ORIGINAL ARTICLE

Medical Journal of Western Black Sea
Batı Karadeniz Tıp Dergisi

Med J West Black Sea 2023;7(3): 318-324
DOI: 10.29058/mjwbs.1328163

Association of Hypervitaminosis D with Thyroid Function in Euthyroid Adult Patients

Ötiroid Erişkin Hastalarda Hipervitaminozis D ile Tiroid Fonksiyonu Arasındaki İlişki

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Cite this article as: Topaloğlu Ö and Müderrisoğlu ŞB. Association of hypervitaminosis D with thyroid function in euthyroid adult patients. Med J West Black Sea. 2023;7(3):318-324.

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Received
16.07.2023
Revision
28.10.2023
Accepted
30.10.2023

ABSTRACT

Aim: No study has investigated the effect of hypervitaminosis D on thyroid function. We aimed to analyze possible associations of hypervitaminosis D with thyroid function in levothyroxine-naive euthyroid patients.

Material and Methods: Levothyroxine-naive euthyroid patients (>18-year-old) with 25(OH) vitamin D level of ≥88 ng/mL after supplementation were analyzed retrospectively. We grouped them as: Group 1, TSH increased above the range; Group 2, TSH increased but in normal range; Group 3, TSH decreased but in normal range; Group 4, TSH decreased below the range; Group A, TSH increased; and Group B, TSH decreased. Before/after levels of TSH, fT4, Ca, P, creatinine, and TSH-change, fT4-change, 25(OH) vitamin D (basal/post-treatment and change), basal AntiTPO levels, and vitamin D dose were analyzed.

Results: TSH-change -0.19±1.03 mIU/L and fT4-change 0.015±0.17 ng/dL were insignificant in total(n=64). Post-treatment 25(OH) vitamin D, TSH-after, and TSH-change were higher in group 1(n=3) than in group 2(n=22), group 3(n=33), or group 4(n=6) ($p<0.05$). Post-treatment 25(OH) vitamin D was positively correlated with vitamin D dose and TSH-after. TSH-change was not associated with findings of intoxication or AntiTPO.

Conclusion: In patients with hypervitaminosis D, there is no linear relationship between 25(OH) vitamin D and TSH levels. In presence of hypervitaminosis D, TSH-change seems to be independent of autoimmunity or intoxication. We suggest monitorization of thyroid function in hypervitaminosis D.

Keywords: Hypervitaminosis, thyroid, thyroid function tests, vitamin D, TSH

ÖZ

Amaç: Hipervitaminozis D'nin tiroid fonksiyonu üzerindeki etkisini araştıran bir çalışma henüz yayınlanmamıştır. Çalışmamızda, levotiroksin-naif ötiroid hastalarda tiroid fonksiyonuyla hipervitaminozis D ilişkisini analiz etmeye çalıştık.

Gereç ve Yöntemler: Suplementasyondan sonra 25(OH) vitamin D düzeyi ≥88 ng/mL olan levotiroksin-naif ötiroid hastalar (>18-yaş) retrospektif analiz edildi. Hastalar şu şekilde gruplandı: Grup 1, TSH düzeyi referans aralığın üzerine çıkanlar; Grup 2, TSH düzeyi artan ancak referans aralığında kalanlar; Grup 3, TSH düzeyi düşen ve referans aralığında kalanlar; Grup 4, TSH düzeyi referans aralığın altına düşenler; Grup A, TSH düzeyi artanlar; Grup B, TSH düzeyi azalanlar. Önceki ve sonraki TSH, sT4, Ca, P, kreatinin değerleri, TSH-değişimi, sT4-değişimi, 25(OH)vitamin D düzeyi (bazal, tedavi sonrası ve değişim), bazal AntiTPO düzeyi ve vitamin D dozu analiz edildi.

Bulgular: TSH-değişimi -0,19±1,03 mIU/L ve fT4-değişimi 0,015±0,17 ng/dL anlamlı değildi (n=64). Tedavi sonrası 25(OH) vitamin D, TSH-son, ve TSH-değişimi grup 1'de(n=3), grup 2(n=22), grup 3(n=33) ve grup 4'e göre(n=6) daha yüksekti (p<0,05). Tedavi-sonrası 25(OH) vitamin D düzeyi, TSH-son ve vitamin D dozu ile pozitif korelasyon gösterdi. TSH-değişimi, intoksikasyon veya AntiTPO ile ilişkili değildi.

Sonuç: Hipervitaminozis D olan hastalarda, TSH düzeyi ile 25(OH) vitamin D arasında lineer bir ilişki yoktur. Hipervitaminozis D durumunda, TSH-değişimi otoimmüniteden veya intoksikasyondan bağımsız görünmektedir. Hipervitaminozis D'de tiroid fonksiyonunun izlemini öneriyoruz.

Anahtar Sözcükler: Hipervitaminozis, tiroid, tiroid fonksiyon testleri, vitamin D, TSH

INTRODUCTION

Vitamin D deficiency (<20 ng/mL) and insufficiency (20-30 ng/mL) are so frequent in all age groups worldwide (1,2). Inadequate exposure to sunlight, obesity, bariatric surgery or medications may lead to vitamin D deficiency, and secondary hyperparathyroidism, bone mineralization defect or osteoporosis may complicate it (3-5). Vitamin D deficiency may be treated by supplementation of active or inactive forms of vitamin D. Given the awareness of the importance of vitamin D deficiency, it is not surprising that some patients replace themselves. High dose vitamin D prescribed by a physician or taken by a patient itself may lead to hypervitaminosis D and/or vitamin D toxicity. Vitamin D intoxication is manifested by hypercalcemia, polyuria, polydipsia or changes in mental status, together with hypervitaminosis D (6). It was defined at 25(OH) vitamin D level of ≥88 ng/mL in older studies, but at a level of ≥100 or ≥150 ng/mL in later reports (5,7-11).

In one study, free T4 (fT4) level was found to be correlated with 25(OH) vitamin D level in Hashimoto's thyroiditis (12). Vitamin D replacement was shown to decrease thyroid stimulating hormone (TSH) level in hypothyroid patients with vitamin D deficiency (13). It was also shown that vitamin D replacement improved autoimmunity but not affect TSH levels in levothyroxine-treated women with Hashimoto's thyroiditis and normal vitamin D status (14). Vitamin D has beneficial effects on thyroid autoimmunity also in euthyroid population (15). Recently, cholecalciferol replacement was shown to decrease TSH level in euthyroid subjects with autoimmune thyroiditis and hypovitaminosis D (16).

No study has investigated the effect of hypervitaminosis D or vitamin D intoxication on thyroid functions or autoimmunity. We aimed to analyze the associations of hypervitaminosis D with thyroid function in vitamin D-supplemented levothyroxine-naive euthyroid adult patients.

MATERIAL and METHODS

Study Design

Euthyroid adult patients who were referred to Adult Endocrinology Clinics of Kocaeli Derince Training and Research Hospital between January 2015 and January 2020 due to hypervitaminosis D (25(OH) vitamin D level of ≥88 ng/mL) were included in this study. This retrospective study was approved by the Ethics Committee of our institution (University of Health Sciences Kocaeli Derince Training and Research Hospital, approval number:2020-1), and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants.

Participants and Data Collection

Patients with normal basal TSH and fT4, and who had hypervitaminosis D (25(OH) vitamin D levels of ≥88 ng/mL) after vitamin D supplementation were analyzed retrospectively.

Patients younger than 18 years, those with diabetes mellitus, cardiovascular diseases, coronary heart disease, chronic renal failure, chronic liver failure, chronic pulmonary disease, thyroid dysfunction, parathyroid dysfunction, malignancy or lacking data were excluded. Patients with previous history of thyroid dysfunction, use of any medications which might have possible effect on thyroid gland or vitamin D metabolism such as levothyroxine, methimazole, anticonvulsants or diuretics also were excluded.

Basic demographic information (age, gender) was analyzed. Total vitamin D dose (unit) was calculated as a sum of dose of vitamin D taken in time elapsed from basal 25(OH) vitamin D measurement to admission. Mean daily dose (unit/day) was calculated as total dose divided by the number of days elapsed from basal 25(OH) vitamin D measurement to admission.

Basal and post-treatment levels of 25(OH) vitamin D, and TSH-before, TSH-after, fT4-before, fT4-after, corrected Ca++(CCa)-before, CCa-after, P-before, P-after, and creatinine(Cre)-before, Cre-after were recorded and analyzed. Serum albumin (g/dL) was not analyzed itself but used to calculate CCa level with a formula of "CCa=Serum calcium+0.8*(4-patient albumin)". Basal AntiTPO level was recorded as positive or negative. TSH-change was calculated as (TSH-after)-(TSH-before), fT4-change as (fT4-after)-(fT4-before), and 25(OH) vitamin D-change as (post-treatment 25(OH) vitamin D)-(basal 25(OH) vitamin D).

TSH (mIU/L), fT4 (ng/dL), and ATPO (IU/mL) were measured by chemiluminescence using a DxI 800 system (Beck-

man Coulter, Inc., Fullerton, CA, USA). We measured the 25(OH) vitamin D level (ng/mL) by immunoassay. Serum CCa (mg/dL), P (mg/dL) and Cre (mg/dL) were measured by using enzymatic method reagents from Olympus Diagnostics (Hamburg, Germany). Laboratory values were evaluated according to normal range in our institution. Normal range of TSH and fT4 was 0.5-4 mIU/L and 0.8-1.6 ng/dL, respectively.

We grouped the patients regarding the change in TSH level between two measurements: Group 1, TSH increased above the range; Group 2, TSH increased but in normal range; Group 3, TSH decreased but in normal range; Group 4, TSH decreased below the range; Group A, TSH increased (Group 1 + Group 2); and Group B, TSH decreased (Group 3 + Group 4).

Indication of vitamin D replacement was vitamin D deficiency/insufficiency, osteoporosis, or bone/muscle/joint pain. Vitamin D was administered via per oral (po) or intramuscular (im) route, or both (po and im).

The patients were grouped also by the presence or absence of findings of vitamin D intoxication (hypercalcemia, nausea, vomiting, musculoskeletal symptoms, polyuria, polydipsia), age (<65 vs. ≥65), hypertension (present vs. absent), total vitamin D dose, post-treatment 25(OH) vitamin D level (<100 vs. ≥100 ng/mL), ATPO positivity, and fT4 (increased vs decreased).

Statistical Analysis

IBM SPSS software (ver. 22.0; IBM Corporation, Armonk, NY, USA) was used for the analysis. Shapiro-Wilk tests were used to assess the normality of the data. Homogeneity of variance was evaluated by Levene tests. When comparing two independent groups on quantitative measures, Independent Samples t-test was used. In comparison of more than two independent groups on quantitative measures, ANOVA was used with post-hoc LSD comparisons. Paired Samples t-test was used in comparison of basal and post-treatment 25(OH) vitamin D, or "before" and "after" measurements of TSH, fT4, CCa, P, or Cre. Pearson's Chi-Square tests were used in comparison of categorical variables each other. To analyze the correlations of variables with each other, Pearson correlation(r) analysis was used. Quantitative variables are reported as means (X) ± standard deviation (SD) in the tables. Categorical variables are reported as number (n) and percent (%), and *p*-values <0.05 were accepted as statistically significant.

RESULTS

Mean age of patients (n=64) was 46.28±16.26 year, and 89% of them was female. TSH remained out-of-range in 9, in-range in 55 patients. Mean post-treatment 25(OH) vitamin D level was 99.18±10.20 ng/mL, and it ranged between 88.1 and 150 ng/mL. Post-treatment 25(OH)D level was higher in group 1 than group 2, group 3 or group 4 (p=0.016, p=0.002, and p=0.002, respectively). Increase in 25(OH) vitamin D level was 80.49±15.76 ng/mL in total (p<0.001).

TSH-before was significantly higher in group 3 than in group 2 or group 4 (p<0.001 and p<0.001, respectively). TSH-after was similar in group 2 and group 3 (p=0.454), and was significantly higher in group 1 than other groups (p<0.001).

TSH-change and fT4-change were -0.19±1.03 mIU/L and 0.015±0.17 ng/dL in total, respectively (p=0.142 and p=0.490, respectively). TSH-change was higher in group 1 than other groups (p<0.001), but similar in group 3 and 4 (p=0.615) (Table 1). TSH-change was similar in males and females (p=0.942), but fT4-change was -0.13±0.18 ng/dL in males, and 0.03±0.16 in females (p=0.018). There was significant increase in CCa and P levels (p=0.009 and p<0.001, respectively), but no change in SCre (p=0.978). The number of days in which vitamin D were supplemented by any route to the patients ranged between 1-250 day. Post-treatment 25(OH) vitamin D level was positively correlated with mean daily dose (r=0.259, p=0.039) and total dose (r=0.256, p=0.041) of vitamin D, TSH-after (r=0.350, p=0.005) and change in 25(OH) vitamin D level (r=0.672, p<0.001) (not shown on the tables).

Vitamin D was given for vitamin D deficiency/insufficiency in 71.87% (n=46) of the patients. TSH did not decrease below the range in any patients taking <300000 unit vitamin D, and did not increase above the range in any patients taking <600000 unit vitamin D (Table 2). The ratio of patients with post-treatment 25(OH) vitamin D of ≥100 ng/mL was higher in group A than group B (p=0.026). The ratio of the patients who had increased fT4 was higher in group B than in group A (p=0.005) (not shown on the tables).

Vitamin D intoxication was observed in 26.56% (n=17) of the patients. TSH-change was similar among the patients with intoxication (-0.12±0.60 mIU/L) or not (-0.21±1.15 mIU/L) (p=0.766). AntiTPO positivity was similar among group A and B (p=0.827). TSH-change was 0.10±2.05 mIU/L in AntiTPO positive group, and -0.22±0.85 mIU/L in AntiTPO negative group (p=0.684) (not shown on the tables).

DISCUSSION

TSH decline was more frequent than TSH elevation, and observed in majority of the patients. Subclinical thyroid dysfunction was detected in minority of them. The patients with elevated TSH had a higher level of post-treatment 25(OH) vitamin D than those with decreased TSH. TSH change was independent of indication of treatment, AntiTPO positivity or intoxication.

Vitamin D supplementation was shown to decrease TSH and anti-thyroglobulin antibody in levothyroxine-treated

Table 1. Comparison of clinical and laboratory parameters among the groups.

	Group 1 (n=3)	Group 2 (n=22)	Group 3 (n=33)	Group 4 (n=6)	p value	Total (n=64)
Parameter	**mean±SD**					**mean±SD**
Age (year)	43.33±18.50	44.41± 16.64	46.36± 16.58	54.17± 13.34	0.625	46.28±16.26
Total dose (unit)	1008000 ±455842	615045 ±474906	703272 ±436734	792000 ±423040	0.492	695546±447984
Mean daily dose (unit/day)	115922.22±159997	37728.93±85417.93	75391.06±118849	60971.32±117207	0.521	62992.75±109302
25(OH) vitamin D (ng/mL)						
Basal	20.56±17.03	18.91±13.03	18.41±11.47	18.40±6.83	0.991	18.68±11.68
Post-treatment	115.53±30.35	101.016±8.74	97.37±7.80	94.26±2.80	0.010	99.18±10.20
Change	94.96±39.56	82.10±16.34	78.95±13.33	75.85±8.30	0.315	80.49 ±15.76
TSH-before (mIU/L)	2.11±1.16	1.60±0.73	2.56±1.11	0.86±0.43	<0.001	2.05±1.10
TSH-after (mIU/L)	4.81±0.64	1.98±0.78	1.81±0.90	0.24±0.19	<0.001	1.86±1.14
TSH-change (mIU/L)	2.69 ±1.75	0.37 ±0.32	-0.75±0.63	-0.61 ±0.58	<0.001	-0.19±1.03
fT4-before (ng/dL)	1.09±0.24	1.24±0.17	1.12±0.14	1.08±0.07	0.034	1.16±0.16
fT4-after (ng/dL)	1.14±0.14	1.20±0.12	1.15±0.16	1.22±0.10	0.483	1.17±0.14
fT4-change (ng/dL)	0.04±0.19	-0.04±0.17	0.02±0.17	0.14±0.09	0.138	0.015±0.17
CCa-before (mg/dL)	8.83±0.28	9.26±0.43	9.39±0.49	9.47±0.72	0.220	9.33±0.50
CCa-after (mg/dL)	9.13±0.08	9.42±0.46	9.53±0.40	9.61±0.37	0.321	9.48±0.42
P-before (mg/dL)	3.57±0.39	3.31±0.51	3.35±0.45	3.75±0.63	0.236	3.38±0.49
P-after (mg/dL)	3.83±0.42	3.68±0.48	3.49±0.46	3.80±0.24	0.241	3.60±0.46
Cre-before (mg/dL)	0.76±0.13	0.75±0.16	0.73±0.10	0.75±0.07	0.939	0.74±0.12
Cre-after (mg/dL)	0.72±0.08	0.76±0.18	0.73±0.12	0.76±0.07	0.849	0.74±0.14

patients with Hashimoto thyroiditis (13). High dose of vitamin D supplementation was shown to be associated TSH decline in autoantibody positive treatment-naïve euthyroid population (16). The effect of vitamin D supplementation on TSH level in euthyroid subjects was controversial (15,16). No study has investigated the effect of vitamin D intoxication or hypervitaminosis D on thyroid function. We revealed that, in hypervitaminosis D, TSH decrease was more frequent than TSH elevation, but we could not analyze the change in thyroid autoantibodies. In total, TSH was slightly decreased and fT4 slightly increased, albeit insignificant. Previous reports suggested possible mechanisms regarding the effects of vitamin D, such as inhibition of iodide uptake by thyroid follicles, or inhibition of TSH secretion via binding of it to pituitary gland (17-19). Immunomodulatory action of vitamin D also was reported as a possible link between improved thyroid function and vitamin D supplementation (16,20). Vitamin D was shown to suppress autoimmunity by regulating the activity of CD4+ T lymphocytes (21). We suggest that the effect of vitamin D on thyroid function may change in different degrees of hypervitaminosis D. Among the patients with hypervitaminosis D in our study, those with higher 25(OH) vitamin D level was further associated with TSH elevation than TSH decline. We theoretically propose that TSH may be decreased by increasing 25(OH) vitamin D level to a threshold and this association may be blunted if 25(OH) vitamin D increases above the threshold. Molecular and clinical impact of different degrees of hypervitaminosis D (25(OH) vitamin D level of ≥88 vs. ≥100 vs. ≥150 ng/mL) on thyroid function remains to be explained. The frequency of AntiTPO positivity in our study was similar to that in general population (22,23). We found that TSH change was independent of AntiTPO positivity. Although the association between vitamin D and non-autoimmune hypothyroidism has not been well-documented, non-immune effects of vitamin D have been implicated in thyroid dysfunction (24). Together with the previous studies, we suggest that serum 25(OH) vitamin D level seems to have importance in the emergence of the effect of hypervitaminosis D on thyroid functions (14,16). Hence, the effect of vitamin D supplementation on thyroid functions may be different at different levels of 25(OH) vitamin D such as in deficiency/insufficiency, sufficiency, hypervitaminosis. Future prospective studies will reveal if the effect of very high 25(OH)D levels on thyroid function is biphasic or nonlinear, at least, or alters according to a possible threshold of 25(OH) vitamin D level or not.

The most of the studies regarding the effect of vitamin D supplementation on thyroid function has been conducted in

Table 2. Comparison of categorical parameters among the groups.

Parameter	Group 1 (n=3)	Group 2 (n=22)	Group 3 (n=33)	Group 4 (n=6)	p	Total
	n					n
Gender (female/male)	3/0	20/2	29/4	5/1	0.874	57/7
Age (<65/>65)	3/0	16/6	27/6	5/1	0.667	51/13
HT (present/absent)	0/3	6/16	11/22	2/4	0.665	19/45
Indications of vitamin D replacement						
Deficiency/insufficiency	1	15	26	4	0.537	46
Osteoporosis	1	4	4	2		11
Bone/muscle/joint pain	1	3	3	0		7
Vitamin D route of administration						
po (yes/no)	3/0	21/1	33/0	5/1	0.176	62/2
im (yes/no)	1/2	1/21	3/30	1/5	0.390	6/58
po and im (yes/no)	1/2	0/22	3/30	0/6	0.108	4/60
Total dose of vitamin D (Unit)						
$<300*10^3/>300*10^3$	0/3	5/17	4/29	0/6	0.401	9/55
$<600*10^3/>600*10^3$	0/3	12/10	11/22	2/4	0.197	25/39
$<900*10^3/>900*10^3$	1/2	16/6	22/11	3/3	0.467	42/22
$<1200*10^3/>1200*10^3$	2/1	18/4	26/7	5/1	0.931	51/13
$<1500*10^3/>1500*10^3$	2/1	19/3	29/4	6/0	0.556	56/8
Post-treatment 25(OH) vitamin D <100/≥100 ng/mL	1/2	10/12	22/11	6/0	0.058	39/25
Intoxication (present) n (%)	0 (0)	7 (31.8)	9 (27.2)	1 (16.6)	0.636	17 (26.5)
AntiTPO (negative/positive)	2/1	20/2	30/3	5/1	0.585	57/7
Group A/Group B	3/0	22/0	0/33	0/6	<0.001	25/39
fT4 (increased/decreased)	2/1	7/15	22/11	6/0	0.009	37/27

levothyroxine-treated patients (13,14). To our knowledge, no study has investigated the effect of vitamin D intoxication or hypervitaminosis D on TSH level in euthyroid or hypothyroid patients. We conducted our study in euthyroid population without known thyroid dysfunction. In our study, TSH change was independent of the presence of vitamin D intoxication, which was observed in approximately one-fourth of the patients. The effect of vitamin D intoxication or hypervitaminosis D on TSH level in hypothyroid patients remains to be elucidated.

The association between TSH and hypervitaminosis D was not affected by the indication of vitamin D supplementation. We excluded the possible confounders such as chronic renal or hepatic failure which may affect the interaction of vitamin D and thyroid gland.

We found that a higher vitamin D dose led to a higher level of post-treatment 25(OH)D. Similar findings also were reported in previous studies (8,9).

In one study, TSH was shown to decrease after high dose supplementation of vitamin D in euthyroid subjects (16). They did not explain if TSH get out-of-range in any patient or not. We did not observe overt thyroid dysfunction, but we found subclinical thyroid dysfunction in approximately 14% of the patients. Subclinical thyrotoxicosis may be complicated with heart failure, atrial fibrillation, and coronary heart disease, and subclinical hypothyroidism may be associated with heart failure, coronary heart disease (25-28). Therefore, the patients with hypervitaminosis D may be suffered from the consequences of subclinical thyroid dysfunction. In previous studies, higher free T4 levels within normal range was found to be further associated with atrial fibrillation even in younger patients than low-normal free T4 levels (29,30). fT4 was increased in more than half of the patients in our study, albeit statistically insignificant. Due to elevated fT4, hypervitaminosis may be associated with an increased risk of arrhythmia. We could not follow up thyroid function tests after hypervitaminosis D was detected until the resolution of it. The association of vitamin D supplementation with development of subclinical or overt thyroid dysfunction in euthyroid subjects with low, normal or high levels of 25(OH) vitamin D remained to be explained in future studies.

Strength and Limitations

To our knowledge, our study is the first to investigate the effect of hypervitaminosis D on thyroid functions in euthyroid adult subjects. We did not analyze the levels of free T3 or anti thyroglobulin antibodies in the study. We could not follow-up the change in the levels of AntiTPO. We could not extend the follow-up of thyroid function tests until resolution of hypervitaminosis D.

Conclusion

TSH declined and fT4 elevated in more than half of the patients. Hence, we propose that hypervitaminosis D may increase the risk of arrhythmia. 25(OH) vitamin D level was higher in subclinical hypothyroidism than in subclinical thyrotoxicosis. TSH change was independent of AntiTPO or intoxication. The association between 25(OH) vitamin D and TSH levels in hypervitaminosis D seems to be nonlinear. We suggest that thyroid functions and electrocardiogram should be followed up until resolution of hypervitaminosis D.

Acknowledgment

None.

Author Contributions

Ömercan Topaloğlu for significant contribution in idea, data collection, analysis, and writing of the manuscript, and second author **Şeyma Büşra Müderrisoğlu** for contribution in data collection and writing of the manuscript.

Conflicts of Interest

None.

Financial Support

No funding or financial support was received.

Ethical Approval

Ethics Committee of University of Health Sciences Kocaeli Derince Training and Research Hospital, approval number: 2020-1.

Review Process

Extremely peer-reviewed and accepted.

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