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Evaluation of the role of thyroid hormones, vitamin B12, vitamin D3, folic acid and ferritin serum levels in pterygium development

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To evaluate the relationship between pterygium and serum thyroid hormone, vitamin B12, vitamin D3, folic acid, and ferritin levels between pterygium patients and control and to assess its correlation with clinical findings. 18–65-year-old 100 pterygium patients and age and sex matched 60 healthy control subjects were included. The peripheric blood sampling results were investigated. Free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH), vitamin B12, vitamin D3, folic acid, and ferritin levels of pterygium and control groups were compared. FT3 level was higher in the patient group compared to the control group, while vitamin B12, vitamin D3, folic acid and ferritin levels were significantly lower in the patient group compared to the control group ($p < 0.05$) No significant difference was found between the patient and control groups in terms of age, gender and body mass index (BMI) ($p = 0.295$, $p = 0.625$, $p = 0.547$, respectively). This study reports that pterygium patients have lower serum vitamin B12, folic acid, ferritin and vitamin D3 levels than healthy individuals.

Keywords Pterygium, folic acid, Ferritin, Thyroid, Vitamin B12, Vitamin D3

Pterygium is a chronic disease of conjunctival fibrovascular tissue invading the cornea, causing ocular irritation, visual impairment and cosmetic problems[1]. Pterygium prevalence rates range from approximately 2.8–23.7% worldwide[2]. Pterygium is often associated with environmental factors, especially ultraviolet (UV) light exposure, which is known to trigger oxidative stress and inflammatory responses, and systemic health factors may also play an important role in its pathogenesis[3]. It is also possible that such a highly prevalent pathology may be triggered by other causes.

In studies aimed at elucidating the pathogenesis of pterygium, irregular ferritin expression have been detected in pterygium tissue and it has been emphasized that this plays an important role in triggering oxidative stress and inflammation[4].

Although pterygium appears to be a localized pathology, it has been shown to be associated with some systemic conditions. Pyo et al. reported that higher blood pressure and total cholesterol levels were associated with the development of pterygium in the South Korean population[5]. This finding is supported by Lee et al., who also noted a high expression of low-density lipoprotein (LDL) receptors in pterygium tissues, suggesting that metabolic diseases could contribute to the condition through mechanisms such as microangiopathy and fibrosis[6].

The relationship between thyroid diseases and pterygium has been a subject of investigation in recent studies, although the direct connections remain ambiguous[7]. Thyroid hormones are known to influence various metabolic processes, and their dysregulation could theoretically affect the cellular environment of the conjunctiva, potentially contributing to pterygium formation.

Moreover, the systemic effects of thyroid dysfunction, particularly in autoimmune thyroid diseases like Graves' disease and Hashimoto's thyroiditis, could potentially influence ocular surface health. For instance, autoimmune conditions are often associated with increased inflammation, which has been implicated in the pathogenesis of pterygium[8]. Chronic inflammation may lead to changes in the ocular surface that could promote

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the development of pterygium, although direct evidence linking specific thyroid diseases to pterygium is still lacking.

The aim of our study is to investigate whether the changes related to oxidative damage and inflammation at the cellular level, which have been shown to be effective in the development of pterygium, have a systemic counterpart, to investigate the existence of differences in serum thyroid hormone, vitamin B12, vitamin D3 and folic acid levels that may have an effect on serum ferritin and ferritin levels in patients with pterygium, and to inspire studies to determine potential treatment and prevention strategies for pterygium.

Materials and methods

This prospective case-control study was conducted at the outpatient ophthalmology clinic in ophthalmology department of Recep Tayyip Erdogan University from March 2023 to November 2023 and the study protocol was approved by the local human research ethics committee from Recep Tayyip Erdogan University. Protocol number and date 2023/77 and 27.03.2023. All patients included in this study provided their informed consent. The study adhered to the tenets of the Declaration of Helsinki, and written informed consent was obtained from all subjects.

All patients presenting to the outpatient clinic for ophthalmological examination were evaluated for eligibility for the study. All participants who met the inclusion criteria and agreed to participate in the study were evaluated for pterygium and newly diagnosed individuals were included in the case group and healthy individuals without pterygium were included in the control group. The inclusion criteria were defined as follows: (1) newly diagnosed pterygium, 2) ≥ 18 years and ≤ 65 years; Exclusion criteria were defined as follows: (1) the presence of any documented systemic disease that may affect the results of peripheral blood sampling (endocrinological diseases, haematological diseases, immunological diseases, rheumatological diseases, malignancy or malnutrition, etc.); (2) the presence of documented hormone, vitamin or iron therapy or supplementation; and (3) the presence of any other documented chronic ophthalmological disease (uveitis, glaucoma, corneal diseases, retinal diseases, etc.) (4) previous ocular surgery.

The diagnosis of pterygium was made by the same physician (FS) using slit lamp biomicroscopy (Topcon Corporation model SL-3G; Topcon, Tokyo, Japan) and the condition was defined as fibrovascular overgrowth of the bulbar conjunctiva on the cornea. All subjects underwent a complete ophthalmic examination, consisting of best corrected visual acuity; slit lamp biomicroscopy of the anterior segment; fundoscopic examination after dilation of the pupils with 0.5% tropicamide and 5% phenylephrine hydrochloride by the same physician (FS). The medical history of all patients was investigated in detail. Patients with a BMI between 18.5 and 24.9 were enrolled in the study.

Blood samples were collected after 12-hour fasting from the antecubital veins, from 08:00 AM to 10:00 AM while in the sitting position from the patients, and those from members of the control group were centrifuged (3500 rpm for 10 min) in serum separator gel tubes (BD Vacutainer; Becton Dickinson, New Jersey, USA) containing serum separator gel. These were saved at -40 °C for analysis. All peripheral blood samples were performed in a single laboratory at the center where the study was conducted. Serum 25 (OH)D, thyroid stimulating hormone (TSH), free T3 (sT3), free T4 (sT4), vitamin B12, folic acid, and ferritin levels were measured by electrochemiluminescence immunoassay (Hitachi High-Technologies Corporation, Tokyo, Japan) in an automatic electrochemiluminescence analyzer (Roche Diagnostics Co. Ltd., Mannheim, Germany). A 25-OHD serum concentration less than 20 ng/mL was considered indicative of vitamin D (VD) deficiency[8].

Statistical analysis

SPSS Windows version 22 programme was used for statistical tests. Continuous variables were evaluated by histogram, Q-Q graph in terms of normal distribution and Shaphiro-Wilk or Kolmogorov-Smirnov tests according to the number of variables. The normally distributed continuous variables were presented as mean ± standard deviation throughout the study and independent-variables t test was used to compare the two groups. Other continuous variables were presented as median (minimum - maximum) values, and the nonparametric Mann-Whitney U test was used to compare the groups. Categorical variables were presented as frequency and percentage, and Pearson Chi-square test or Fischer's exact probability test was used to compare the groups. Tests with a p value of 0.05 and below at 95 per cent confidence interval were considered statistically significant.

Results

In this prospective case control study, serum parameters of 100 pterygium patients and age and sex matched 60 healthy control subjects were compared. All patients had nasal-sided pterygium. Baseline characteristics of patients were reported in Table 1. 68 (42.5%) of the patients were male and 92 (57.5%) were female. The mean age of the patients was 52.99 ± 5.84 years. None of the patients were smoking. There was no statistically significant difference between the groups in systolic ($p = 0.209$) and diastolic ($p = 0.659$) blood pressure. No significant difference was found between the patient and control groups in terms of age, gender and body mass index (BMI) ($p = 0.295$, $p = 0.625$, $p = 0.547$, respectively).

While no significant difference was found between the patient group with pterygium and the healthy control group in FT4 and TSH levels ($p > 0.05$), FT3 level was higher in the patient group compared to the control group, while vitamin B12, vitamin D3, folic acid and ferritin levels were significantly lower in the patient group compared to the control group ($p < 0.05$) (Table 2) (Fig. 1).

Variable	Patient	Control	*p*
Men/Women, n (%)	41 (41) / 59 (59)	27 (45) / 33 (55)	0,625[a]
Age, mean ± SD, year	53,37 ± 5,79	52,37 ± 5,92	0,295[b]
BMI, median (IQR)	22,1 (1,72)	22,4 (1,82)	0.547[c]
Smoking	100/0	60/0	
Systolic blood pressure (mmHg)	120.0 (115.0/125.0)	120.0 (115.0/125.0)	0.209
Diastolic blood pressure (mmHg)	80.0 (80.0/85.0)	84.0 (80.0/85.0)	0.659

Table 1. Demographic characteristics of the patients and control groups. *SD: Standard deviation, BMI: Body mass index (kg/m^2), a: Fisher's exact test, b: T-test, c: Mann-Whitney U, $p < 0.05$ statistically significant.

Variable, median (IQR)	Patients	Control	*p*
FT_3, pg/mL	3,15 (0,37)	3,12 (0,27)	**0,047[a]**
FT_4, ng/dL	1,19 (0,13)	1,21 (0,17)	0,678[a]
TSH, IU/mL	1,21 (0,80)	1,21 (0,29)	0,250[a]
Vitamin B_{12}, pg/dL	321 (40)	415,5 (41)	**< 0,001[a]**
Vitamin D_3, ng/mL	16,25 (2,4)	21,1 (1,68)	**< 0,001[a]**
Ferritin, ng/dL	38,17 (18,52)	87,42 (20,83)	**0,004[a]**
Folik asit, ng/mL	9,35 (4,54)	11,65 (6,20)	**< 0,001[a]**

Table 2. Laboratory values of the patient and control groups. FT3: Free T3, FT4: Free T4, TSH: Thyroid stimulating hormone, a: Mann-Whitney U, $p < 0.05$ statistically significant.

Discussion

To our knowledge, this study is the first attempt to demonstrate an association between serum thyroid hormone, ferritin, folic acid, vitamin B12 levels and the risk of pterygium in human population-based study. The cause of pterygium remains unknown despite numerous investigations. The following have been proposed as risk factors: oxidative stress, viral involvement, ocular surface alterations, genetics, ultraviolet radiation (UVR), viral inheritance, and environmental variables[9]. Our results suggest that subjects with high total serum T3 tend to have a significantly increased risk of developing pterygium. The association between serum thyroid hormones and pterygium is not fully understood. One of the possible reasons for the higher serum T3 levels in pterygium patients compared to the control group may be that thyroid hormones, including T3, play a role in many physiological processes such as cell proliferation, metabolism and inflammation. Although there are no studies on the relationship between high serum thyroid hormones and pterygium, this result may be possible in pterygium where chronic inflammation is thought to be predominant. In addition, research has shown that thyroid hormones may regulate the antioxidant defense system. For example, they can increase the expression and activity of antioxidant enzymes such as superoxide dismutase (SOD) and catalase, which play important roles in reducing oxidative stress[10]. This protective effect supports the finding of high T3 values in the development of pterygium in which oxidative stress is blamed.

Other possible causes include proptotic appearance due to thyroid hormones and higher exposure to UV radiation due to lid retractions. This assumption is actually a statement of summary inference from the literature. In their study, Ozer et al.[11] found that the prevalence of pingeacula formation, which is accepted to have a similar pathophysiology with pterygium, was higher in patients with thyroid orbitopathy compared to the control group.

Angiogenesis, cell proliferation, tissue invasion, and inflammation are all important factors in the production of pterygiums, as demonstrated by a recent study that found that pterygium epithelial cell cultures exposed to UVR release pro-inflammatory cytokines like interleukin IL-6 and IL-8[12]. The use of topical vitamin D (VD) has also been demonstrated to suppress ocular surface inflammation and corneal neovascularization by preventing the migration of Langerhans cells from the conjunctiva to the cornea and the release of IL-1a, IL-1b, IL-6, and IL-8 by corneal epithelial cells respectively.[13] While 25(OH)D(D_3) is the predominant form of VD in the circulatory system, 1,25(OH)(D_2) is the active intracellular binding form. Serum 25(OH)D levels are used to determine the state of VD[14]. Season, skin pigmentation, age, sex, and obesity are risk factors for vitamin D insufficiency[8]. Age, sex, and BMI of the groups in our study were comparable ($p < 0.05$). It can be expressed as an indicator that there is a balanced distribution between groups. The same amount of time was used to gather the blood samples. The fact that vitamin D levels were lower in patients with pterygium compared to the control group in our study supports the presence of anti-inflammatory effect of vitamin D in pterygium, which is accepted to develop due to chronic inflammation, and may mean that inadequate protection from inflammation may be effective in the development of pterygium.

The inflammatory response and wound healing process in pterygium are clearly dysregulated. This was supported by a study on pterygium tissue. In this study, it was accepted that acute inflammation could not be controlled due to disruption of the oxidant-antioxidant balance; the HO1-HO2 expression ratio was disrupted, and the event turned into chronic inflammation.[15] Exposure to UVA and UVB is linked to photochemical cell damage. Lipid peroxidation, a reduction in mitochondrial viability, and direct damage to DNA are examples of

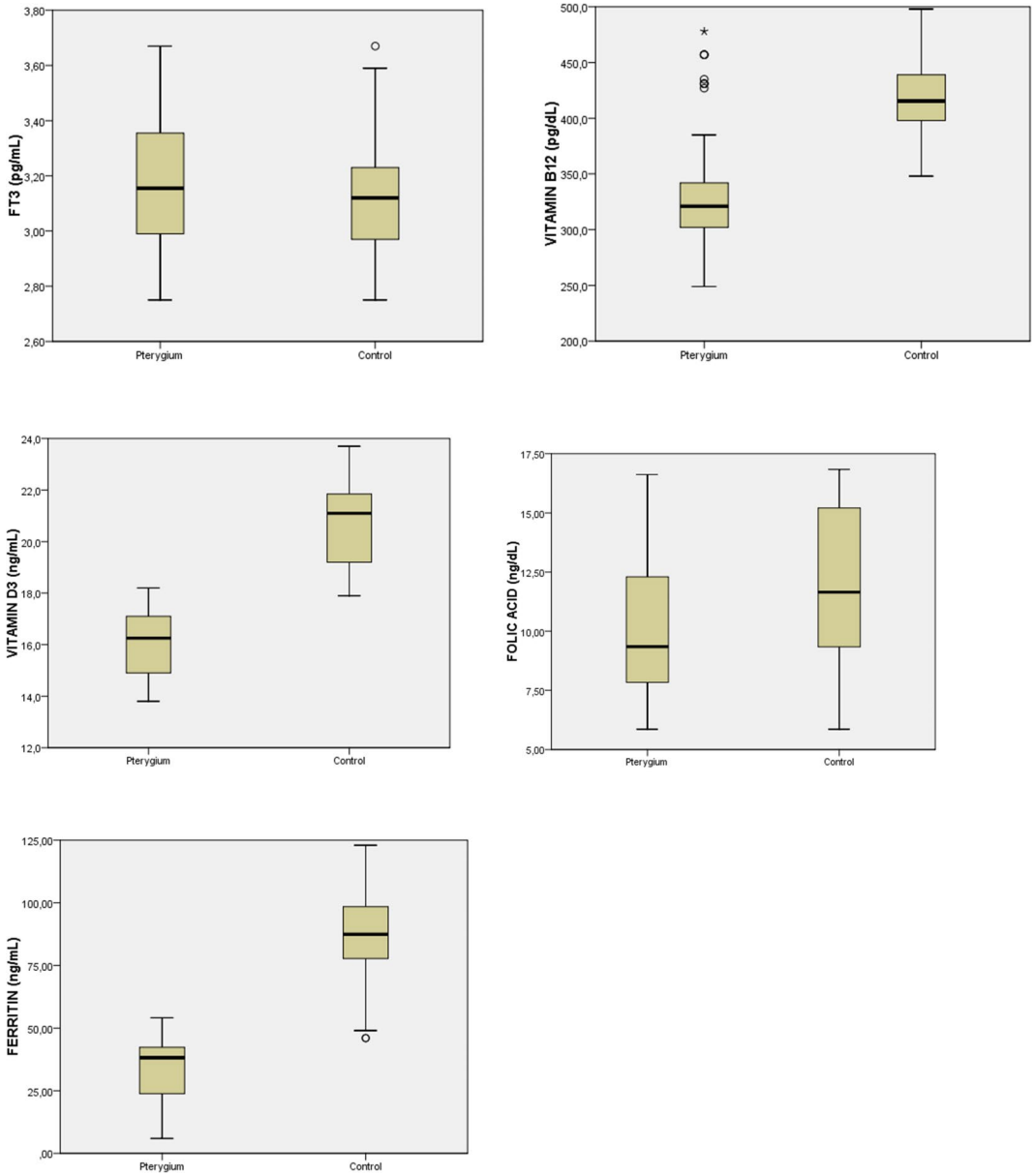

Fig. 1. Box plot graphs of laboratory analyses of the patient and control groups.

this damage. By breaking down ferritin, UV-A radiation increases the amount of free iron that is immediately detectably present in the cytoplasm of human skin fibroblasts and keratinocytes. It also reduces the binding activity of iron regulatory protein 1 (IRP-1)[16] The Fenton reaction uses the freed iron to catalyze the production of ROS caused by UV radiation[17]. The iron-scavenging action of ferritin is primarily responsible for maintaining the low level of intracellular free iron concentration, which is generally strictly regulated. Ferritin, which was previously believed to be restricted to the cytoplasm, has been discovered in the avian corneal epithelium's nuclei and may protect DNA from UV-induced free radical damage.[18] In the study conducted by Fox et al.[16] on pterygium tissue, ferritin mRNA levels were found to be 3 times lower in pterygium compared to controls, suggesting that ferritin plays a role in the pro-oxidant and inflammatory status of pterygium tissue. Although pterygium is thought to be a local pathology in our study, the fact that serum ferritin levels were significantly lower in the pterygium group compared to the control group supports that the anti-inflammatory mechanism deficiency is also affected systemically. This may be related to the severity of the condition in the cornea, and in this regard, it may be useful to compare cellular and tissue samples with serum values.

Vitamin B12 is a water-soluble vitamin that is essential for the proper functioning of the human body. The main rationale for evaluating vitamin B12 levels in this study was to understand whether there is a change in vitamin B12 levels in the pathogenesis of pterygium, a fibrovascular inflammation. There is insufficient data to support the hypothesis that vitamin B12 levels and inflammation are directly correlated. In a large population-based investigation, Young et al.[19] found a comparable association between vitamin B12 level and C-reactive protein (CRP) for some races, whereas Al-Daghri et al.[20] observed a substantial negative link between vitamin B12 level

and tumor necrosis factor-α (TNF-α). Studies conducted on experimental animals have demonstrated that a deficit in vitamin B12 initiates proinflammatory pathways via interleukin-10 (IL-10), monocyte chemoattractant protein-1 (MCP-1), and interleukin-1β (IL-1β)[21]. However, opinions differ about the mechanism and potential severity of the body's inflammation caused by a vitamin B12 shortage.

A vitamin B12 shortage can lead to mucocutaneous illnesses such as vitiligo, aphthous stomatitis, and atopic dermatitis[22]. Serum vitamin B12 levels in pterygium have never been studied, as far as we are aware. In this study, serum vitamin B12 levels were significantly lower in pterygium patients than in controls, and gender had no effect on the outcomes. The large sample size enhanced the conclusion's strong statistical power. This result can be interpreted in two ways: (1) By causing inflammatory processes in the corneal and conjunctival tissue, low vitamin B12 levels may have a role in the pathophysiology of certain disorders. Recent studies have shown a connection between low vitamin B12 levels and inflammation in a number of organs, including the liver, gut, and bone.[23] It's not clear enough right now, though, therefore additional future experimental work is required to clarify the exact mechanism. (2) In the same general systemic inflammatory disease, pterygium and low vitamin B12 levels may be independent results. Given that pterygium or low vitamin B12 levels are known to be linked to some systemic disorders, this theory may also be deemed plausible.In those with a systemic illness brought on by low vitamin B12 levels, pterygium and related ophthalmologic disorders may go unnoticed[9,21].This may help to clarify the association. Physicians who are keeping an eye on the patient should ask about any ocular surface complaints and seek consultation from an ophthalmologist as needed.

According to Bresscoll et al.[22], vitamin B12 may be utilized therapeutically to treat a few mucocutaneous conditions. Based on the findings of this investigation, it is plausible that elevated levels of vitamin B12 may serve as a preventive measure or a therapeutic approach for pterygium. However, given the number of documented side effects from vitamin B12 supplementation and the need for more prospective randomized trials to confirm its efficacy and safety, this is currently a very compelling argument[19].

Like vitamin B12, folic acid is a water-soluble vitamin that the body is unable to produce on its own and must get from food or supplements[24]. Serum folic acid levels in pterygium have never been studied, as far as we are aware. The study's findings indicate that, in comparison to healthy controls, pterygium patients had decreased serum folic acid levels. This result can be interpreted as follows; (1) There is limited evidence of the presence of a direct association between vitamin folic acid level and inflammation. Supplementing with vitamin B12 and folate through food may have therapeutic potential to prevent or treat nonalcoholic steatohepatitis, according to research done on mice, primates, and people. Our results are consistent with the literature, and the inflammatory nature of pterygium is supported by the fact that folic acid can be utilized to prevent the known inflammatory condition nonalcoholic steatohepatitis. (2) Given our similar interpretation of vitamin B12, it is also possible that low folic acid levels and pterygium are distinct outcomes described in the same broad systemic inflammatory illness. Given the documented associations between pterygium and low folic acid levels and various systemic disorders, this explanation may have some merit.

The study has also some important limitations. Firstly, the subjects were selected from a single center, which can cause a selection bias. Generally, the incidence of ptrygium is influenced by genetic background[25]. In addition, further research should be conducted on the systemic inflammatory status of patients with recurrent pterygium. Only patients with primary pterygium were included in our study. The clinical classification of pterygium according to TAN was evaluated according to lesion size, corneal invasion, optic zone involvement and vascularization and was noted by the same physician (FS). Comparison between subgroups could not be made because there were not enough people to make a statistical difference between the groups, which is another limitation of this study. Another limitation was that we did not use additional biomarkers to assess systemic inflammatory cytokines and did not perform histopathological examinations. These are much more costly than biochemical tests but provide similarly reliable results. There are studies suggesting that high neutrophil-to-lymphocyte ratios (NLR) may serve as a biomarker for systemic inflammation in pterygium patients and that systemic inflammatory processes may contribute to the local inflammatory environment on the ocular surface.(26) Another limitation of our study is that NLR values were not examined in our study and it was not investigated whether they supported the factors examined. Comparisons between subgroups with a larger number of patients will provide valuable information to the literature as the subject of future studies.

In conclusion, this study reports that pterygium patients have lower serum vitamin B12, folic acid, ferritin and vitamin D3 levels than healthy individuals. Further histological prospective studies should be designed to clarify the relationship between vitamin B12 and vitamin D3 levels and pterygium pathophysiology and the feasibility of vitamin B12 and vitamin D3 supplementation for treatment or prevention of recurrence. This may be the subject of a new study.

Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Author contributions

F.Sumer have constructed/constructed the main idea and hypothesis of the study. F.S. and BK, F.S and developed the theory and arranged/edited the material and method section. F.S.and A.S have evaluated the data in the Results section. Discussion section of the article. Written by F.S., E.Y. and B.K reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

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Declarations

Ethics approval and consent to participate

The study protocol was approved by the local human research ethics committee from Recep Tayyip Erdogan University. Protocol number and date 2023/77 and 27.03.2023. All patients included in this study gave their informed consent, which adhered to the tenets of the Declaration of Helsinki, and written informed consent was obtained from all subjects. Consent was obtained from the patients. Consent was also obtained from our

institution.

Consent for publication
Consent was obtained from the patients. Consent was also obtained from our institution.

Competing interests
The authors declare no competing interests.

Additional information
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