Behavior of hyperreflective spots noted on optical coherence tomography following intravitreal therapy in diabetic macular edema: A systematic review and meta-analysis

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Purpose: Hyperreflective spots (HRS) are considered as spectral domain optical coherence tomography biomarkers in predicting response to intravitreal therapy (IVT) in diabetic macular edema (DME). We aimed to determine if there was a quantitative reduction in HRS following IVT in DME, if the response to antivascular endothelial growth factor (anti-VEGF) drugs was different from steroids, and if HRS-response was associated with improvement in visual acuity (VA) or reduction in central macular thickness (CMT).

Methods: PubMed/MEDLINE, Scopus, ProQuest, CINAHL, Wiley online, and Web of Science were searched (between January 1, 2011 and July 1, 2020). Publication bias and heterogeneity were assessed. Meta-analysis was done using the random-effects model. Results: Totally, 1168 eyes from 19 studies were eligible for inclusion. IVT was associated with a reduction in quantitative HRS (z = -6.3, P < 0.0001). Studies, however, showed heterogeneity (I² = 93.2%). There was no difference between anti-VEGF and steroid therapies (P = 0.23). The evidence on predicting VA and CMT outcomes were limited by the number of analyzable studies, owing to the wide variation in individual study designs, and lack of randomized controlled trials.

Conclusion: We could conclude that there is a definite reduction in quantitative HRS following either form of IVT. We highlight the lacunae in the existing literature on HRS in DME and propose goals for future studies to harness the advantage of this promising biomarker.

Key words: Biomarker; Diabetic macular edema; Hyperreflective spots; Macular thickness; Optical coherence tomography; Prognosis; Visual acuity

Intravitreal antivascular endothelial growth factor (anti-VEGF) therapy emerged as the first-line treatment for diabetic macular edema (DME) in the last decade after the landmark RISE/RIDE trials and Diabetic Retinopathy Clinical Research Network (DRCR.net) studies demonstrated a significant visual acuity (VA) improvement in ~60% of the eyes treated with IVT.[1,2] However, ~50% of the eyes in protocols I and T of DRCR.net did not respond adequately to these injections.[3,4] Intravitreal steroids are being used in such patients not responding to anti-VEGF injections.[5,6] The rationale behind using steroids is based on the role inflammation has in the pathogenesis of DME.[7,8] However, a subset of patients can show suboptimal response to steroids as well.[9] In a real-life scenario, predicting which patient will or will not respond to intravitreal treatment has become a challenging task.

Various biomarkers are being evaluated on optical coherence tomography (OCT) scans to predict responses like neurosensory detachment,[10,11] ellipsoid zone (EZ) line integrity, cystoid macular edema (CME),[10,12] hyperreflective spots (HRS),[12,13] and disorganization of retinal inner layers.[12,13] HRS are small, dot-like lesions with absent back shadowing on OCT [Fig. 1].[12-14,17] The pathogenesis of these spots is still unclear. These spots are thought to be extravasated lipoproteins (precursors of hard exudates),[10,13] inflammatory cells (leucocytes, activated microglia),[14,15,18,19] migrated retinal pigment epithelium (RPE) cells,[18,20] or photoreceptor fragments.[21] Research is underway to estimate the predictive value of this biomarker in determining the final VA, reduction in central macular thickness (CMT), and duration of action of intravitreal implants.[14,15,22-25]

The current literature on HRS in DME consists of small retrospective/prospective cohort studies with a small proportion of studies showing conflicting results. Majority of the studies, however, point that HRS could be a candidate marker in predicting response to therapy in DME. Hence, we tried to synthesize the available information on HRS to (1) investigate if there was a reduction in quantitative HRS following IVT, (2) if the HRS-response to anti-VEGF drugs...
was different from steroids, and (3) if change in posttreatment quantitative HRS/baseline HRS counts were associated with improvement in VA and/or reduction in CMT. Finally, we highlight the lacunae in the existing literature on HRS in DME and suggest goals for future studies.

Methods

A systematic review was conducted in accordance with Meta-Analyses and Systematic Reviews of Observational Studies guidelines. The protocol was registered in International Prospective Register of Systematic Reviews (CRD42020186820).

This review included all articles that described HRS as an outcome predictor after IVT in DME from peer-reviewed journals published in electronic databases (between January 1, 2011 and July 1, 2020).

We excluded studies: (1) not available in English, (2) published in books, conference abstracts, review, comments, letter to editor, case series (<5 subjects), (3) with insufficient quality, (4) where the results of DME were combined with other causes of macular edema like vein occlusion, (5) where additional interventions were done during the study period like laser, vitrectomy, etc., (6) performed in nonhuman subjects, and (7) where time-domain OCT machines were used.

Search strategy

The following databases were searched: PubMed/MEDLINE, Scopus, ProQuest, CINAHL, Wiley online, and Web of Science. PICO (participants, intervention, and comparison and outcomes) format search strategy was used to search databases mentioned.

The full search strategy for MEDLINE using keywords is detailed in Appendix 1.

Assessment of methodological quality and risk of bias

The quality and risk of bias of the articles included in the full-text review was assessed by PG and SK using the National Institute of Health Study Quality Assessment Tool. Questions with answer “yes” were scored 1 and those with an answer “no”/“cannot determined”/“not reported” were scored 0. The total score for each study = (the total number of questions answered as “yes”/the total number of questions) × 100. Studies were graded as high quality (80–100%), moderate quality (60–80%), and low quality (<60%).

Statistical analysis

Meta-analysis

We performed a random-effects meta-analysis. All the outcomes of interest (i.e., quantitative HRS reduction, difference in quantitative HRS reduction between steroid and anti-VEGF therapy, and posttreatment change in VA) were set as continuous variables. The variances of combined true effect sizes among the studies were estimated using Hedge’s g for all outcomes (with 95% CI). Heterogeneity among studies was estimated using P statistic. Subgroup analysis was performed using analysis of variance of sum of squares. Publication bias was analyzed using Begg and Mazumdar rank correlation test (Δx–y, Kendall Tau a, and CI limits).

Results

Included studies

Fig. 2 shows the flow diagram to summarize inclusion of studies.

Quality of the studies

The quality scores of the 19 studies (13 retrospective cohort studies, 3 prospective cohort studies, 2 case series, and 1 case-control study) are enumerated in Table 1.

Baseline characteristics

A total of 1168 eyes of 942 patients (mean age: 64.3 ± 4.9 years, males: 59.4%) were analyzed for HRS from the above 19 studies. Eight studies evaluated the response to anti-VEGF injections [intravitreal ranibizumab (IVR), intravitreal bevacizumab (IVB), and conbercept], 11 studies...
to dexamethasone implant,\textsuperscript{[12,14,26-30,32-34,36-40]} and 2 studies to sequential use of anti-VEGF and dexamethasone.\textsuperscript{[15,17]} The measurement of HRS was done over different area sizes in the macula (12 studies used 3000 µm area,\textsuperscript{[12,14-17,26,32-34,36,38,39]} 4 studies used 1000 µm area,\textsuperscript{[24,30,35,40]} 2 studies used 1500 µm area,\textsuperscript{[31,37]} and 1 study used area between 500 and 1500 µm from the center of the fovea) [Table 1].\textsuperscript{[41]}

Change in quantitative HRS with IVT

Twelve studies with HRS counts before and after IVT were analyzed. All seven studies where anti-VEGF injections were used\textsuperscript{[16,17,30-32,35,41]} and six out of the seven studies where dexamethasone was used\textsuperscript{[17,26,32,34,37,40]} reported a decrease in quantitative HRS. In the subgroup of patients whose macular edema did not respond to dexamethasone or IVB, there was no significant HRS reduction [Table 2].\textsuperscript{[17]}

Retinal-layer-wise analysis was done in six studies. However, the definition of retinal layers was variable across the studies. Inner retina (IR) was defined as extending from internal limiting membrane (ILM) to outer nuclear layer (ONL) in three studies,\textsuperscript{[17,31,35]} ILM to inner nuclear layer (INL) in one study,\textsuperscript{[26]} and as INL in one study.\textsuperscript{[16]} Similarly, outer retina (OR) was defined as extending from external limiting membrane (ELM) to RPE in two studies,\textsuperscript{[17,31]} ELM to photoreceptors in one study,\textsuperscript{[35]} and ELM to outer plexiform layer (OPL) in two studies.\textsuperscript{[16,26]} One study analyzed HRS in three layers, i.e., ILM to inner plexiform layer, INL to OPL and ONL.\textsuperscript{[41]}

HRS change in steroid versus anti-VEGF-treated eyes

Two studies compared the change in HRS counts between these two classes of drugs, in treatment naive eyes.\textsuperscript{[32,36]} Vujosevic \textit{et al.}\textsuperscript{[32]} showed a greater reduction in HRS in dexamethasone-treated eyes ($n = 15$) versus IVT-treated eyes ($n = 18$) (24.7% versus 8.0%, $P = 0.03$) when all baseline parameters were matched. In another study by the same author, the decrease in HRS was not found to be different between the two treatment groups ($P = 0.135$).\textsuperscript{[36]} However, in this study, the baseline HRS counts were significantly higher in the dexamethasone group compared to the IVR group ($P = 0.003$). Hwang \textit{et al.}\textsuperscript{[17]} noted that baseline HRS numbers were higher in eyes that did not respond to IVB. When such eyes were treated with dexamethasone implant, the HRS count decreased [Table 2 and Fig. 3a].

Baseline HRS and change in VA

A total of 14 studies were analyzed. Five studies made a qualitative reporting of HRS as present or absent at baseline.\textsuperscript{[12,14,24,38,39]} three studies had categorized the patients into those with HRS $<$10–15 and those with HRS $>$10–15 on baseline scans.\textsuperscript{[15,33,40]} In the remaining six studies, baseline HRS counts were correlated with final VA using regression/correlation statistics.\textsuperscript{[16,30,31,35,37,41]} Three studies showed that higher HRS counts at baseline were associated with worse final VA.\textsuperscript{[31,35,38]} Five studies showed no correlation between baseline HRS counts and final VA.\textsuperscript{[13,16,33,40,41]} In a study by Cavalleri \textit{et al.},\textsuperscript{[15]} dexamethasone therapy resulted in a greater gain in VA in eyes with high baseline HRS.
### Figure 3:

(a) Forest plot showing the change in quantitative HRS following intravitreal injection. There were a total of 12 studies among which there were 20 effect sizes to be analyzed. The box and whisker plot for individual studies represent the effect size (Hedges’ g) and 95% confidence intervals (CI95%). Subgroup analyses for dexamethasone and anti-VEGF groups are summarized within the plot. The overall effect size is represented by the polygon.

(b) Forest plot showing the association between HRS at baseline and change in VA. [*G = Hedges’ g; LCL = lower confidence limit; UCL = upper confidence limit; WGHT = weight of the study; dotted vertical line = overall effect size; I^2 = heterogeneity of the studies; within parenthesis = therapeutic group; VEGF = vascular endothelial growth factor; DEX = dexamethasone; DRT = diffuse retinal thickening; CME = cystoid macular edema; SRD = serous retinal detachment; R = responder; NR = nonresponder; ER = early recurrence; LR = late recurrence*]
Table 1: Baseline characteristics of the studies and participants included in the systematic review

| Author (year)          | Study design | Study population                                       | *Eyes* | **Mean age (years)** | *Follow up (months) | Macular area analyzed (µm) | Intervention | Study quality |
|------------------------|-------------|-------------------------------------------------------|--------|----------------------|---------------------|---------------------------|--------------|---------------|
| Framme et al. (2012)[21]| Retrospective cohort | DME (previously no anti-VEGF)                      | 51     | 67                   | 1                   | 1000                      | IVR=30, IVB=21 | Moderate      |
| Vujosevic et al. (2016)[41]| Prospective case control | Treatment naive DME                                  | 40     | 63.0                 | 6                   | 500-1500                  | IVR          | High          |
| Kang et al. (2016)[31]| Retrospective cohort | Treatment naive DME                                  | 97     | 60.11                | 6.71±3.7            | 1500                      | DEX          | Moderate      |
| Vujosevic et al. (2017)[32]| Retrospective cohort | Treatment naive DME                                  | 49     | 66.0                 | Unclear             | 3000                      | DEX (23)/ IVR (26) | Moderate      |
| Chatziralli et al. (2017)[38]| Prospective cohort | Refractory DME                                       | 54     | 69.2                 | 12                  | 3000                      | DEX          | Moderate      |
| Hwang et al. (2017)[17]| Retrospective cohort | Treatment naive DME                                  | 82     | 55.13                | 3 m post IVB/1 m post DEX | 3000                      | 3 IVB; if no response add DEX | Moderate      |
| Zur et al. (2018)[12]| Retrospective cohort | Treatment naive and refractory DME                   | 299    | 64                   | 4                   | 3000                      | DEX          | High          |
| Schreur et al. (2018)[16]| Retrospective cohort | Treatment naive DME                                  | 54     | 67                   | 3                   | 3000                      | IVR          | High          |
| Hatz et al. (2018)[42]| Case series    | Refractory DME                                       | 40     | 68.3                 | 2                   | 1000                      | DEX          | Moderate      |
| Bonfiglio et al. (2019)[14]| Case series    | Refractory DME                                       | 44     | 69.7                 | 6                   | 3000                      | DEX          | High          |
| Fonollosa et al. (2019)[33]| Retrospective cohort | Naive or previously treated DME patients             | 64     | 67.5                 | 6                   | 3000                      | DEX          | High          |
| Karttunen et al. (2019)[24]| Retrospective cohort | Refractory DME                                       | 24     | 65.6                 | 2                   | 3000                      | DEX          | Moderate      |
| Menezo et al. (2019)[39]| Prospective cohort | Treatment naive DME                                  | 50     | 66.4                 | 12                  | 3000                      | DEX          | Moderate      |
| Liu et al. (2019)[23]| Retrospective cohort | DME (previously no anti-VEGF)                       | 26     | 53.9                 | 3                   | 1000                      | Conbercept   | High          |
| Kim et al. (2019)[29]| Retrospective cohort | Refractory DME                                       | 29     | 58.3                 | 12                  | 3000                      | DEX          | Moderate      |
| Vujosevic et al. (2020)[38]| Retrospective cohort | Treatment naive DME                                  | 33     | 63.3                 | 3 m post IVR/2 m post DEX | 3000                      | DEX (15 eyes)/IVR (18) | Moderate      |
| Cavalleri et al. (2020)[15]| Retrospective cohort | Treatment naive DME                                  | 28     | 72.1                 | 12                  | 3000                      | Loading dose of IVR followed by DEX | Moderate      |
| Yoshitake et al. (2020)[24]| Retrospective cohort | DME (unspecified)                                    | 77     | 69                   | 12                  | 1000                      | IVR          | High          |
| Narnaware et al. (2020)[27]| Prospective cohort | Treatment naive and refractory DME                  | 27     | 61.11                | 4                   | 1500                      | DEX          | Low           |

IVR: intravitreal ranibizumab; IVB: intravitreal bevacizumab; DEX: dexamethasone implant; *: number of eyes with respect to HRS analysis; refractory DME: diabetic macular edema unresponsive to previous anti-VEGF injections, µm: micrometers; m: months

HRS counts compared to IVB. Bonfiglio et al.[14] and Yoshitake et al.[24] compared eyes with and without HRS at baseline and showed a greater gain in VA following dexamethasone and anti-VEGF injections, respectively, in eyes with HRS. Zur et al.[12] reported a greater gain in eyes without HRS at baseline[12] and Menezo et al.[39] showed no association between gain in VA and the presence of HRS at baseline [Appendix 2 and Fig. 3b].

Baseline HRS and CMT change

A total of 10 studies were included for this analysis. Bonfiglio et al.[14] and Yoshitake et al.[24] reported greater reduction in CMT in eyes with HRS compared to those without. Menezo et al.[39] found no association between the two parameters. Two studies which evaluated the association between a decrease in HRS and change in CMT showed contrasting results, with Liu et al.[23] reporting a significant correlation between the
Table 2: Quantitative HRS change following intravitreal therapy

| Author (year)          | Drug (Number of eyes) | HRS (Mean±SD) | baseline | After treatment | P value |
|------------------------|-----------------------|---------------|----------|----------------|---------|
| Framme et al. (2012)   | IVR (30); IVB (21)    |               | 16.02±8.0| 14.32±8.46     | 0.000*  |
| Vujosevic et al. (2016) | IVR                   |               | 16.02±8.0| 8.0±2.8        | 0.02*   |
| Kang et al. (2016)     | IVB                   |               | 16.02±8.0| 14.32±8.46     | 0.000*  |
| Vujosevic et al. (2017) | DEX (23); IVR (26)    |               | 16.02±8.0| 14.32±8.46     | 0.000*  |
| Hwang et al. (2017)    | 3 IVB; if no response |               | 16.02±8.0| 14.32±8.46     | 0.000*  |
| Schreur et al. (2018)  | IVR                   |               | 16.02±8.0| 14.32±8.46     | 0.000*  |
| Hatz et al. (2018)     | DEX                   |               | 16.02±8.0| 14.32±8.46     | 0.000*  |
| Kim et al. (2019)      | DEX                   |               | 16.02±8.0| 14.32±8.46     | 0.000*  |
| Karttunen et al. (2019)| DEX                   |               | 16.02±8.0| 14.32±8.46     | 0.000*  |
| Shulin Liu et al. (2019)| Conbercept           |               | 16.02±8.0| 14.32±8.46     | 0.000*  |
| Vujosevic et al. (2020)| DEX (15); IVR (18)    |               | 16.02±8.0| 14.32±8.46     | 0.000*  |
| Narnaware et al. (2020)| DEX                   |               | 16.02±8.0| 14.32±8.46     | 0.000*  |

IVR: intravitreal ranibizumab; IVB: intravitreal bevacizumab; DEX: dexamethasone implant; IR: inner retina; OR: outer retina; TR: total retina; SRF: subretinal fluid; ILM: internal limiting membrane; INL: inner nuclear layer; IPL: inner plexiform layer; OPL: outer plexiform layer; ONL: outer nuclear layer; DRT: diffuse retinal thickening; CME: cystoid macular edema; SRD: subretinal detachment; *P<0.05, NA=not available; †data obtained after contacting author.
reduction in inner and total retinal HRS and the decrease in CMT at 3 months (r = 0.422, P = 0.032 and r = 0.429, P = 0.029, respectively) and Framme et al.[30] reporting no significant association between the two variables at the end of 1 month. Vujosevic et al.[31] showed greater CMT reduction in eyes with more HRS (>87) at baseline than those with less HRS (<87) (p = 0.28, P = not reported). Schreur et al.[32] reported that the number of HRS at baseline was independently associated with a decrease in CMT (βstandardized = -2.61, P = 0.006). On the contrary, Fonollosa et al.[33] found that the CMT reduction was not significantly different between groups with scarce (<10) or abundant (>21) HRS. Finally, Kang et al.[34] and Vujosevic et al.[35] found no significant correlation between the baseline HRS counts and the final retinal thickness [Appendix 2].

Meta-analysis

From the systematic review, we found (i) that the qualities of the studies were moderate, (ii) result reporting was inconsistent across studies, and (iii) conflicting results across various studies. Hence, results summarized using a random effects meta-analysis on 12 studies testing the quantitative HRS change following IVT [Fig. 2a] showed high heterogeneity in the studies (I² = 93.16%) and significant publication bias (Δ = -100; Kendall’s Tau = -0.526, CI95% = -0.47 to -0.36, P = 0.001). There was no significant difference between dexamethasone (Hedges’ g = -1.1, CI95% = -1.22 to -0.57) and anti-VEGF groups (Hedges’ g = -0.69, CI95% = -0.99 to -0.38) in terms of HRS reduction (Q² = 1.4, df = 1, P = 0.23).

To analyze the association between HRS and VA, we performed a meta-analysis on three studies [Fig. 3b].[12,14,39] The presence/absence of HRS at baseline was not associated with improved VA at the end of treatment (Hedges’ g = 0.237, CI95% = -1.39 to 1.87, P = 84%, P = 0.5) [Fig. 3b].

We could not perform a meta-analysis to see the effect of HRS on CMT reduction due to heterogeneity in reporting results.

Discussion

In this review, we found that there is a definite reduction in HRS counts following IVT and no significant difference between anti-VEGF and steroid groups. The role of HRS in predicting VA outcome and CMT change was limited by the number of analyzable studies owing to the wide variation in the study designs and reporting.

Various theories have been proposed regarding the exact nature of HRS.[18-22,42] Of these, the hard exudate and inflammatory theories are most popular in DME. Cusick et al.[43] using immunochemistry found apolipoprotein-B deposits corresponding to the HRS. An inflammatory basis for HRS was postulated by Lee et al.[44]Shen et al.[45] The authors found that soluble CD14 (sCD14) levels in the aqueous humor and HRS counts in inner retina on OCT were raised in patients with DME compared to controls. Hence, they concluded that since sCD14 is released by retinal microglia, HRS might represent aggregates of activated microglial cells in DME eyes. Intravitreal dexamethasone is a potent antiinflammatory agent. Anti-VEGF injections, although not as potent as steroids in their antiinflammatory action, have been shown to have antiactivated microglial activity.[46] The reduction in HRS within 3 months of starting IVT as seen in most studies of this review strongly points toward their inflammatory origin. If HRS were to be hard exudates, we do not expect such rapid regression.

Although HRS are mainly located in the inner retina, with progressing retinopathy, HRS reach the outer retinal layers. Studies have shown that OR-HRS were associated with ELM and EZ disruption[49] and that there was a positive correlation between OR-HRS counts and final EZ and ELM disruption length.[51] Further studies have shown that HRS in OR had greater shortening of EZ line disruption following intravitreal anti-VEGF therapy than those without HRS at baseline.[24] Nishijima et al.[57] showed that HRS in OR were predictive of photoreceptor damage and poor vision after vitrectomy for DME. Kang et al.[34] found that in the DRT and CME groups, the final VA was worse in those with greater number of OR-HRS. Yoshihake et al.[24] reported that eyes with HRS in OR had greater VA improvement and greater CSF thickness reduction. HRS in the inner retinal layers were not associated with VA improvement in this study. In an observational study on treatment naive DME patients, Arthi et al.[40] found that there were no differences in CMT, BCVA, ELM, and EZ continuity between those with and without IR-HRS or OR-HRS.

A recent study showed that greater proportion of diabetics with HRS had coexistent hypertension compared to those who did not have HRS and those with higher number of HRS had significantly lower levels of serum triglycerides.[48] However, Davoudi et al.[49] showed that the presence of HRS was associated with higher total cholesterol and higher low-density lipoprotein levels. Framme et al.,[30] Wong et al.,[50] and De Benedicto et al.[18] have shown that poor glycemic control is associated with more HRS. They postulate that hyperglycemia could activate retina microglial cells in diabetic patients, which are seen as HRS on OCT. On the contrary, Arthi et al.[40] showed no association of HRS with glycemic control.

HRS noted in the inner wall of cystoid spaces have been called the “pearl necklace sign.”[71] This sign indicates the presence of lipoproteins or lipid-laden macrophages in patients with chronic CME. In a study by Ajay et al.,[52] this sign was seen in 13.1% of the eyes with DME. In 75% of such eyes, clinically visible hard exudates developed in exactly the same location as the pearl necklace sign after the resolution of DME. This could cause irreversible damage to photoreceptors if present subfoveally. Terada et al.[53] noted that HRS were accompanied by hyperreflective walls in foveal cystoid spaces. Eyes with hyperreflective walls in foveal cystoid spaces had poorer VA, more severe photoreceptor disruption, and poorer DME remissions than did those without such findings.

In DME, SD-OCT often shows HRS at the outer border of the detached neurosensory retina and/or within the subretinal space. Arthi et al.[40] showed that a greater proportion of eyes with HRS also had SRF. Ota et al.[54] compared eyes with no/few subretinal HRS and eyes with many subretinal HRS. While there was no difference in the baseline foveal thickness between the groups, foveal thickness of the group with few dots was significantly thicker than that of the group with many dots at 6 months, and this difference was abolished at 12 months. However, the VA at
12 months was significantly poorer in the groups with many HRS owing to the subfoveal deposition of hard exudates.

This meta-analysis could not bring out a significant effect of baseline HRS on the change in VA. However, on closer look, eyes with treatment naive DME as against those with refractory DME showed a positive correlation between HRS and VA gain (5/8 studies versus 0/3 studies) and CMT reduction (7/8 studies versus 1/3 studies) implying a significant role of inflammation in treatment naive DME as against a multifactorial pathogenesis in refractory-DME eyes.

The limitations of the studies included in this review include the following: retrospective designs, inadequate sample sizes, varied HRS measurements (i.e., HRS measured in different macular areas, manual versus automated counting, inconsistent definition of retinal layers), short follow-up duration, lack of adjustment for confounders (blood lipid/sugar levels), and varying statistical reporting methods and significant publication bias. Also, there has been a lack of uniform definition of HRS in these studies.

There is a need to standardize such variability in quantitative research when evaluating a biomarker to ensure reproducibility and test-retest reliability. Hence, we recommend a stage-wise approach to understand the exact nature and the role of this biomarker in DME [Table 3].

**Conclusion**

In conclusion, there is a definitive quantitative reduction in HRS after intravitreal anti-VEGF or intravitreal steroid therapy for DME. However, its correlation with reduction in CMT and VA change is inconclusive. HRS appear to be a promising biomarker in predicting therapeutic response to intravitreal treatment in DME.

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**Conflicts of interest**

There are no conflicts of interest.
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### Appendix 1: Pubmed search strategy (searched on July 4, 2020)

| No. | Search no | Query | Results |
|-----|-----------|-------|---------|
| 1.  | #S1       | Search ((("DMO" OR "DME" OR "macular oedema" OR "Macular edema" OR "Center-involving" OR "Maculopathy")) OR (("DMO"[Title/Abstract] OR "DME"[Title/Abstract] OR "macular oedema"[Title/Abstract] OR "Macular edema"[Title/Abstract] OR "Center-involving"[Title/Abstract] OR "Maculopathy" [Title/Abstract])) OR (("DMO" OR "DME" OR "macular oedema" OR "Macular edema" OR "Center-involving" OR "Maculopathy")[MeSH Terms]) Filters: Humans | 14561 |
| 2.  | #S2       | Search ((("DMO" OR "DME" OR "macular oedema" OR "Macular edema" OR "Center-involving" OR "Maculopathy")) OR (("DMO" OR "DME" OR "macular oedema" OR "Macular edema" OR "Center-involving" OR "Maculopathy") OR "Optical coherence tomography" OR "Anti VEGF" OR "ranibizumab" OR "SD-OCT" OR "Intravitreal" OR "antiangiogenic endothelial growth factor" OR "OCT" OR "BVZ" OR "dexamethasone" OR "steroid" OR "Intra vitreal" OR "avastin" OR "Lucentis" OR "accentrix" OR "Aflibercept" OR "Eyelea" OR "ozurdex" OR "Triamcinolone acetonide" OR "IVTA" OR "Conbercept" OR "Anti-VEGF" OR "AntiVEGF") OR ("Bevacizumab" OR "Optical coherence tomography" OR "Anti VEGF" OR "ranibizumab" OR "SD-OCT" OR "Intravitreal" OR "antiangiogenic endothelial growth factor" OR "OCT" OR "BVZ" OR "dexamethasone" OR "steroid" OR "Intra vitreal" OR "avastin" OR "Lucentis" OR "accentrix" OR "Aflibercept" OR "Eyelea" OR "ozurdex" OR "Triamcinolone acetonide" OR "IVTA" OR "Conbercept" OR "Anti-VEGF" OR "AntiVEGF")[MeSH Terms]) Filters: Humans | 1738178 |
| 3.  | #S3       | Search ((("Hyper" OR "reflective" OR "foci" OR "central macular thickness" OR "macular volume" OR "CST" OR "CMT" OR "FT" OR "hyperreflective" OR "foveal thickness" OR "spots" OR "HRS" OR "HF" OR "Small" OR "Dense" OR "Best" OR "Corrected" OR "Visual" OR "acuity" OR "BCVA" OR "outcomes" OR "Hyper-reflective" OR "dots" OR "material" OR "points" OR "aggregates" OR "particles" OR "clumps" OR "retinal" OR "HRF" OR "HS" OR "HRD" OR "inflammatory" OR "biomarkers" OR "Prognostic" OR "markers") OR ("Hyper" OR "reflective" OR "foci" OR "central macular thickness" OR "macular volume" OR "CST" OR "CMT" OR "FT" OR "hyperreflective" OR "foveal thickness" OR "spots" OR "HRS" OR "HF") OR "Small" OR "Dense" OR "Best" OR "Corrected" OR "Visual" OR "acuity" OR "BCVA" OR "outcomes" OR "Hyper-reflective" OR "dots" OR "material" OR "points" OR "aggregates" OR "particles" OR "clumps" OR "retinal" OR "HRF" OR "HS" OR "HRD" OR "inflammatory" OR "biomarkers" OR "Prognostic" OR "markers")[MeSH Terms]) Filters: Humans | 3886156 |
| 4.  | #S1 AND S2 AND S3 | Search ((("DMO" OR "DME" OR "macular oedema" OR "Macular edema" OR "Center-involving" OR "Maculopathy")) OR ("DMO"[Title/Abstract] OR "DME"[Title/Abstract] OR "macular oedema"[Title/Abstract] OR "Macular edema"[Title/Abstract] OR "Center-involving"[Title/Abstract] OR "Maculopathy"[Title/Abstract])) OR ("DMO" OR "DME" OR "macular oedema" OR "Macular edema" OR "Center-involving" OR "Maculopathy")[MeSH Terms] AND Humans[Mesh]) AND ((("Bevacizumab" OR "Optical coherence tomography" OR "Anti VEGF" OR "ranibizumab" OR "SD-OCT" OR "Intravitreal" OR "antiangiogenic endothelial growth factor" OR "OCT" OR "BVZ" OR "dexamethasone" OR "steroid" OR "Intra vitreal" OR "Intra-vitreal" OR "avastin" OR "Lucentis" OR "accentrix" OR "Aflibercept" OR "Eyelea" OR "ozurdex" OR "Triamcinolone acetonide" OR "IVTA" OR "Conbercept" OR "Anti-VEGF" OR "AntiVEGF") OR ("Bevacizumab" OR "Optical coherence tomography" OR "Anti VEGF" OR "ranibizumab" OR "SD-OCT" OR "Intravitreal" OR "antiangiogenic endothelial growth factor" OR "OCT" OR "BVZ" OR "dexamethasone" OR "steroid" OR "Intra vitreal" OR "Intra-vitreal" OR "avastin" OR "Lucentis" OR "accentrix" OR "Aflibercept" OR "Eyelea" OR "ozurdex" OR "Triamcinolone acetonide" OR "IVTA" OR "Conbercept" OR "Anti-VEGF" OR "AntiVEGF")[MeSH Terms]) OR ("Bevacizumab"[Title/Abstract] OR "Optical coherence tomography"[Title/Abstract] OR "Anti VEGF"[Title/Abstract] OR "ranibizumab"[Title/Abstract] OR "SD-OCT"[Title/Abstract] OR "Intravitreal"[Title/Abstract] OR "antiangiogenic endothelial growth factor" OR "OCT" OR "BVZ" OR "dexamethasone" OR "steroid" OR "Intra vitreal" OR "Intra-vitreal" OR "avastin" OR "Lucentis" OR "accentrix" OR "Aflibercept" OR "Eyelea" OR "ozurdex" OR "Triamcinolone acetonide" OR "IVTA" OR "Conbercept" OR "Anti-VEGF" OR "AntiVEGF")[Title/Abstract]) | 888178 |

Contd...
### Appendix 1: Contd...

| No. | Search no | Query                                                                 |
|-----|-----------|----------------------------------------------------------------------|
|     |           | "ranibizumab"[Title/Abstract] OR "SD-OCT"[Title/Abstract] OR "Intravitreal"[Title/Abstract] OR "antivascular endothelial growth factor"[Title/Abstract] OR "OCT"[Title/Abstract] OR "BVZ"[Title/Abstract] OR "dexamethasone"[Title/Abstract] OR "steroid"[Title/Abstract] OR "Intra vitreal"[Title/Abstract] OR "avastin"[Title/Abstract] OR "Lucentis"[Title/Abstract] OR "accentrix"[Title/Abstract] OR "Allibercept"[Title/Abstract] OR "Eyelea"[Title/Abstract] OR "ozurdex"[Title/Abstract] OR "Triamcinolone acetonide"[Title/Abstract] OR "IVTA"[Title/Abstract] OR "Conbercept"[Title/Abstract] OR "Anti-VEGF"[Title/Abstract] OR "AntiVEGF"[Title/Abstract]) AND Humans[Mesh]) AND ((((("Hyper" OR "reflective" OR "foci" OR "central macular thickness" OR "macular volume" OR "CST" OR "CMT" OR "FT" OR "hyperreflective" OR "foveal thickness" OR "spots" OR "HRS" OR "HF" OR "Small" OR "Dense" OR "Best" OR "Corrected" OR "Visual" OR "acuity" OR "BCVA" OR "outcomes" OR "Hyper-reflective" OR "dots" OR "material" OR "points" OR "aggregates" OR "particles" OR "clumps" OR "retinal" OR "HRF" OR "HS" OR "HRD" OR "inflammatory" OR "biomarkers*" OR "Prognostic" OR "markers")) OR ((("Hyper" OR "reflective" OR "foci" OR "central macular thickness"[Title/Abstract] OR "macular volume"[Title/Abstract] OR "CST"[Title/Abstract] OR "CMT"[Title/Abstract] OR "FT"[Title/Abstract] OR "hyperreflective"[Title/Abstract] OR "foveal thickness"[Title/Abstract] OR "spots"[Title/Abstract] OR "HRS"[Title/Abstract] OR "HF"[Title/Abstract] OR "Small"[Title/Abstract] OR "Dense"[Title/Abstract] OR "Best"[Title/Abstract] OR "Corrected"[Title/Abstract] OR "Visual"[Title/Abstract] OR "acuity"[Title/Abstract] OR "BCVA"[Title/Abstract] OR "outcomes"[Title/Abstract] OR "Hyper-reflective"[Title/Abstract] OR "dots"[Title/Abstract] OR "material"[Title/Abstract] OR "points"[Title/Abstract] OR "aggregates"[Title/Abstract] OR "particles"[Title/Abstract] OR "clumps"[Title/Abstract] OR "retinal"[Title/Abstract] OR "HRF"[Title/Abstract] OR "HS"[Title/Abstract] OR "HRD"[Title/Abstract] OR "inflammatory"[Title/Abstract] OR "biomarkers*" OR "Prognostic" OR "markers")[Title/Abstract]) OR ((("Hyper" OR "reflective" OR "foci" OR "central macular thickness" OR "macular volume" OR "CST" OR "CMT" OR "FT" OR "hyperreflective" OR "foveal thickness" OR "spots" OR "HRS" OR "HF" OR "Small" OR "Dense" OR "Best" OR "Corrected" OR "Visual" OR "acuity" OR "BCVA" OR "outcomes" OR "Hyper-reflective" OR "dots" OR "material" OR "points" OR "aggregates" OR "particles" OR "clumps" OR "retinal" OR "HRF" OR "HS" OR "HRD" OR "inflammatory" OR "biomarkers*" OR "Prognostic" OR "markers")[MeSH Terms]) AND Humans[Mesh]) Filters: Journal Article; Publication date from 2011/01/01 to 2020/06/01; Humans; English |

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Results: 524
### Appendix 2: Summary of studies reporting association between HRS and VA/CMT

| Author (Year) | Results |
|---------------|---------|
| **Association between HRS and VA/CMT** | |
| Framme et al. (2012)[21] | No correlation between the HRS reduction and the course of VA/decrease in CMT |
| Vujosevic et al. (2016)[41] | Weak correlation between the number of HRS and BCVA ($r = -0.37$)/CMT (data not shown) |
| Kang et al. (2016)[31] | Positive association between baseline number of HRS in OR and final VA (LogMAR) in DRT ($\beta_{\text{standardized}}$=0.037; $P=0.004$) and CME groups ($\beta_{\text{standardized}}$=0.048; $P=0.002$) and between baseline number of HRS in IR and OR and final VA (LogMAR) in the SRD group ($\beta_{\text{standardized}}$=0.014, 0.024, respectively; $P<0.04$) |
| The final foveal thickness showed no association with the baseline HRS counts ($P>0.2$ in all three groups) |
| Chatziralli et al. (2017)[38] | Presence of HRS at baseline was associated with poorer visual outcomes (coefficient = - 6.02; CI $95\%$ = -10.12 to -2.21; $P<0.001$) |
| Zur et al. (2018)[12] | Absence of HRS at baseline predicted increased odds to gain >10 letters after 4 months (OR=5.33; CI $95\%$ = 1.81-15.72; $P=0.002$) and good clinical response at 4 months (absent vs. present HRS: OR=3.66; CI $95\%$ = 1.40-9.62; $P=0.01$) |
| Schreur et al. (2018)[16] | No effect of baseline number of HRS on change in VA (3 m) ($\beta_{\text{standardized}}$ = -0.002; CI $95\%$ = -0.009 to -0.004; $P=0.473$) |
| The number of HRS at baseline was independently associated with a decrease in CMT (3 m) ($P=0.006$) Adequate responders had higher numbers of HRS at baseline than insufficient responders (21.6±9.5 versus 12.7±8.8; OR=1.106; CI $95\%$ = 1.012-1.210; $P=0.030$) |
| Hatz et al. (2018)[40] | HRS <15 HRS >15 $P$ |
| Change in VA | 8.0±7.7 3.1±12.0 0.163 |
| Fonollosa et al. (2019)[33] | HRS<10 HRS>21 |
| Change in VA | 4.1 (0.3-7.9) 4.4 (1.3-7.5) 0.336 |
| Change in CMT | -106.3 (59.8-152.7) - 94.2 (34.7-153.7) NA |
| Cavalleri et al. (2020)[15] | HRS<13 HRS>13 |
| IVR (VA) | Baseline | Final | Baseline | Final |
| 63.3±24.2 | 76.3±17.1 | 63.9±16.7 | 63.1±21.3 | NA |
| DEX (VA) | HRS present at baseline | HRS absent at baseline |
| 79±15.4 | 84.1±15 | 59.6±22.2 | 70.1±15.6 | NA |
| Bonfiglio et al. (2019)[14] | VA |
| HRS present at baseline | HRS absent at baseline |
| 52.3±6.4 | 55.2±8.4 | 51.4±8.9 | 51.8±8.0 | NA |
| Menezes et al. (2019)[39] | CMT |
| HRS present at baseline | HRS absent at baseline |
| 607±69 | 493±123 | 569±94 | 510±125 | NA |
| Yoshitake et al. (2020)[26] | HRS present at baseline | HRS absent at baseline |
| Change in VA (LogMAR) (6 m) | 0.140±0.0138 | 0.074±0.110 | 0.022* |
| Change in VA (LogMAR) (12 m) | 0.179±0.150 | 0.048±0.124 | <0.001* |
| Change in CMT | 171±138 | 110±86 | 0.028* |
| Shulin Liu et al. (2019)[35] | Positive correlation between the baseline number of HRS in OR and baseline VA ($r=0.42$; $P=0.034$) Positive correlation between the baseline number of HRS in the IR, OR, and SRD and final VA ($r=0.571$, $P=0.002$; $r=0.464$, $P=0.017$; $r=0.405$, $P=0.04$, respectively) No correlation between the HRS reduction in OR and TR and increase in VA ($r=0.40$, $P=0.043$ and $r=0.393$, $P=0.04$, respectively) Positive correlation between the HRS reduction in IR and TR and decrease in CMT ($r=0.422$, $P=0.032$ and $r=0.429$, $P=0.029$, respectively) |
| Narnaware et al. (2020)[37] | Positive but not significant correlation between the change in HRS and change in VA (LogMAR) ($r=0.3343$; $P=0.05$) |
| Vujosevic et al. (2017)[32] | Inverse correlation between the HRS number at baseline and CMT change ($q = -0.28$, $P=NA$) |

All CMT values are measured in micrometers, VA measured in ETDRS letters unless specified; m: months; IVR: intravitreal ranibizumab; DEX: dexamethasone implant; IR: inner retina; OR: outer retina; TR: total retina; DRT: diffuse retinal thickening; CME: cystoid macular edema; SRD: subretinal detachment; NA: not available