Risk factors for recurrent vitreous haemorrhage in patients with proliferative diabetic retinopathy.

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Abstract

Background : To investigate which demographic and clinical factors are related to the presence of recurrent vitreous haemorrhage in a population of diabetic patients diagnosed with proliferative diabetic retinopathy [PDR]. Methods: This was a retrospective review-based study. We studied 285 eyes from 165 patients with PDR. We recorded age, gender, type of diabetes mellitus [DM] , type of DM treatment, history of hypertension and body mass index, panretinal photocoagulation status and the presence of concomitant anticoagulant or antiplatelet treatment. We evaluated the mean glycosylated haemoglobin, mean haemoglobin, the urine albumin to creatinine ratio and the estimated glomerular filtration rate in each patient. In addition, we recorded the smoking history [pack-years] and the systemic complications related to DM. We used the logistic regression analysis to study which independent variables were significantly related to the presence of recurrent vitreous haemorrhage. Results: In total, 183 eyes [64%] with PDR had vitreous haemorrhage, of which 68 [37%] underwent recurrent vitreous haemorrhage. In our study, tobacco consumption [OR= 1.21, 95% CI, 1.10- 1.32, P <0.001], duration of diabetes [OR= 1.03, 95% CI, 1.0-1 .07 P = 0.04] and haemoglobin level [OR= -0.24 , 95% CI, -0.16, -0.06 , P <0 .001] had an independently significant associaton with recurrent vitreous haemorrhage. There was a positive correlation between pack-years consumed and the number of vitreous haemorrhages [r=0.339; p<0.001]. In addition, patients with diabetic polineuropathy, myocardial infarction and ischemia in lower limbs had more vitreous haemorrhage events [p<0.001]. Conclusion s : In our study, those patients with PDR who smoked, with longer duration of their diabetes, anaemia and that had previously suffered from cardiovascular events were more prone to suffer from recurrent vitreous haemorrhage.

Background

Diabetic retinopathy [DR] is the leading cause of visual loss in the working-age population in developed countries.[1] This is due mainly to ocular complications, such as diabetic macular edema [DME] and vitreous haemorrhage. The latter occurs in patients with proliferative diabetic retinopathy [PDR]. The main two, well-established, risk factors related to PDR development are diabetes duration[2-4] and the degree of metabolic control of the disease. The Diabetes Control and Complications Trial[5] [DCCT] and the United Kingdom Prospective Diabetes Study[6] [UKPDS] reported that the poorer the metabolic control, the higher the risk of suffering from PDR, both in type 1 [T1DM] and type 2 diabetic patients [T2DM]. Regarding blood pressure, the UKPDS noted that the risk of PDR development was lower for T2DM patients if blood pressure was controlled.[7]

The role of smoking as a risk factor for T2DM development is contentious. On one hand, Moss et al.[8] reported that smoking did not have a significant role in T2DM patients whereas more recent studies have found a significant increase in T2DM in smokers. A report by the United States Surgeon General in 2014, based on a meta-analysis, concluded that cigarette smoking is indeed a causal factor of T2DM.[9] This conclusion has been supported by a more recent systematic review and meta-analysis of 88 prospective studies conducted by Pan et al.[10] In line with these results, Akter et al.[11] found a significant 38% higher

risk of T2DM for current smokers compared with non-smokers among the Japanese population. Furthermore, these authors were able to establish a positive correlation between cigarette consumption and the risk of developing T2DM.

The association between smoking and DR is not clear. On one hand, the UKPDS[6] suggests that current smoking status is associated with a reduced incidence of DR in T2DM, and current smokers have a lower risk of progression of their retinopathy. Similarly, Xiaoling et al.[12] based on a recent extensive meta-analysis, found that T2DM patients, compared with non-smokers, the risk of both DR and PDR was significantly lower in smokers. However, this meta-analysis showed that T1DM patients who currently smoked had a significantly higher risk of DR incidence and progression of retinopathy.

On the other hand, Moss et al.[13] reported no association between smoking and DR except in older-onset insulin taking subjects, for whom pack-years and progression to PDR was established.

It is well known that diabetic patients are more prone to have the vitreous attached to the retina throughout life[31] and those patients are predisposed to retinal neovascularization since the gel acts as a scaffolding for the new vessels to grow, especially in those patients with poor metabolic control. Patients with PDR that undergo pan-retinal photocoagulation seem to be more prone to suffer posterior vitreous detachment [PVD] thus reducing the future risk of vitreous haemorrhage.[17] However, there is a group of patients with PDR that have several episodes of vitreous haemorrhage despite having previously suffered vitreous detachment along with pan-retinal photocoagulation.

In our experience,[4] three groups of patients with PDR can be separated according to their clinical evolution. The first group are patients who never develop vitreous haemorrhage [NVH] once pan-retinal photocoagulation is carried out; the second group are patients who have had one single episode of vitreous haemorrhage [SVH] in either eye and do not re-bleed after performing pars plana vitrectomy

surgery in which the posterior vitreous is completely detached from the retina and retinal laser photocoagulation is usually completed; the third group are patients who develop recurrent vitreous haemorrhage [RVH] in either eye even after performing vitrectomy where the vitreous is detached and the retinal laser photocoagulation is widely applied.

The aim of this study was to evaluate the different risk factors related to the existence of RVH episodes in patients with PDR.

Methods

Setting:

We evaluated 285 eyes diagnosed with PDR from 165 diabetic patients of whom 40 eyes belonged to 21 T1DM patients [14%] and 245 eyes were from 144 T2DM patients [86%]. There were 197 eyes of 113 males [69%] and 88 eyes of 52 females [31%]. All patients proceeded from the reference population of University Hospital Sant Joan, Tarragona, Spain.

Study design:

This study is part of our line of research on diabetic retinopathy described elsewhere.[4]

We conducted a retrospective review of all diabetic patients with PDR who attended for treatment at our hospital.

Inclusion criteria:

- All patients with T1DM or T2DM diagnosed with PDR in our health care areas. The minimum duration of follow up required was 7 years.

Exclusion criteria:

- Patients with any previous type of retinal vascular occlusion.
- Patients with proliferative retinopathy of causes other than diabetes.
- Patients who had previously been operated on for other retinal conditions.

Methods:

All eyes were initially assessed by fundus examination, optical coherence tomography [OCT] and fluorescein angiography [FA] to ensure the presence of PDR and to classify the type of DME if no vitreous haemorrhage was present, in which case the diagnosis was made after pars plana vitreoretinal surgery.

We conducted a comprehensive review of the medical report documentation for all patients, including age, gender, type of DM, DM treatment [insulin or oral antidiabetic drugs], DM duration and blood pressure. We recorded the body mass index [BMI], estimated glomerular filtration rate [eGFR], the

existence of urine albumin to creatinine ratio [UACR] and the mean HbA1c and haemoglobin levels, measured at one year before having been diagnosed with PDR and through the whole study period. We identified the patients treated with anticoagulant or antiplatelet drugs and those diagnosed with chronic pulmonary obstructive disease [CPOD]. Furthermore, we quantified the cigarette consumption in pack-years. Former smokers were those who don't smoke now but have smoked at some time within the last 10 years and non-smokers were those who had never smoked or have not smoked at any time within the last 10 years, based on Akter et al.[11] Finally, we identified the patients who had suffered from polineuropathy, stroke, ischemic cardiopathy and ischemia in the lower limbs.

All eyes were evaluated for the existence and type of DME using the SD-OCT [TOPCON 3D OCT-2000]. We classified the patients into three groups:

- No DME
- Focal or multifocal DME: whether one or multiple areas of exudative microaneurysms were identified along with increased retinal thickness.
- Diffuse DME [whether more than 75% of the fluorescein leakage observed was not related to the presence of microaneurysms].

All eyes were classified into two subgroups depending on whether or not the vitreous was attached to the posterior pole. In addition, we recorded the patients treated with anti-VEGF drugs.

We classified all the eyes with PDR into three groups depending on their vitreous haemorrhage behaviour: the first group were eyes which had never bled [NVH], the second group were eyes that had bled just once [SVH] and the third group were eyes which had bled more than once [RVH]. In addition, we further classified them into two subgroups, depending on the time of recurrence. Early recurrence was considered within 30 days after pars plana vitreoretinal surgery and late recurrence after this period.

The severity of all vitreous haemorrhage episodes was scored on a 5-point scale according to Lieberman et al[16] : Grade 0 (no vitreous haemorrhage); Grade 1 (minimal vitreous haemorrhage, optic disk and retinal vessels were clearly visible); Grade 2 (mild vitreous haemorrhage, most of the optic disk and retinal vessels were visible); Grade 3 (moderate vitreous haemorrhage, optic disk or retinal vessels were barely visible); Grade 4 (severe vitreous haemorrhage, too dense to allow visualization of the optic disk).

In our study, those eyes which showed vitreous haemorrhage of grade 3 or 4 and did not clear after 2 months, underwent vitreoretinal surgery along with aditional retinal laser photocoagulation.

Finally, all eyes were classified into another two subgroups according to whether or not patients had previously undergone pan-retinal photocogulation before the beginning of the study period.

Statistical methods:

Data was analysed using the SPSS software package, version 25.0. In this study, the dependent variable was the presence of recurrent vitreous haemorrhage. The independent variables were: age, gender, DM duration, type of DM, type of DM treatment, arterial hypertension, existence of UACR, eGFR, mean HbA1c, mean haemoglobin, pan-retinal photocoagulation status, smoking status and cigarette consumption [pack-years], the presence of CPOD, treatment with anti-VEGF intravitreal injections and treatment with anticoagulant or antiplatelet drugs.

A descriptive statistical analysis was made of the quantitative data. For qualitative data, we used the analysis of frequency and percentage in each category. The normal data curve was evaluated using the Kolmogorov-Smirnov test. Differences between quantitative variables with normal distribution were examined using Student's t-test, in other cases we used the Mann-Whitney *U* test. To compare the mean of one quantitative variable in more than two groups of patients with normal distribution we used one-way ANOVA. Otherwise, the Kruskal-Wallis test was used. Inferential analysis for qualitative data was carried out using the chi-squared table and the determination of the Phi test. To correlate two continuous quantitative variables with normal distribution we used Pearson's parametric coefficient. For categorical variables we used Spearman's coefficient. We used the logistic regression analysis to study which independent variables were significantly related to the presence of RVH. Finally, we used the Kaplan-Meier estimator to compare the probability of occurence of RVH among smokers, former smokers and non-smokers in a specific interval of time. P<0.05 was considered statistically significant.

Results

Diabetic patients with PDR were recruited between 1st June 2004 and 30th June 2015. The mean follow-up period was 8.47 ± 1.17 years [7-21]. Patient demographics are shown in **Table 1**.

The majority of participants were men [197/69%] and 88 were women [31%]. Approximately one third of eyes with PDR had NVH for both genders. Women had a greater proportion of eyes with SVH and men had double the number of eyes with RVH [p=0.001].

In the present study, 183 eyes with PDR had vitreous haemorrhage [64%], of which 68 eyes [37%] had RVH. The majority of eyes that had RVH re-bled once [61%] and twice [33%]. Sixty-four eyes [85%] had late RVH and 11 eyes [15%] had early RVH.

Study of risk factors

As shown in **Table 1**, the groups of patients that suffered from NVH and SVH were mainly the non-smokers whereas the group with RVH were mainly smokers [p<0.001]. The mean pack-years of those who smoked in the NVH group was 10.13 ± 18.61, in the SVH group was 25.32 ± 35.94 and in the RVH group 49.34 ± 44.42, this result being statistically significant [p<0.001]. Therefore, there was a greater proportion of smokers in the RVH group who smoked more. In addition, there was a positive correlation between the number of vitreous haemorrhage episodes and the pack-years consumed [r=0.339; p<0.001] [**Figure 1**].

By contrast, there was no significant difference observed in the vitreous haemorrhage between former smokers and non-smokers.

Patients in the RVH group had longer duration of DM compared with the SVH and NVH groups. The longer the duration, the greater number of vitreous haemorrhage episodes [r=0.128; p=0.031] [**Table 1, Figure 1**].

The mean of haemoglobin was different among groups: NVH = 13.21 ± 1.70, SVH = 12.60 ± 1.55 and RVH = 11.71 ± 1.89 [p<0,001]. The lower the haemoglobin level the more episodes of vitreous haemorrhage [r= - 0.260; p<0.001] [**Figure 1**]. In the present study, as shown in **Table 2**, tobacco consumption, duration of diabetes and haemoglobin level had an independently significant associaton with the presence of recurrent vitreous haemorrhage. The Kaplan-Meier survival analysis estimated that after 25 years of diabetes duration, 40% of smokers had recurrent vitreous haemorrhage while only 14% of former smokers and 10% of non smokers [Log Rank=22.15; p< 0.005] [**Figure 2**].

Regarding the status of the vitreous, there were significant differences among the three groups of patients at the beginning of the study [p<0.001]. In total, 177 eyes [62%] had the vitreous attached to the retina whereas 108 eyes [38%] showed PVD. Twice as many eyes of the patients in the NVH group had the vitreous attached to the retina. Patients in the SVH group had the same proportion of eyes with and without the vitreous attached to the retina whereas three-quarters of the number of eyes of patients in the RVH group had the vitreous attached to the retina. Patients with the vitreous attached to the retina were younger [57.86 ± 11.77] than those with PVD [72.65 ± 9.79] and there was no relationship between the presence of recurrent vitreous haemorrhage and the status of the vitreous (OR= 2.15, 95% CI, 0.93-4.93, *P*= 0.07).

Patients diagnosed with COPD were more likely to show vitreous re-bleeding. Nevertheless, once this variable was studied through the logistic regression analysis it could not be considered an independent risk factor for RVH because it correlated positively with smoking.

Nearly all patients [95%] who took anticoagulant drugs in our series had SVH or RVH whereas that was the case for only 60% of those patients in the non-anticoagulant group. However, anticoagulants was not an independent risk factor for RVH since it correlated negatively with haemoglobin and positively with pack-years in our series. The proportion of patients that took antiplatelet drugs was similar among the three groups and was not a risk factor for eye re-bleeding.

In the present study, the mean of HbA1c was similar among the three group of patients and we did not observe a correlation between the level of HbA1c and the number of vitreous haemorrhage events. However, men showed a lower mean HbA1c level [8.49 ± 1.70] than women [9.10 ± 1.49] [p=0.004].

We included 40 eyes of T1DM patients in our study. Sixteen eyes had NVH [40%], 11 eyes [27.5%] had SVH and 13 eyes [32.5%] had RVH. Also, 245 eyes came from T2DM patients of whom 86 eyes [35%] did not bleed, 104 eyes [42.5%] had SVH and 55 eyes [22.5%] had RVH. There was no significant difference in terms of vitreous haemorrhage behaviour between T1DM and T2DM patients. Regarding treatment, 30 patients were treated with oral antidiabetic drugs [18.5%] and 135 were treated with insulin [81.5%]. The mean of vitreous haemorrhage episodes observed was similar for both groups of patients.

The BMI was similar among groups at the start of the study and did not correlate with the tendency to show vitreous haemorrhage.

In relation to both the UACR and the eGFR, there were no differences among the three groups at the start of the study and there was no significant tendency to suffer from RVH.

In the present study, 175 eyes with PDR [61,4%] were referred with no previous PRP carried out. Eighty-one eyes [46.3%] did not have VH, 65 eyes [37.1%] had SVH and 29 eyes [16.6%] developed RVH. By constast, 110 eyes [38.6%] had previously undergone PRP of which 21 eyes [19.1%] did not develop vitreous haemorrhage, 50 eyes [45.5%] developed SVH and 39 eyes [35.5%] developed RVH. Therefore, a greater percentage of eyes that had previously undergone PRP, developed SVH and RVH [$p<0.001$].

Diabetic macular oedema.

We evaluated the presence and type of DME in the three groups of eyes with PDR at the start of the study. Twenty-eight eyes [27.5%] in the NVH group did not have DME, 44 eyes [43,1%] had focal DME and 30 eyes [29,4%] had diffuse DME. In the SVH group, 31 eyes [27%] did not have DME, 52 eyes [45.2%] had focal DME and 32 eyes [27.8%] had diffuse DME. Finally, in the RVH group, 12 eyes [17.6%] did not present with DME, 17 eyes [25%] had focal DME and 39 eyes [57.4%] had diffuse DME. Therefore, eyes with RVH presented with diffuse DME significantly greater percentage than the others [$p<0.001$].

Study of anti-VEGF.

One hundred and four eyes included in the study [36.5%] had previously received anti-VEGF injections [mostly ranibizumab] for DME. Most eyes received 3 injections [37.5%]. The mean number of vitreous haemorrhages in the group of eyes that received anti-VEGF injections was 0.46 ± 0.823 compared to 0.38 ± 0.755 in those that did not. Therefore, the previous treatment with anti-VEGF therapy, independently of the number of injections, did not influence the tendency to re-bleeding.

Relationship with other diabetes complications.

The existence of systemic complications was recorded in all patients. Approximately one third of patients [38%] with diabetic polineuropathy developed RVH, which is a higher percentage than the others

[p<0.001]. Similarly, those patients diagnosed with some type of ischemia in lower limbs [35%] were more prone to show RVH when compared to the others [p<0.001]. In the same way, those patients who had ischemic cardiopathy [25%] were more prone to suffer from RVH [p<0,001]. The rate of occurrence of stroke was similar among groups and did not relate with eye re-bleeding.

Discussion

This study included a significantly greater number of men and in population-based studies of prevalence other authors found a greater proportion of men with severe PDR. Klein et al.[17] found that men were twice as likely to suffer from PDR as women in southern Wisconsin whereas Nittala et al.[18] reported that being male together with duration of diabetes were the strongest risk factors for the development of PDR in a Latin-American population. Finally, Hammes et al. reported that being male was a risk factor for developing DM2 in a large prospective study in Central Europe.[19]

Regarding smoking, we found that smokers with PDR were twice as likely to suffer vitreous haemorrhage episodes than former smokers and three times as likely as non-smokers. These findings must be a strong motivation for diabetics with PDR to stop smoking in order to avoid the risk of vitreous re-bleeding.

The role of smoking as a risk factor for developing DM appears to be contentious. On one hand, Moss et al.[8] reported that smoking had no direct affect on T2DM patients and Will et al. found a dose-response relationship between smoking and incidence of diabetes in a large prospective study conducted by the American Cancer Society.[20] More recent studies, have found a significant increase in T2DM in smokers. Hence, The United States Surgeon General's report, based on a meta-analysis, concluded that cigarette smoking is a cause of T2DM.[9] This conclusion has been supported by a more recent systematic review and meta-analysis conducted by Pan et al[10]. In line with these results, Akter et al. found a significantly higher risk of T2DM for smokers compared with non-smokers among the Japanese. Furthermore, this author was able to establish a positive correlation between cigarette consumption and the risk of T2DM.[11]

The role of cigarette smoking with respect to DR has not been clear. There have been several studies aimed at evaluating the degree of their relationship having obtained different results. The UKPDS suggested that current smoking status was associated with a reduced incidence and progression of retinopathy in T2DM patients. Moss et al. established an association between pack-years consumed and progression to PDR in older-onset insulin-taking diabetic patients. Xiaoling et al.[12] found a significantly higher risk of developing DR and PDR in T1DM patients who currently smoked, compared with non-smokers. At the same time, Xiaoling found a significantly lower risk for developing DR and PDR in T2DM patients who currently smoked, compared to the others. Therefore, it seems that the risk factors for DR might be different in T1DM and T2DM.

Our study showed that diabetic patients with PDR who currently smoke, had a significantly higher risk of developing multiple vitreous haemorrhage episodes compared to the others. One possible explanation of the potential role of smoking as a risk factor for RVH might be the vasoconstrictive effect of nicotine, which can cause retinal hypoxia mediated through the activation of the sympathetic nervous system.[21] In addition, the retinal and choroidal vessels seem to be less able to autoregulate their flow immediately after smoking.[23] On this topic, Maugeri et al. found that nicotine alters the outer blood retinal barrier and upregulates hypoxia inducible factor [HIF-1α and HIF-2α], which determine VEGF expression.[25] Finally, smoking has been shown to increase the level of carboxyhaemoglobin, thereby reducing the oxygen-carrying capacity of blood delivery to the retina,[24] hypoxia being the main factor linked to progression of the DR.

In the present study, we observed that patients with RVH had a significantly lower blood haemoglobin level compared to the others. In this sense, Qiao et al. in Finland found that the DM patients with haemoglobin levels lower than 12 mg/dl were twice as likely to develop DR.[26] Similarly, Bahar et al.[27] found that anaemic DM patients were 2.4 times more likely to develop DR. It seems logical, therefore, to suppose that patients with PDR with lower haemoglobin levels aggravate their retinal hypoxia, which could lead to a greater formation of new vessels. The etiology and pathogenesis of anaemia in DM patients is multifactorial. Chronic hyperglycemia causes oxidative stress, autonomic neuropathy and sympathetic denervation leading to renal hypoxia and finally a reduction in the erythropoietin production.[28]

Patients with a longer duration of their DM were more prone to suffer RVH. It is well known that duration of diabetes is probably the strongest predictor for development and progression of DR.[29] The longer the duration of the diabetes the more likely it is to develop inflammatory factors, such as platelet derived growth factor and VEGF, which have an active role in the evolution of DR and the development of new vessels.[30]

Arterial hypertension is a well-established risk factor for the progress of DR in T2DM patients. The UKPDS reported that the better the blood pressure control in T2DM patients, the lower the risk for developing PDR.[7] The majority of participants in our study were diagnosed with high blood pressure and as a result we found no differences among groups.

Unexpectedly, we found that patients who had previously undergone retinal laser photocoagulation were more prone to present with SVH or RVH. Those patients might have initially had more severe PDR and consequently showed a greater tendency to re-bleed afterwards [$p<0.001$]. We highlight that most eyes in our study were referred with no previous PRP carried out and for the majority of eyes that previously underwent retinal laser photocoagulation, this was not completed.

In the present study, the majority of eyes in the NVH and RVH groups of patients had the vitreous attached to the retina. Patients in the NVH had shorter duration of their diabetes than the others, which might explain a lesser tendency to bleed. On the contrary, patients in the RVH group had longer duration of their diabetes than the others, which might facilitate their tendency to re-bleed. Although the posterior hyaloid was removed in the first vitreoretinal surgery undergone in those eyes that bled, the likely existance of peripheral vitreous remnants attached to the retina, along with the retinal ischemia, might facilitate the growth of new vessels and the occurence of subsequent episodes of vitreous haemorrhage in the RVH group of patients.

The type of DME reported in the three group of patients was quite different. The most common type of DME in the NVH and SVH groups were focal DME whereas in the RVH group it was the diffuse DME. Those eyes with higher level of VEGF were possibly more prone to suffer from both a higher level of growth of new vessels and an alteration of the inner blood retinal barrier, leading to RVH and diffuse DME.

Patients in our study with RVH had more myocardial and lower limb ischemia compared to NVH and SVH groups. However, the incidence of stroke was similar among the three groups. Xiao-Rong et al. [34] found a graded relationship between severity of DR and the risk of all-cause mortality in patients with T2DM, mainly due to heart failure and stroke, which is indicative that PDR individuals have more risk factors than those with non-proliferative DR. Similarly, Cheung et al. found in a prospective cohort study that DR was an independent risk factor for ischemic stroke.[35] However, other studies are inconclusive about the association between DR and stroke. The UKPDS[36] reported that DR was not a significant risk factor for stroke and the Wisconsin Epidemiological Study of Diabetic Retinopathy concluded that only PDR was associated with stroke in T2DM patients, not NPDR.[14] Unlike non-diabetic patients, the type of stroke in diabetic patients mainly affect microvascular circulation instead of large vessels.[37]

To our knowledge this is the first study aimed at evaluating clinical and epidemiological differences between the patients with PDR whose eyes do not bleed once the PRP is carried out compared to those patients who tend to re-bleed despite being treated with retinal laser photocoagulation or vitrectomy.

The limitations of our study are its retrospective design and the small sample size.

Conclusions

Our study found that the patients with PDR who are the most prone to eye re-bleeding are men who smoke, have a longer duration of their diabetes, have anaemia and have previously suffered from a cardiovascular event. At the same time, our study showed that non-smokers and former smokers had a lower tendency to suffer RVH than smokers. Therefore, we can make some recommendations in order to

reduce the likelihood of re-bleeding. In particular, smokers with PDR, must be encouraged to stop and anaemia needs to be treated.

Abbreviations

RVH: recurrent vitreous haemorrhage

PDR: proliferative diabetic retinopathy

BMI: body mass index

UACR: urine albumin to creatinine ratio

eGFR: estimated glomerular filtration rate

DR: diabetic retinopathy

DM: diabetes mellitus

DME: diabetic macular edema

DCCT: Diabetes Control and Complications Trial

UKPDS: United Kingdom Prospective Diabetes Study

T1DM: type 1 diabetes mellitus

T2DM: type 2 diabetes mellitus

PRP: pan-retinal photocoagulation

PVD: posterior vitreous detachment

NVH: non-vitreous haemorrhage

SVH: single vitreous haemorrhage

PPVS: pars plana vitreoretinal surgery

OCT: optical coherence tomography

FA: fluorescein angiography

COPD: chronic obstructive pulmonary disease

VEGF: vascular endothelial growth factor

Declarations

Ethics approval and consent to participate

The study was carried out according to local legal requirements [local ethics committee of *Hospital Universitari Sant Joan de Reus. approval no. 13-01-31/proj6*] and the revised guidelines of the Declaration of Helsinki. The study was approved and supported by *Instituto de Investigaciones Carlos III [IISCIII]. Spain. nos.* PI15/001150 July 15 and PI18/000169 July 2018.

Consent for publication

All patients included in the study signed our institutional consent form.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions:

[*MBB*] contributed to study conception and design. collected research data. reviewed the statistical analysis. wrote the discussion and edited the manuscript contributing to the final approval of the version sent for publication.

[*PRA*] contributed to ophthalmology data collection, carried out retinographs and OCT procedures and interpreted the research data, contributing to the final approval of the version sent for publication.

[*JMG*] contributed to ophthalmology data collection. carried out fluorescein angiographs and OCT procedures and interpreted the research data, contributing to the final approval of the version sent for publication.

[*ABP*] contributed to ophthalmology data collection, carried out retinographs and OCT procedures and interpreted the research data, contributing to the final approval of the version sent for publication.

[*NSL*] contributed to medical history data collection, carried out OCT procedures and interpreted the research data, contributing to the final approval of the version sent for publication.

[*RNG*] contributed to ophthalmology data collection, carried out retinographs and OCT procedures and interpreted the research data, contributing to the final approval of the version sent for publication.

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Tables

Table 1.

Title: Baseline differences of the all independent variables among the 3 groups of patients with proliferative diabetic retinopathy [PDR] studied.

Variable	No vitreous haemorrhage (NVH)	Single vitreous haemorrhage (SVH)	Recurrent vitreous haemorrhage (RVH)	Significance
Gender:	71 [69%]	70 [61%]	56 [82%]	
Men	31 [31%]	45 [39%]	12 [18%]	Phi=0.180, p=0.01*
Women				
T1DM	16 [16%]	11 [17%]	13 [19%]	Phi=0.112, p=0.16*
T2DM	86 [84%]	104 [83%]	55 [81%]	
Age [yrs]	61.11 ± 12.54 [34-94]	66.08 ± 11.81 [28-88]	62.59 ± 15.51 [34-91]	F=4.131, p=0.017**
DM duration [yrs]	20.88 ± 9.02 [19.1-22.6]	22.02 ± 9.30 [20.3-23.7]	24.35 ± 10.65 [21.7-26.9]	F=2.721, p=0.043**
Arterial hypertension	70 [24.6%]	84 [29.5%]	43 [15.1%]	Phi=0.083, p=0.37*
DM treatment:				Phi=0.082, p=0.38*
Insulin	80 [78%]	93 [81%]	59 [87%]	
Oral drugs	22 [22%]	22 [19%]	9 [13%]	
Anticoagulant users	2 [0.7%]	18 [6.3%]	18 [6.3%]	Phi=0,279, p<0.001*
Antiplatelet users	44 [15.4%]	59 [20.7%]	37 [13%]	Phi=0,093, p=0.295[1]
No Previous PRP	81 [79%]	65 [52%]	29 [43%]	Phi=0,297, p<0.001*
Previous PRP	21 [21%]	50 [48%]	39 [57%]	
No COPD	96 [94%]	84 [73%]	44 [65%]	Phi=0.293, p<0.001*
COPD	6 [6%]	31 [27%]	24 [35%]	
Haemoglobin [g/dL]	13.21 ± 1.70 [12.8-13.5]	12.60 ± 1.55 [12.3-12.8]	11.71 ± 1.89 [11.2-12.1]	F=15.99, p<0.0001**
Mean HbA1c	8.40 ± 1.63 % [8-8.7]	8.81 ± 1.61 % [8.5-9.1]	8.88 ± 1.77 % [8.4-9.3]	F=2.271, p=0.105***
No UACR	61 [60%]	63 [55%]	30 [44%]	Phi=0.120, p=0,131*
UACR	41 [40%]	52 [45%]	38 [56%]	
eGFR [ml/min/1.73^2]	69.71 ± 25.74 [64.65-74.76]	66.25 ± 25.66 [61.51-70.99]	60.63 ± 25.55 [54.71-66.55]	F=2.607, p=0.07**

Smoking status:				Phi=0.284, p<0.001*
Non smoker	61 [60%]	65 [56%]	20 [29%]	
Former smoker	15 [15%]	18 [16%]	9 [13%]	
Smoker	26 [25%]	32 [28%]	39 [58%]	
Pack-years smoked	10.13 ± 18.61 [6.5-13.8]	25.32 ± 35.94 [18.7-31.9]	49.34 ± 44.42 [38.6-60]	F=28.123, p<0.0001**
No PVD	70 [69%]	57 [49%]	50 [73%]	Phi=0.216, p=0.001*
PVD	32 [31%]	58 [51%]	18 [27%]	

Legend: Patients that suffered multiple vitreous haemorrhage smoked more, showed lower levels of haemoglobin and had longer duration of their diabetes compared to the others. UACR= urine albumin to creatinine ratio; eGFR= estimated glomerular filtration rate; COPD=chronic obstructive pulmonary disease; PRP=panretinal photocoagulation; PVD: posterior vitreous detachment. *=Chi-squared test; **=Kruskal-Wallis test; ***=one-way ANOVA.

Table 2.

Title: Study of each independent variable in relation to the occurrence of vitreous haemorrhage recurrence assessed by means of logistic regression analysis.

Independent Variables	Exp(B)	CI 95%	Significance*
Sex	-0.004	-0.231-0.228	p=0.31
Type DM	1.21	0.33-4.42	p=0.48
Age	-0.221	-0.023-(-0.004)	p=0.09
DM duration	1.03	1.0-1.07	p=0.04
Body Mass Index	0,726	-0.022-0.15	p=0.44
Arterial hypertension	1.73	0.78-3.84	p=0.17
DM treatment	-0.058	-0.343-0.111	p=0.31
Anticoagulant therapy	0.265	-0.046-0.494	p=0.11
Antiplatelet therapy	0.259	0.010-0.392	p=0.48
Panretinal photocoagulation	0.090	-0.031-0.318	p=0.10
COPD	-0.023	-0.285-0.196	p=0.65
Haemoglobin	-0,243	-0.16 -(-0.06)	p<0.001
HbA1c	0.905	-0.061-0.049	p=0.82
UACR	0.885	0.45-1.73	p=0.72
eGFR	-0.087	-0.007-0.002	p=0.21
Pack-years smoked	1.21	1.10-1.32	p<0.001
Previous Anti-VEGF therapy	0.010	-0.157-0.188	p=0.47
Posterior Vitreous Detachment	2.15	0.93-4.93	p=0.07

Legend: The pack-years smoked, the duration of the diabetes and the level of haemoglobin were the risk factors in our population of diabetic patients with proliferative diabetic retinopathy that significantly related to recurrent vitreous haemorrhage. eGFR= estimated glomerular filtration rate; COPD=chronic obstructive pulmonary disease; VEGF=vascular endothelial growth factor; PRP=panretinal photocoagulation; PVD: posterior vitreous detachment.

Figures

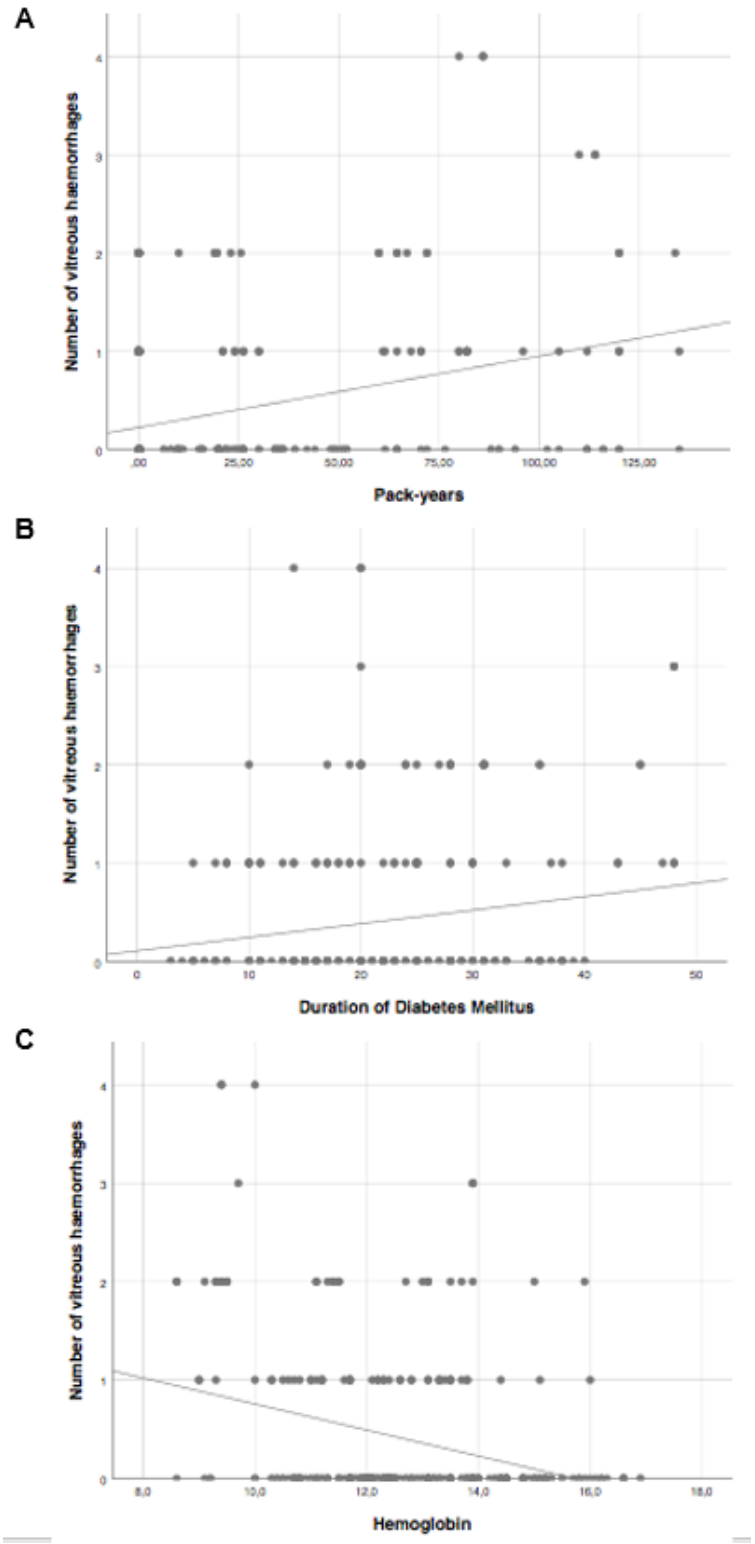

Figure 1

Number of vitreous haemorrhage events as a function of the pack-years smoked, duration of diabetes and the level of haemoglobin. Legend: Tobacco consumption [OR= 1.21, 95% CI, 1.10-1.32, P< 0.001], diabetes duration [OR= 1.03, 95% CI, 1.0-1.07, P= 0.04] and haemoglobin level [OR= -0.24, 95% CI, -0.16, -0.06, P< 0.001] ad an independently significant associaton with recurrent vitreous haemorrhage in a sample of 285 eyes with proliferative diabetic retinopathy. Statistical analysis was performed using the

logistic regression analysis. [1A] Scatter plot that shows positive correlation between the number of vitreous haemorrhage episodes and the pack-years smoked. [1B] Scatter plot that shows positive correlation between the duration of diabetes and the number of vitreous haemorrhage events. [1C] Scatter plot that shows negative correlation between the haemoglobin level and the number of vitreous haemorrhage episodes.

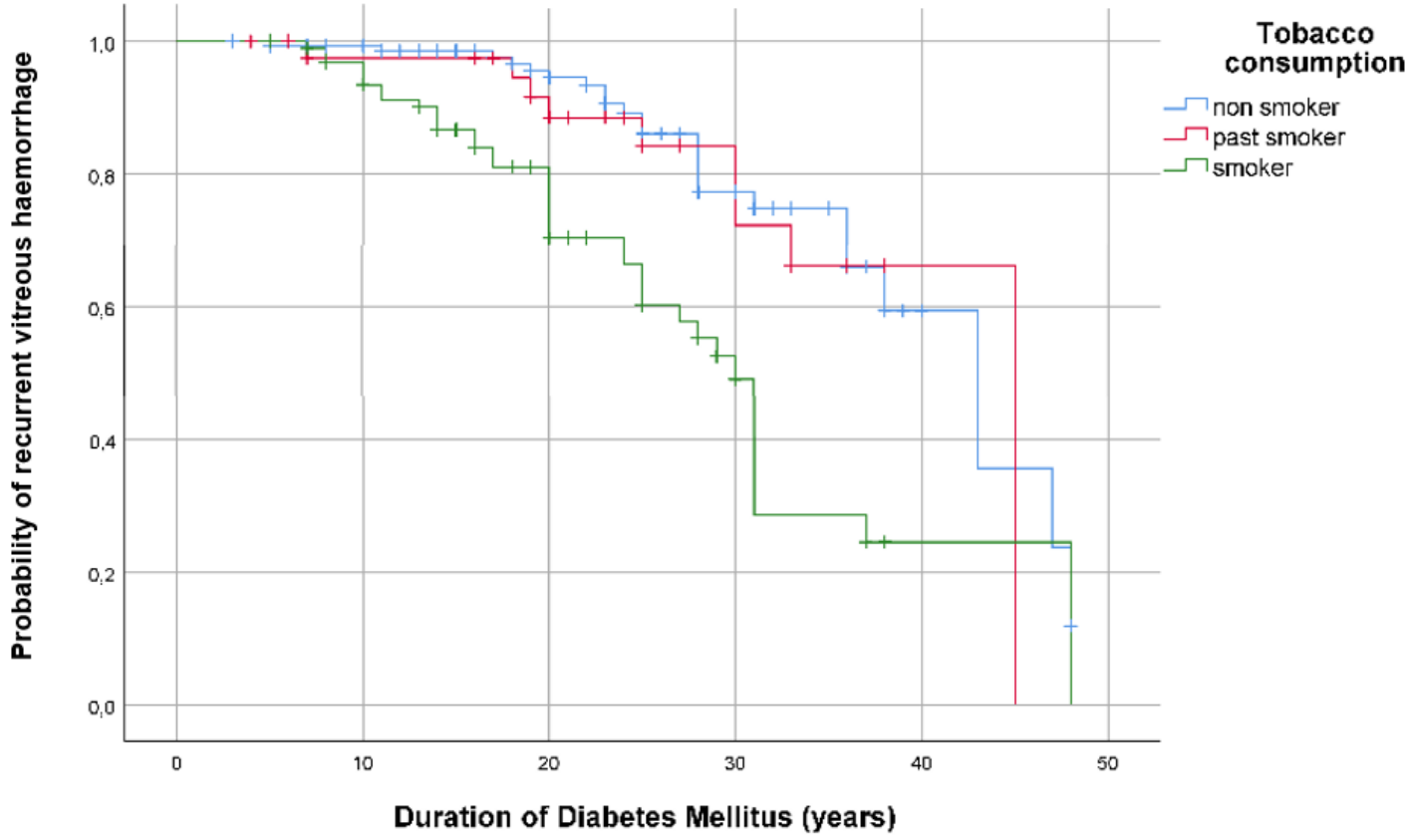

Figure 2

Kaplan-Meier plot.