Original Article

Impact of systemic parameters before commencing anti-vascular endothelial growth factor therapy for diabetic macular edema – Pan-Indian survey of retina specialists

Mahesh Shanmugam P, Payal Shah, Rajesh Ramanjulu, Divyansh Mishra

Purpose: Intravitreal anti-vascular endothelial growth factor (VEGF) injection therapy has emerged as the mainstay of treatment in the management of diabetic macular edema (DME) today. Various systemic risk factors have to be considered before initiating anti-VEGF therapy. The aim of our study was to form a consensus on various systemic factors to consider before starting anti-VEGF therapy for DME. **Methods:** A questionnaire was created and sent across to various retina specialists across India. A Google™ form with various questions pertaining to what systemic parameters would one consider before giving anti-VEGF therapy for DME was sent to each of them by email/WhatsApp™/direct telephonic interview. **Results:** Of the 650 retina specialists contacted, 322 responded to the questionnaire. There was no difference in responses between private and institutional practitioners. The majority would consider RBS (85%), HbA1c (61%), blood pressure (63%), and renal function (57%) as a routine before administering the anti-VEGF injection, while the majority would not consider hemoglobin (63%) or lipid profile (55%) of the patient as a routine practice prior to administering the injection. **Conclusion:** In our study, most VR specialists prefer to consider RBS, HbA1c, BP, and renal profile (creatinine) routinely prior to anti-VEGF injection. We suggest that it is important to consider blood pressure control, glycemic control, HbA1c, Hb, lipid profile, and renal profile (UACR, eGFR, and creatinine) prior to anti-VEGF therapy in all diabetic patients and to discuss the need for statins in patients with dyslipidemias with the physician.

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Diabetic macular edema (DME) is a common vision-threatening complication of diabetes mellitus. Among various systemic factors, male gender, diabetes duration, insulin, smoking, alcohol, high HbA1c, uncontrolled hypertension, dyslipidemia, nephropathy, neuropathy, sleep apnea, glitazone usage, pregnancy, severity of diabetic retinopathy (DR), and previous cataract surgery are associated with higher risk of DME.[1-3]

Intravitreal anti-vascular endothelial growth factor (VEGF) injection therapy has emerged as the mainstay in the management of DME.[4] This study is designed to understand the consensus among various vitreoretinal specialists regarding the systemic considerations before commencing anti-VEGF therapy.

Methods

Contacting retina specialists

This was a survey conducted among vitreoretinal (VR) specialists in India. A questionnaire was sent across to 650 retina specialists across India. Contacts were collected from various sources like RETNET directory, WhatsApp™ retina groups, Telegram™ retina groups, and other personal contacts. Approximately 1200 phone calls were made by our retina team to interview them and send reminders.

Creating the questionnaire

Based on the published literature, we framed the questionnaire. A Google™ form with various questions was created and sent. Questionnaires were sent via either email or SMS or WhatsApp™ or directly interviewed via phone calls. The responses from the form and telephonic interviews were collected and analyzed. Eighteen questions [Supplement File] were framed which pertained to experience (in years), type of practice (private or institute), systemic considerations, that is, blood pressure (BP), random blood sugar (RBS), glycosylated hemoglobin (HbA1c), hemoglobin (Hb), lipid profile, renal function before giving anti-VEGF, anti-VEGF in pregnancy, urinary tract infection (UTI)/diabetic foot, and recent history of cerebrovascular accident (CVA) or myocardial ischemia (MI).

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The institutional ethics committee board ruled that approval was not required for the study as it was an expert opinion poll and did not involve any patients or patients' data.

Responses were analyzed using SPSS software. Mean cut-off values, standard deviation, confidence interval, Chi-square test, and *P* values were calculated.

Results

Of the 650 specialists contacted, 322 responded to the questionnaire. The mean experience as a retina specialist was 8.03 years (range: 1–34 years). They were grouped into three categories based on experience (<5, <10, and ≥10 years) to understand if there was any difference in practice patterns. Institutional practitioners were 156, while 166 were private practitioners.

We found no significant difference in responses between private and institute practice [Fig. 1]. The majority preferred to consider RBS (85%), HbA1c (61%), blood pressure (63%), and renal function (57%) as a routine before giving an anti-VEGF injection, while the majority did not consider hemoglobin (63%) or lipid profile (55%) levels as a routine practice prior to injection. We used a cut-off value of 200 mg/dl for RBS, based on AIOS guidelines of RBS performed in last 1 week.[5] We found that ~ 85% considered RBS cut-off of 200 mg/dl for giving injection [Table 1] and ~61% considered HbA1c levels before injection with a mean cut-off value of 7.8% (range: 5.5%–12%). Approximately 2/3rd of retina specialists (~63%), considered BP before injection. While there were variations between systolic and diastolic cut-off values, most would not inject above a mean systolic of 166 and a diastolic of 96 mm Hg. In regards with renal function tests, 57% considered them before injection

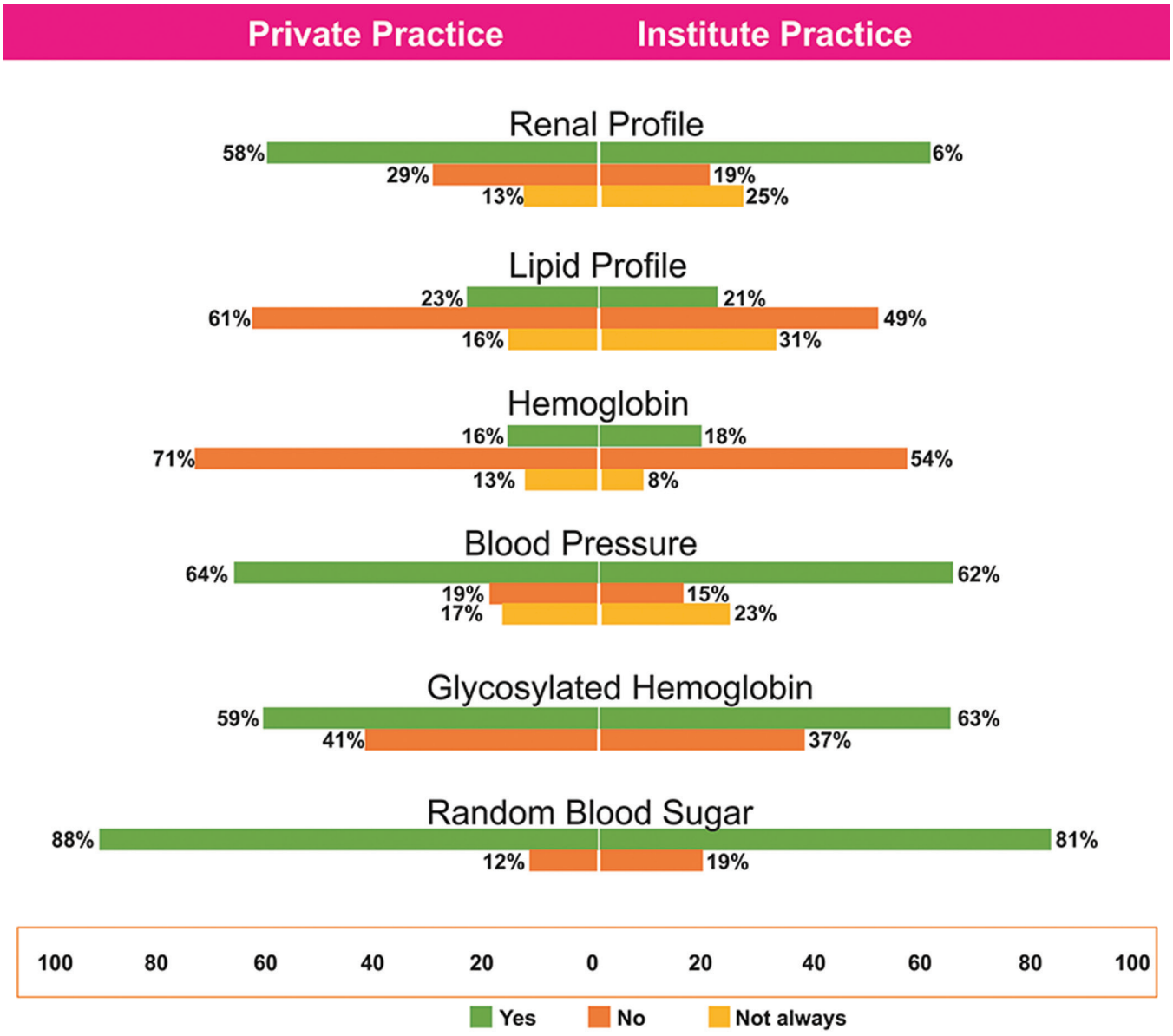

Figure 1: Comparison of responses of basic systemic parameters based on private and institute practice

with a mean serum creatinine cut-off value of 2.5 mg/dl for injection. Only 13% preferred a physician clearance for renal function before injection. There was no significant difference between responses of retina specialists based on the years of experience, as can be seen in Fig. 2.

While considering lipid profiles [Table 2], 55% did not consider them in the routine practice before the first injection. Serum triglyceride was the most chosen parameter. Lipid profile was recommended when "significant" hard exudates were noted. In dyslipidemia, 24% said they would inject anyway, 32% preferred to start statins along with injection and refer to a physician, and 44% preferred to refer to a physician or start statins and then decide upon injection. In patients with normal serum lipids but fundus revealed significant hard exudates, 29% wanted to start anti-lipid therapy, 29% wanted to discuss with a physician, and 42% did not consider anti-lipid therapy.

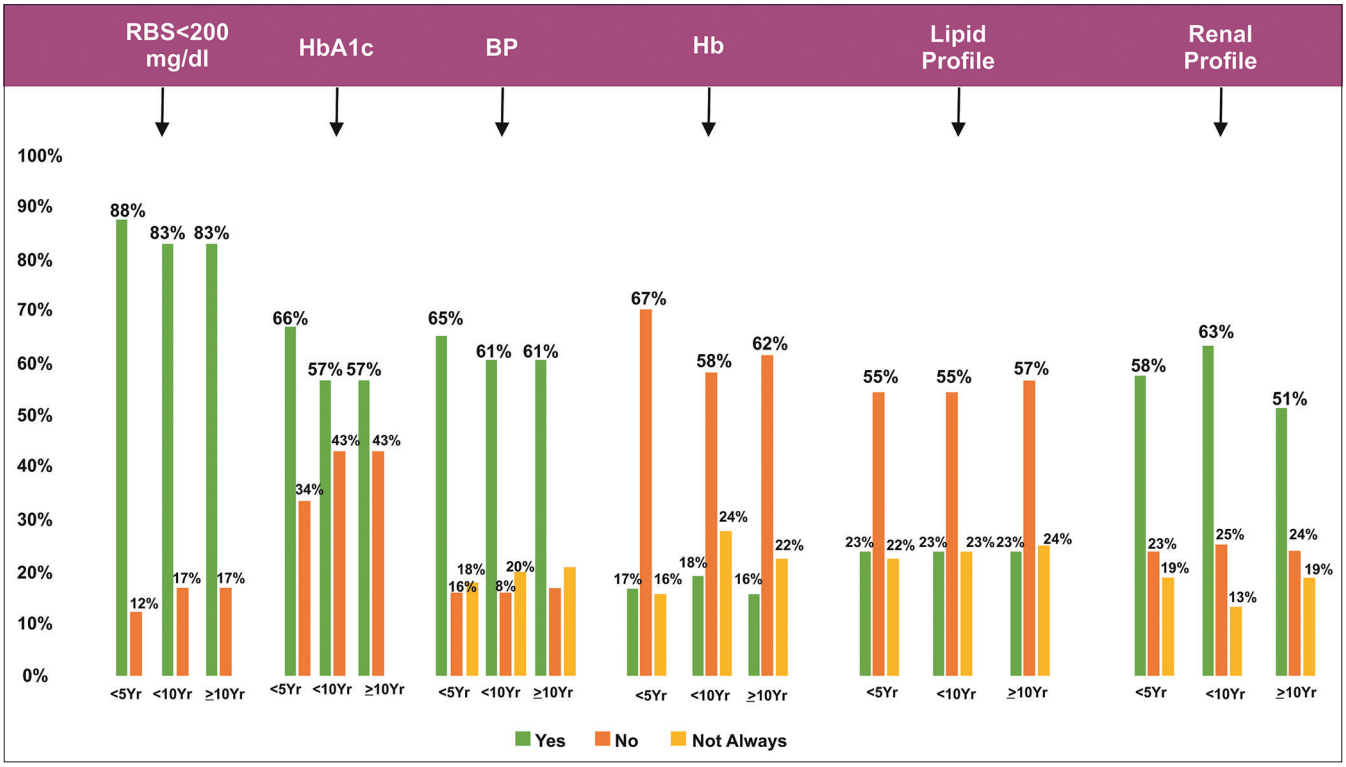

Figure 2: Comparison of responses of basic systemic parameters based on years of experience (Group 1 <5 years as retina specialist, Group 2 <10 years, Group 3 <10 years of experience)

Table 1: Responses of VR specialists for considering basic systemic parameters (BP, Hb, lipid profile, renal profile, and RBS cut-off for 200 mg/dl and HbA1c)

Systemic Parameter	Consider	Not always	Do not consider	Mean cut-off when considered (95% CI)
Blood Pressure	63% (203)	19.9% (64)	17.1% (55)	Systolic: 166.3 (168.8-163.9) Diastolic: 96.2 (95.3-97.2)
Hemoglobin	17.1% (55)	20.2% (65)	62.7% (202)	8.17 mg/dl (7.73-8.60)
Lipid profile (Serum Triglyceride)	21.7% (70)	23% (74)	55.3% (178)	255.19 mg/dl (229.98-280.40)
Renal function test (Serum Creatinine)	57.1% (184)	18.9% (61)	23.9% (77)	2.47 mg/dl (2.25-2.69)
Random Blood Sugar (Cut-off: 200 mg/dl)	84.8% (273)	-	15.2% (49)	200 mg/dl
Glycosylated Hemoglobin (HbA1c)	60.9% (196)	-	39.1% (126)	7.8%

Table 2: Responses of VR specialists in regards to dyslipidemia and oral anti-lipid therapy

Considerations for lipid profile and anti-lipid therapy (statins) in DME patients			
Do you consider lipid profile before injection?	Yes: 21.7% (70)	Not always: 23% (74)	No: 55.3% (178)
If serum lipids are normal, but you find lot of hard exudates, do you start anti-lipid therapy?	Yes: 29.2% (94)	May be: 28.6% (92)	No: 42.2% (136)
If serum lipids are elevated, what would you do?	Inject: 24% (77)	Anti-lipid therapy + inject: 32.3% (105)	Anti-lipid therapy and then decide: 43.7% (140)

Table 3: Responses while considering anti-VEGF therapy in cases with recent cardiac/cerebral history and DME in pregnancy

Question	Response
Practice patterns in case of recent cardiac/ cerebral ischemia*	
Avoid anti-VEGF and inject steroids	8.7% (28)
Physician clearance and inject	17.4% (56)
3 months, then inject	45.6% (147)
6 months, then inject	30.4% (98)
1 year, then inject	1.8% (6)
Anti-VEGF for DME in pregnancy	
"No" to injection in 2nd trimester	70.2% (226)
"No" to injection in 3rd trimester	60.9% (196)
"Yes" to injection in 2nd trimester	12.1% (39)
"Yes" to injection in 3rd trimester	22.4% (72)
Based on obstetrician's decision	2.2% (7)
Refused to comment due to lack of experience	13.3% (43)

In patients with UTI/diabetic foot, two-third of respondents preferred to wait; 13% preferred urine culture to decide, 15% preferred to inject anyways, and the rest preferred physician's clearance. In CVA or MI, 45% preferred to inject after 3 months. In pregnancy, the majority preferred not to give anti-VEGF [Table 3].

Discussion

Systemic control can cause regression of DME[6,7] and reduce the frequency of injections.[8] It is important to consider managing diabetic retinopathy from a systemic perspective as well rather than treating edema alone.

In a survey by AIOS,[9] 82% of doctors preferred RBS cut-off at 200 mg/dl for anti-VEGF injection, which is similar to our study, wherein 85% considered a cut-off at 200 mg/dl. The long-term benefits of improving glycemic control are well established by DCCT[10] and UKPDS.[11]

While several studies suggest, lower baseline HbA1c is associated with better resolution of edema,[8,12,13] few studies[14,15] suggest that HbA1c does not impact the outcome. Increase in HbA1c by 1 unit increases the time to resolution of DME by 1.28 times.[16] A very high threshold of HbA1c (<6.5% or 7%) is not warranted for injections, especially in older patients (>65 years), as the risk of severe hypoglycemia and mortality increases with intensive therapy.[17] In our study, 21% of the respondents had set a very high threshold (<6%–7%).

Uncontrolled hypertension is another well-known risk factor. Berger *et al*.[18] found that 31% of patients undergoing anti-VEGF injection experienced transient hypertensive urgency, mostly following preparation of the patient prior to injection or during the procedure. Thus, anxiety-induced and white-coat hypertension should be kept in mind preoperatively. In our study, 4%, 5%, and 54% of the respondents considered systolic BP, diastolic BP, or both, respectively. Although very rare, there are few case reports of worsening hypertension and proteinuria with bevacizumab injection.[19,20] Thus, bevacizumab should be used more cautiously in uncontrolled hypertensive with nephropathy. Elevated systolic BP is associated with need for multiple anti-VEGF injections.[21]

Presence of high HbA1c levels,[22] high blood pressure,[23] and renal impairment can be associated with neurosensory detachment in DME. Eyes with neovascular glaucoma (NVG) and DME are at a higher risk of losing vision and hence can receive injection despite higher RBS and HbA1c levels.

In our study, 29% of retina specialists used serum creatinine levels (1–6 mg/dl cut-off range) as a measure of renal function. Of the 13% who sought clearance, 9% preferred nephrologist clearance while 4% sought physicians'. A spot urine albumin/ creatinine ratio (UACR), preferably in a first-morning void, is the first-line renal screening test for diabetic patients, and estimated Glomerular filtration rate (eGFR) is the best overall indicator over serum creatinine as the former considers age, sex, race, and body size.[24] Baseline urinary albumin excretion levels can help in predicting treatment frequency in DME.[25]

One-quarter of diabetics are anemic.[26] In DR, anemia is associated with a five-fold risk of progression.[27] Spontaneous closure of microaneurysms following management of anemia has been reported.[28] Ranil *et al*.[29] have also suggested anemia evaluation prior to anti-VEGF therapy. In our study, 63% did not recommend hemoglobin routinely. Although nephropathy and anemia are often not considered before giving anti-VEGF injections, not addressing these issues may not give optimal results.

Elevated lipid levels are associated with increased hard exudates and DME severity. In our study, 58% preferred to use statins in patients with elevated lipid levels. Gupta *et al*.[30] concluded that atorvastatin helps to reduce the severity and subfoveal migration of hard exudates. AIOS DME guidelines also suggest that in patients with foveal clumps of hard exudates, statins can be advised under the physician's guidance.[5] Statins protected against the development of DME.[31] FIELD[32] and ACCORD[33] studies showed that adding fenofibrates helps to reduce the progression of DR. It is important to assess lipid profile and start statins in diabetic patients with dyslipidemias after discussing with the primary physician and calculating cardiovascular risk assessment score.

While managing glycemic and lipid profile can be planned concomitantly, it is important to correct uncontrolled hypertension, severe nephropathy, and severe anemia prior to initiation of DME therapy as the risk of micro and macrovascular complications is very high. Uncontrolled hypertension can also increase the risk of thromboembolic events post anti-VEGF therapy.[34] In recalcitrant DME cases, it is also worthwhile to look for obstructive sleep apnea, use of glitazones, and rule out hematological malignancies.

AIOS guidelines recommend avoiding anti-VEGF in pregnancy and instead use intravitreal steroids.[5] Studies have reported miscarriage when bevacizumab was given in the first trimester and none in the second and third trimester.[35] In our study, the majority (two-thirds) avoided anti-VEGF in pregnancy, while 9% preferred to inject steroids. Only, 12% and 22% agreed to give anti-VEGF injections in second and third trimesters, respectively.

In the case of CVA or MI, while 45% preferred to avoid anti-VEGF following the first three months, 32% preferred to

wait longer (6 months/1 year). Patients who receive multiple injections are at higher risk.[36]

The strengths of our study are as follows: 1) It includes a large number of retina specialists across the country. 2) It involves equal participation of private and institutional practitioners. 3) It includes almost an equal number of young and senior ophthalmologists; we found that similar practice patterns prevail irrespective of experience. 4) It gives a consensus among VR specialties in uncertain situations such as pregnancy/UTI/diabetic foot and statins in hard-exudates with normal lipid levels. These responses can guide young ophthalmologists. 5) Our study was unbiased as the participants cannot view others' responses.

Our study is limited to the expert opinion of retina specialists across India. Despite having over 1500 retina specialists across the country, we were able to collect responses only from 322 specialists.

Several studies on systemic considerations in DR[37,38] and DME[2,39] are published. However, this is the first real-world survey of retina specialists and their perspective on systemic considerations before giving anti-VEGF injections in DME.

Conclusion

From our survey, most VR specialists consider RBS, HbA1c, BP, and renal profile (creatinine) routinely prior to anti-VEGF injection.

We suggest that it is important to consider blood pressure control, glycemic control, HbA1c, Hb, lipid profile, and renal profile (UACR, eGFR, and creatinine) prior to anti-VEGF therapy in all diabetic patients and to discuss the need for statins in dyslipidemias with the physician.

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Conflicts of interest

There are no conflicts of interest.

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Supplement File

Questionnaire

The following questions are pertaining to the practice of intravitreal anti-VEGF injection for diabetic macular edema (DME)

1. How many years of experience do you have as a retina specialist
2. Where do you practice – private or institute
3. Do you consider random blood sugars cut off as <200 or >200 mg/dl for giving intravitreal anti-VEGF injection?
4. Do you consider HbA1c prior to anti-VEGF injection?
5. If yes, what is the cut-off value for HbA1c you consider?
6. Do you consider blood pressure prior to anti-VEGF injection?
7. If yes, what is the cut-off value for bp you consider?
8. Do you consider hemoglobin prior to anti-VEGF injection?
9. If yes, what is the cut-off value for bp you consider?
10. Do you consider renal profile prior to anti-VEGF injection? Which parameter?
11. If yes, what is the cut-off value you consider?
12. Do you consider lipid profile prior to anti-VEGF injection?
13. If serum lipids are normal, but you find a lot of hard exudates, do you start anti-lipid therapy?
14. If serum lipids are elevated, what would you do?
15. In presence of urinary tract infection and the patient has DME, what would you do?
16. In presence of diabetic foot and the patient has DME, what would you do?
17. If a patient has history of cerebrovascular accident/stroke/cardiac ischemia, when would you inject?
18. If a patient has DME in pregnancy when would you inject?