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Metformin therapy as a strategy to compensate anti-VEGF resistance in patients with diabetic macular edema

Alexandre Uwimana, MD[a], Cong Ma, MD[a], Shengyao Chen, MD[a], Xiang Ma, MD, PhD[a,*]

Abstract

Diabetic macular edema (DME) is the complication of diabetic retinopathy, the leading cause of vision loss among diabetic patients. Metformin is the main antidiabetic treatment. It is preferable for its great anti-angiogenic and anti-inflammatory effects. Anti-vascular endothelial growth factor (VEGF) therapy is the preferable treatment for DME despite its lack of convincing results in some patients. To assess whether the combination of metformin and anti-VEGF drugs may decrease the risk of anti-VEGF resistance among DME patients. We included DME patients with a central retinal thickness (CRT) ≥ 250 μm who consecutively underwent at least 3 anti-VEGF therapies from January 1, 2020, to December 30, 2021. Anti-VEGF resistance was defined as persistent macular edema with decreased CRT ≤ 25% after 3 anti-VEGF injections. 109 patients were considered for this research, of whom 65 (59.6%) were resistant to anti-VEGF therapy. The mean CRT of the non-metformin group decreased from 344.88 ± 129.48 to 318.29 ± 123.23 (20.85%) and from 415.64 ± 144.26 to 277.11 ± 99.25 (31.51%) (P = .031) in the metformin group. Moreover, the metformin group had fewer resistant patients than the non-metformin, 24 (45.3%) versus 41 (73.2%). Furthermore, a considerable gain in visual acuity was observed in both groups, with a BCVA gain of 40.41% in the metformin group and 39.9% in the non-metformin group. Metformin may be combined with an anti-VEGF drug to minimize the risk of anti-VEGF resistance among DME patients. Moreover, it can serve to design effective therapeutic deliveries.

Abbreviations: BCVA = best-corrected visual acuity, CRT = central retinal thickness, DM = diabetes mellitus, DME = diabetic macular edema, DR = diabetic retinopathy, LogMAR = logarithm of the minimal angle of resolution, OCT = optical coherence tomography, RPE = retinal pigment epithelial, VA = visual acuity, VEGF = vascular endothelial growth factor.

Keywords: anti-VEGF treatment resistance, central retinal thickness, diabetic macular edema, diabetic retinopathy, logMAR best-corrected visual acuity, metformin, optical coherence tomography.

1. Introduction

The world health organization (WHO) reported an estimation of 422 million people worldwide living with diabetes mellitus (DM).[1] The long-term onset of DM is associated with the risk of developing vascular complications that lead to patient fatality. Uncontrolled glycemia results in large vessel complications such as stroke and coronary heart disease (CHO) and small vessel complications such as diabetic neuropathy, nephropathy, and retinopathy.[2] The developmental processes of diabetic retinopathy (DR) are associated with inflammation-mediated and angiogenesis pathways, capillary breakdown, and ischemia, causing neovascularization and microhemorrhages.[3] Moreover, ischemia promotes the thickness of the macula due to the permeability of the retinal capillaries, causing visual acuity impairment.[4] Other risk factors of DME include elevated glycosylated hemoglobin (HbA1c) levels, a long durability of DR, poor glycemic control, and hypertension.

Metformin hydrochloride is the main antidiabetic treatment acting without causing hypoglycemia,[5] with a considerable effect of reducing body weight, protecting cardiac diseases, decreasing the rate of fatality from cancer, enhancing lifespan, and involving in vascular protection such as amelioration of inflammation, coagulation process, oxidative stress (OS), reactive oxygen species (ROS), endothelial impairment, and hemostasis.[6,7] Metformin inhibits the overexpression of VEGF-A during hyperglycemia-hypoxia conditions and protects retinal vascular endothelial cells. Moreover, metformin stimulates the adenosine monophosphate-activated protein kinase (AMPK)

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University. Patient consent was not applicable and waived due to the study's retrospective nature.

[a] *Department of Ophthalmology, First Affiliated Hospital of Dalian Medical University, Dalian, China.*

**Correspondence: Xiang Ma, Department of Ophthalmology, First Affiliated Hospital of Dalian Medical University, 222 Zhongshan Road, Xigang District, Dalian 116044, China (e-mail: xma9467@vip.sina.com).*

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pathway to protect against the deterioration of photoreceptor cells and retinal pigment epithelial cells by increasing mitochondrial biogenesis and decreasing OS.[8]

Anti-VEGF agents are the preferable drugs to treat the complications of DR and have the primary function in managing DME. Although anti-VEGF therapy has considerable advantages on retinal tissues, some patients have little (if any) improvement in vision and persistent macular edema despite continuous anti-VEGF injections.[9] Furthermore, due to the short duration of action of anti-VEGF drugs, patients require monthly or bimonthly injections to ascertain efficacy; in consequence, limitations such as nonadherence to the treatment, financial burden, and impairment of quality of life are complained by patients.[10–12] Up to date, there has been no agreement on the definition of anti-VEGF treatment resistance.[13] However, most studies have defined anti-VEGF treatment resistance as the absence of anatomical improvement after 3 to 4 consecutive anti-VEGF injections.[14–16] Therefore, the present study defined anti-VEGF resistance as persistent macular edema with a ≤25% decrease in CRT after 3 consecutive anti-VEGF therapies. Optical coherence tomography (OCT) and various retinal imaging tools assist physicians in properly diagnosing macular disorders and offer a highly detailed view of different retinal layers, allowing precise measurements of their thicknesses.[17–20]

The present study aims to assess whether the combination of metformin and anti-VEGF drugs may decrease the risk of anti-VEGF resistance among DME patients. We hypothesized that patients under systemic metformin treatment would respond better to anti-VEGF therapy than patients receiving other anti-diabetic drugs. Previously, the anti-VEGF treatment resistance has been poorly understood and investigated. This research will provide new insights into the management of DM and its retinal complications. Through this study, clinicians and diabetic researchers will further realize the benefits of the concomitant therapy of metformin and anti-VEGF agents as an effective strategy to reduce anti-VEGF resistance among DME patients. Given the large unmet need for DME treatment, further studies are warranted. Our findings will draw attention to future research, which can lead to novel therapeutic approaches.

2. Methods

2.1. Study design

This is a retrospective observational study conducted in a single hospital. The patients were retrospectively included and prospectively controlled throughout the study period. All patients who were first diagnosed with DME between January 1, 2020, and December 30, 2021, were identified and closely followed their response to the anti-VEGF treatment. Data were consecutively recorded and maintained in the computerized electronic database, and analysis started after the set period for data collection was reached. The recorded patients' information included age, gender, alcohol or tobacco consumption status, diabetes duration, history of diabetes medications from the diagnosis up to date, history of insulin therapy, previous systemic and ocular disorders, and previous general and ocular surgeries.

On the first visit, a clinical laboratory report was required. Patients were sent to our hospital's laboratory for testing complete blood count (CBC), anti-HIV antibody (anti-HIV), hepatitis C antibody (anti-HCV), hepatitis B surface antigen (HBsAg), total protein (TP), activated partial thromboplastin time (APTT), thrombin time (TT), prothrombin time and international normalized ratio (PT/INR), and fibrinogen activity (FIB).

At each hospital visit, a complete eye examination was conducted. First, we performed preliminary tests such as visual acuity, tonometry, keratometry, depth perception, extraocular muscle function, topography, color blindness, peripheral vision, pupillary light reflex, and refraction. Then a wide slit-lamp examination and fundoscopy were evaluated by an ophthalmologist, followed by complementary tests, including digital retinal imaging, OCT, and fluorescein angiography. Moreover, measurements of HbA1C, blood pressure, height, weight, and temperature were taken in our department during all follow-up visits.

The intravitreal anti-VEGF treatment followed similar procedures, the same dosage, and was operated by a single experienced retinal specialist. Four independent assessors collected the data, and 3 assessors blindly analyzed them. However, randomization would not be possible since this was a retrospective study. Patients were divided into the metformin group and the non-metformin group. The patients in both groups received at least 3 injections of one of the following anti-VEGF drugs: Aflibercept (4.0 mg/0.1 mL), Conbercept (1.0 mg/0.2 mL), or Ranibizumab (1.0 mg/0.2 mL). The anti-VEGF treatment was scheduled every 4 to 8 weeks. Patients with injection intervals longer than 8 weeks were not considered. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University. Patient consent was not applicable and waived due to the study's retrospective nature.

2.2. Inclusion and exclusion criteria

This study included naïve patients newly diagnosed with DME and who had never received other retinal treatments. Moreover, patients with any form of chronicity of the disease were not considered to ensure accurate results of our analysis. For this, we excluded all patients with advanced stages of DME, tractional retinal detachment, diffuse hard or circinate exudates, intraretinal hemorrhages, and intraretinal cystic spaces. It is worth mentioning that when both eyes met the inclusion criteria, we considered the eye with high CRT.

Therefore, the present study included patients who: aged 18 years or more; with CRT ≥ 250 μm, received at least 3 consecutive anti-VEGF therapies throughout the study period, and with complete ophthalmic examination and the OCT records on follow-up following each anti-VEGF therapy. On the other hand, patients who received one of the following treatments were excluded: intravitreal or sub-tenon injection of steroidal or nonsteroidal anti-inflammatory, pan-retinal photocoagulation, pars plana vitrectomy, ≤6 months history of any non-retinal surgery such as cataract and glaucoma, and any history of retinal impairment such as optic nerve disorders, branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO), and age-related macular degeneration. In addition, we also excluded patients who had a history of metformin less than 6 months, poor glycemic control (HbA1C > 9%), with missing or incomplete data on follow-ups, and who were not adherent to diabetes treatment.

2.3. Definition of outcomes

Anti-VEGF treatment resistance was defined as persistent macular edema with a ≤25% decrease in CRT after 3 consecutive anti-VEGF therapies.[21] However, due to assorted visual acuity outcomes after anti-VEGF therapy, literature does not have a unanimous definition of effective vision after anti-VEGF treatment. The present study defined improved vision as gaining best-corrected visual acuity (BCVA) ≥15% after 3 anti-VEGF injections. Two groups were created: the metformin group and the non-metformin group. Patients in the metformin group had to be on oral metformin treatment for at least 6 months before the study entry.[22] The logarithm of the minimal angle of resolution (LogMAR) BCVA was measured by a standardized Snellen chart at each follow-up and was correlated with the macular thickness outcome. The data of OCT images were kept from the hospital imagery database, and the CRTs were measured by the Spectralis domain OCT

(Heidelberg Engineering, Carlsbad, California). OCT allows the evaluation of macular edema changes following anti-VEGF treatments.[23,24]

2.4. Statistical analysis

Data was collected using XLS Excel (Microsoft Excel, Washington), and all statistics were performed by IBM SPSS version 25.0 (IBM Corp, Armonk, New York). The multivariate analysis of variance (MANOVA) was conducted to assess whether there are relationships between factors and resistance. We presented data by mean ± SD (standard deviation) and number/percentage of patients (n, %). A normality test (Shapiro–Wilks test) was determined for each parameter. The Chi-square test was used to compute differences between groups. Two-tailed paired *t* test was performed to compare the results of CRT and BCVA before and after treatment. Two-way ANOVA analysis was used to determine the significance of increased CRT, improved VA, and IOP changes in both groups after treatment. Wilcoxon signed-rank tests were used for non-normal distribution. $P < .05$ was considered significant across our statistics.

3. Results

Overall, 233 patients were eligible for the study. However, after applying all our inclusion criteria, only 109 patients (109 eyes) were considered for the final analysis. The average age was 56.9 ± 11.1 years (range from 23 to 81). Fifty-eight (53.2%) were male and 51 (46.8%) were female. The total mean BCVA before and after 3 anti-VEGF treatments was 0.32 ± 0.25 logMAR and 0.23 ± 0.24 logMAR, respectively ($P < .000$). The total mean CRT before and after treatment was 379.28 ± 140.78 µm and 298.27 ± 113.59 µm, respectively ($P < .000$). Of all patients, 53 were in the metformin group and 56 in the non-metformin group. The characteristics of each group are outlined in Table 1. A high degree of interrater reliability was found between assessors. The intraclass correlations (ICC) was 0.866 (95% CI = 0.794–0.902; F test = 3.665; $P = .0043$).

After 3 anti-VEGF therapies, both groups observed an important improvement in the BCVA. The mean logMAR BCVA of the non-metformin group (before treatment: 0.30 ± 0.23 versus after treatment: 0.21 ± 0.22, and the metformin group (before treatment: 0.34 ± 0.28 versus after treatment: 0.25 ± 0.26); $P = .668$. Moreover, an important amelioration of the retinal thickness was noticed for both groups. The mean CRT of the non-metformin group decreased from 344.88 ± 129.48 to 318.29 ± 123.23, and in the metformin group, the decrease was from 415.64 ± 144.26 to 277.11 ± 99.25; $P = .001$.

Our results found that the mean CRT in the metformin group was slightly higher than in the non-metformin group, but the 2 groups were comparable ($P = .397$). The initial analysis of the sample showed that this increased CRT from 6 patients in the metformin group with a higher baseline CRT, > 600 µm (614, 651, 672, 713, 747, and 883). However, all these 6 patients met the inclusion criteria; therefore, the authors decided to include them in the study.

Part of this research aimed to ascertain the advantages of metformin treatment on intraocular pressure (IOP). We observed a slight increase in IOP in the non-metformin group compared to the metformin group (Fig. 1). The mean IOP of non-metformin group (before treatment: 17.16 ± 7.9 vs after treatment: 17.64 ± 11.4), and metformin group (before treatment: 17.15 ± 4.5 vs after treatment: 17.04 ± 5.3); $P = .919$.

According to our definition, a total of 65 eyes (59.6%) were resistant to anti-VEGF treatment, and 44 eyes (40.4%) were responsive to treatment. Comparing both groups, we observed that the metformin group had fewer resistant patients than the non-metformin. Our results showed 24 (45.3%) versus 41 (73.2%), $P = .003$ resistant eyes for metformin group and non-metformin group, respectively. Moreover, our results showed that the overall CRT in both groups decreased by 26.03%. However, a significant decrease was observed in the metformin group compared to the non-metformin group (respectively 31.51% and 20.85%, $P = .031$). Furthermore, according to the definition of visual outcome (gain of BCVA ≥ 15%), we observed a considerable gain of visual acuity in both groups (40.2%), with a BCVA gain of 40.41% in the metformin group and a BCVA gain of 39.9% in the non-metformin group ($P = .956$).

In addition, we determined whether other studied factors influenced the patients' resistance to anti-VEGF therapy. The results showed that there is no statistical relationship between CRT outcomes and age (SE: 1.07; 95% CI: 54.77–59.01; $P = .466$), duration of DM (SE: 0.65; 95% CI: 12.72–15.31; $P = .716$), HbA1C (SE: 0.12; 95% CI: 7.30–7.79; $P = .506$), systolic blood pressure (SE: 2.09; 95% CI: 138.62–146.90; $P = .207$), diastolic blood pressure (SE: 1.04; 95% CI: 81.46–85.58; $P = .543$), BMI (SE: 0.28; 95% CI: 24.55–25.67; $P = .522$), gender

Table 1

Group characteristics.

	Metformin group	Non-metformin group	*P*	All
Number (male/female)	53(25/28)	56(33/23)	.219	109(58/51)
Age (yrs)	57.64 ± 10.74	56.18 ± 11.57	.472	56.89 ± 11.15
Duration of DM (years)	14.68 ± 6.59	13.39 ± 7.05	.361	14.02 ± 6.83
Insulin treatment, n(%)				
Insulin users	23(43.4)	12(21.4)	.014	35(32.1)
Non-insulin users	30(56.6)	44(78.6)		74(67.9)
BP (mm Hg)				
IOP (mm Hg)	143/82	143/85	.483	143/83
HbA1C (%)	17.15 ± 4.52	17.16 ± 7.91	.361	17.16 ± 6.45
BMI	7.56 ± 1.40	7.54 ± 1.19	.448	7.55 ± 1.29
Smoking status, n (%)	25.12 ± 3.11	25.11 ± 2.80	.782	25.12 ± 2.94
Yes	11(20.8)	8(14.3)	.374	19(17.4)
No	42(79.2)	48(85.7)		90(82.6)
Alcohol consumption, n (%)				
Yes	34(64.2)	30(53.6)	.262	64(58.7)
No	19(35.8)	26(46.4)		45(41.3)

Values are expressed as means ± standard deviations or numbers (%).

BMI = body mass index, BP = blood pressure, DM = diabetes mellitus, HbA1C = glycated hemoglobin, IOP = intraocular pressure.

(P = .873), insulin treatment (P = .580), type of anti-VEGF (P = .558), smoking status (P = .498), and alcohol consumption (P = .743).

Finally, we conducted Pearson's correlation analysis to investigate whether the outcomes of CRT are correlated with the outcomes of logMAR BCVA. The following hypotheses were made; the null hypothesis (H_0) hypothesized no difference in outcome between BCVA and CRT, and the alternative hypothesis (H_1) hypothesized a difference in outcome between BCVA and CRT in terms of resistance to anti-VEGF. From the results of this analysis, we observed a very low, negative, and non-statistically significant correlation between BCVA and CRT (r = –0.26, P = .789). Therefore, H_1 was rejected, and H_0 was considered.

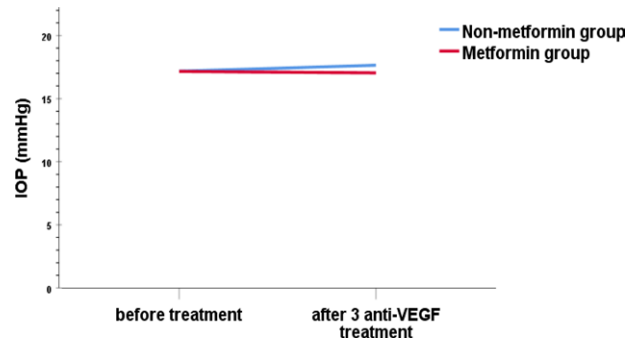

Figure 1. Change of intraocular pressure (IOP) before and after treatment. IOP was measured in mm Hg before and after each intravitreal anti-VEGF treatment.

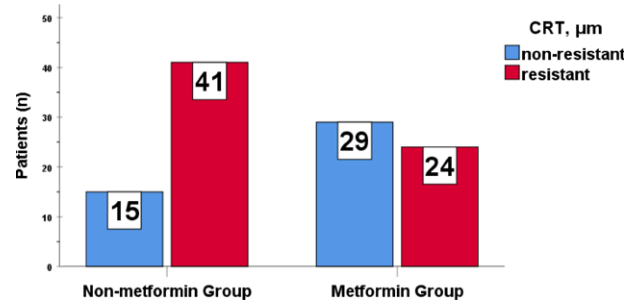

Figure 2. The proportion of resistant patients in both groups. Data are presented as number of patients (n). The total number of patients in non-metformin group (n = 56) and in metformin group (n = 53).

4. Discussion

The present study investigated whether the combination of metformin with anti-VEGF agents may decrease the risk of anti-VEGF resistance among DME patients. DME is the commonest complication of DR, conducting to the visual sequelae of diabetic patients, and poses a considerable burden to the working-age population. Anti-VEGF drugs have become the golden therapy for managing DME.[25] However, although anti-VEGF agents are the standardized therapy for DME, some patients lack an effective response to this therapy, with a possibility of worsening, a phenomenon called tachyphylaxis or tolerance.[26,27] It is believed that resistance to anti-VEGF occurs due to the chronicity of the disease, with long-lasting impairment applied to retinal tissues during the developmental process of DME; therefore, sustained treatment might be required to achieve effective results. The pathophysiology of DME has undoubtedly been linked to elevated VEGF levels and many inflammatory reactions;[28] however, the anti-inflammatory effects of anti-VEGF agents are still not ascertained.[16] Thus, some patients resist anti-VEGF treatment and require different approach therapies such as intravitreal dexamethasone (DEX) implant.[29–32] Moreover, a slow-release DEX implant is favorable for continuous drug release and decreases the treatment burden.[33–35]

We demonstrated that concomitant use of metformin and anti-VEGF agents could decrease the risk of anti-VEGF resistance in DME patients. The incidence of anti-VEGF treatment resistance was higher in non-metformin users compared to metformin users (P = .003) (Fig. 2). Previous studies found similar results. For instance, in a retrospective study of 234 eyes, Maleškić et al (2017)[36] reported that oral metformin combined with anti-VEGF therapy results in strong protective effects against diabetes complications in the eye. Similarly, Li et al (2018)[37] monitored 335 types 2 diabetes mellitus (T2DM) patients for 15 years and demonstrated that 47% of non-metformin users progressed to severe DR, compared to 25% of metformin users (P < .001). Moreover, animal model experiments have indicated the beneficial protection of metformin against degeneration and aggravation of DR and DME.[38–42]

A recent study by Fan et al (2020)[22] has reported a lower possibility of developing sight-threatening diabetic retinopathy (STDR) among metformin users. However, in our study, the VA has significantly ameliorated among metformin takers and non-metformin takers, and we did not remark a significant VA difference in both groups. The BCVA improved by 40.41% and 39.9% (Fig. 3a) in the metformin and non-metformin group, respectively. Furthermore, the retinal thickness in the metformin group decreased significantly compared to the non-metformin group (31.51% vs 20.85%, respectively) (Fig. 3b). Some studies have discussed discrepancies between anatomic improvement and functional outcomes, which may be attributed to the subretinal scars and photoreceptor loss at an earlier stage of Dr[15] In the same way, the Pearson analysis in our study

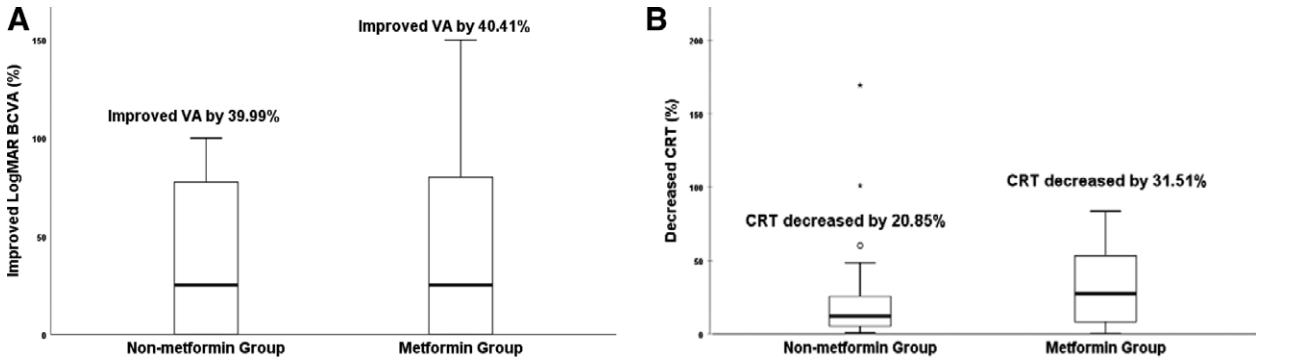

Figure 3. Group outcomes after 3 intravitreal anti-VEGF treatments. (a) improved visual acuity (LogMAR, %), and (b) decreased central retinal thickness (µm, %).

revealed a non-correlation between BCVA and CRT. This was consistent with the findings of a clinical trial, which showed an insignificant correlation between CRT and BCVA among DME patients.[43] This may explain the higher proportion of patients who improved VA in both groups (Fig. 4), which was not correlated to the proportion of those who improved CRT. Interestingly, Kokame et al (2019)[14] have linked anti-VEGF treatment resistance to gender (male), younger age, and smoking status. In contrast to our findings, no relationship was found between anti-VEGF treatment resistance and age, duration of DM, HbA1C, blood pressure, insulin treatment, type of anti-VEGF, smoking status, and alcohol consumption.

In the light of phase III RISE and RIDE clinical trials, Brown et al (2013)[44] revealed that DME patients treated with anti-VEGF maintained the improved vision and retinal thickness until 36 months. However, our study set up the cut point of 3 consecutive anti-VEGF therapies because it has been speculated that most non-responsive eyes after 3 anti-VEGF injections will stay non-responsive even when the treatment is continued. Even Busch et al (2019)[45] questioned the importance of keeping the anti-VEGF treatment since 72 percent of eyes were still non-responsive when continued on anti-VEGF therapy alone. Moreover, 2 separate clinical trials conducted by Bressler et al (2016 and 2018)[46,47] have demonstrated that approximately 40 percent of patients don't respond to anti-VEGF therapy.

Of note, the conception of anti-VEGF treatment resistance was originally acquainted through cancer studies.[48] Currently, no common definition of anti-VEGF treatment resistance has been agreed upon.[49] The description of responsiveness to DME therapy and the universal definition of responsiveness to anti-VEGF therapy has been contradicted among studies and has not yet achieved agreement. The literature discrepancy is based on whether the definition should be based on visual or anatomic measures. Notwithstanding, retrospectively, there is no available definition of early treatment diabetic retinopathy study (ETDRS) refraction; hence the anatomic definition is more practical. To explain the ranges of DME outcomes following anti-VEGF treatment, the diabetic retinopathy clinical research network (DRCR.net) defined the success of anti-VEGF therapy as a gain of VA of 10/10 and decrease of CRT lesser than 250 μm; improvement of anti-VEGF therapy as VA gain of 5 or more letters and reduction of CRT of greater than 10%; and no improvement anti-VEGF therapy as VA gain of lesser than 5 letters and CRT of lesser than 10%.[50] Furthermore, it is worth mentioning that anti-VEGF treatment resistance can happen at any time from the beginning of treatment and later following initially successful treatment.[51] To the best of our knowledge, our research is the first to investigate whether the combination of metformin and anti-VEGF agents decreases the risk of anti-VEGF treatment resistance among DME patients.

The predominant limitation of this research was its retrospective design. While 2 years of the follow-up period were relatively short, extending to a longer follow-up was not possible because of the diverging variety of treatments after this period, especially in the resistant eyes. Also, the mean baseline CRT in the metformin group was quite higher compared to the non-metformin group due to few patients (n = 6) in the metformin group who had initial elevated CRT (>600 μm) while meeting all defined inclusion criteria. Moreover, another limitation was the deficiency of the standard definition of anti-VEGF treatment resistance. The last limitation was that many patients did not meet our inclusion criteria due to the prepotency of cataracts, which might have impacted BCVA results.

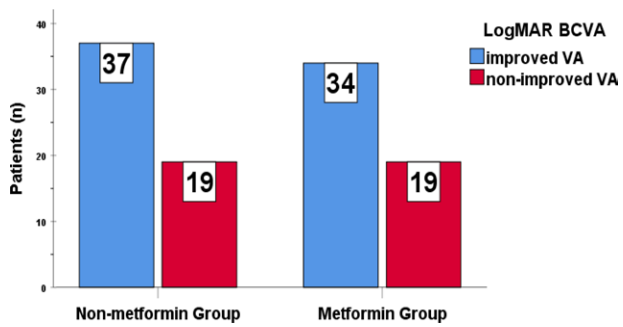

Figure 4. The proportion of patients that gained ≥15% best-corrected visual acuity (BCVA) from baseline to 3 anti-VEGF treatments.

5. Conclusions

This study identified that combining oral metformin with intravitreal anti-VEGF drugs is advantageous to anti-VEGF therapy resistance among DME patients. Metformin is a very effective therapy for cardiovascular and nervous system diseases. However, its beneficial effects on ocular-related diabetic complications are still poorly understood.[40] Retinal researchers have recently focused on ameliorating DME management through anti-VEGF, steroids, laser, and surgical approaches. Nonetheless, the systemic approach is still disvalued. We imply that retinal specialists ought to collaborate with endocrinologists for better systemic considerations and the design of efficient delivery methods to reach the successful treatment of DR complications, including DME.[52] Metformin could substantially serve this design for its safety and effectiveness. In short, our study suggests that systemic metformin therapy might be used concomitantly with anti-VEGF treatment to achieve effective results. Our results revealed a significant decrease in retinal thickness and a lower proportion of resistant eyes among DME metformin users compared to non-metformin users. To conclude, randomized trials are highly recommended for future research to support our study.

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Author contributions

Conceptualization: Alexandre Uwimana, Xiang Ma, Cong Ma, Shengyao Chen.
Data curation: Xiang Ma, Alexandre Uwimana, Cong Ma, Shengyao Chen.
Formal analysis: Alexandre Uwimana, Shengyao Chen, Cong Ma.
Investigation: Alexandre Uwimana, Xiang Ma, Shengyao Chen.
Methodology: Xiang Ma, Cong Ma, Alexandre Uwimana.
Project administration: Xiang Ma.
Resources: Alexandre Uwimana, Xiang Ma, Cong Ma, Shengyao Chen.
Supervision: Xiang Ma, Cong Ma.
Validation: Alexandre Uwimana, Xiang Ma, Shengyao Chen, Cong Ma.
Writing – original draft: Alexandre Uwimana.
Writing – review & editing: Xiang Ma, Alexandre Uwimana.

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