Crocin Monotherapy in Non-Central Diabetic Macular Edema

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Abstract

Background: Crocin can be utilized as an anti-inflammatory component of Saffron in diabetic macular edema (DME), which is known as the most common cause of vision loss in patients with diabetes mellitus (DM). Although anti-vascular endothelial growth factor (VEGF) agents are common in non-center involving DME (NCI-DME), there is no consensus on NCI-DME treatment.

Methods: This before-after study was performed from October 2019 to August 2021. Twenty-six eyes of 16 patients with type 2 DM in Baghayipoor Clinic in Yazd, were treated with 15 mg crocin per day for 90 days. Patients had at least one eye with non-proliferative DR (NPDR) and NCI-DME along with no adherence to intravitreal injection or a contraindication of intravitreal injection. Central subfield thickness (CST), visual acuity, fasting blood sugar (FBS), and HbA1c were assessed once before and once after the study (day 90).

Results: After 90 days of therapy, the mean CST significantly decreased to 2.8 µm (P-value=0.030), four patients had increased CST and 1 patient had a significantly decreased CST (≥25µm). The mean Logarithmic Minimum angle of resolution increased during the study. The Mean (±SD) FBS showed a significant improvement during the study from 174.7 (±60.41) at baseline up to 161.8 (±47.7) at day 90 (P-value = 0.012). HbA1c had no significant reduction. Nausea/vomiting and insomnia were among the reported adverse effects. Nevertheless, no one withdrew from the study because of the adverse effects.

Conclusion: This study suggests Crocin's positive impact on NCI-DME. It may also improve the glycemic profile of diabetic patients; however, more high-quality randomized clinical trials with larger sample sizes and longer durations are needed for validation.

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Keywords: Diabetic Retinopathy; Macular Edema; Crocin; Visual Acuity

Introduction

It is estimated that nearly 600 million people will develop diabetes by 2040, and one-third of them will progress to diabetic retinopathy (DR) (1). DR, as a microvascular and neurovascular complication of diabetes, is the leading cause of blindness through retinal ischemia, neovascularization, and macular edema (ME) (2, 3). It

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is classified as both proliferative DR (PDR) and non-proliferative DR (NPDR) (4).

The most common cause of vision loss in DR is ME (5). A healthy retina is dehydrated and transparent to transmit light. However, in ME, intra or sub-retinal fluid accumulation develops. As well, it is diagnosed by increased thickness of the retina and/or exudates within the macula (6). ME is developed by various retinal diseases such as retinal vein occlusion (RVO), choroidal neovascularization, posterior uveitis, postoperative inflammation, and central serous chorioretinopathy (7).

The new classification of DME is categorized based on OCT into three classes, including center-involving DME (CI-DME), retinal thickening in the macula that involves a central subfield zone in a 1mm diameter ring, and non-center-involving DME (NCI-DME) that is retinal thickening in the macula with no central subfield zone in 1mm in diameter ring (8, 9). Accordingly, in this definition, normal macular thickening in a 1mm diameter ring is ≥250 μm (10).

DR is caused by biochemical mechanisms that may be due to hyperglycemia (3). Hyperglycemia can induce metabolic abnormality and oxidative stress in DME, furthermore; the retina is the most metabolically active tissue, so it is susceptible to reactive oxygen species damage (ROS). ROS can cause cellular apoptosis, inflammation, lipid peroxidation, neurodegeneration, and structural and functional abnormalities in the retina. All these abnormalities can provide multiple chances for therapeutic targets (2).

The most important cornerstone in DME treatment is the control of systemic risk factors. Laser therapy, pharmacological or surgical modalities can only reduce fluid leakage. The goal is intensive control of blood glucose, especially HbA1c (6). Previously, laser therapy was the only proven effective treatment of DME, but only in NCI-DME (3, 11). Laser therapy can decrease fluid leakage from retinal vessels (6). Vitrectomy is only effective in patients with macular traction due to improper contouring of the macula (3).

The dramatic effects of intravitreal corticosteroids at the early stage of DR is known as a clue for an inflammatory process (3). Corticosteroids can reduce capillary permeability and DME through different mechanisms, including decreasing pro-inflammatory cytokines, altering endothelial cells' tight junctions, inhibiting vascular endothelial growth factor (VEGF) gene expression, and inhibiting VEGF receptors. As well, VEGF can increase retinal capillary endothelial cell permeability (3, 6). Anti-VEGF agents are the first-line treatment in both CI-DME and PDR (4, 12). Bevacizumab (Avastin®) and Ranibizumab are the two efficient and low-cost antibodies that bind to all isoforms of VEGF-A. Aflibercept (Eyelea®) is a fusion protein binding to VEGF-A and placental growth factor, it has a tighter binding affinity to VEGF compared to the current anti-VEGF therapies and it may require less frequent dosing than other anti-VEGF agents (3, 6).

Although anti-VEGF agents' usage is common in NCI-DME, there is no consensus on NCI-DME treatment and no guidelines for the management of DME are still under investigation (13). It should be noted that all the above-mentioned modalities in NCI-DME management could prevent deterioration. Perhaps a visible microvascular change in the retina and its related complications are irreversible and late for performing any intervention (3, 4).

Crocin is a bioactive natural product extracted from Gardenia Jasminoides Ellis and Crocus Sativus (saffron). Additionally, it is related to hydrophilic carotenoids that are either monoglycosyl or diglycosyl polyene esters of crocetin. A Crocin mechanism of action is pleiotropic, and it can alleviate oxidative stress by decreasing ROS generation, neutralizing them, and improving of anti-oxidant defense system through modulation of glutathione peroxidase (GPx), glutathione S-transferase (GST), catalase (CAT), and superoxide dismutase. Furthermore, Crocin can suppress pro-inflammatory cytokines and improve blood flow to the retina. It showed some protective effects on photoreceptors of the retina in some animal samples. Significant adverse effects with routine dosages have not been reported in any previous study (2, 14). Figure 1 shows the Crocin probable mechanism of action (3). As reported in both animal and human studies, Crocin can reduce fasting blood glucose by increasing glucose uptake, and insulin sensitivity and secretion due to β-cells protection against oxidative stress (8, 15-17). Consequently, Sepahi et al. showed Crocin has the potency of being a part of DM treatment and managing its comorbidities and complications, particularly diabetic retinopathy and DME (8). This information represents the logic for investigating the Crocin effect on NCI-DME.

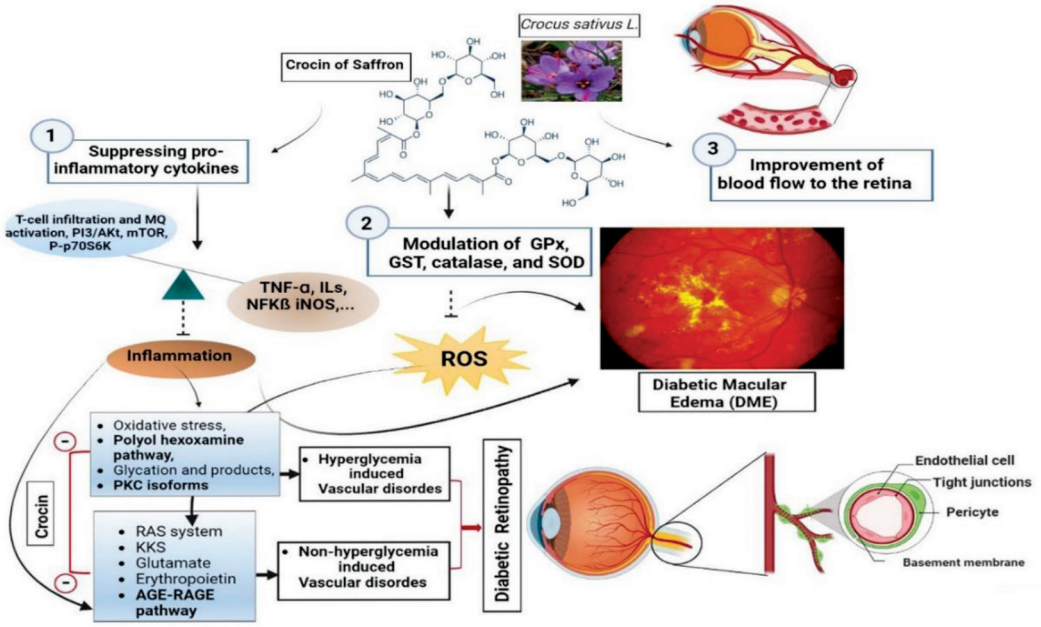

Figure 1. Crocin pleotropic mechanism of action in diabetic retinopathy

Methods

The current before-after study was performed from October 2019 to August 2021. The Study participants were provided with written informed consent. The ethics committee of Shahid Sadoughi University of Medical Sciences approved this study (Ethic ID: IR.SSU.MEDICINE.REC.1398.129).

Patient Selection and Procedure

Patients with type 2 DM referred to Baghayipoor Clinic, a university-affiliated clinic in YAZD, were prospectively enrolled in the study. The study participants were at least 18 years old. All the included participants had at least one eye with NPDR and refractory NCI-DME, which was diagnosed by ophthalmologist, along with no adherence to intravitreal injection or a contraindication of intravitreal injection, especially hypertension safety considerations after vascular accidents.

Major exclusion criteria were having a history of eye surgery, receiving intravitreal corticosteroids or anti-VEGF agents, or previous retinal photocoagulation 6 months prior to the study. Other exclusion criteria were the following: age-related macular degeneration (AMD), retinal artery occlusion (RAO), pregnancy or lactation period, anti-coagulation use and coagulopathies, cholelithiasis or biliary ducts obstruction, active peptic ulcer, immunologic reaction to saffron, severe cataract, and acute glaucoma.

Thereafter, baseline demographic characteristics were obtained. Refraction was evaluated by an optometrist using an auto refractometer. Best-corrected visual acuity (BCVA) was determined by the Snellen E chart, directional optotype test, used at a standard distance (6 m) and in standard light by an ophthalmologist. Anterior segment and intraocular pressures were examined by an ophthalmologist with HAAG-STREIT BM 900 slit lamp (koeniz, Switzerland) and HAAG-STREIT AT 900 ocular tonometer, respectively. Heidelberg engineering pecterialis (Vista, CA, USA) optical coherence tomography (SD-OCT), through the six-radial scans, centered at the fovea at equally spaced angular orientations was used for investigating posterior segment for determination of central subfield thickness (CST) in 1mm diameter zone of the fovea (18). Study maps were available in the SD-OCT machine.

Patients received Krocina® tablet (Pouyesh Darou Sina, Mashhad, Iran) 15 mg per day for a duration of 90-day.

Study Endpoints

The primary outcome in this study was CST′s difference in the 1mm diameter zone of fovea between the first and second visits after 90 days with a clinical target of ≥25μm reduction (10). Secondary outcomes were visual acuity (VA), fasting blood glucose (FBS), and HbA1c compression between these two visits. As a part of the

safety evaluation, some known adverse effects of Crocin, including sleep disorders, nausea/vomiting, feet swelling, stomachache, increased appetite, redness, swelling or burning of eyes, and sub-conjunctival hemorrhage were asked weekly. In addition, drug compliance was evaluated using the 8-item Morisky Medication Adherence Scale (MMAS-8) (19).

Sample size

The sample size was estimated as 25 eyes based on an earlier experience (20) and CST standard deviation of 30 to reach a mean difference of 25 μm after 90 days with the following specifications and using the sample size, as in the following formula:

$$n = \frac{\left(z_{1-\alpha/2} + z_{1-\beta}\right)^2 * 2S^2}{d^2}$$

Statistical analysis

The quantitative and qualitative variables were reported as mean (SD) and number (%), respectively. The effect of Crocin on both primary and secondary outcomes before and after the procedure was assessed using the Wilcoxon rank-sum test. Moreover, a paired T-test was used to compare the changes in variables over 90 days, and repeated measurements to compare the changes in variables over time. All the statistical analysis was conducted by Statistical Package for Social Science (SPSS) software version 25 and two-tailed P-values < 0.05 were considered statistically significant.

Results

Twenty-seven eyes of 17 patients were enrolled in the study. One patient was excluded from the study due to a lack of oral treatment compliance (Figure 2). The patients' demographic characteristics are shown in Table 1. The mean (SD) age was 59.43 years old (6.39) with a minimum and maximum of 38 and 69 years old, respectively. 37.5% of the patients were female and the mean (SD) duration of diabetes was 14.0 (5.39) years. Ischemic heart disease was the most common comorbidity of the participants and the majority of the study patients were insulin users.

Table 1. Baseline characteristics of the study participants

Parameter		N= 16
Age, mean (SD), y		59.43 (6.39)
Sex, N (%)	Male	10 (62.5)
	Female	6 (37.5)
Duration of diabetes, N (%), y	< 10	4 (25)
	10-20	11 (68.75)
	> 20	1 (6.25)
Other comorbidities, N (%)	HTN	8 (15)
	IHD	3 (18.75)
	Hypothyroidism	1 (6.25)
HbA1C		6.85 (1.32)
Insulin used, N (%)		13 (81.25)

N: Number; y: year; SD: Standard Deviation; HTN: Hypertension; IHD: Ischemic Heart Disease, HbA1C: Hemoglobin A1C

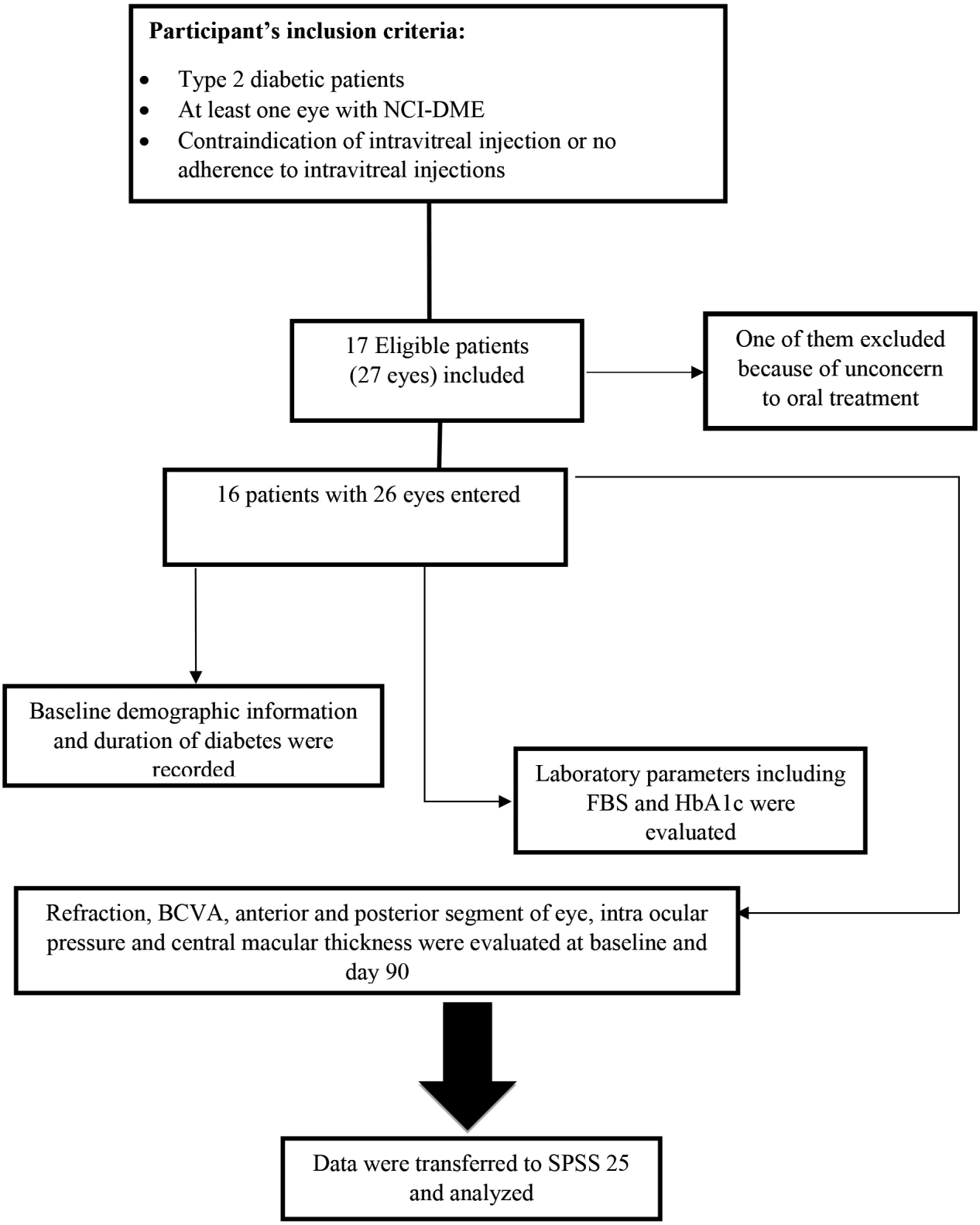

Figure 2. Flow diagram of the study process

Primary and secondary outcomes

Clinical characteristics at baseline as well as primary and secondary outcomes after 90 days of oral Crocin monotherapy are shown in Table 2. At day 90, a statistically significant mean reduction of 2.8 µm in CST in a 1mm diameter zone of the fovea was observed compared to the baseline (P-value = 0.030) (Table 2). Four patients (25%) had increased CST and one patient (6%) had significantly decreased CST (≥25µm).

The mean LogMAR of VA increased during the study process, however, it was not significant (P-value = 0.801). Only one eye had visual acuity reduction and others were invariable. The mean (SD) of FBS showed a significant improvement during the study from 174.7 (60.41) at baseline up to 161.8 (47.7) at day 90 (P-value = 0.012). HbA1c changes were invariable during the study, which did not show any significant reduction (P-value = 0.265) (Table 2). Mild adverse effects in the form of nausea/vomiting and insomnia were observed in 2 and 1 of the included patients treated with Crocin, respectively. However, none of the patients discontinued the therapy because of these adverse effects. According to MMAS-8, seven patients (43.75%), eight patients (50%), and one patient (6.25%) had high, medium, and low adherence to treatment, respectively.

Table 2. Primary and secondary outcomes at baseline and after 90 days

Parameter	Baseline	Day 90	*P-Value*
	Mean (SD)		
CST, µm	282.1 (75.65)	279.30 (61.14)	**0.030***
VA, LogMAR	0.0969 (0.1132)	0.1024 (0.1200)	0.801
FBG, mg/dl	174.7 (60.41)	161.8 (47.71)	**0.012***
Hgb A1C, %	7.26 (1.026)	7.26 (0.882)	0.265

SD: Standard Deviation; CST: Central subfield thickness; µm: micrometer; mg/dl: Milligrams per deciliter; LogMAR: Logarithm of the Minimum Angle of Resolution; FBG: Fasting blood glucose.

* Specifies statistically significant.

Discussion

The results of this before-after study on NPDR patients with NCI-DME showed that daily consumption of 15 mg Crocin for 90 days could reduce CST levels and improve the FBS level. Although we had a statistically significant CST mean reduction, 25 percent of patients had thickened macula after 90 days. This finding can be explained by the increased HbA1c and medium or low adherence to the treatment according to MMAS-8 in these patients.

The results of an in-vivo study illustrated that 100 mg/kg of Crocin can decrease photoreceptors damage and 50 mg/kg of Crocin can save retinal ganglion cells (14). Sepahi et al. in their study showed that consumption of 5-15 mg Crocin daily can improve VA in refractory DME (8), while the results of the current study showed no significant improvement in VA. A systematic review and meta-analysis revealed a decreasing trend in visual outcomes improvement by aging, increasing diabetes duration, and baseline visual acuity (21) that is consistent with the high mean letter score (≈80) of the participants of this study (Snellen chart 20/24, 0.0969 LogMAR) and higher mean of age beside to the Sepahi et al.'s study. Furthermore, a short period of follow-up can be another cause of unchanged visual acuity. Only one patient had increased LogMAR which can be rationalized by thickening of CST due to the increased HbA1c.

Sample analysis of our study demonstrated that daily consumption of 15 mg Crocin can improve FBS, but it did not have a significant effect on HbA1c, which was in agreement with previous studies (8, 15). Rahmani et al. in a systematic review and meta-analysis of clinical trials have demonstrated that FBS significantly reduces when the intervention period of Crocin is more than 12 weeks (15). Short follow-up can be a feasible cause of HbA1c's unchanging results. Human studies do not have the same favorable results compared to animal studies, which may probably be due to Crocin's way of extraction, used doses, study duration, diet, and lifestyle that were not adjusted in human studies (17).

The results of a trial showed that although laser photocoagulation in patients with NCI-DME could improve visual acuity and median retinal thickness, VA was stable after 12 months (10). Despite its effects, laser therapy can cause chorioretinal scars, reduced color vision, retinal pigment epithelium fibrous metaplasia, and inadvertent photocoagulation of the center of the macula (6).

Bevacizumab monotherapy caused no significant effect on visual acuity and CST of NCI-DME patients in the Cuervo-Lozano's study. They had an inclusion criterion

of LogMAR ≤0.3, so they did not have any potential for a significant VA improvement. Although they have evaluated loading phase effect of bevacizumab, CST reduction was not statistically significant (22). Bevacizumab can improve visual acuity and retinal thickness in CI-DME, but it is less effective compared to both Ranibizumab and Aflibercept based on the results of a two-year clinical trial (23). Furthermore, Vriti et al. in their systematic review reported statistically significant superior results of Aflibercept over Bevacizumab, while Ranibizumab was not statistically significant (21).

Although the Ranibizumabʾs effect on NCI-DME has not been studied, it was found that it can improve VA and macular thicknesses and prevent PDR in CI-DME. Systemic adverse effects such as cerebrovascular accident and myocardial infarction were reported in RISE/RIDE and Wellsʾs studies, but it was inconsistent with the RESTORE study (23, 24). Despite the beneficial effect of Aflibercept on VA and macular thickness improvement in comparison to a laser control group in CI-DME in VISTA and VIVID studies during 148 weeks, no data are available in NCI-DME (25).

No study has been done to evaluate the effects of corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) on NCI-DME patients. NSAIDs have no significant effect on CI-DME patients' VA, but some studies demonstrated that topical NSAIDs and intravitreal anti-VEGFs combination therapy can better reduce macular thickness than monotherapy (26). Mehtaʾs systematic review showed that intravitreal steroids do not improve VA and macular thickness compared with monotherapy. Moreover, it can increase intra-ocular pressure and cataracts (27).

A significant reduction in macular thickness and visual acuity improvement in DME was recorded at a six-month follow-up with the supplementations involving Curcumin, Artemisia, Bromelain, and Black Pepper in a case-control study. Nevertheless, they did not ameliorate glycemia and HbA1c as the most important systematic risk factor of DME (13). Mazzolaniʾs before -after a study suggested that curcumin may be feasible in the improvement of visual acuity and the reduction of macular edema in CSME (27).

Although we obtained no significant results due to a small number of participants, oral modalities hold a huge advantage of being a non-invasive therapy with apparently no damaging effects versus intravitreal injections that can cause endophthalmitis, anterior chamber reactions, Intraocular pressure elevation, lens opacity, rhegmatogenous retinal detachment, and Ocular hemorrhage (28, 29). Accordingly, this can be convincing to design more high-quality RCTs with larger sample sizes and duration in the future.

Strength and limitations

To the best of our knowledge, this was the first study evaluating the Crocin monotherapy's effects on NCI-DME patients. All the participants were evaluated for routine ophthalmologic physical exams to investigate probable side effects.

The type of study, lack of placebo group, short-term follow-up, and relatively small sample size was due to corona virus pandemic interference that can cause spurious results and lack of statistical power. We did not assess the foveal avascular zone (FAZ) area and vessel density, but we quantified the number of micro aneurysms in each layer. Bioavailability is an important parameter in nutraceutical studies; however, we did not consider it as an effective factor on our participants' status and using agent. The study population was type II diabetic patients who use anti-diabetic agents; we did not consider these agents' effects as a confounder factor. There is a clear need for high-quality RCTs with a larger sample size and duration. Of note, evaluating other confounding factors including participants' diet, weight, smoking, and physical activity during intervention could be helpful.

Conclusion

In conclusion, this preliminary study recommends the positive impact of Crocin on NCI-DME. Accordingly, it can be used as monotherapy or combination therapy mainly in the beginning of DME. Additionally, it may improve the glycemic profile of diabetic patients. Crocin can be an armamentarium for ophthalmologists and endocrinologists, but it needs to be confirmed by performing more high-quality RCTs with larger sample sizes and longer duration.

Conflicts of Interest

The authors declare that they have no competing interests.

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