bigger picture. A recent review on this was aptly titled: Thyroid and female infertility: more questions than answers [14]. This study was hence undertaken to understand the involvement of autoimmune factor in causing the subclinical hypothyroidism leading to female infertility and see if a causal relationship can be established. The study is designed to screen the infertile female population for the prevalence of SCH and look for AITD and see if we can establish a correlation between SCH with infertility and AITD, which in turn can be consider as an important step in treatment of infertility. Very few studies documenting this for Indian population exists.

Materials and Methods

Ethical consideration

It was ensured that the study design complies with the ethical standards of the Institutional Ethical Committee for Human Research (IECHR), Faculty of Science, The Maharaja Sayajirao University of Baroda, Vadodara, Gujarat, India (FS/IECHR/BC/PR/1) and with the 1964 Helsinki declaration.

Study population

The present retrospective study is a matched, case-control study and includes female subjects only. The study population consists of a total 1000 infertile females with primary infertility as case subjects and 135 healthy females as controls. Control females were selected

from general public by arranging health-checkup camps through newspaper advertisements as well by the means of field work. Infertile female patients were taken from the Ghanshyam Clinic (of Dr. Mahesh Pandya, Vadodara), which is a very well known and highly recognized infertility treatment center which receives a large number of female infertility cases from all over Gujarat and neighboring states (India). Rational of the study was explained in details to controls as well as patients and only the females who show willingness to participate were enrolled as study population. The inclusion criteria for controls were: healthy fertile females who have at least once delivered healthy full term babies and are non-pregnant for the duration of this study. Infertile females at their first visit to the clinic and those who have not gone to any other infertility center before were selected only to avoid any interruption from the previous medical treatment. The patients coming for the treatment of secondary infertility were not selected in the study population. Patient inclusion criteria were primary infertility diagnosis and duration of more than one year of unprotected intercourse without pregnancy. The exclusion criteria were male factor infertility, any tubal anomaly, congenital or urogenital tract anomaly and history of thyroid disease/medication/surgery, PCOS (Polycystic Ovarian Syndrome) or any other disorders or diseases. Infertile subjects taking antidepressants, antipsychotics and females with liver and kidney diseases were also excluded. Because females are the most fertile in the age of 20 - 40 years; the subjects which are within this age group were selected for the study. General information such as contact details, health characteristics, menopausal status, smoking and/or tobacco addiction, medical history of family, residential details, alcohol consumption and dietary habits (particularly as related to preference) were investigated by the questionnaire.

To find out the geographical difference in the reference range of thyroid hormones, the study protocol was discussed with local endocrinologists and gynecologists of private as well as government hospitals and with their suggestions the reference range of TSH, fT_3 and fT_4 for euthyroid, overt hypothyroid, SCH and hyperthyroid were decided which was further confirmed with the literature.

Sample collection

Blood was drawn from overnight fasting subjects by venous puncture. 135 control females and 1000 infertile females were recruited in this study. The control subjects having serum TSH levels in the normal/euthyroid range (0.35 - 3.5 µIU /ml) and infertile females with TSH levels above normal range (3.5 - 10 µIU/ml) were requested to continue as subjects for this study. The control and study subjects were requested to come during the 3^{rd} - 5^{th} day of their menstruation cycle for estimation of levels of reproductive hormones.

The subjects were further classified into normal (euthyroid-ET), above normal (subclinical hypothyroid-SCH), high (overt/clinical hypothyroid-OHT) or low (hyperthyroid-HYPT) depending on reference range of TSH and thyroid hormone levels as given in table 1. Patients with TSH value between 3.5 to 10 µl/ml were considered as subclinical hypothyroid (270 infertile female subjects were turned out to be SCH out of total 1000) and selected as the study population. While on the other hand euthyroid (112 control female subjects were tested euthyroid out of total 135) controls were included in the study. The euthyroid control subjects and Subclinical hypothyroid (SCH) infertile subjects were the final study population of the present study and were further characterized by the thyroid function test (TFT).

Diagnosis	TSH Levels (µIU/ml)	fT_3 (pg/ml)	fT_4 (ng/dl)
Euthyroid (ET)	0.35 - 3.5	2.3 - 4.2	0.9 - 1.76
Subclinical hypothyroidism (SCH)	3.5 - 10 (High)	Normal	Normal
Overt/Clinical Hypothyroid (OHT)	> 10	Low	Low
Hyperthyroid (HYPT)	< 0.35	High	High

Table 1: *Reference (normal) range of TSH, fT3 and fT4 levels followed for the selecting the subjects (TSH: Thyroid Stimulating Hormone; fT3: Free Triiodothyronine; fT4: Free Thyroxine).*

A total of 270 infertile and 110 controls were further subjected to TFT which includes the test for the serum TSH, free T_3 (fT_3) and fT_4 by enzyme-linked fluorescence immunoassay (ELFA) on mini VIDAS® immuno-analyzer (BioMérieux India Pvt. Ltd., India).

Strategies for screening and management of IF-SCH

Infertile females having TSH values between 3.5 and 10 µIU/ml with normal fT4 were considered as infertile subclinical hypothyroid female and named as IF-SCH females. Fertile females having TSH values within the normal/euthyroid range (i.e. 0.35-3.5 µIU/ml) and fT_4 levels within the normal range were included as controls in the present study. IF-SCH females/case group are defined as the infertile females who have subclinical hypothyroidism with no other clinical difficulty. In addition, they should not be under any type of medication, including thyroid disorder. And the control group includes fertile, parous, healthy euthyroid females with no medical history of thyroid or any other disorder. Control group does not include any subclinical hypothyroid female.

Anti-TPO antibody test

Estimation of Anti TPO antibodies was done by Enzyme Linked Immunosorbent Assay (ELISA). The calibration of the calibrators for the quantitative detection is based on WHO reference serum - 1st International Reference Preparation MRC 66/387|| for TPO -Antibodies. The estimation was done at 450 nm within 30 after completion of assay. TPO values smaller than 70 IU/ml was judged as negative (Cut off = 70 IU/ml).

Sampling method

The sampling method for selecting the participants was purposive (also called convenience method) sampling method as this provides the best information by the members of the selected community. Sample size for the present study was calculated using G-Power software with Alpha 0.05 and effect size of 0.9.

Statistical analysis

All the statistical analysis was done by using Prism 5 software (GraphPad Software Inc.; 2007). The tests done were Non-parametric unpaired t-test, Fishers exact test for retrospective data and One-way ANOVA test whichever is applicable. The correlation studies were done by using Pearson correlation coefficients to find out the correlation between TSH and fT_3, fT_4 and Anti-TPO Abs. Pearson's correlation coefficient was calculated to determine the relationship. A two-tailed, at minimum 95% confidence intervals and a p-value < 0.05 was considered statistically significant.

Results and Discussion

To determine the prevalence rate of SCH in the selected study population TSH levels were estimated in 135 control and 1000 infertile female volunteers. Out of total 135 controls females enrolled for the present study 110 (82%) females were euthyroid, 8 (6%) were overt/clinical hypothyroid (CT-OHT), 7 (5%) females (CT- SCH) were subclinical hypothyroid and 10 (7%) were tested as hyperthyroid (CT-HYPT) (Table 2). Whereas out of 1000 infertile females who were participated in the study in which 664 females (66%) were euthyroid (IF-ET), 20 (2%) were overt/clinical hypothyroid (IF-OHT), 270 (27%) infertile females (IF-SCH) were tested as SCH and 46 (5%) females were showing hyperthyroid (IF-HYPT) status (Table 2). Thus, the present study reports a significantly high prevalence rate of 27% SCH in infertile females as against 5% in control females. Diagnosis and when to start treatment of subclinical hypothyroidism (SCH) is a challenge which is usually left up to the physician in clinical practice due to the differing upper limits of normal TSH [15]. We continued this study with 270 SCH infertile females who were nominated as IF-SCH females for Infertile with SCH (the case subjects) with 112 euthyroid control females.

Researchers have opined that diagnosis of SCH should be based on an understanding of geographic and demographic differences in biochemical criteria versus a global reference range for TSH that is based on the 95% confidence interval for a population [16]. The de-

Subjects	Control N (%) (Type)	Infertile N (%) (Type)
Total Number	135 (CT)	1000 (IF)
Euthyroid (ET)	110 (82) (CT-ET)	664 (66) (IF-ET)
Subclinical Hypothyroid (SCH)	7 (5) (CT-SCH)	270 (27) (IF-SCH)
Overt/clinical Hypothyroid (OHT)	8 (6) (CT-OHT)	20 (2) (IF-OHT)
Hyperthyroid (HYPT)	10 (7) (CT-HYPT)	46 (5) (IF-HYPT)

Table 2: *Screening of SCH in study population.*

mographic details of all the subjects were checked to account for contribution of confounding variables such as Body Mass Index (BMI), the levels of Hemoglobin (Hb) and smoking habits. The age of IF-SCH females were significantly higher with p value = 0.0007 (mean ± SEM: 31.58 ± 0.266) as compared to controls (mean ± SEM: 29.85 ± 0.447). BMI of the case subjects was also higher with p value = 0.0245 (mean ± SEM: 23.63 ± 0.130) as compared to control subjects (mean ± SEM: 23.09 ± 0.196). We do not found any difference between IF-SCH subjects (p = 0.394; mean ± SEM: 11.69 ± 0.167) and controls (mean ± SEM: 11.56 ± 0.080) with respect to Hemoglobin (Hb) levels (Table 3). The IF-SCH group subjects were divided into two subgroups group A and B to on the basis of the TSH levels to find out the more prevailing sub range for the subclinical hypothyroidism in the selected population. The data revealed that the group A subjects with the TSH levels 3.5 - 7 µIU/ml represents a significantly higher prevalence with 221 out of total 270 subjects at 82% as compared the group B with 49 out of 270 IF-SCH subjects at 18% with TSH levels 7.1-10 µIU/ml (Table 4).

Study subjects	Control	IF-SCH	p value
Total subjects	110	270	-
Age (years)	29.85 ± 0.45	31.58 ± 0.27	0.0007 (***)
BMI ($kg/m^{2)}$	23.09 ± 0.20	23.63 ± 0.13	0.0245 (*)
Hb (gm/dl)	11.69 ± 0.17	11.56 ± 0.08	NS
Age at menarche (Yrs)	13.1 ± 0.12	13.3 ± 0.17	NS
Smokers (%)	0	0	-
Alcohol addiction	0	0	-
Tobacco addiction	0	0	-

Table 3: *Demographic details of population. Data presented as Mean ± SEM.*

	TSH levels (µIU/ml)	Prevalence n (%)
Group -A	3.5 - 7	221(82)
Group-B	7.1 - 10	49 (18)

Table 4: *Prevalence of SCH in infertile females (IF-SCH).*

The IF-SCH subjects were further divided into four age groups to compare the prevalence of infertility between different age groups. The group I, II, III and IV were consisting of the IF-SCH females of 20 - 25, 26 - 30, 31 - 35 and 36 - 40 years of age respectively. We found that the group III with IF-SCH females of 31 - 35 years of age group with the highest infertility prevalence with 39% followed by group II

with 31% and group IV at 21%. The IF-SCH females with the age group of 20 - 25 years of age with 9% were reported the lowest infertility prevalence amongst the all four groups (Table 5).

Group	Age group (Yrs)	Infertility prevalence n (%)
Group-I	20 - 25	24 (9)
Group-II	26 - 30	84 (31)
Group-III	31 - 35	106 (39)
Group-IV	36 - 40	56 (21)

Table 5: *Prevalence of infertility in different age groups of IF-SCH subjects.*

Further to find out the duration of infertility years of IF-SCH subjects the group was divided into four subgroups, group 1, 2, 3 and 4. The data revealed that the infertility duration was highest in group 2 with 5 - 7 yrs of duration showing 42% followed by group 3 having 8 - 10 yrs at 26%, group 1 at 20% and group 4 at 12% showing 11-13 yrs of infertility duration (Table 6).

Group	Duration of infertility (Yrs)	Total cases (%)
Group 1	2 - 4	55 (20)
Group 2	5 - 7	112 (42)
Group 3	8 - 10	70 (26)
Group 4	11 - 13	33 (12)

Table 6: *Duration of infertility in years of IF-SCH subjects.*

Correlation analysis was done to find out the correlation of TSH with various cofounders. The correlation (Pearson) of TSH with age was found to be r = -0.033 and p = 0.734 in control subjects and r = -0.068 and p = 0.268 for IF-SCH subjects indicating no significant correlation (Table 7).

	TSH with Age	
	Control subjects	IF-SCH subjects
No. of XY pairs	110	270
Pearson r	-0.03	-0.07
95% Confidence	-0.22 to 0.16	-0.19 to 0.05
P value	0.73	0.27
Significance of correlation	NS	NS

Table 7: *Correlation between TSH and age.*

Analysis of TSH, fT_3 and fT_4 levels revealed that IF-SCH subjects had significantly very high ($p < 0.0001$) TSH levels (mean ± SEM: 5.364 ± 0.115 µIU/ml; Table 8) compared to the control females (mean ± SEM: 1.908 ± 0.068 µIU/ml) and they had no significant difference in fT_3 levels ($p = 0.5532$, mean ± SEM: 2.7± 0.025 pg/ml; Table 8) compared to the controls (mean ± SEM: 2.8 ± 0.065 pg/ml). There was no

significant difference in fT_4 levels (p = 0.2227, mean ± SEM: 1.22 ± 0.0249; Table 8) between IF-SCH and control subjects (mean ± SEM: 1.195 ± 0.0318 ng/dl). Many cohort studies have looked at TSH levels in age and gender specific manner and a pattern in changes in TSH levels in Iodine replete and deficient regions have been reported [17,18].

	Reference Value	Control subjects	IF-SCH subjects	p value (p value summary)
TSH (µIU/ml)	0.35 - 4.00	1.908 ± 0.0680 (n = 100)	5.364 ± 0.115 (n = 270)	< 0.0001 (****)
fT_3 (pg/dl)	0.9 - .1.76	2.8 ± 0.065 (n = 100)	2.7± 0.025 (n = 270)	0.553 (ns)
fT_4 (ng/dl)	2.3 - 4.2	1.14 ± 0.024 (n = 100)	1.15 ± 0.010 (n = 270)	0.545 (ns)
Anti-TPO Abs	0 - 9 IU/ml	9 % (n = 50)	20 % (n = 100)	0.0432 (*)

Table 8: *Levels of TSH, fT3, fT4 and anti-TPO prevalence in the study population. Data presented as Mean ± SEM.*

On comparing TSH levels in controls (mean ± SEM; 1.908 ± 0.068) and IF-ET (mean ± SEM; 1.888 ± 0.041) subjects we found no significant difference (p = 0.8483) (Table 8). While the levels of TSH in IF-ET subjects (mean ± SEM; 1.888 ± 0.041) and IF-SCH (p = < 0.0001, mean ± SEM; 5.364 ± 0.115) showed significant difference (Table 8). The IF-OHT subjects were having very high TSH levels (p = < 0.0001; mean ± SEM; 31.53 ± 4.345) as compared to IF-SCH (mean ± SEM; 5.364 ± 0.115) (Table 9). A significantly high TSH levels in IF-SCH subjects as compared to the Control and IF-ET subjects was seen. The prevalence rate of Anti-TPO Abs in the study population revealed 9%, 11% and 20% rate in control, IF-ET and IF-SCH subjects respectively (Table 9). The difference in percentage of IF-ET and control was not significant (p = 0.814) and the trend was also same for the IF-ET and IF-SCH though significant with p = 0.117 (Table 9). Studies have found that patients with positive TPOAb have higher TSH levels [15].

Groups/Comparison	TSH (µIU/ml)	Anti-TPO Ab prevalence	p value
Control	1.91 ± 0.07 (n = 100)	9% (n = 50)	-
IF-ET	1.89 ± 0.04 (n = 664)	11% (n = 100)	-
IF-SCH	5.36 ± 0.12 (n = 270)	20% (n = 200)	-
IF-OHT	31.53 ± 4.35 (n = 20)	-	-
Control vs IF-ET	-	-	0.8483 (ns)
IF-ET vs IF-SCH	-	-	<0.0001 (****)
IF-OHT vs IF-SCH	-	-	<0.0001 (****)

Table 9: *TSH levels and Anti-TPO Abs prevalence.*

Thyroid autoimmunity could be an underlying cause of subclinical hypothyroidism so thyroid peroxidase antibody (TPOAb) was measured. Studies have found that patients with positive TPOAb have higher TSH levels and an association has been found between thyroid autoimmunity and recurrent loss in pregnancy [15]. Studies have shown that those with positive TPOAb without hypothyroidism have improved pregnancy outcomes when treated with levothyroxine [15]. Normally, TSH increases very minimally in patients ages 18 - 65 [16]. In the population with positive TPOAb, it is likely that TSH would rise over time in the pathogenesis of hypothyroidism. Correlation analysis of TSH with fT_3, fT_4 and Anti-TPO Abs was carried out to find out the correlation of TSH with thyroid hormones and anti-TPO Abs in primary infertile females. The study revealed that there is no significant correlation of TSH with fT_3 in control (Pearson r = 0.116 and p = 0.229) as well as in IF-SCH subjects (Pearson r = 0.036 and p = 0.561) (Table 10). This is a typical SCH scenario where fluctuations in TSH levels are not reflected in the levels of fT_3, fT_4.

	TSH with fT_3		TSH with fT_4	
	Control	IF-SCH	Control	IF-SCH
No. of XY pairs	110	270	110	270
Pearson r	0.116	0.036	-0.053	0.0168
95% confidence	-0.073 to 0.296	-0.084 to 0.154	-0.238 to 0.136	-0.103 to 0.136
P value	0.229	0.561	0.582	0.784
Significance of correlation	NS	NS	NS	NS

Table 10: *Correlation of TSH with fT3 and fT4 in the study population.*

Various studies have shown potential association of a mildly elevated TSH concentration with frequency of abortion, problems in pregnancy, unexplained infertility [4,17-19].

Conclusion

Role played by thyroid hormones in reproduction can be too subtle to easily identify. A systematic approach to rule out contribution of thyroid hormones in any physiological process is of utmost importance. Therefore, assessment of thyroid dysfunction has been considered as an important component in the infertility work-up of women. Evaluation of Thyroid status should be made mandatory for infertile females wanting to conceive. The panel of tests for thyroid evaluation should consist of triiodothyronine (T_3), thyroxine (T_4), thyroid stimulating hormone (TSH), and thyroid peroxidase antibodies (TPOAb), thyroglobulin antibodies (TgAb), and thyroid stimulating immunoglobulin (TSI). SCH cases can be transient and hence easily reversible in nature. In SCH patients the decision to use levothyroxine has to be with restrain as there are contradictory reports on its benefits. This study shows that incidences of SCH are significantly high in infertile females and the treatment regimen should factor in thyroid hormones rather than go for hyper-stimulation of ovaries.

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Conflict of Interest

The authors declare no financial interests/personal relationships which may be considered as potential competing interests.

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