Intravitreal Ranibizumab Alone or in Combination with Calcium Dobesilate for the Treatment of Diabetic Macular Edema in Nonproliferative Diabetic Retinopathy Patients: 12-Month Outcomes of a Retrospective Study

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Objective. This study investigates the efficacy of CaD combined with intravitreal ranibizumab for the treatment of diabetic macular edema (DME) in patients with nonproliferative DR. Methods. This retrospective, observational, case-control study enrolled consecutive patients newly diagnosed with DME. The patients were treated with 3-monthly loading dose injections of intravitreal ranibizumab (IVR) followed by pro re nata injections (3+PRN), with or without daily oral CaD. The patients were treated and followed up for 12 months. We reviewed their medical records to determine the optical coherence tomography (OCT) findings, number of injections, best-corrected visual acuity (BCVA), and central macular thickness (CMT) at 3, 6, and 12 months after the first injection. Results. We reviewed 102 eyes of 102 patients; 54 patients received IVR combined with oral CaD (IVR+CaD group) and 48 received only IVR (IVR group). In both groups, BCVA was higher, and CMT was lower, at 3, 6, and 12 months after the injection compared to those at the baseline (p < 0.05 for all), while there were no significant differences in BCVA improvement or CMT reduction between the two groups (p > 0.05). The mean number of IVR injections was significantly lower in the IVR+CaD group than the IVR group (5.4 ± 1.1 vs. 6.7 ± 1.6 injections, p < 0.05) during 1 year of treatment. No adverse events were noted in either group. Conclusions. Compared to IVR alone, the addition of oral CaD to IVR in DME patients was safe and effective for improving visual function and restoring the retinal anatomy and was associated with the need for fewer injections.

1. Introduction

Diabetic macular edema (DME) is the leading cause of visual impairment in patients with diabetes mellitus and is characterized by exudative fluid accumulation in the macula [1, 2]. The blood-retinal barrier (BRB) is vital for maintaining normal structure and function of the retina. DME is caused by damage to the BRB [3]. BRB disruption is associated with increased production of the vascular endothelial growth factor (VEGF), intercellular adhesion molecule-1, interleukin-6, monocyte chemotactic protein-1, and other inflammatory factors [3]. Therefore, anti-VEGF [4, 5] and anti-inflammatory agents [6] are the main treatment methods for DME after laser photocoagulation. Although the Diabetic Retinopathy Clinical Research Network randomized clinical trial [7] reported that intravitreal aflibercept, bevacizumab, and ranibizumab injections improved vision in eyes with center-involved DME (CIDME), a significant number of patients have a poor or short-duration response to anti-VEGF treatment. Although anti-VEGF therapy is a cost-effective way to improve vision loss in DME [8], frequent intravitreal injections impose a high economic burden on patients, particularly in developing countries. Therefore, studies have investigated combination therapy using intravitreal anti-VEGF agents with intravitreal triamcinolone acetonide [9], Rho kinase inhibitors [10], methotrexate [11], subthreshold micropulse lasers [12, 13], macular grid laser photocoagulation [14], and subtenon...
2. Materials and Methods

2.1. Study Design and Participants. This retrospective study enrolled treatment-naïve patients with nonproliferative DR and CIDME, who received IVR at the Department of Ophthalmology, Changyi People’s Hospital. The patients were followed up for 1 year. All patients had type 2 diabetes mellitus and clinically significant DME. According to the ETDRS criteria [26], clinically significant macular edema is defined as retinal thickening that involves or threatens the center of the macula (even if visual acuity is not yet reduced). Figure 1 presents the flowchart of patient selection.

This study adhered to the Declaration of Helsinki and was approved by the Ethics Committee of Changyi People’s Hospital. Informed consent was obtained from the patients or their guardians before IVR. The medical records were retrospectively reviewed after approval was received from the Institutional Review Board of Changyi People’s Hospital.

2.2. Data Collection. The data retrieved from the medical records included demographic information, medical history, history of ocular conditions, and previous treatments for DME. The participants underwent detailed ophthalmological examination, including BCVA, slit-lamp biomicroscopy, intraocular pressure measurement, fundus examination under pupil dilation, and macular scans using spectral domain optical coherence tomography (OCT; Cirrus HD-OCT [software version 6.0]; Carl Zeiss Meditec, Dublin, CA, USA), before treatment and at each follow-up. The CMT was defined as the retinal thickness of the central 1.0 mm, as determined using an OCT B-scan. Complications during the perioperative and postoperative period were also recorded.

2.3. Treatment Protocol. A 3-monthly loading dose of IVR, followed by pro re nata injections (3 + PRN), was used for anti-VEGF treatment of patients. The criteria for reinjection were similar to those described previously [27]. At each visit, patients underwent visual acuity assessment and OCT to determine the macular thickness. If BCVA and OCT were stable over two consecutive visits, and reinjection was suspended; reinjection was considered in cases showing deterioration of BCVA (loss of >5 letters) or OCT (CMT increase by >10%) at follow-up.

In the IVR group, patients received IVR injections only, while in the IVR + CaD group, patients received oral CaD (1,500 mg per day in three 500 mg doses) and IVR injections.

2.4. Statistical Analysis. The data were analyzed using SPSS software (version 20.0; IBM Corp., Armonk, NY, USA). The BCVA measurements were converted to logMAR equivalents for statistical analysis. The Pearson chi-square test was used for comparative analyses of categorical variables. The independent sample t-test and paired t-test were performed to analyze changes in BCVA and CMT. P < 0.05 was considered statistically significant.

3. Results

Between January 2017 and March 2020, 102 patients (102 eyes; mean age: 57.72 ± 9.91 years; range: 42–69 years) were enrolled in this study, of whom 63 (61.76%) were males and 39 (38.24%) were females. The IVR + CaD and IVR groups included 54 and 48 patients, respectively.

Table 1 presents the baseline characteristics of the study participants. There were no significant differences between the groups in sex, age, smoking, alcohol use, or comorbidities, except in terms of the presence, treatment course, and control (i.e., HbA1c) of diabetes.

After 3-monthly loading doses of IVR, BCVA (logMAR) significantly increased from 0.35 ± 0.12 to 0.24 ± 0.09 (p < 0.05) in the IVR group and from 0.32 ± 0.15 to 0.23 ± 0.10 in (p < 0.05) in the IVR + CaD group (Table 2). The BCVA remained stable in both treatment groups until the end of the follow-up (Table 2). Furthermore, the CMT significantly decreased from 427 ± 185 to 277 ± 92 μm (p < 0.05) in the IVR + CaD group. The CMT remained stable in both treatment groups until the end of the follow-up. No significant difference was observed in BCVA or CMT between the two groups at the baseline or follow-up visits.

After 1 year of IVR treatment, the mean number of injections was 6.7 ± 1.6 in the IVR group, which was significantly greater than that in the IVR + CaD group (5.4 ± 1.1, p < 0.05). There were no ocular complications (such as endophthalmitis, vitreous hemorrhage, and retinal detachment) or serious systemic adverse effects (such as cerebral or myocardial infarction) in either group.

steroid injections [15], as well as switching from anti-VEGF treatment to intravitreal dexamethasone implantation [6, 16–18], for DME patients.

Calcium dobesilate (calcium 2, 5-dihydroxymbenzesulfonate; CaD) is a vascular-protective drug used for the treatment of diabetic retinopathy (DR) [19–21] due to its ability to prevent oxidative stress and inflammation [22]. It protects blood vessels and improves the circulation by lowering blood viscosity, inhibiting platelet activity, and reducing capillary permeability [23, 24]. A previous randomized, double-blind, placebo-controlled, multicenter clinical trial reported that CaD did not reduce the risk of development of DME [25]. However, the potential beneficial effects of combined use of CaD and intravitreal anti-VEGF agents on DME patients are not clear. Therefore, we investigated the effectiveness and safety of combination therapy with CaD and anti-VEGF agents for the treatment of DME in nonproliferative DR patients. The primary outcomes of this study were the change in best-corrected visual acuity (BCVA) and central macular thickness (CMT) after treatment. The secondary outcome was the number of intravitreal ranibizumab (IVR) injections administered during the study period.
4. Discussion

DME is a type of diabetic maculopathy and an important cause of vision loss among individuals with diabetes worldwide [2]. The advent of anti-VEGF therapy has significantly improved the outcomes of DME patients, and intravitreal anti-VEGF injections are considered the first-line therapy for DME. However, some patients respond poorly to treatment.

CaD is a vascular-protective drug with beneficial effects for vascular diseases, such as chronic venous insufficiency [28], hemorrhoids [25], DR [29–31], and multiple microangiopathic diseases [32]. Previous studies have suggested that several mechanisms underlie the improvement in microcirculation and reduction in microvascular injury associated with CaD use [21]. First, CaD reduces platelet aggregation caused by thrombin or collagen [33]. Second, it significantly protects the peritoneal vessels from the penetrative effects of reactive oxygen species [34]. Third, it inhibits capillary permeability [35]. Fourth, it alleviates chronic inflammation and improves endothelial cell function [36, 37]. Fifth, it reduces endothelial shedding by increasing the synthesis and release of nitric oxide [38]. Sixth, it inhibits prostaglandin production to reduce platelet aggregation, erythrocyte aggregation, and suspension viscosity [24]. Seventh, it downregulates the expression of the VEGF and fibroblast growth factor to inhibit vascular endothelial

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**Table 1: Baseline characteristics of total study population.**

|                | IVR (n = 48) | IVR + CaD (n = 54) | p value |
|----------------|--------------|--------------------|---------|
| Gender (male/female) | 31/17        | 32/22              | 0.581   |
| Age (years)       | 56.98 ± 11.62 | 57.65 ± 12.79     | 0.784   |
| Smoking (yes/no)  | 28/20        | 29/25              | 0.638   |
| Drinking (yes/no) | 19/29        | 25/29              | 0.494   |
| Comorbidity (yes/no) | 17/31      | 18/36              | 0.825   |
| Course (years)    | 10.58 ± 6.00 | 11.51 ± 6.16       | 0.440   |
| HbA1c (%)         | 7.72 ± 0.88  | 7.80 ± 1.01        | 0.645   |

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**Table 2: Changes of CMT and BCVA after the treatment.**

|                | BCVA (logMAR) | CMT (μm) |                |               |
|----------------|---------------|----------|----------------|---------------|
|                | IVR (n = 48)  | IVR + CaD (n = 54) | p value | IVR (n = 48)  | IVR + CaD (n = 54) | p value |
| Baseline       | 0.35 ± 0.04   | 0.34 ± 0.04 | 0.416 | 428.21 ± 100.68 | 282.06 ± 26.55   | 0.188   |
| At 3 month     | 0.24 ± 0.04*  | 0.23 ± 0.04* | 0.253 | 288.27 ± 19.83* | 274.33 ± 31.74*  | 0.234   |
| At 6 month     | 0.26 ± 0.04*  | 0.25 ± 0.04* | 0.436 | 281.40 ± 27.34* | 264.93 ± 27.16*  | 0.429   |
| At 12 month    | 0.25 ± 0.03*  | 0.24 ± 0.04* | 0.696 | 269.33 ± 28.82* | 264.06 ± 27.16*  | 0.429   |

*represents p < 0.05 when compared with the corresponding parameters at the baseline.
cell proliferation [39]. Finally, it restores autophagy by inhibiting the VEGF/Pi3K/AKT/mTOR signaling pathway [40]. Therefore, CaD acts through several mechanisms and is effective in the treatment of DME. However, in a previous study, CaD did not reduce the risk of development of DME [25]. Furthermore, in another study, CaD combined with laser photocoagulation did not decrease macular thickness in DME patients compared to placebo [41]. Both of the aforementioned studies were published before the anti-VEGF agents became popular. No previous studies have investigated the effectiveness and safety of oral CaD combined with anti-VEGF treatment. Therefore, our study is the first to demonstrate that, and compared to anti-VEGF monotherapy, CaD combined with anti-VEGF agents had similar effects in terms of improving visual function and reducing CMT in DME patients, and it reduced the number of intravitreal injections and economic burden during the 1-year follow-up period.

Although the exact mechanism underlying the effects of DME is still unclear, abnormally increased levels of VEGF and inflammatory mediators, and subsequent breakdown of BRB, play a vital role in the development of DME [2]. Accordingly, anti-VEGF and anti-inflammatory agents are considered the first-line treatments for DME [42, 43] and show good outcomes [44, 45]. CaD downregulates VEGF and inhibits VEGF-related pathways and may work synergistically with anti-VEGF agents [46]. This might partly explain why oral CaD alone has no therapeutic effect on DME, but it reduced the number of intravitreal injections required when combined with anti-VEGF agents during the 1-year follow-up period of this study. In addition, the treatment combination was safe, with no systemic or local complications observed. Although CaD inhibited VEGF expression by acting synergistically with anti-VEGF agents and prolonging their effect duration, it did not increase the risk of adverse events due to VEGF inhibition.

This study has some limitations. First, it was a retrospective study with a relatively small sample size, which may have made it difficult to detect small but significant changes in visual and retinal structure improvement. Secondly, the follow-up period was relatively short, and this may not have allowed for enough time to detect the efficacy and safety of CaD during long-term treatment. Thirdly, this study only included type 2 diabetes DME patients in the NPDR stage, and the results could not give more information to type 1 diabetes DME patients or DME patients in the PDR stage.

In summary, oral CaD combined with IVR has similar effectiveness and safety as anti-VEGF monotherapy for improving visual function and restoring the retinal anatomy in DME patients and reduced the need for IVR injections. The addition of oral CaD can reduce the number of IVR injections required and the economic burden of treatment in DME patients receiving anti-VEGF therapy.

Data Availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because of privacy or ethical restrictions.

Additional Points

What is already known about this topic? CaD is a vascular-protective drug used for the treatment of DR. It protects blood vessels and improves the circulation by lowering blood viscosity, inhibiting platelet activity, and reducing capillary permeability. Although a previous study reported that CaD did not reduce the risk of development of DME, the potential beneficial effects of the combined use of CaD and intravitreal anti-VEGF agents on DME patients are not clear. What does this article add? Within one year of IVR treatment by 3+PRN regimen, adding oral CaD to intravitreal ranibizumab might be a feasible way to reduce the injection number and decrease the economic burden of treatment in DME patients who received anti-VEGF therapy.

Ethical Approval

This study adhered to all relevant tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Changyi People’s Hospital, Changyi, China.

Consent

Informed consent was obtained from all patients or their guardians. All medical records and patient demographics were retrospectively reviewed after approval was received from the Institutional Review Board of Changyi People’s Hospital.

Disclosure

The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see https://www.textcheck.com/certificate/APcagO.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

S. W. and D. W. conceptualized and designed the study. S. W., D. W., and H. W. drafted the manuscript. S. W., D. W., H. W., X. Y., and J. X. were involved in the acquisition, analysis, and interpretation of the data and approved the final version of the manuscript.

References

[1] N. M. Holekamp, “Overview of diabetic macular edema,” American Journal of Managed Care, vol. 22, no. 10 Suppl, pp. s284–s291, 2016.
[2] G. S. Tan, N. Cheung, R. Simo, G. C. M. Cheung, and T. Y. Wong, "Diabetic macular oedema," Lancet Diabetes & Endocrinology, vol. 5, no. 2, pp. 143–155, 2017.

[3] A. Daruich, A. Matet, A. Moulin et al., "Mechanisms of macular edema: beyond the surface," Progress in Retinal and Eye Research, vol. 63, pp. 26–68, 2018.

[4] P. Massim, F. Bandello, J. G. Garweg et al., "Safety and efficacy of ranibizumab in diabetic macular edema (resolve study): a 12-month, randomized, controlled, double-masked, multicenter phase II study," Diabetes Care, vol. 33, no. 11, pp. 2399–2405, 2010.

[5] S. Akkaya, B. Acikalin, Y. E. Dogan, and F. Coban, "Sub-threshold micropulse laser versus intravitreal anti-vegf for diabetic macular edema patients with relatively better visual acuity," International Journal of Ophthalmology, vol. 13, no. 10, pp. 1606–1611, 2020.

[6] A. Rosenblatt, P. Udaondo, J. Cunha-Vaz et al., "A collaborative retrospective study on the efficacy and safety of intravitreal dexamethasone implant (ozurdex) in patients with diabetic macular edema: the European DME registry study," Ophthalmology, vol. 127, no. 3, pp. 377–393, 2020.

[7] The Diabetic Retinopathy Clinical Research Network, J. A. Wells, A. R. Glassman et al., "Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema," New England Journal of Medicine, vol. 372, no. 13, pp. 1193–1203, 2015.

[8] N. Hodgson, F. Wu, J. Zhu et al., "Economic and quality of life benefits of anti-vegf therapy," Molecular Pharmaceutics, vol. 13, no. 9, pp. 2877–2880, 2016.

[9] M. Riazi-Esfahani, H. Riazi-Esfahani, A. Ahmadraji et al., "Intravitreal bevacizumab alone or combined with 1 mg triamcinolone in diabetic macular edema: a randomized clinical trial," International Ophthalmology, vol. 38, no. 2, pp. 585–598, 2018.

[10] H. Ahmadieh, R. Nourinia, A. Hafezi-Moghadam et al., "Intravitreal injection of a rho-kinase inhibitor (fasudil) combined with bevacizumab versus bevacizumab monotherapy for diabetic macular oedema: a pilot randomised clinical trial," British Journal of Ophthalmology, vol. 103, no. 7, pp. 922–927, 2019.

[11] F. Fazel, B. Oliya, M. Mirmohammadkhani, M. Fazel, G. Yadegarfar, and M. Pourazizi, "Intravitreal injections of bevacizumab plus methotrexate versus bevacizumab alone for the treatment of diabetic macular edema: a randomized, sham-controlled trial," Journal of Current Ophthalmology, vol. 32, no. 2, pp. 164–169, 2020.

[12] M. G. Altinel, B. Acikalin, M. G. Alis et al., "Comparison of the efficacy and safety of anti-VEGF monotherapy versus anti-VEGF therapy combined with subthreshold micropulse laser therapy for diabetic macular edema," Lasers in Medical Science, vol. 36, no. 7, pp. 1545–1553, 2021.

[13] H. S. Kanar, A. Arsan, A. Altun, S. F. Aki, and A. Hacisalihoglu, "Can subthreshold micropulse yellow laser treatment change the anti-vascular endothelial growth factor algorithm in diabetic macular edema? A randomized clinical trial," Indian Journal of Ophthalmology, vol. 68, no. 1, pp. 145–151, 2020.

[14] K. A. M. Solaiman, M. M. Diab, and M. Abo-Elenin, "Intravitreal bevacizumab and/or macular photoagulation as a primary treatment for diffuse diabetic macular edema," Retina, vol. 30, no. 10, pp. 1638–1645, 2010.

[15] E. Eris, I. Perente, E. Vural et al., "Evaluation of the effect of combined intravitreal ranibizumab injection and sub-tenon steroid injection in the treatment of resistant diabetic macular edema," International Ophthalmology, vol. 39, no. 7, pp. 1575–1580, 2019.

[16] A. Sharma, K. Bellala, P. Dongre, and P. Reddy, "Anti-vegf versus dexamethasone implant (ozurdex) for the management of centre involved diabetic macular edema (CiDME): a randomized study," International Ophthalmology, vol. 40, no. 1, pp. 67–72, 2020.

[17] V. Castro-Navarro, E. Cervera-Taulet, C. Navarro-Palop, C. Monferrer-Adsuara, L. Hernandez-Bel, and J. Montero-Hernandez, "Intravitreal dexamethasone implant ozurdex® in naïve and refractory patients with different subtypes of diabetic macular edema," BMC Ophthalmology, vol. 19, no. 1, p. 15, 2019.

[18] P. Mello Filho, G. Andrade, A. Maia et al., "Effectiveness and safety of intravitreal dexamethasone implant (ozurdex) in patients with diabetic macular edema: a real-world experience," Ophthalmologica, vol. 241, no. 1, pp. 9–16, 2019.

[19] H. Allain, A. A. Ramelet, E. Polard, and D. Bentue-Ferrer, "Safety of calcium dobesilate in chronic venous disease, diabetic retinopathy and haemorrhoids," Drug Safety, vol. 27, no. 9, pp. 649–660, 2004.

[20] P. Berthet, J. C. Farine, and J. P. Barras, "Calcium dobesilate: pharmacological profile related to its use in diabetic retinopathy," International Journal of Clinical Practice, vol. 53, no. 8, pp. 631–636, 1999.

[21] J. Liu, S. Li, and D. Sun, "Calcium dobesilate and microvascular diseases," Life Sciences, vol. 221, pp. 348–353, 2019.

[22] P. Bogdanov, C. Sola-Adell, C. Hernandez et al., "Calcium dobesilate prevents the oxidative stress and inflammation induced by diabetes in the retina of db/db mice," Journal of Diabetes and Its Complications, vol. 31, no. 10, pp. 1481–1490, 2017.

[23] M. L. Ribeiro, A. I. Seres, A. M. Carneiro et al., "Effect of calcium dobesilate on progression of early diabetic retinopathy: a randomised double-blind study," Graefes Archive for Clinical and Experimental Ophthalmology, vol. 244, no. 12, pp. 1591–1600, 2006.

[24] B. Akbulut, "Calcium dobesilate and oxerutin: effectiveness of combination therapy," Phlebology, vol. 25, no. 2, pp. 66–71, 2010.

[25] C. Haritoglou, J. Gerss, C. Sauerland, A. Kampik, M. W. Ulbig, and C. S. Group, "Effect of calcium dobesilate on occurrence of diabetic macular oedema (caldiret study): randomised, double-blind, placebo-controlled, multicentre trial," The Lancet, vol. 373, no. 9672, pp. 1364–1371, 2009.

[26] Photocoagulation for Diabetic Macular Edema," Early treatment diabetic retinopathy study report number 1. Early treatment diabetic retinopathy study research group," Archives of Ophthalmology, vol. 103, no. 12, pp. 1796–1806, 1985.

[27] D. G. P. James, D. Mitkute, G. Porter, and D. Vayalambrone, "Visual outcomes following intravitreal ranibizumab for diabetic macular edema in a pro re nata protocol from baseline: a real-world experience," Asia-Pacific Journal of Ophthalmology (Phila.), vol. 8, no. 3, pp. 200–205, 2019.

[28] E. Rabe, K. A. Jaeger, M. Bulitta, and F. Pannier, "Calcium dobesilate in patients suffering from chronic venous insufficiency: a double-blind, placebo-controlled, clinical trial," Phlebology, vol. 26, no. 4, pp. 162–168, 2011.

[29] X. Zhang, W. Liu, S. Wu, J. Jin, W. Li, and N. Wang, "Calcium dobesilate for diabetic retinopathy: a systematic review and meta-analysis," Science China Life Sciences, vol. 58, no. 1, pp. 101–107, 2015.

[30] R. Graber, J. C. Farine, and G. A. Losa, "Calcium dobesilate protects human peripheral blood mononuclear cells from
oxidation and apoptosis,” *Apoptosis*, vol. 3, no. 1, pp. 41–49, 1998.

[31] M. E. Szabo, D. Haines, E. Garay et al., “Antioxidant properties of calcium dobesilate in ischemic/reperfused diabetic rat retina,” *European Journal of Pharmacology*, vol. 428, no. 2, pp. 277–286, 2001.

[32] J. F. Hall, “Modern management of hemorrhoidal disease,” *Gastroenterology Clinics of North America*, vol. 42, no. 4, pp. 759–772, 2013.

[33] M. Michal and C. Gotti, “Effect of calcium dobesilate on platelet function,” *Thrombosis Research*, vol. 51, no. 6, pp. 593–605, 1988.

[34] J. Brunet, J. C. Farine, R. P. Garay, and P. Hannaert, “Angioprotective action of calcium dobesilate against reactive oxygen species-induced capillary permeability in the rat,” *European Journal of Pharmacology*, vol. 358, no. 3, pp. 213–220, 1998.

[35] R. Rota, C. Chiavaroli, R. P. Garay, and P. Hannaert, “Reduction of retinal albumin leakage by the antioxidant calcium dobesilate in streptozotocin-diabetic rats,” *European Journal of Pharmacology*, vol. 495, no. 2-3, pp. 217–224, 2004.

[36] Y. Zhou, J. Yuan, C. Qi, X. Shao, S. Mou, and Z. Ni, “Calcium dobesilate may alleviate diabetessinduced endothelial dysfunction and inflammation,” *Molecular Medicine Reports*, vol. 16, no. 6, pp. 8635–8642, 2017.

[37] Y. Zhou, C. Qi, S. Li, X. Shao, S. Mou, and Z. Ni, “Diabetic nephropathy can be treated with calcium dobesilate by alleviating the chronic inflammatory state and improving endothelial cell function,” *Cellular Physiology and Biochemistry*, vol. 51, no. 3, pp. 1119–1133, 2018.

[38] Y. Zhou, C. Qi, S. Li, X. Shao, and Z. Ni, “Investigation of the mechanism underlying calcium dobesilate-mediated improvement of endothelial dysfunction and inflammation caused by high glucose,” *Mediators of Inflammation*, vol. 2019, Article ID 9893682, 12 pages, 2019.

[39] J. Angulo, C. Peiro, T. Romacho et al., “Inhibition of vascular endothelial growth factor (VEGF)-induced endothelial proliferation, arterial relaxation, vascular permeability and angiogenesis by dobesilate,” *European Journal of Pharmacology*, vol. 667, no. 1-3, pp. 153–159, 2011.

[40] Y. Wang, Y. H. Lu, C. Tang et al., “Calcium dobesilate restores autophagy by inhibiting the VEGF/PI3K/AKT/mTOR signaling pathway,” *Frontiers in Pharmacology*, vol. 10, p. 886, 2019.

[41] M. Feghhi, F. Farrahi, M. Abbaspour, and A. Takhtaeian, “Effect of adding oral calcium dobesilate to laser photocoagulation on the macular thickness in patients with diabetic macular edema: a randomized clinical trial,” *Advanced Pharmaceutical Bulletin*, vol. 4, no. 4, pp. 375–378, 2014.

[42] E. J. Kim, W. V. Lin, S. M. Rodriguez, A. Chen, A. Loya, and C. Y. Weng, “Treatment of diabetic macular edema,” *Current Diabetes Reports*, vol. 19, no. 9, p. 68, 2019.

[43] L. Kodjikian, D. Bellocq, F. Bandello et al., “First-line treatment algorithm and guidelines in center-involving diabetic macular edema,” *European Journal of Ophthalmology*, vol. 29, no. 6, pp. 573–584, 2019.

[44] A. Garcia Layana, A. Adan, F. J. Ascaso et al., “Use of intravitreal dexamethasone implants in the treatment of diabetic macular edema: expert recommendations using a Delphi approach,” *European Journal of Ophthalmology*, vol. 30, no. 5, pp. 1042–1052, 2020.

[45] S. K. Mahapatra and S. Kumari, “Long-term results of a single injection of intravitreal dexamethasone as initial therapy in diabetic macular edema,” *Indian Journal of Ophthalmology*, vol. 68, no. 3, pp. 490–493, 2020.

[46] F. Njau, N. Shushakova, H. Schenk et al., “Calcium dobesilate reduces VEGF signaling by interfering with heparan sulfate binding site and protects from vascular complications in diabetic mice,” *PLoS One*, vol. 15, no. 1, Article ID e0218494, 2020.

[47] W. Dongxuan, W. Hui, W. Shuang, Y. Xueqiu, and Y. Xueqiu, “Effect of calcium dobesilate (CaD) on diabetic macular edema treated by intravitreal ranibizumab,” 2021, https://www.researchsquare.com/article/rs-830956/v1.