·文献综述·

糖尿病性干眼发病机制及治疗进展

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摘要

糖尿病是一种主要以损害微血管为主的病变。随着生活水平的提高,糖尿病患者的数量也逐渐增加,据最新数据显示,全球的糖尿病患病率高达 9.3%(4.63 亿人)。糖尿病相关的视网膜病变是导致工作人群视力障碍最主要的原因,近年来人们逐渐认识到高糖也可以引起眼表泪膜的不稳定、角膜神经功能障碍、角膜感知功能下降、泪液渗透压升高。糖尿病引起的眼表功能障碍原因复杂,机制多样,包括高糖导致泪膜各层结构破坏、树突状细胞-神经沟通障碍、炎性因子破坏泪腺分泌泪液等。本文就糖尿病性相关干眼的发生机制、研究进展进行综述,以期眼科医师在诊疗糖尿病干眼患者时更多考虑全身情况。

关键词:糖尿病;干眼;发病机制;治疗;眼表
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Pathogenesis and advances in treatment of diabetic dry eye

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Abstract

• Diabetes is a disease that leads primarily to microvascular damage. In recent years, with the improvement of living standards, the number of diabetes patients has been increasing. The latest data is shown that about 9.3% (463 million people) globally have diabetes. Diabetic retinopathy is a leading cause of visual impairment and blindness among the working - age population. What have been progressively recognized in recent years is hyperglycemia can also lead to tear film instability, corneal nerve dysfunction, corneal sensitivity decreased, and tear osmolarity increased. The etiology and mechanisms of ocular surface dysfunction caused by diabetes are diverse and complex, including hyperglycemia destabilizing the tear film, disturbances in connectivity between dendritic cells and neurons, and inflammatory cytokines inducing damage to the lacrimal glands, leading to impaired tear secretion. This article is intended to review recent progress and mechanisms in diabetic dry eye and the general conditions of patients that ophthalmologists should consider during the diagnosis and treatment of the diabetic dry eye.

• KEYWORDS: diabetes; dry eye; pathogenesis; treatment; ocular surface

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0 引言

糖尿病属一种慢性代谢性、炎症性疾病[1],其对眼部的损害可以涉及视网膜、视神经以及眼表的相关结构。糖尿病视网膜病变的患病率及干预措施已得到广泛研究,但糖尿病患者的眼表受损机制及治疗报道不多。干眼是一种多因素共同参与而诱发的眼表疾病,其特征在于泪膜动态平衡的丧失,表现为泪膜不稳定和泪液高渗,伴随着各

种眼部不适症状、眼表的炎症以及角膜神经感觉异常在干眼的发病中发挥着重要作用。

1 糖尿病性干眼的发病率及影响因素

糖尿病是干眼的诱因之一,糖尿病与干眼的发病显著相关[2]。Manaviat 等[3]研究中,糖尿病患者的干眼患病率约为 54.3%,但儿童及青少年的糖尿病性干眼的发生率为 28.95%[4],患者病程长、年龄大、维生素 D 缺乏、心理压力过度都会导致泪河高度越低,泪膜稳定性差[5]。血糖控制不佳、波动较大或血糖极速变化增加干眼发病[6];糖化血红蛋白(HbA1c)值越高,说明患者长期控制血糖欠佳,泪膜稳定性也越差[7-8];在绝经期糖尿病女性因为缺乏雌激素对泪腺腺泡细胞中的线粒体保护作用,导致局部氧化应激反应升高破坏泪膜稳定性,干眼增多[9]。一部分患者口服如非那雄胺等 5-α-还原酶抑制剂或抗抑郁药物也增加干眼的患病风险[10-11];在有饮酒史的患者中发现有代谢的酒精出现在泪液中,升高泪液渗透压,溶解泪液中的脂质,破坏泪膜稳定性[12-13];既往有过手术史包括屈光手术、全视网膜激光光凝也会增加糖尿病患者泪膜不稳定性[14-15]。尽管发生干眼的危险因素极其多,但泪膜稳定性的破坏是影响糖尿病患者干眼的主要原因。

2 糖尿病性干眼的发病机制

2.1 泪膜稳定性下降 泪膜由最外层脂质层,内层的水液层及中间黏蛋白层组成,任何一层结构被破坏都会导致泪膜的不稳定。在临床上广泛应用泪膜破裂时间来衡量泪膜的质量及稳定性,现目前可以使用眼表综合分析仪与传统侵袭性荧光素钠测量泪膜破裂时间,后者检查需在结膜囊滴注荧光素钠,常导致泪膜的稳定性下降,使其测量值偏低[16];而眼表综合分析仪表现出更高的准确性,且是无接触式,在临床中的使用逐渐增加。

睑板腺脂质含量影响泪膜脂质层稳定性。糖尿病患者局部睑板腺脂质聚集除受全身高血脂影响外,Yu 等[17]发现睑板腺管壁的增厚,腺泡单位扩张、萎缩,腺体密度降低,炎细胞浸润,纤维组织增生,腺管开口狭窄、闭塞、纤维化,均引起睑板腺脂质的分泌下降。

高血脂诱导泪腺腺泡细胞凋亡,泪液分泌量减少,水液层结构被破坏[18]。高血糖相关的自主神经病变、交感和副交感神经支配障碍损伤泪腺微血管、杯状细胞分泌黏蛋白及泪液分泌量下调[19-20],泪液处于相对高渗状态,最终可以导致结膜和角膜细胞凋亡,同时也引发炎症级联反应,也可以触发流泪反射的反应——“干反应”被抑制,瞬目及反射性泪液分泌减少[21]。

糖尿病患者长期高血糖和脂质代谢紊乱以各种形式导致泪膜结构异常[22],泪膜的稳定性破坏,泪液蒸发增加,导致炎症反应加重,进一步促进干眼发生[23]。

2.2 角膜感知功能下降 糖尿病患者角膜神经纤维长度缩短和变细,分支、密度减少[24-25],周围高浓度树突状细胞聚集都导致角膜敏感度和知觉降低[26],从而在临床上常出现患者的症状与体征常不相符。活体激光扫描共聚焦显微镜(*in vivo* confocal microscopy, IVCM)可以量化角膜神经形态,如密度、纤维长度、分支等,常用于评估角膜神经状态[27]。

泪液中的成分变化可降低角膜感知功能。糖尿病患者的泪液中胰岛素样生长因子结合蛋白 3(IGFBP-3)浓度约为非糖尿病组的 3 倍,泪液中 IGFBP-3 浓度的显著增加与角膜基底下神经丛中神经纤维丢失和神经纤维分支减少显著相关[28];有学者发现三叉神经感觉神经末梢释放的 P 物质在糖尿病患者泪液中明显降低,不能正常维持角膜感知功能,瞬目平均次数减少,泪膜稳定性下降[29],但 Taketani 等[30]研究发现通过拮抗 P 物质受体,可恢复干眼中的调节性 T 细胞功能,进而减轻干眼症状。故对于泪液中成分变化的作用有待进一步探究。

角膜感知功能障碍使得糖尿病性干眼患者的症状与体征不符合,症状容易被忽视,建议糖尿病患者应该定期进行干眼的相关检查,同时可口服某些药物改善泪液成分,缓解角膜感觉减退,避免延误病情诊断及治疗。

2.3 炎症机制参与眼表完整性的破坏 前期大量研究表明糖尿病患者全身氧化应激反应增高。2 型糖尿病小鼠的睑板腺中氧化应激、炎症和凋亡相关基因表达上调,防御反应等相关基因和基因本体表达下调,机体炎症-防御机制的破坏损伤泪腺线粒体功能,杯状细胞能量代谢障碍,泪液分泌减少[31-32]。氧化应激条件下过氧化物酶体增殖物激活受体 γ(PPARγ)表达降低,激活 MAPK 和 NF-κB信号通路,促使眼睑局部炎症因子如白细胞介素-6(IL-6)、白细胞介素-1β(IL-1β)、肿瘤坏死因子-α(TNF-α)表达上调[33-34],同时诱导细胞间黏附分子-1(ICAM-1)表达[35],或与基质金属蛋白酶-9(MMP-9)DNA 启动子结合,增加 MMP-9 mRNA 的含量,降解细胞外基质,破坏角膜上皮细胞间的紧密连接,损害眼表完整性[36]。但最近的一项研究发现部分糖尿病性干眼患者与非糖尿病性干眼患者的泪液中炎症因子无明显差异[37]。伴有炎症因子升高的患者局部阿奇霉素治疗可显著改善症状[38]。

3 糖尿病性干眼的治疗

3.1 一般情况控制 控制高糖、高血脂异常,改变饮酒、抽烟不良习惯;对于服用抗抑郁药物或服用如非那雄胺等 5-α-还原酶抑制剂患者,可在专科医师的建议下更改全身药物或加用人工泪液改善症状。

3.2 物理治疗 局部热敷、睑板腺按摩、泪点闭塞及理疗等治疗方法可以改善干眼症状[39]。睑板腺按摩(meibomian gland expression, MGX)联合强脉冲光(intense pulsed light, IPL)可以融化腺口的脂栓,减少结膜血管释放炎症因子来改善泪膜稳定性[40]。泪点闭塞最大限度减少泪液的流失,改善以泪液分泌减少为主型的患者症状,但可能会发生栓子丢失和眼部刺激症状[41],甚至有的患者会出现泪小管炎或泪囊炎[42],其安全性有待商榷,并且泪点闭塞对于干眼的炎症并无治疗作用[43]。鼻腔泪液神经刺激器(intranasal tear neurostimulator, ITN)是一种以刺激筛前神经,激活鼻泪反射,从而刺激泪液、黏蛋白和脂质的分泌,增加瞬时泪液分泌量,降低泪液渗透压,可能成为一种潜在可推广的治疗方式[44-45],但因其副作用有轻度鼻出血和自限性鼻部不适等,在临床上的应用尚未得到推广。

3.3 控制炎症 环孢素(cyclosporine-A, CSA)是亲脂性抗炎药,通过下调 Toll 样受体 4(TLR4)、上调转化生长因子β1(TGFβ1)等相关炎症基因的机制来拮抗炎症[46]。临床应用 0.05%和 0.1%CSA 两种浓度治疗难治性干眼,0.05% CSA 除了可以显著改善干眼症状外,早期规律使用还可以减缓干眼疾病的进展[47-48],但 CSA 具有高疏水性,目前作为油基乳液使用,有其自身的缺点。为增加 CSA 渗透性,将 CSA 与纳米材料相结合后,其生物利用度及疗效显著提高,在促进干眼患者泪液产生和改善眼表完整性均明显优于 CSA 乳剂[49]。

不饱和脂肪酸(Omega-3)能降低干眼的炎症因子生成[50],增加干眼患者的基础泪液分泌量,增强泪膜稳定性,用于治疗干眼[51]。α-硫辛酸(alpha-lipoic acid, ALA)不饱和脂肪酸,通过抑制活化 T 细胞因子 5(NFAT5)表达,减弱其与 p65 之间相互作用[52-53],减轻 NF-κB 活性,下调 IL-1β 和 IL-6 的表达,降低炎症反应[54]。ALA 还可以通过下调角膜上皮细胞基质金属蛋白酶-9(MMP-9)[55],清除 ROS 和激活眼表抗氧化状态,预防干眼的发生[56]。此外,ALA 直接抗氧化作用还可以防止氧化应激引起的角膜损伤和泪腺损伤,维持眼表的完整性。但有研究报道[57]4 例服用 Omega-3 脂肪酸补充剂的干眼患者中有 2 例发生消化道不良反应,且患者耐受性以及治疗干眼的合理疗程尚未有定论。

虽然胰蛋白酶样丝氨酸蛋白酶抑制剂(UAMC-00050)明显减少眼表炎性细胞浸润,降低泪液中 IL-1α 和 TNF-α 的浓度,减少基质金属蛋白酶(MMPs)对眼表的损伤[58],但并未在患者中验证其安全,故其安全性还有待论证。Zhang 等[59]最新研究发现糖尿病性干眼患者较正常人眼表的微生物群复杂多样,或许日后能为糖尿病性干眼的诊治提供依据。

总之,糖尿病患者干眼治疗是一个针对多机制参与的病理过程,不仅局部要对症缓解症状,而且全身或局部的炎症也不容忽视。

4 总结

糖尿病性干眼是糖尿病眼部常见并发症,其发病机制复杂,除了炎症及全身代谢异常参与其中,患者基因表型差异、各种非功能基因的异常也可能包含在其中,需进一步的研究证实。且现尚无具有针对性的诊断标准,对糖尿病性干眼的诊断及治疗诊疗时需更多考虑全身情况等因素。未来与糖尿病性干眼相关的靶点性抗炎治疗及基因研究与探索,或许会为临床工作者在防治糖尿病性干眼带来新的理念。

参考文献

1 Lontchi-Yimagou E, Sobngwi E, Matsha TE, *et al*. Diabetes mellitus and inflammation. *Curr Diabetes Rep* 2013;13(3):435-444

2 Yoo TK, Oh E. Diabetes mellitus is associated with dry eye syndrome: a meta-analysis. *Int Ophthalmol* 2019;39(11):2611-2620

3 Manaviat MR, Rashidi M, Afkhami-Ardekani M, *et al*. Prevalence of dry eye syndrome and diabetic retinopathy in type 2 diabetic patients. *BMC Ophthalmol* 2008;8:10

4 Chen ZL, Xiao Y, Qian Y, *et al*. Incidence and risk factors of dry eye in children and adolescents with diabetes mellitus: a 3-year follow-up study. *Front Med* (*Lausanne*) 2021;8:760006

5 He FL, Zhao ZL, Liu Y, *et al*. Assessment of ocular surface damage during the course of type 2 diabetes mellitus. *J Ophthalmol* 2018; 2018:1206808

6 Masmali AM, Maeni YA, El-Hiti GA, *et al*. Investigation of ocular tear ferning in controlled and uncontrolled diabetic subjects. *Eye Contact Lens* 2018;44(Suppl 2):S70-S75

7 di Zazzo A, Coassin M, Micera A, *et al*. Ocular surface diabetic disease: a neurogenic condition? *Ocul Surf* 2021;19:218-223

8 Chen LL, Chen ZL, Xu GH, *et al*. Evaluation of the tear film function in diabetic patients using the Keratograph 5M. *Zhonghua Yan Ke Za Zhi* 2018;54(10):762-766

9 da YM, Niu KY, Wang K, *et al*. A comparison of the effects of estrogen and Cimicifuga racemosa on the lacrimal gland and submandibular gland in ovariectomized rats. *PLoS One* 2015; 10 (3):e0121470

10 Traish AM. Healthrisks associated with long-term finasteride and dutasteride use: it's time to sound the alarm. *World J Mens Health* 2020; 38(3):323-337

11 Rakofsky JJ, Rakofsky SI, Dunlop BW. Dry Those Crying Eyes: The Role of Depression and Antidepressants in Dry Eye Disease. *J Clin Psychopharmacol* 2021 ;41(3):295-303

12 You YS, Qu NB, Yu XN. Alcohol consumption and dry eye syndrome: a Meta-analysis. *Int J Ophthalmol* 2016;9(10):1487-1492

13 Kim JH, Kim JH, Nam WH, *et al*. Oral alcohol administration disturbs tear film and ocular surface. *Ophthalmology* 2012; 119(5): 965-971

14 Shehadeh-Mashor R, Mimouni M, Shapira Y, *et al*. Risk factors for dry eye after refractive surgery. *Cornea* 2019;38(12):1495-1499

15 Jamali H, Eslami J, Kalashipour F, *et al*. Effect of panretinal photocoagulation on corneal sensation and tear function in patients with diabetic retinopathy. *Retina* 2021;41(2):338-344

16 Wang MTM, Craig JP. Comparativeevaluation of clinical methods of tear film stability assessment: a randomized crossover trial. *JAMA Ophthalmol* 2018;136(3):291-294

17 Yu T, Han XG, Gao Y, *et al*. Morphological and cytological changes of meibomian glands in patients with type 2 diabetes mellitus. *Int J Ophthalmol* 2019;12(9):1415-1419

18 He X, Zhao ZY, Wang SP, *et al*. High-fat diet-induced functional and pathologic changes in lacrimal gland. *Am J Pathol* 2020;190(12): 2387-2402

19 Dogru M, Katakami C, Inoue M. Tear function and ocular surface changes in noninsulin-dependent diabetes mellitus. *Ophthalmology* 2001; 108(3):586-592

20 Misra SL, Patel DV, Mc Ghee CN, *et al*. Peripheral neuropathy and tear film dysfunction in type 1 diabetes mellitus. *J Diabetes Res* 2014; 2014:848659

21 Hirata H, Mizerska K, Marfurt CF, *et al*. Hyperosmolar tears induce functional and structural alterations of corneal nerves: electrophysiological and anatomical evidence toward neurotoxicity. *Invest Ophthalmol Vis Sci* 2015;56(13):8125-8140

22 Zeng XY, Lv Y, Gu ZX, *et al*. The effects of diabetic duration on lacrimal functional unit in patients with type Ⅱ diabetes. *J Ophthalmol* 2019;2019:8127515

23 Pflugfelder SC, Stern ME. Biological functions of tear film. *Exp Eye Res* 2020 ;197:108115

24 Lyu Y, Zeng XY, Li F, *et al*. The effect of the duration of diabetes on

dry eye and corneal nerves. *Cont Lens Anterior Eye* 2019; 42(4): 380-385

25 De Mill DL, Hussain M, Pop-Busui R, *et al*. Ocular surface disease in patients with diabetic peripheral neuropathy. *Br J Ophthalmol* 2016; 100(7):924-928

26 Richdale K, Chao C, Hamilton M. Eye care providers' emerging roles in early detection of diabetes and management of diabetic changes to the ocular surface: a review. *BMJ Open Diabetes Res Care* 2020; 8(1):e001094

27 Jiang MS, Yuan Y, Gu ZX, *et al*. Corneal confocal microscopy for assessment of diabetic peripheral neuropathy: a meta-analysis. *Br J Ophthalmol* 2016;100(1):9-14

28 Stuard WL, Titone R, Robertson DM. Tearlevels of insulin-like growth factor binding protein 3 correlate with subbasal nerve plexus changes in patients with type 2 diabetes mellitus. *Invest Ophthalmol Vis Sci* 2017;58(14):6105-6112

29 Markoulli M, You JJ, Kim J, *et al*. Corneal nerve morphology and tear film substance P in diabetes. *Optom Vis Sci* 2017;94(7):726-731

30 Taketani Y, Marmalidou A, Dohlman TH, *et al*. Restoration of regulatory T-cell function in dry eye disease by antagonizing substance P/neurokinin-1 receptor. *Am J Pathol* 2020;190(9):1859-1866

31 Yıldız E, Zibandeh N, Özer B, *et al*. Effects of type 2 diabetes mellitus on gene expressions of mouse meibomian glands. *Curr Eye Res* 2020;45(1):72-80

32 Qu ML, Wan L, Dong MC, *et al*. Hyperglycemia-induced severe mitochondrial bioenergetic deficit of lacrimal gland contributes to the early onset of dry eye in diabetic mice. *Free Radic Biol Med* 2021;166: 313-323

33 Vallée A, Lecarpentier Y. Crosstalkbetween peroxisome proliferator-activated receptor gamma and the canonical WNT/β-catenin pathway in chronic inflammation and oxidative stress during carcinogenesis. *Front Immunol* 2018;9:745

34 Fabiani C, Sota J, Tosi GM, *et al*. The emerging role of interleukin (IL)-1 in the pathogenesis and treatment of inflammatory and degenerative eye diseases. *Clin Rheumatol* 2017;36(10):2307-2318

35 Tsou TC, Yeh SC, Tsai FY, *et al*. Zinc oxide particles induce inflammatory responses in vascular endothelial cells via NF-κB signaling. *J Hazard Mater* 2010;183(1-3):182-188

36 Jamerson EC, Elhusseiny AM, ElSheikh RH, *et al*. Role of matrix metalloproteinase 9 in ocular surface disorders. *Eye Contact Lens* 2020;46 (Suppl 2):S57-S63

37 Liu RJ, Ma BK, Gao YF, *et al*. Tear inflammatory cytokines analysis and clinical correlations in diabetes and nondiabetes with dry eye. *Am J Ophthalmol* 2019;200:10-15

38 Ren TY, Lin XY, Zhang QY, *et al*. Encapsulation of azithromycin ion pair in liposome for enhancing ocular delivery and therapeutic efficacy on dry eye. *Mol Pharm* 2018;15(11):4862-4871

39 Wang MTM, Feng J, Wong J, *et al*. Randomised trial of the clinical utility of an eyelid massage device for the management of meibomian gland dysfunction. *Cont Lens Anterior Eye* 2019;42(6):620-624

40 Arita R, Fukuoka S, Morishige N. Therapeutic efficacy of intense pulsed light in patients with refractory meibomian gland dysfunction. *Ocul Surf* 2019;17(1):104-110

41 Ervin AM, Law A, Pucker AD. Punctal occlusion for dry eye syndrome: summary of a Cochrane systematic review. *Br J Ophthalmol* 2019;103(3):301-306

42 Smart Plug Study Group. Management of complications after insertion of the SmartPlug punctal plug: a study of 28 patients. *Ophthalmology* 2006;113(10):1859.e1-6

43 Tong L, Beuerman R, Simonyi S, *et al*. Effects of punctal occlusion on clinical signs and symptoms and on tear cytokine levels in patients with dry eye. *Ocul Surf* 2016;14(2):233-241

44 Sheppard JD, Torkildsen GL, Geffin JA, *et al*. Characterization of tear production in subjects with dry eye disease during intranasal tear neurostimulation: results from two pivotal clinical trials. *Ocul Surf* 2019; 17(1):142-150

45 Brinton M, Kossler AL, Patel ZM, *et al*. Enhanced tearing by electrical stimulation of the anterior ethmoid nerve. *Invest Ophthalmol Vis Sci* 2017;58(4):2341-2348

46 Daull P, Barabino S, Feraille L, *et al*. Modulation of inflammation-related genes in the cornea of a mouse model of dry eye upon treatment with cyclosporine eye drops. *Curr Eye Res* 2019;44(5):476-485

47 Wan KH, Chen LJ, Young AL. Efficacy andsafety of topical 0.05% cyclosporine eye drops in the treatment of dry eye syndrome: a systematic review and meta-analysis. *Ocul Surf* 2015;13(3):213-225

48 Leonardi A, van Setten G, Amrane M, *et al*. Efficacy and safety of 0.1% cyclosporine A cationic emulsion in the treatment of severe dry eye disease: a multicenter randomized trial. *Eur J Ophthalmol* 2016;26(4): 287-296

49 Zhang AN, Sun R, Ran MX, *et al*. A novel eyes topical drug delivery system: CsA-LNC for the treatment of DED. *Pharm Res* 2020; 37(7):146

50 Hampel U, Krüger M, Kunnen C, *et al*. *In vitro* effects of docosahexaenoic and eicosapentaenoic acid on human meibomian gland epithelial cells. *Exp Eye Res* 2015;140:139-148

51 Georgakopoulos CD, Makri OE, Pagoulatos D, *et al*. Effect of *Omega*-3 fatty acids dietary supplementation on ocular surface and tear film in diabetic patients with dry eye. *J Am Coll Nutr* 2017;36(1): 38-43

52 Roth I, Leroy V, Kwon HM, *et al*. Osmoprotective transcription factor NFAT5/TonEBP modulates nuclear factor-kappa B activity. *Mol Biol Cell* 2010;21(19):3459-3474

53 Kim H, Yoo WS, Jung JH, *et al*. Alpha-lipoic acid ameliorates radiation-induced lacrimal gland injury through NFAT5-dependent signaling. *Int J Mol Sci* 2019;20(22):E5691

54 Dinicola S, Proietti S, Cucina A, *et al*. Alpha-lipoic acid downregulates IL-1β and IL-6 by DNA hypermethylation in SK-N-BE neuroblastoma cells. *Antioxidants (Basel)* 2017;6(4):74

55 Ajith TA. Alpha-lipoic acid: a possible pharmacological agent for treating dry eye disease and retinopathy in diabetes. *Clin Exp Pharmacol Physiol* 2020;47(12):1883-1890

56 Attia M, Essa EA, Zaki RM, *et al*. An Overview of the Antioxidant Effects of Ascorbic Acid and Alpha Lipoic Acid (in Liposomal Forms) as Adjuvant in Cancer Treatment. *Antioxidants (Basel)* 2020;9(5):359

57 Oleñik A, Jiménez-Alfaro I, Alejandre-Alba N, *et al*. A randomized, double-masked study to evaluate the effect of *Omega*-3 fatty acids supplementation in meibomian gland dysfunction. *Clin Interv Aging* 2013;8:1133-1138

58 Joossen C, Baún A, Moreno-Cinos C, *et al*. A novel serine protease inhibitor as potential treatment for dry eye syndrome and ocular inflammation. *Sci Rep* 2020;10(1):17268

59 Zhang Z, Zou XR, Xue WW, *et al*. Ocular surface microbiota in diabetic patients with dry eye disease. *Invest Ophthalmol Vis Sci* 2021;62 (12):13