

ARTICLE



Increased intravitreal glucose in rhegmatogenous retinal detachment

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PURPOSE: Altered glucose metabolism, along with low-grade inflammation, has been proposed to be involved in retinal detachment (RD)-induced cone loss. Here, we assessed intravitreal glucose and cytological profile in patients with macula-off RD.

METHODS: Glucose concentration was analysed in vitreous samples from 137 non-diabetic patients undergoing vitrectomy for either primary macula-off RD ($n = 73$) or epiretinal membrane (ERM; $n = 64$). Cellularity was assessed in vitreous cytopsin preparations by a semi-quantitative immunostaining approach.

RESULTS: Intravitreal glucose concentration was higher in the RD group (2.28 mmol.L⁻¹ $n = 73$ vs 1.6 mmol.L⁻¹ $n = 64$; $p < 0.0001$). Overall cellularity and density of macrophages were significantly higher in the vitreous of RD patients (respectively $p = 0.003$ and $p < 0.0001$). Among the RD patients, intravitreal glucose concentration correlated with macrophages density ($p = 0.002$): its levels remained significantly higher in eyes in which macrophages were innumerable compared to lower macrophages densities RD eyes ($p = 0.0095$).

CONCLUSIONS: We observed a strong relationship between intravitreal glucose concentration and vitreous macrophage density. Additional indicators for vitreous glycation and low-grade inflammation should be further studied.

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INTRODUCTION

As a consequence of age, the vitreous liquefies, detaches from the retina. This can lead to peripheral vitreo-retinal traction, retinal tear formation and rhegmatogenous retinal detachment (RD) or to vitreo-macular traction and epiretinal membrane (ERM) formation [1, 2]. In spite of the frequent anatomical success of RD surgery, photoreceptor cell death may limit postoperative visual recovery [3]. Modulation of these cell death signalling pathways is an interesting therapeutic strategy to prevent blindness [4]. The precise mechanisms leading to photoreceptor cell death remain poorly understood, although many studies have shown the critical role of macrophage accumulation in the subretinal space, associated with changes in chemokine and cytokine levels in RD-associated vitreous [5, 6].

Interestingly, increased levels of intravitreal glucose and advanced glycation endproducts (AGE) have been observed in the vitreous of both non-diabetic and diabetic RD patients, with significantly higher concentrations in the latter [7–10]. AGEs are associated with mononuclear chemotaxis, and activation of macrophages through specific receptors (R-AGE) could be responsible for low-grade inflammation [11]. Over the last decade it has been shown that in several types of human retinal diseases, cone function and viability as well as inflammatory cells such as intravitreal macrophages are highly dependent on glucose metabolism [12–14]. Recently, Conart et al. [15] described a new mechanism by which inflammation induces retinal detachment-

cone death through cone starvation, a mechanism that could be reversed by insulin.

The purpose of this study was to investigate a possible link between intravitreal glucose metabolism, low-grade inflammation and photoreceptor loss in an existing cohort of non-diabetic macula-off RD patients compared to control non-diabetic ERM patients.

PATIENTS AND METHODS

The vitreous of patients undergoing vitrectomy is routinely collected at Reims University Hospital. Patients with macula-off RD or ERM requiring vitrectomy between March 2015 and November 2017 were consecutively enrolled. Patients with diabetes, vitreous haemorrhages, previous history of vitreo-retinal surgery or uveitis, were excluded, as were patients who did not complete the follow-up period of 3 months. Written informed consent was obtained from all the patients. The study adhered to the tenets of the Declaration of Helsinki.

At the beginning of the 25-gauge pars plana vitrectomy, a 0.2 mL sample of undiluted vitreous fluid was collected by aspiration with a syringe before opening the infusion line. After the opening of the infusion line, a 5 mL-diluted vitreous sample was collected. All surgeries were performed by the same physician (CA).

Undiluted samples were analysed within 45 min in the laboratory of biochemistry at Reims University Hospital, using GOD-PAP colorimetric procedures. Perioperative capillary glycaemia and intravitreal glucose concentration were monitored as a standard procedure in all patients,

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regardless of diabetes status, with validated routine enzymatic assays with automated spectrophotometric detection (hexokinase method, Cobas 8000, ROCHE, Switzerland). Cytological examination was performed at the Department of Pathology at Reims University Hospital on the diluted samples (5 mL volume). Samples were first centrifuged using cytospin and six slides were prepared for microscopy as follows. Two slides were used for Papanicolaou and May–Grünwald–Giemsa stainings. The four remaining slides were treated with Merckofix® fixative spray (Millipore, MERCK, Germany), then stained by immunocytochemistry with the BenchMark XT automated slide stainer (Ventana Medical System, Tucson, USA), using with the following antibodies: AE1/AE3 (1:50) for epithelial cells identification, CD68-KP1 (1:100) for macrophages identification, GFAP (1:400) for glial cells identification and CD45 (1:50) for hyalocytes identification (all antibodies from DAKO, USA). All slides were microscopically evaluated by an experienced pathologist (CB) blinded to ophthalmological information. Macrophages, hyalocytes, lymphocytes, neutrophils, glial cells, red cells and epithelial cells were scored using a semi-quantitative scale: 0 = acellular vitreous sample, 1 = less than 10 cells on the whole slide, 2 = more than 10 cells on the slides but less than 10 on the most cellular field at high magnification (x40 magnification), 3 = innumerable cells.

Patient's age, gender, preoperative best corrected visual acuity (BCVA) were obtained from their medical files. In case of RD, median number of retinal tears, Proliferative Vitreoretinopathy (PVR) stage (none, A, B or C) and RD extent (clock hours) were collected. Postoperative follow-up was performed at three weeks and three months and included BCVA, slit-lamp biomicroscopy, fundus view and OCT (Spectralis, Heidelberg engineering, Heidelberg, Germany), to measure the Mean Foveal Thickness (MFT). The main outcome measure was intravitreal glucose concentration. Cellularity, postoperative BCVA and MFT at three months were secondary outcome measures. For descriptive analysis, variables were expressed as mean values with standard deviation. Mann–Whitney tests were performed to compare quantitative variables. The correlation between intravitreal glucose concentration and different clinical or paraclinical parameters was evaluated with Pearson's correlation tests after testing both variables for normality. Fisher exact tests and Chi² tests were used to compare qualitative variables of cytologic findings. The relation between cytological findings and intravitreal glucose concentration was evaluated with ANOVA and Kruskal–Wallis tests with pairwise Bonferroni correction for multiple comparisons. Any *p* value below 0.05 was considered statistically significant.

RESULTS

General findings

A total of 137 patients who underwent pars plana vitrectomy between March 2015 and November 2017 were included in the study: seventy-three eyes with primary macula-off RD and 64 with ERM. Details are given in Table 1. RD patients had a lower mean age than ERM patients (61 vs. 71 years; *p* = 0.002). Both far and near preoperative visual acuity were worse in the RD group, whereas post-operative visual acuity was not significantly different between the two groups. The RD extended between 1 to 12 clock hours (mean 8.2 ± 3.1). The postoperative mean MFT was significantly lower in the RD group.

Intravitreal glucose

Although RD patients were significantly younger than ERM patients, no correlation was found between patient's age and intravitreal glucose level in neither RD (*r* = 0.04; *p* = 0.75) nor ERM

(*r* = 0.12; *p* = 0.34) group. Intravitreal glucose concentration was on average 40% higher in the RD group compared to the ERM group (mean 2.28 vs 1.60 mmol.L⁻¹; *p* < 0.0001). A significant correlation between blood glucose levels and intravitreal glucose concentration was found only in the ERM group (*r* = 0.7; *p* = 0.0071; Table 2). In the RD group, intravitreal glucose concentration was inversely correlated with post-operative MFT (*r* = -0.51; *p* = 0.0001). We also observed a significant (*r* = 0.38; *p* = 0.013) correlation between intravitreal glucose concentration and RD

Table 1. Clinical, ophthalmological and biochemical data of RD and ERM patients.

	RD (n = 73) mean (SD)	ERM group (n = 64) mean (SD)	<i>p</i> values
Age	61 (±15.9)	71 (±6.8)	0.002
Sex ratio (M/F)	1.4	0.73	
Preoperative far BCVA (logMAR)	1.41 (±1.02)	0.47 (±0.24)	<0.0001
Preoperative near BCVA (logMAR)	1.42 (±1.08)	0.46 (±0.17)	<0.0001
Postoperative MFT (µm)	202 (±24, 2)	322 (±47, 6)	<0.0001
Postoperative far BCVA (logMAR)	0.70 (±0.51)	0.36 (±0.22)	0.12
Postoperative near BCVA (logMAR)	0.70 (±0.49)	0.43 (±0.27)	0.53
Median number of retinal tears	1 (±1.02)	NA	NA
Mean RD extent (clock hours)	8.2 (±3.1)	NA	NA
PVR			
None	n = 25	NA	NA
Stage A	n = 13	NA	NA
Stage B	n = 22	NA	NA
Stage C	n = 13	NA	NA
Intravitreal glucose concentration (mmol.L ⁻¹)	2.28 (±0.67)	1.60 (±1.1)	<0.0001
Glycaemia (mmol.L ⁻¹)	4.1 (±1.0)	4.6 (±1.1)	0.12

Mann–Whitney tests.

BCVA Best Corrected Visual Acuity, MAR Minimum Angle of Resolution, MFT Mean Foveal Thickness, PVR Proliferative Vitreoretinopathy, RD Rhegmatogenous Retinal Detachment, ERM Epiretinal Membrane, SD Standard Deviation, NA Non-Applicable.

Table 2. Correlation between intravitreal glucose concentration and different clinical and OCT parameters.

Correlation between intravitreal glucose and the listed parameters	RD group (n = 73)	ERM group (n = 64)
Postoperative BCVA	<i>r</i> = -0.36 (<i>p</i> = 0.001)	<i>r</i> = -0.14 (<i>p</i> = 0.25)
Postoperative MFT	<i>r</i> = -0.51 (<i>p</i> = 0.0001)	<i>r</i> = -0.17 (<i>p</i> = 0.21)
RD extent	<i>r</i> = 0.38 (<i>p</i> = 0.013)	NA
Number of retinal breaks	<i>r</i> = 0.25 (<i>p</i> = 0.07)	NA
Blood glucose concentration	<i>r</i> = -0.1 (<i>p</i> = 0.23)	<i>r</i> = 0.7 (<i>p</i> = 0.0071)

Pearson's correlation tests.

RD Rhegmatogenous Retinal Detachment, ERM Epiretinal Membrane, NA Non-Applicable.

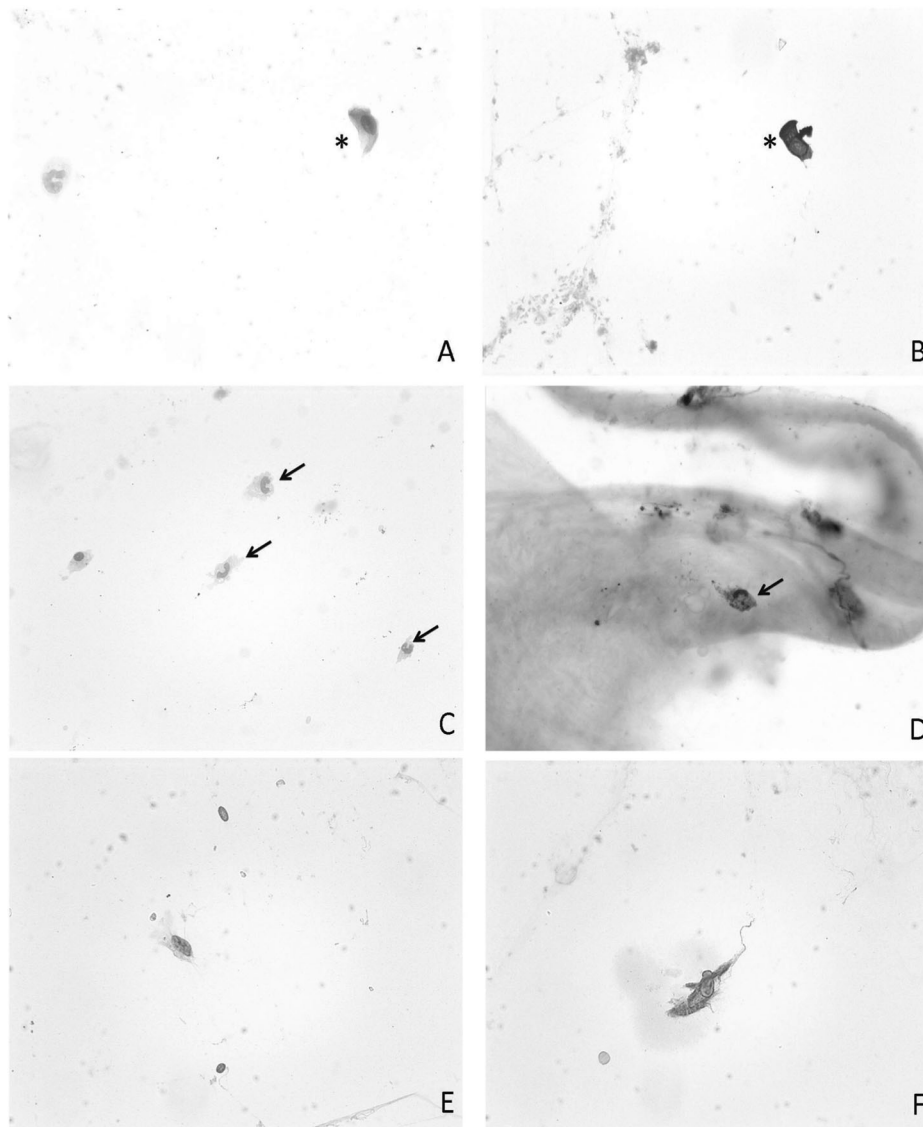


Fig. 1 Photomicrographs (x400) of different cell types observed in the vitreous of patients who underwent surgery for rhegmatogenous retinal detachment or epiretinal membrane peeling. **A, B** Epithelial cell. **A** May-Grünwald-Giemsa stain; **B** AE1/AE3 immunolabelling. **C, D** Macrophages. **C** May-Grünwald-Giemsa stain; **D** CD68 immunolabelling. **E, F** Hyalocyte. **E** Papanicolaou stain; **F** CD45 immunolabelling.

extent, while a tendency with no statistically significant correlation was noticed between the intravitreal glucose concentration and the number of retinal breaks ($r = 0,25$; $p = 0,07$; Table 2).

Vitreous cellularity

Macrophages, hyalocytes, lymphocytes, neutrophils, glial cells, red cells and epithelial cells were scored using a semi-quantitative immunostaining approach (Fig. 1, Table 3). The overall cellularity and the number of macrophages were significantly higher in the RD group compared to the corresponding values in the ERM group (Table 3). Macrophage density increased with RD extent ($p < 0.0001$, ANOVA test), while no such correlation was found for epithelial cells ($p = 0.21$, ANOVA test). No relationship between the density of macrophages and PVR was found ($p = 0.98$ CHI^2 test). However, the density of epithelial cells was consistently higher in cases with PVR stage C compared with cases with no PVR ($p = 0.002$ CHI^2 test).

Table 3. Cytologic findings in RD and ERM patients.

	RD (n = 73) Mean score [range]	ERM (n = 64) Mean score [range]	p values
Cellularity	1.21 [0–3]	0.68 [0–3]	0.003
Macrophages	1.2 [0–3]	0.42 [0–2]	<0.0001
Hyalocytes	0.43 [0–3]	0.30 [0–2]	0.09
Red cells	0.62 [0–3]	0.33 [0–3]	0.06
Epithelial cells	0.37[0–3]	0.33 [0–3]	0.89
Lymphocytes	0.24 [0–3]	0.13 [0–1]	0.21
Neutrophils	0.31 [0–3]	0.17 [0–2]	0.053

Fisher exact tests.

RD Rhegmatogenous Retinal Detachment, ERM Epiretinal Membrane.

Table 4. a. Correlation between macrophages density and intravitreal glucose concentration in patients with Retinal Detachment. b. Correlation between epithelial cells density and intravitreal glucose concentration in patients with Retinal Detachment.

Macrophages density score	Intravitreal glucose concentration (mmol.L ⁻¹) mean (SD)	p value
0 (n = 28)	2.03 ± 0.14	0.002
1 (n = 17)	2.19 ± 0.11	
2 (n = 13)	2.14 ± 0.12	
3 (n = 15)	2.98 ± 0.13	
Epithelial cells density score	Intravitreal glucose concentration (mmol.L ⁻¹) mean (SD)	p value
0 (n = 53)	2.25 ± 0.09	0.498
1 (n = 15)	2.25 ± 0.18	
2 (n = 3)	3.01 ± 0.45	
3 (n = 2)	2.27 ± 0.15	

SD Standard Deviation. Kruskal–Wallis test with pairwise Bonferroni correction for multiple comparisons.

Relationship between intravitreal glucose and cellularity

Among the RD patients, there was a direct link between glucose concentration and the density of vitreal macrophages ($p = 0.0001$, ANOVA test). The intravitreal glucose concentration was 50% higher in eyes in which macrophages were innumerable compared to RD eyes with no macrophages ($2.98 \pm 0.13 \text{ mmol.L}^{-1}$ vs $2.03 \pm 0.14 \text{ mmol.L}^{-1}$, $p < 0.0001$; Table 4a), though no correlation was noticed with any other cell type (Table 4b and data not shown).

DISCUSSION

In this study, both intravitreal glucose concentration and cytology were analysed in non-diabetic patients who underwent surgery for macula-off RD or ERM treatment. In RD patients, intravitreal glucose concentration and cytological findings were correlated to RD extent. Intravitreal glucose concentration was found to be strongly correlated with the density of vitreal macrophages. This is, to our knowledge, the first study describing and comparing intravitreal glucose concentration and cytology in human non-diabetic patients with RD and ERM.

Intravitreal glucose concentration was 40% higher in RD patients compared to ERM patients, in spite of the fact that none of the patients was diabetic. These values were lower than those previously reported in non-diabetic patients ($3.5 \pm 1.8 \text{ mmol.L}^{-1}$) by Lundquist and Österlin [8]. It has been demonstrated that intravitreal glucose reflects glycaemia, owing to the influx of glucose through the blood retina barrier through GLUT-1 transporters [7–9]. Glucose concentration in the vitreous is about half its plasma concentration. We observed a correlation between intravitreal glucose and glycaemia in ERM patients, but not in RD patients. This indicates that glycaemia solely cannot explain this difference of intravitreal glucose levels between RD and ERM patients and suggests that intravitreal glucose concentration can depend on the underlying retinal disease, i.e. RD or ERM in our study, and not only on the diabetic status. This is also the first study to show no correlation between age and intravitreal glucose level.

In parallel, we observed significantly higher levels of overall cellularity, as well as higher macrophage density in the vitreous of RD patients compared to ERM patients. In contrast, the density of epithelial cells was similar in the two groups. In the RD eyes, increased epithelial cell density was significantly associated with a higher PVR stage. This is in accordance both with previous data and with the hypothesis that PVR could be associated with the

migration of pigment epithelial cells out of the subretinal space [16, 17]. Macrophages are known to be either vitreous resident microglial cells or blood-borne cells that enter the vitreous following activation by multiple stimuli e.g., injury [18]. For this reason, patients with macroscopic vitreous haemorrhage were not included in this study. Since the number of red cells detected in RD eyes was not significantly higher than in ERM eyes, the augmentation that we observed in both the number of macrophages and the intravitreal glucose in the vitreous of RD patients could result from a non-haemorrhagic breakdown of the blood-ocular barrier, as already reported by Hiscott et al. [19]. This hypothesis is further supported by the correlation between the RD extent and both the higher density of macrophages and the increased intravitreal glucose. Cantrill and Pederson previously described such a breakdown of the blood-retinal barrier in rhegmatogenous RD [20]. It is likely that these permeability changes induced by some local effect are partly mechanical in nature, possibly involving fluid displacement through the retinal break, and physical disruption of tissues caused by the separation of the neurosensory retina and retinal pigment epithelium. In addition, permeability changes may also be brought about by locally increased vascular permeability [21], such as an increased influx of glucose into the vitreous via GLUT-1 transporters through the subretinal space [22]. However, our data do not support that hypothesis, since we observed no correlation between intravitreal glucose and glycemia in the RD group compared with the ERM group.

Another explanation for our findings could be a pre-existing higher intravitreal glucose level in eyes eventually developing RD. Stitt and al. suggested that the exposure to high glucose concentrations in diabetic patients could result in increased levels of advanced glycation end products (AGE) in the vitreous [23]. Indeed, AGE are formed through the non-enzymatic glycation of proteins by aldehyde or keto groups of reducing sugars in a process known as the Maillard reaction [24]. Further, AGE-induced cross-links in the vitreous collagen of extracellular matrix are known to cause tissue rigidity [9, 24–26]. Such irreversible cross-links persist on long-lived proteins and have been shown to accumulate with aging and at an accelerated rate in diabetes [27, 28]. This could also be the case in rhegmatogenous RD and proliferative diabetic retinopathy, as recently demonstrated by Fokkens et al. [10] and Coral et al. [29, 30].

To summarize, the increased intravitreal glucose concentration in the RD group could be associated with the loss of collagen elasticity through glycation and therefore an increase in vitreoretinal traction. As mentioned above, RD extent was significantly associated with both intravitreal glucose and macrophage density. However, no relationship was found between the number of retinal breaks and either intravitreal glucose or the score of macrophages, in spite of the fact that the number of tears could be an indicator of vitreoretinal traction and loss of elasticity.

Although we could not assess cone functionality using electrophysiology, this deserves further explorations. Indeed, previous electrophysiological studies of RD human eyes have reported reduced amplitudes and increased latencies compared to normal values, in full field electroretinograms (ERGs) [31], focal ERGs [32] or multifocal ERGs [33], with evidence for retinal dysfunction due to outer retinal alterations in primary macula-off RD.

Our study did not investigate low-grade inflammation associated with the release of cytokines and chemokines. Such a mechanism could also contribute to macrophage proliferation [5, 15]. Several studies in mammalian model systems have demonstrated that, in response to retinal damage, bone-marrow-derived cells are homed to the eye where they proliferate, accumulate in the retina and in the subretinal space, contributing to retinal pathology following RD [6, 18, 34]. It has also been shown that monocyte chemoattractant protein 1 mediates RD-induced photoreceptor apoptosis by triggering macrophage accumulation and promoting oxidative stress [35]. Finally, apoptotic photoreceptors in a rat RD-induced

model were found to be selectively eliminated from the original nuclear layer of the retina and directed into the subretinal space where they were phagocytosed by infiltrating monocyte-derived macrophages [36]. In parallel with the extent of the retinal detachment, low-grade inflammation is likely to be increased [37]. Additional indicators for vitreous glycation and low-grade inflammation, such as inflammatory cytokines, which could not be assessed in the setting of our study, should be further studied. Conart et al. [15] recently evaluated these inflammatory cytokines levels in RD eyes, and their data strongly suggested a link between insulin signalling and cone malfunction or death.

Summary

What was known before:

- Inflammation induces retinal detachment-cone death through cone starvation, a mechanism that could be reversed by insulin.

What this study adds:

- This study shows increased intravitreal glucose levels and macrophage cells density in non-diabetic patients with rhegmatogenous retinal detachment compared to patients with epiretinal membrane. First report showing that intravitreal glucose concentration can depend on the underlying retinal disease and not only on the diabetic status.

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AUTHOR CONTRIBUTIONS

CA, BH, FH, MA, were responsible for designing the protocol, performing surgeries, collecting samples and data, interpreting results, and writing. CB performed statistical analyses and provided feedback on the report. PG and LR were responsible for designing the protocol, performed biochemical analyses, and contributed to writing the report. AH was responsible for extracting and analysing data, interpreting results, updating reference lists, and contributed writing the report. CBR was responsible for designing the protocol, conducted immunohistochemistry on samples, and contributed to interpreting results and writing the report.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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