Research Square

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Oral Vitamin D3 Supplementation for Femtosecond LASIK–Associated Dry Eye

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Research Article

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Abstract

Purpose: To assess the effect of oral vitamin D_3 supplementation in dry eye after femtosecond laser-assisted in situ keratomileusis (FS-LASIK).

Setting: Liuzhou Worker's Hospital.

Design: This prospective study included 90 patients selected between January and December in 2019, who underwent fs-lasik operation in our hospital and had obvious symptoms indicating dry eyes one month after operation. The subjects were randomly divided into two groups: the experimental group (n = 45) received vitamin D3 2000 IU / D continuously for 12 weeks; the control group (n = 45) did not take vitamin D3 orally. Ocular surface disease index（OSDI）, tear breakup time（TBUT）and Schirmer's Test I were evaluated pre-medication and 1,3,6 months after treatment. Serum vitamin D level, and the mean concentration of cytokine IL-6, IL-17, IL-23 in tears were also measured.

Results: One month after treatment, the mean OSDI score of the experimental group (11.67 ± 8.53) was significantly lower than that of the control group (23.82 ± 13.22) (P = 0.007). TBUT (10.71±1.02s) and Schirmer I (9.36±0.40mm) of the experimental group were higher than those of the control group (7.49±1.29 s and 7.51±0.44 mm). The OSDI (10.25 ± 5.49), TBUT (10.75±1.09 seconds) and Schirmer I test value (11.34±0.39 mm) of the experimental group were significantly lower than those of the control group (20.22±6.23, 8.36±1.23， 8.12±0.50) at 3 months after treatment. There were significant differences in OSDI, TBUT (P ＜ 0.05) and Schirmer I test value between the two groups at 6 months after treatment. Serum vitamin D3 level was negatively correlated with OSDI score (r=-0.90，P=0.00), and positively correlated with Schirmer I test (r=0.88，P=0.00), TBUT score (r=0.89，P=0.00) and TMH (r=0.80，P=0.00). IL-17 level was shown to be significantly correlated with TBUT (r=-0.25, P=0.014) and Schirmer I test (r=-0.21, P=0.018). IL-6 level was significantly correlated with OSDI (R=0.18, P = 0.020) and TBUT (R=0.20, P = 0.019).

Introduction

Femtosecond laser-assisted in situ keratomileusis (FS-LASIK) is a current mainstream of keratorefractive surgery because of its predictability and stability [1-2]. FS-LASIK has many advantages: fast visual rehabilitation, less regression and subepithelial corneal haze, less postoperative dry eye symptoms. However, tear functions worsened approximately 40% at 1 month post-operation, and 20% to 40% at 6 months post-operation[3-4]. Although it is temporary, patients still complained about decreased visual acuity or residual refractive errors. These symptoms may be caused by post-LASIK dry eye [5]. Conventional treatment of post-LASIK dry eye includes the use of artificial tears to lubricate the ocular surface, but sometimes, it would be ineffective. Several studies have reported that punctual plugs and corticosteroids are effective for the post-LASIK dry eye [6]. However, the long-term treatment showed they may have potential side effects, including higher intraocular pressure and cataract.

Vitamin D_3 is a fat-soluble vitamin which produced by ultraviolet light. L. Adorini [7] and J. Marcotorchino [8] found that elevated vitamin D_3 levels could reduce inflammatory mediators and improve anti-oxidative functions [9]. A recent study found that vitamin D_3 can protect patients from dry eye syndrome (DES) [10], but inconsistent with Da- Hye Jeon's result [11].

The aims of this study were to investigate whether there was an association between low vitamin D_3 levels and post-LASIK dry eye, and whether dry eye symptoms could be alleviated by oral vitamin D_3 supplement. If so, then how cytokine concentrations would change via taking oral vitamin D supplement.

1. Materials And Methods

1.1 Participants

This prospective study included 90 patients selected between January and December in 2019, who underwent fs-lasik operation in our hospital and had obvious symptoms indicating dry eyes one month after operation. The subjects were randomly divided into two groups: the experimental group (n = 45) received vitamin D3 2000 IU / D continuously for 12 weeks 1month after operation; the control group (n = 45) did not take vitamin D3 orally. The inclusion criteria were as follows 1) Myopic patients, aged 18 to 30 with no dry eye history and volunteered to take the refractive surgery; 2) Stable refractive error for at least 2 years (within ±0.5D); 3) No long-term history of wearing contact lenses. The exclusion criteria were 1) Inflammatory diseases of eyelid and its appendages and conjunctiva that have adverse effects on tear film; 2) lacrimal gland diseases or surgery; 3) abnormal eyelid structure or function; 4) eye diseases such as cataract, glaucoma, keratoconus, uveitis, retinal detachment, optic neuritis, etc.; 5) systemic diseases such as diabetes, hypertension, etc.; 6) Use of drugs that affect corneal metabolism.

Vitamin D_3 deficiency was assessed through classifying serum 25(OH)D_3. The fasting serum samples of patients were collected pre medication, 1 、3 and 6 months after medication to analyze serum 25-hydroxyvitamin D levels. The serum samples were pre-processed and stored at −80 °C until later analysis. Then, serum 25-hydroxyvitamin D levels were determined using a radioimmunoassay kit (DiaSorin Inc., Stillwater, MN, USA).[11] The serum 25(OH) D levels < 20 ng/mL was diagnosed as vitamin D deficiency. [12]

1.2 Ethical approval

Ethical approval (the protocol of the study and informed consent) was obtained from the human Ethics Committee of Liuzhou Worker's hospital. All the patients or their legal guardians signed written informed consent. All procedures were in accordance with the Declaration of Helsinki.

1.3 Surgical procedure and Postoperative pharmacotherapy

All FS-LASIK procedures were performed by two experienced surgeons. The WaveLight FS200 femtosecond laser (Alcon, Germany) was used to create the corneal flap and the diameter of optical zone ablation was 6.5 mm (EX500, Alcon, Germany).

Both groups of subjects were treated with polyethylene glycol ophthalmic solution (Alcon, USA) which were treated 4 times a day for 12 weeks.

In addition, the experimental group took vitamin D3 soft capsules orally, each contained 2000 IU of vitamin D3 (Confidence Inc., America) [12], one capsule once a day, with meal. The administration of vitamin D3 lasted 12 weeks, while the control group remained conventional treatment.

1.4 **Clinical Examination**

Patients were examined in detail by the same ophthalmologist. The following parameters were observed pre-medication, 1 、3 and 6 months after surgery: 1) Fill out the ocular surface disease index(OSDI) questionnaire, a 12-question scale for evaluating dry eye symptoms, before the start of clinical examinations; 2) Tear meniscus height (TMH), which indirectly qualify tear film volume, non-invasive tear break-up time (NITBUT), an estimate of tear stability using Keratograph 5M(Oculus GmbH, Wetzlar, Germany); 3) Schirmer I test, a tear secretion test, using Schirmer paper; 4) Observe corneal and conjunctival staining using fluorescein. Sodium fluorescein test paper and Schirmer test paper were purchased from Tianjin Jingming New Technology Development Co., Ltd.

Keratograph 5M measurement method: (1) TMH: the patients placed head position in front of the central dot as required, setup TMH mode, instructed the patient to blink before collecting images. A TMH of less than 0.35mm is regarded as lower tear quantity; (2) NITBUT: instructed the patient to blink twice, and recorded the first tear film rupture time and average tear film rupture time when the Placido ring broke.

1.5 Tear samples

Tear samples were collected non-traumatically and quickly from the inferior fornix of both eyes in case reflex tear secretion. Tear samples, collected by glass capillary micropipettes, from two eyes (1 μl total) were fully eluted into a sterile collection tube containing 9 μl of 0.1% bovine serum albumin (Sigma-Aldrich, St. Louis, MO). Tubes were then stored at -80°C until experiment performed. Cytokin concentrations in tears of patients were measured using a Milliplex immunobead assay (Human Th17 Magnetic Bead Panel, Millipore, Billerica, MA) and the Bio-Plex Luminex 200 XYP instrument (Bio-Rad Laboratories).

1.6 Statistical analysis

All data were conducted using SPSS 22.0 software. Kolmogorov-Smirnov was used to evaluate the normality of data. The changes of clinical parameters between the experimental group and the control group were compared at every follow-ups (pre- medication, 1、 3 and 6 months after medication). The data of normal distribution were tested by t test and non-normal distribution were tested by Mann-whitney u test. For the parameters observed at different time points in the two groups, repeated measurements of variance analysis were used. Pearson correlation analysis was used to assess the correlation between clinical data and serum vitamin D3 level levels. A p value ≤ 0.05 was considered significant.

2. Results

Ninety eyes of 90 Chinese patients who underwent fs-lasik operation with obvious dry eyes after operation were included in the study and randomized into experimental group and control group. The general information of the patients are shown in Table 1. Parameters are all at the baseline, and there is no statistical significance between the two groups.

Table 1. Preoperative general data between the two groups

	experimental group	control group	t	p
Age/years	27.35±4.42	26.85±5.11	-1.73	>0□05
Preoperative spherical power / D	-5.54±1.35	-5.60±1.30	1.56	>0□05
Preoperative cylinder power / D	-1.15±0.64	-1.13±0.61	1.34	>0□05
BCVA	0.06±0.05	0.07±0.04	1.15	>0□05
Ablation deph /um	80.55±11.41	-80.68±11.37	1.62	>0□05
Serum VITD3 ng/ml	23.80±3.26	23.76±3.11	1.50	>0□05

2.1 Visual acuity

One month after medication, the uncorrected visual acuity (UCVA) of the experimental group was - 0.11 ± 0.15, and that of the control group was 0.01 ± 0.14. There was no significant difference between the two groups (t = 2.14, P = 0.030). At 3 months UCVA of the experimental group was - 0.12 ± 0.13, which was higher than - 0.09 ± 0.11 of the control group. There was significant difference between the two groups (t = 1.95, P = 0.042). There was no significant difference between the two groups after 6 months.

2.2 Ocular surface disease index□OSDI□

There was no significant difference in OSDI score between the two groups before medication (see Table 2). The OSDI scores of the experimental group at 1, 3 and 6 months after taking the medicine were lower than those before taking the medicine. One month after treatment, the OSDI scores of the experimental group was 11.67 ± 8.53, which was lower than those of the control group (23.82 + 13.22, t = 3.693, P = 0.024). Six months after treatment, the experimental group was significantly lower than the baseline, and the control group was slightly lower than the baseline.

Table 2. Changes in OSDI of the two groups of after medication

	experimental group	control group	t	p
Pre medication	26.54±8.39	26.63±8.40	0.751	0.067
1 month Post- medication	11.67±8.53	23.82±13.22	4.323	0.007
3 months Post- medication	10.25±5.49	20.22±6.23	2.502	0.010
6 months Post- medication	10.40±5.26	18.54±7.60	2.311	0.025

2.3 Tear breakup time（TBUT）

The TBUT of the experimental group was significantly higher than that of the control group (10.71 ± 1.02) s vs. (7.49 ± 1.29) s (t = 2.84, P = 0.025). The TBUT of the experimental group was close to the normal level at 3 months after treatment. TBUT of the experimental group was significantly higher than that of the control group at any time point. The control group did not return to the normal level (t = 3.71, P = 0.033) during the 6-month follow-up (see Figure 1). There was significant difference in TBUT at different time points between the two groups (F = 27.32, P < 0.02).

2.4 Schirmer's I Test（SIT）

One month after taking the medicine, the SIT of the experimental group was higher than that of the control group (t = 2.78, P = 0.030). Three months after treatment, the SIT values of the experimental group increased significantly and recovered to 11.34 ± 0.39s. The SIT values of the control group increased to 7.51 ± 0.44 and 8.12 ± 0.50 at 1 and 3 months after treatment (see Figure 2). There was significant difference in SIT at different time points between the two groups (F = 9.10, P = 0.017).

2.5 Tear meniscus height (TMH)

One month after medication, TMH of the experimental group was 0.35 ± 0.03, which was significantly higher than that before taking the medicine (P = 0.028). The TMH value was 0.39 ± 0.08 in the experimental group and 0.29 ± 0.08 in the control group at 3 months after medication, with statistical significance (P = 0.035) (Table 3)

Table 3. Changes in TMH of the two groups

	experimental group	control group	P
Pre medication	0.27±0.05	0.28±0.04	0.322
1 month Post- medication	0.35±0.03	0.29±0.07	0.038
3months Post- medication	0.39±0.08	0.29±0.08	0.030
6months Post- medication	0.39±0.05	0.31±0.06	0.035

2.6 Serum 25(OH) D_3 level

In the experimental groups the mean serum 25(OH)D_3 level increased from 12.85±5.24 (9.57–18.89) preoperatively to 46.83±8.52 (38.41–58.12) and 56.51±10.36 (44.78–69.14) at 1month and 3 months after medication, respectively. There were significant differences between preoperative and 1, 3months follow-up ($P < 0.05$). At 3 months after medication, serum 25(OH) D_3 level was negatively correlated with OSDI score (r=-0.90;P=0.00) and positively with Schirmer I test (r=0.88，P=0.00), TBUT (r=0.89，P=0.00), and TMH (r=0.80，P=0.00). The relationship between serum 25(OH)D_3 level and clinical data are summarized in Figure 3.

2.7 Cytokine concentrations

The mean concentration of cytokine concentrations in tears between two groups were shown in table 5. The IL17, IL6 and IL23 levels of control group significant increased at 3 months after treatment, whereas cytokine concentrations of experimental group were slight increased (Table 5). IL-17 level was shown to be significantly correlated with TBUT (r=-0.25, P=0.014) and Schirmer I test (r=-0.21, P=0.018). IL-6 level was significantly correlated with OSDI (r=0.18, P = 0.020) and TBUT (r=0.20, P = 0.019).

Table 5. Changes in cytokine concentrations

		IL-17	IL-6	IL-23
Pre medication	experimental group	191.21±50.10	28.62±12.78	8.36±4.12
	control group	188.45±48.36	25.75±14.33	9.64±6.50
	t	2.09	1.72	1.11
	p	0.08	0.14	0.21
3months Post- medication	experimental group	225.78±35.63	30.36±17.18	11.21±8.09
	control group	821.22±45.28	45.79±20.09	16.60±7.34
	t	23.77	5.59	3.87
	p	0.001	0.02	0.03

3. Discussion

Post-LASIK dry eye is becoming an increasingly important health problem. Dry eye patients usually suffered from symptoms such as grittiness, pain, ocular fatigue, redness, or burning. Although it is temporary, it affects patients' functional visual acuity (such as reading visual acuity, keeping the eyes open after 10 seconds reading or driving).

In our study, the Schirmer score decreased after surgery. Many patients complain of noticeable grittiness and fluctuating vision. The process of corneal flap cut off all the subepithelial plexus of cornea, which leads to a significant reduction in the reflex tear secretion [13]. The transection of corneal subepithelial plexus impair corneal sensations and disrupt the interaction between the autonomic nerves and the lacrimal gland [14-15]. The research found that tear secretion was correlated with serum vitamin D3 levels [16-17]. The patients with lower serum vitamin D3 levels get lower Schirmer score. A research by Lu, X et al showed that vitamin D3 were found in tear, and vitamin D3 transporters were expressed in lacrimal and accessory glands [18]. Our research also confirmed that patients who treated with vitamin D_3 have higher Schirmer score.

OSDIs in both the experimental group and the control group were significantly higher at 1-month post-operation. The OSDI score in the experimental group was significantly lower after 3 months of vitamin D3 supplement, which increased with the serum levels of vitamin D_3. Our finding supports the idea that vitamin D_3 levels are correlated with post-LASIK dry eye. Chih-Huang Yanga [19]et al also found an association between OSDI and vitamin D_3. Vitamin D_3 supplementation may be useful for dry eye symptoms[17]. We discovered that the OSDI in the control group still not reach to preoperative level. Previous studies have shown that the density of nerve fibers remained less compared to the preoperative levels, even 5 years after operation, which caused the persistence of dry eye symptoms [20]. Cruzat[21] et al

found that corneal immune cells can affect the density of corneal nerve, and Vitamin D_3 promotes corneal nerve regeneration by reducing the levels of inflammatory factors.

We observed that the patients in the control group complained about the pain, while there were not any in the experimental group. We speculated that inflammatory mediators can decrease the sensory nerve thresholds in the ocular surface which lead to the pain and hyperalgesia 22.

According to our results, increases in IL-17 concentration were observed in both groups, supporting the possibility of an important role for IL-17 in dry eye inflammation processes. Vitamin D_3 is well known for modulating the expression of various inflammatory cytokines in various cells, including corneal epithelial cells [23]. Wei & Christakos [24] illustrated that vitamin D_3 played an important immunomodulatory role in the immune system. The IL-17, which play the pathologic role in inflammatory disorders was found to be reduced in the tear of patients who were treated with vitamin D_3[25]. Lam and associates7 also suggested a correlation between IL-6 levels in tears of dry eye patients, such as OSDIs and TBUT. In the further study, we will study the mechanism of the vitamin D_3 in reducing dry symptoms and discover the role of IL-17 and its relationship with vitamin D_3 in FS-LASIK dry eye.

Post-LASIK dry eye had been reported its effects on functional visual acuity. Our results showed that, BCVA, photopic contrast sensitivity and scotopia contrast sensitivity were significantly improved after LASIK in the experimental group, while the control group remained the same. These findings suggest that the oral vitamin D_3 supplementation could be effective for the prevention of postoperative dry eye induced by LASIK compared to treatment with only conventional eye drops. The mechanism of vitamin D_3 improving post-LASIK dry eye symptom is not very clear. More studies with a larger patient base and longer follow-up durations may help to determine the role of vitamin D_3 in decreasing the incidence and severity of the post-LASIK dry eye.

Value Statement

WHAT WAS KNOWN

LASIK may induce post surgery dry eye, which can affect decreased visual acuity or residual refractive errors.

Conventional treatment of post-LASIK dry eye includes the use of artificial tears to lubricate the ocular surface, punctal plugs and corticosteroids , but sometimes, it can be ineffective or have long-term side effect.

WHAT THIS PAPER ADDS

Vitamin D_3 can increase serum 25(OH) D3 level and alleviate dry eye syndrome, and improve visual quality.

References

1. Somani S, Tuan KA, Chernyak D (2004) Corneal asphericity and retinal image quality: a case study and simulations. J Refract Surg 20:S581–S585
2. Amigó A, Bonaque-González S, Guerras-Valera E (2015) Control of induced spherical aberration in moderate hyperopic LASIK by customizing corneal asphericity. J Refract Surg 31:802–806. DOI:10.3928/1081597X-20151111-03
3. De Paiva CS, Chen Z, Koch DD et al (2006) The incidence and risk factors for developing dry eye after myopic LASIK. Am J Ophthalmol 141:438–445. DOI:10.1016/j.ajo.2005.10.006
4. Shoja MR, Besharati MR (2007) Dry eye after LASIK for myopia: incidence and risk factors. Eur J Ophthalmol 17:1–6. DOI:10.1177/112067210701700101
5. Behrens A, Doyle JJ, Stern L et al (2006) Dysfunctional tear syndrome: a Delphi approach to treatment recommendations. Cornea 25:900–907. DOI:10.1097/01.ico.0000214802.40313.fa
6. Stern ME, Pflugfelder SC (2004) Inflammation in dry eye. Ocul Surf 2:124–130
7. Adorini L, Penna G (2008) Control of autoimmune diseases by the vitamin D endocrine system. Nat Clin Pract Rheumatol 4:404–412. DOI:10.1038/ncprheum0855
8. Marcotorchino J, Gouranton E, Romier B, Tourniaire F, Astier J, Malezet C, Amiot MJ, Landrier JF (2012) Vitamin D reduces the inflammatory response and restores glucose uptake in adipocytes. Mol Nutri Food Res 56:1771–1782. DOI:10.1002/mnfr.201200383
9. Alvarez JA, Chowdhury R, Jones DP, Martin GS, Brigham KL, Binongo JN et al (2014) Vitamin D status is independently associated with plasma glutathione and cysteine thiol/disulfide redox status in adults. Clinical endocrinology. Clin Endocrinol 81:458–466. doi:10.1111/cen.12449
10. Mangge H, Weghuber D, Prassl R, Haara A, Schnedl W, Postolache TT, Fuchs D (2015) The role of vitamin D in atherosclerosis inflammation revisited: more a bystander than a player? Curr Vasc Pharmacol 13:392–398. DOI:10.2174/1570161111666131209125454
11. Jeon D-H, Yeom H, Yang J, Song JS, Lee HK (2017) Hyeon Chang Kim. Are Serum Vitamin D Levels Associated With Dry Eye Disease? Results From the Study Group for Environmental Eye Disease. J Prev Med Public Health 50:369–376. DOI:10.3961/jpmph.17.089
12. Muhammed Kizilgul S, Kan O, Ozcelik S, Beysel M, Apaydin BU & Erman Cakal. Vitamin D Replacement Improves Tear Osmolarity in Patients with Vitamin D Deficiency. Seminars in Ophthalmology, 2017,Early Online, 1–6. DOI: 10.1080/08820538.2017.1358752
13. Chao C, Golebiowski B, Stapleton F (2014) The role of corneal innervations in LASIK-induced neuropathic dry eye. Ocul Surf 12:32–45. DOI:10.1016/j.jtos.2013.09.001
14. Darwish T, Brahma A, O'Donnell C et al (2007) Sub basal nerve fiber regeneration after LASIK and LASEK assessed by noncontact esthesiometry and in vivo confocal microscopy: prospective study. J Cataract Refract Surg 33:1515–1521. DOI:10.1016/j.jcrs.2007.05.023
15. Aras C, Ozdamar A, Bahcecioglu H et al (2000) Decreased tear secretion after laser in situ keratomileusis for high myopia. J Refract Surg 16:362–364

16. Jin KW, Ro JW, Shin YJ et al (2016) Correlation of vitamin D levels with tear film stability and secretion in patients with dry eye syndrome. Acta Ophthalmol. doi:10.1111/aos.13241
17. Pelin YILDIRIM, Yes_im GARIP, Ayse Aslihan KARCI, Tuba GULER (2016) Dry eye in vitamin D deficiency: more than an incidental Association. International Journal of Rheumatic Diseases 19:49–54. DOI:10.1111/1756-185X.12727
18. Lu X, Elizondo RA, Nielsen R, Christensen EI, Yang J, Hammock BD, Watsky MA (2015) Vitamin D in tear fluid. Invest Ophthalmol Vis Sci 56:5880–5887. DOI:10.1167/iovs.15-17177
19. Yang C-H, Albietz J, Harkin DG, Kimlin MG, Schmid KL (2018) Impact of oral vitamin D supplementation on the ocular surface in people with dry eye and/or low serum vitamin D. Contact Lens and Anterior Eye. Cont Lens Anterior Eye 41:69–76. DOI:10.1016/j.clae.2017.09.007
20. Ikuko Toda (2018) Dry Eye After LASIK. Invest Ophthalmol Vis Sci 59:DES109–DES115. DOI:10.1167/iovs.17-23538
21. Cruzat A, Witkin D, Baniasadi N et al (2011) Inflammation and the nervous system: the connection in the cornea in patients with infectious keratitis. Invest Ophthalmol Vis Sci 52:5136–5143. DOI:10.1167/iovs.10-7048
22. Rohit Shetty S, Sethu P, Chevour et al. Lower Vitamin D Level and Distinct Tear Cytokine Profile Were Observed in Patients with Mild Dry Eye Signs but Exaggerated Symptoms. DOI: 10.1167/tvst.5.6.16
23. Segond von, Banchet G, Boettger MK, Konig C et al (2013) Neuronal IL-17 receptor upregulates TRPV4 but not TRPV1 receptors in DRG neurons and mediates mechanical but not thermal hyperalgesia. Mol Cell Neurosci 52:152–160. DOI:10.1016/j.mcn.2012.11.006
24. Wei R, Christakos S (2015) Mechanisms underlying the regulation of innate and adaptive immunity by vitamin D. Nutrients 7:8251–8260. DOI:10.3390/nu7105392
25. Kim CF, Moalem-Taylor G (2011) Interleukin-17 contributes to neuroinflammation and neuropathic pain following peripheral nerve injury in mice. J Pain 12:370–383. DOI:10.1016/j.jpain.2010.08.003

Figures

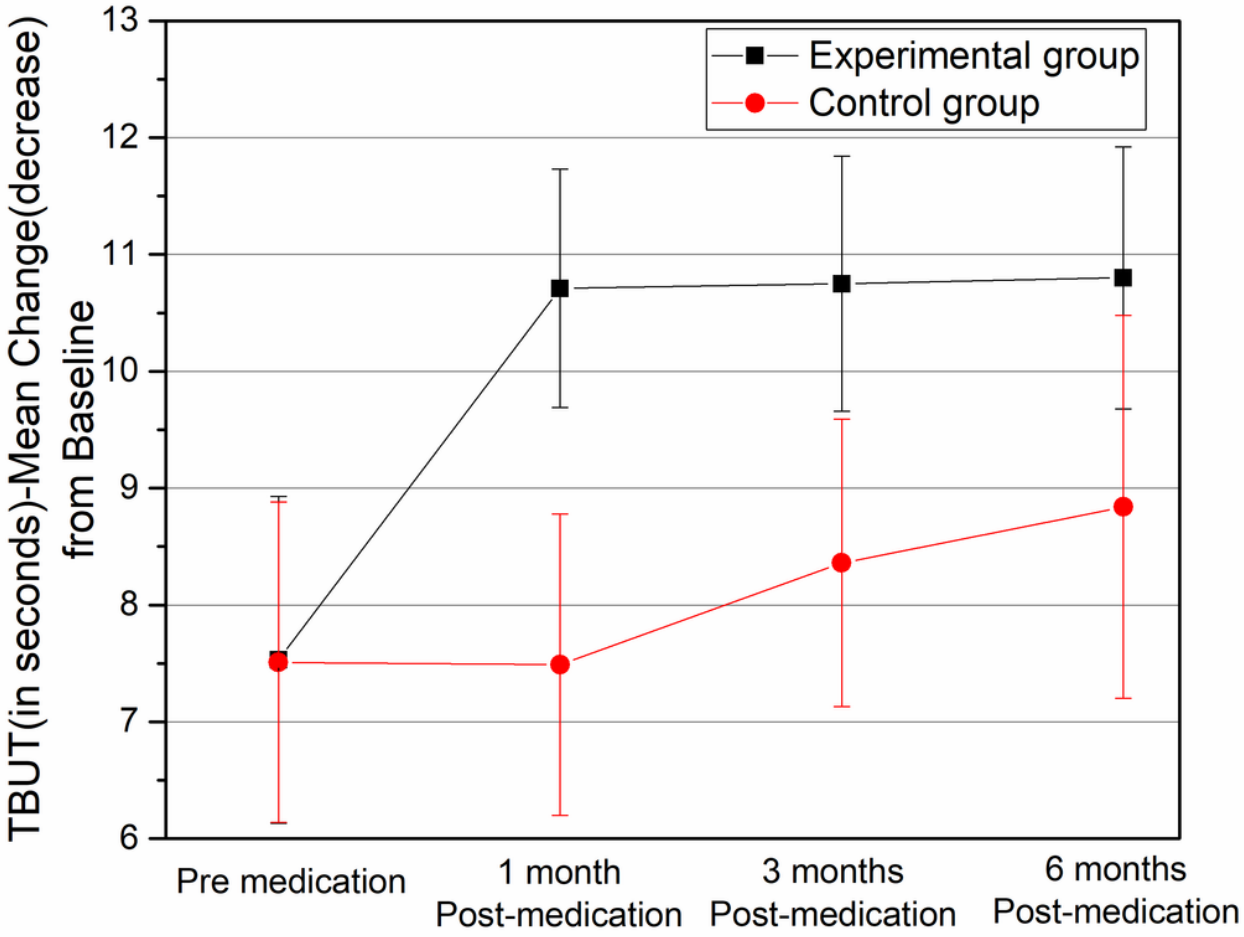

Figure 1

Changes in TBUT of the two groups after medication

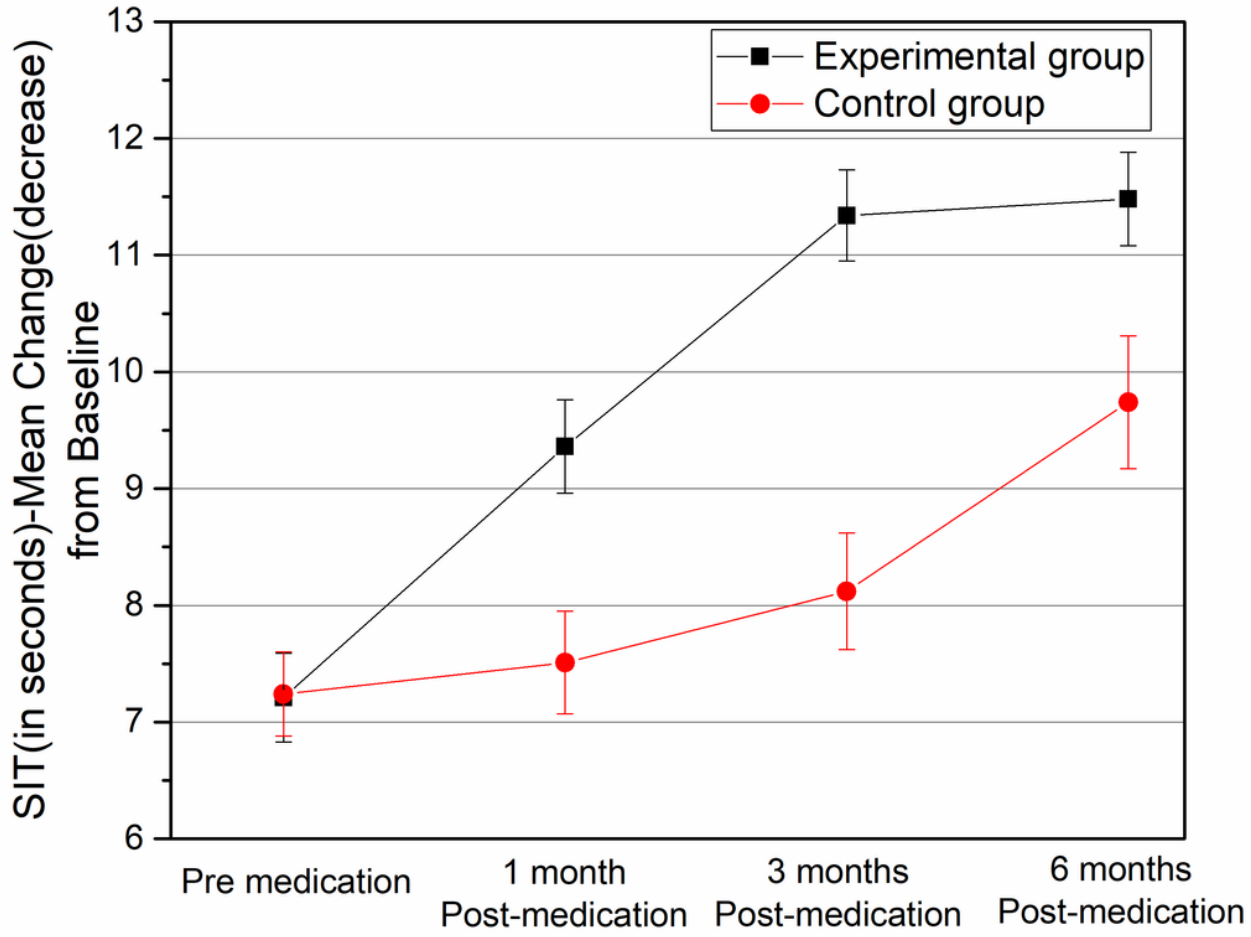

Figure 2

Changes in SIT of the two groups after medication

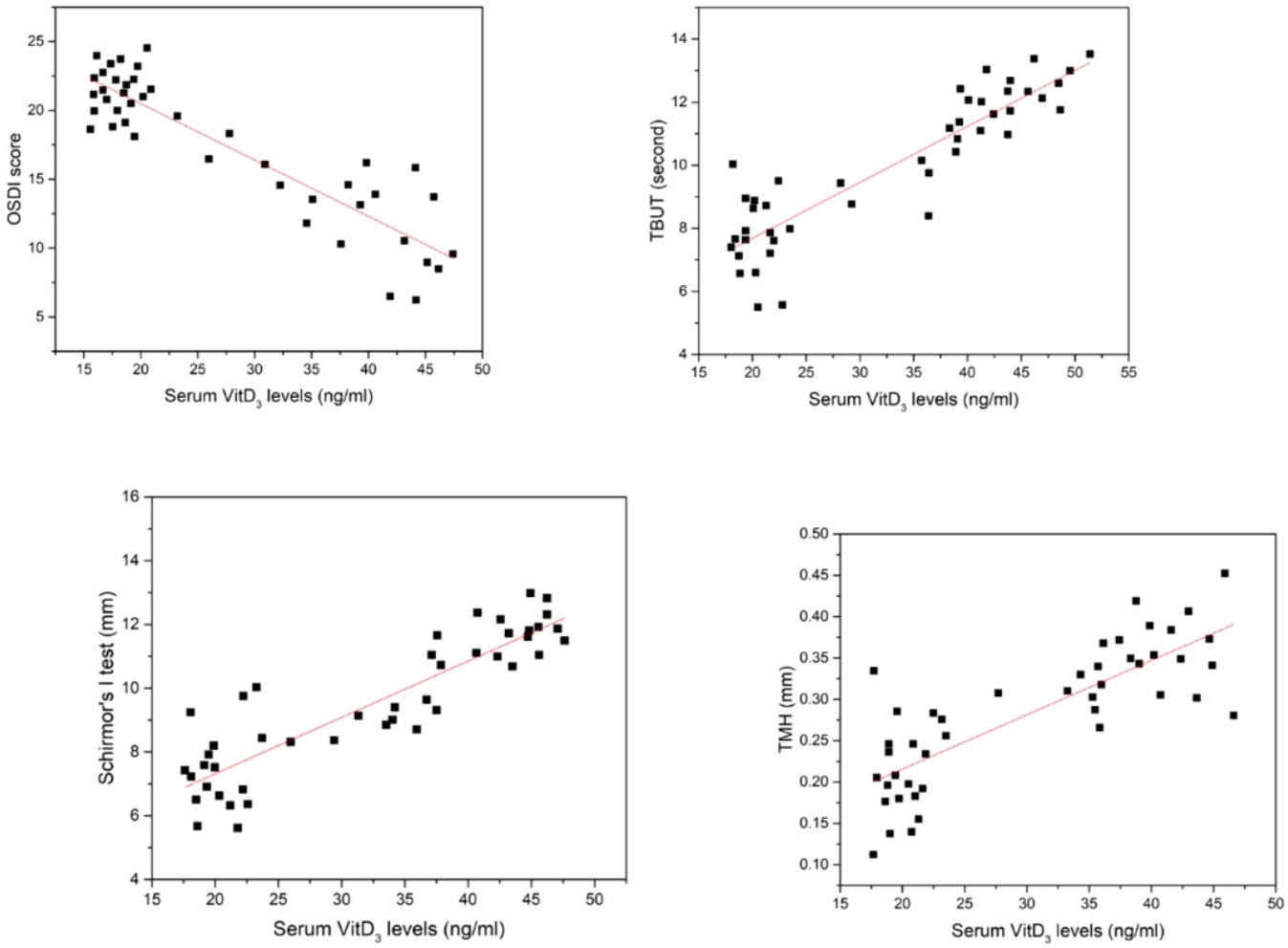

Figure 3

Correlation between Serum vitamin D3 level and TBUT, OSDI, SIT, TMH