

# Clinical Pathology of Diabetic Retinopathy and Macular Edema

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**Review Article**

Volume 1 Issue 1

**Received Date:** July 08, 2016

**Published Date:** July 22, 2016

## Abstract

Diabetic retinopathy and macular edema is multifactorial complex disease, VEGF can play central role in non-chronic diabetic macular edema pathogenesis and VEGF blockade agents may improve vision, where in chronic diabetic macular edema inflammatory cytokines are the main driver of edema and intravitreal steroids may result in edema resolution, however vascular element is not always the cause of macular thickening and visual loss from non-vascular elements such as vitreomacular abnormalities which needs to be managed surgically, while diabetic retinopathy can be non-proliferative or proliferative in the presence of neovascularization which they managed by pan retinal laser photocoagulation and proliferation can complicate in to tractoinal retinal detachment and vitreous hemorrhage, which may require surgical management in certain cases.

**Keywords:** Cytokines; Pericytes; Ischemia; Diabetic retinopathy; Diabetic maculopathy

## Introduction

Diabetic retinopathy and macular edema is responsible for vision loss in working age group due to hyperglycemia, when approaching patients with diabetic retinopathy, it is essential to understand the underlying pathological mechanisms in order to individualized treatment as diabetic retinopathy and macular edema is multifactorial complex disease. A lot of agents or procedures are available for targeting various pathological mechanisms, such as VEGF, inflammatory, or vitreomacular abnormality, however optimum treatment results can be achieved by using the right agent or procedure at the right place.

## Macular Edema

Macular thickening and cyst formation are due to fluid accumulation because of increased vascular permeability

as a result of inner blood retinal barrier break down after loss of pericytes and thickened basement membrane induced by hyperglycemia, this process is governed by multiple and complex factors and mechanisms such as vascular, inflammatory and biochemical [1].

Macular edema can be induced by one or multiple factors at the same time, and it is important to understand that pathogenesis mechanism can be changed from one to another. The best way to target pathological factors in clinical practice is to understand its mechanism verities, diabetic macular edema can be induced by vascular and non-vascular (vitreomacular abnormality) elements and sometimes mixed where vascular is in term can be presented as ischemic or non-ischemic, where the latter can be as chronic or non-chronic course (Figure 1).

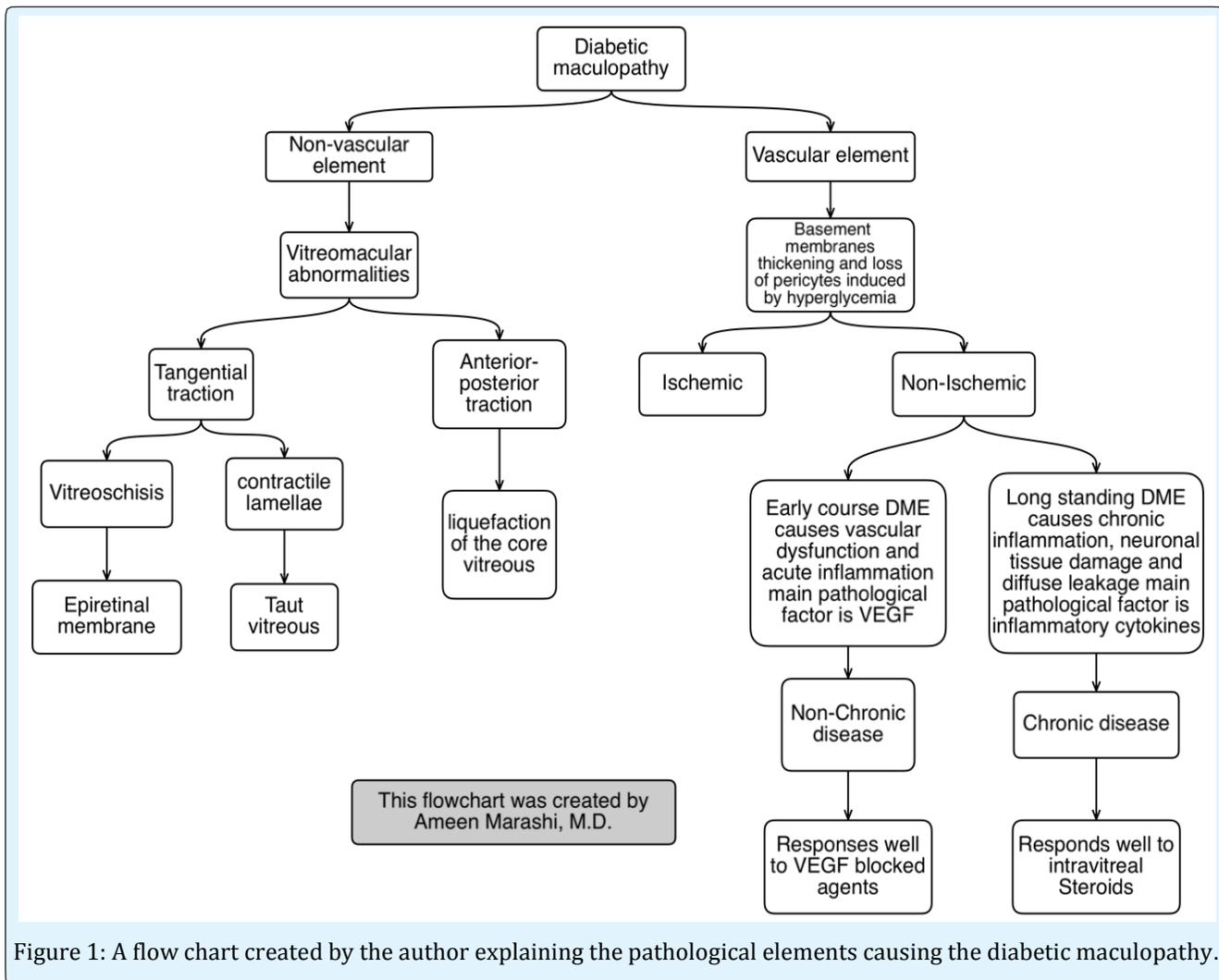


Figure 1: A flow chart created by the author explaining the pathological elements causing the diabetic maculopathy.

## Vascular Element

### Non-ischemic

**Non-chronic disease:** When diabetic macular edema starts to develop the main mechanism is vascular dysfunction, and acute inflammation causing hypoxia and thus governed by upregulated vascular endothelial growth factor (VEGF) and other inflammatory cytokines [2] such as IL-1b, IL-6, IL-8, and MCP-1, where in non-chronic disease VEGF may play major role in pathogenesis and targeting it by VEGF blockade agents can cause macular edema resolution. VEGF can be targeted by blocking the VEGF receptor using monoclonal antibodies such as Ranibizumab or Bevacizumab which they inhibit VEGF-A isoforms, or by trapping VEGF using fusion proteins such as Aflibercept, ziv-aflibercept, or conbercept which they inhibit VEGF-A VEGF-B, and PlGF.

Clinical trials have evaluated the safety and efficacy of intravitreal VEGF-blockade agents for diabetic macular edema treatment and compared it head to head and with other treatment modalities such as laser and steroids. The main outcome of these clinical trials is the following:- VEGF blockade agents are safe and effective to use for diabetic macular edema [3] (Figure 2).-VEGF blockade agents are superior to laser treatment alone and to steroids in a long term follow-up [4]. -There is not much deference in visual out come when combining intravitreal VEGF blockade agents with laser treatment in contrast to intravitreal VEGF blockade agents alone [5]. -Patients with central diabetic macular edema that received intravitreal VEGF blockade agents as differed treatment didn't gain visual benefits as those who received VEGF blockade agents at baseline maybe due to permanent functional damage or diabetic macular edema has

adopted chronic course [6]. -Patients may benefit equally to all VEGF blockade agents when BCVA is good at baseline where Aflibercept showed more efficacies in the 1<sup>st</sup> 12 months follow up when BCVA is worse at baseline [7].

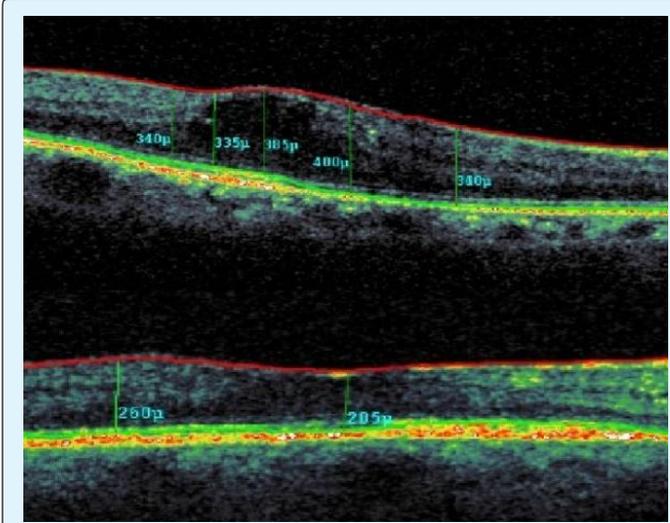


Figure 2: Shows thickening of the macula and cyst formation as a result of diabetic macular edema (above) where (bottom) shows resolution of diabetic macular edema after injecting intravitreal VEGF blockade.

**Chronic disease:** As the diabetic macular edema becomes long standing the fluid leakage become diffuse and cause photoreceptor loss (Figure 3) inflammation governed by mediators such as MCP-1, TNF- $\alpha$ , IL-1b, IL-6, IL-8, and IP-10 where VEGF may not play a significant role and thus explain the poor response to intravitreal VEGF blockade agents in chronic DME. The process of chronic inflammation itself is not self-resolving leading to tissue stress and it further damage with increased sub retinal microglia accumulation which will cause more fluid leak induced by leukostasis and cytotoxic effect (8).

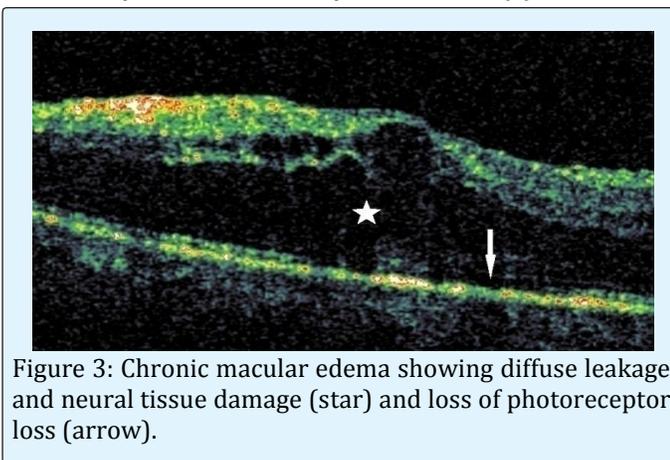


Figure 3: Chronic macular edema showing diffuse leakage and neural tissue damage (star) and loss of photoreceptor loss (arrow).

This cascade of events can be shot down using intravitreal steroids, commercially intravitreal steroids are available in three forms: Triamcinolone Acetonide, dexamethasone 0, 7 mg biodegradable implant and Fluocinolone Acetonide Implant 0.19 mg non-biodegradable implant.

A lot of trials have studied the safety and efficacy of intravitreal steroids and they concluded the following Intravitreal steroids are safe and effective for diabetic macular edema treatment [9].-Intravitreal steroids can resolve persistent diabetic macular edema which may not respond well to other treatment modalities [10]. Intravitreal steroids induce risk of increased intra ocular pressure and cataract formation [11,12].

### Ischemic

Ischemic maculopathy is not caused by increased by vascular leakage, it is induced by microvascular blockage and enlargement, with capillary loss and adjacent edema. Clinically diabetic ischemic maculopathy appears as feature less retina and diagnosed using fluoresce in angiography which appears as enlarged or irregular FAZ (foveal avascular zone) (Figure 4). In cases of substantial ischemia, visual prognosis is poor and unfortunately no beneficial treatment is available.

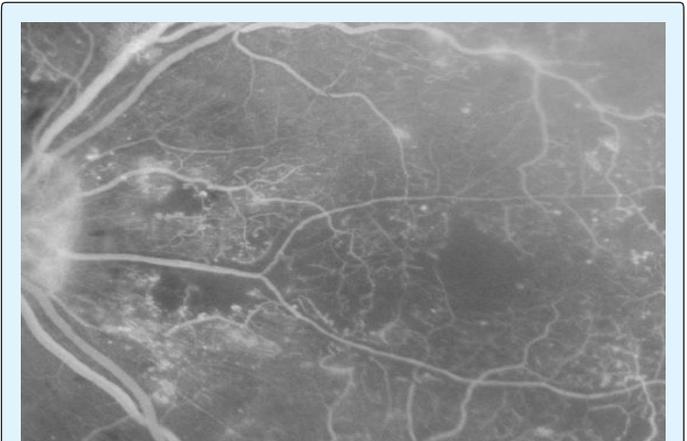


Figure 4: Shows enlarged FAZ and capillary loss and blockage.

### Non-Vascular Element

Not all macular thickening in diabetic patients are originated from vascular elements sometimes non-vascular element can cause macular thickening and visual loss, the most common non vascular element is vitreomacular abnormality which cause macular traction. Macular traction can be presented as anterior posterior traction due to liquefied core vitreous or tangential

traction which can feature either epiretinal membrane due to vitreoschisis, or taut vitreous due to glial cell proliferation or contracted lamellae. These vitreomacular abnormalities are governed by several mechanisms such as non-enzymatically cross linking of vitreous collagen along with glial cells and inflammatory cells infiltration and deposition of glial fibrillary acidic protein and cytokeratin.

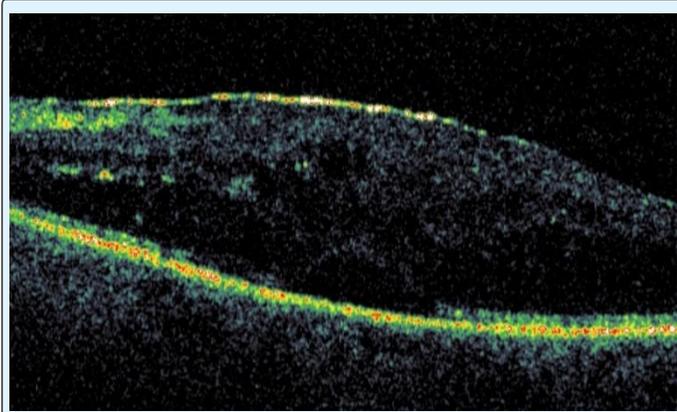


Figure 5: Shows macular thickening due to vitreomacular thickening with focal disturbance of inner retinal layers.

The best way to diagnose vitreomacular abnormality is by OCT showing focal disturbance of inner retinal layers (Figure 5) however clinically in the absence of vascular element and presence of vitreomacular abnormalities, treatment with VEGF blockade agents, intravitreal steroids and laser may not reduce macular thickening and improve vision, as this abnormality should be addressed surgically by performing pars plana vitrectomy with ILM peeling in cases of moderate visual loss [13].

## Diabetic Retinopathy

The metabolic and retinal microenvironment causes pericytes, endothelium and capillary damage due to agglutinated erythrocyte and thrombus, all that forms hyper cellular sacs in the capillary wall and thus forms micro aneurysms which is the main feature of non-proliferative stage of diabetic retinopathy as this process progress more micro aneurysms forms and retinal tissue reaches state of relative ischemia and thus will trigger VEGF production and interim will induce neovascularization which is the main feature of proliferative stage (Figure 6) which may lead eventually to vitreous hemorrhage or/ and tractional retinal detachment and blindness (Figure 6).

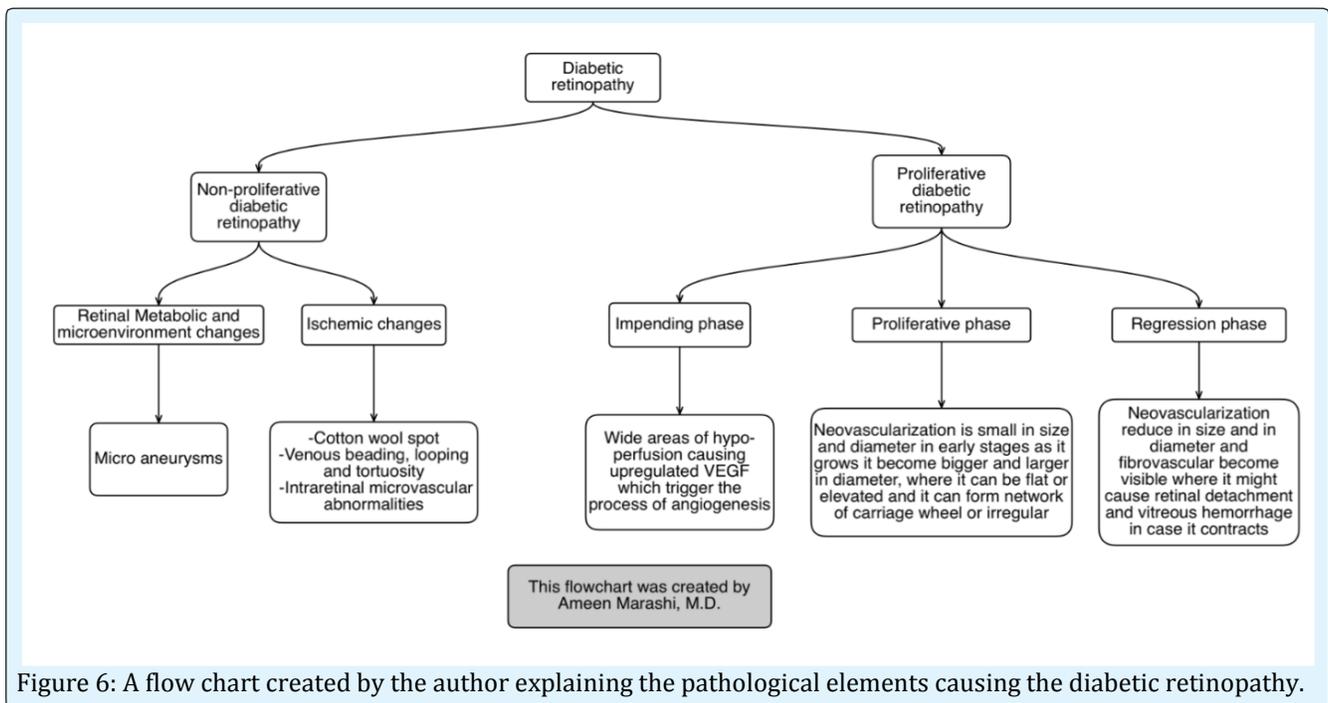


Figure 6: A flow chart created by the author explaining the pathological elements causing the diabetic retinopathy.

### Non-proliferative stage

In non-proliferative stage the main features are:

*Microaneurysms* formed from hyper-cellular sacs in the capillary wall and as the disease progress they increase in number and retinopathy become more severe (Figure 7).



Figure 7: Intra retinal Microaneurisms.

**Cotton-Wool spots:** Ischemia causes cystic bodies changes in the RNFL and interim will cause swelling RNFL ends with neural deposits and thus will form cotton-wool spots (Figure 8) *Venous beading*, looping and tortuosity, may proceeds proliferative stage as ischemia increases (Figure 9). *Intraretinal microvascular abnormalities (IRMA)* is a shunt runs from retinal arteriols to venule bypassing capillary bed, usually associated next to retinal ischemia (Figure 10).

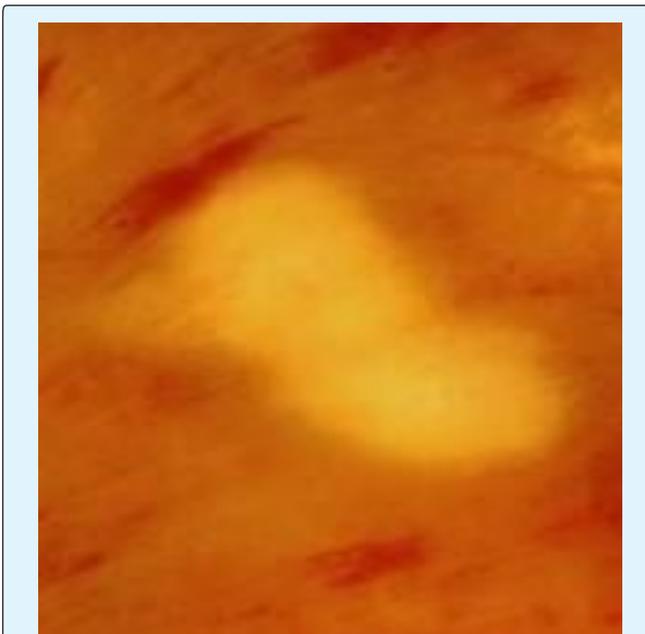


Figure 8: Cotton wool spots.



Figure 9: Venous looping.



Figure 10: Intraretinal microvascular abnormalities (IRMA).

### Proliferative stage

The proliferation has a cycle of three phases

**The impending phase:** VEGF is upregulated when the retinal tissue reaches the state of relative ischemia and thus initiates the process of angiogenesis, in this stage level of VEGF concentration is high in the vitreous [14], and this can be noted clinically as areas of hypo perfusion on fluorescein angiograms (Figure 11).

**The proliferative phase:** Neo-vessels are developed as process of angiogenesis began, in it is early stages neo vessel is hard to see but as it matures, the diameter enlarges to reach  $\frac{1}{4}$  of retinal vein diameter [15] in which it drains, neo vessels can grow in different patterns (irregular or as network forming carriage wheel), positions (flat, or anchored to the posterior hyaloid) and speed (fast or slow) (Figure12).

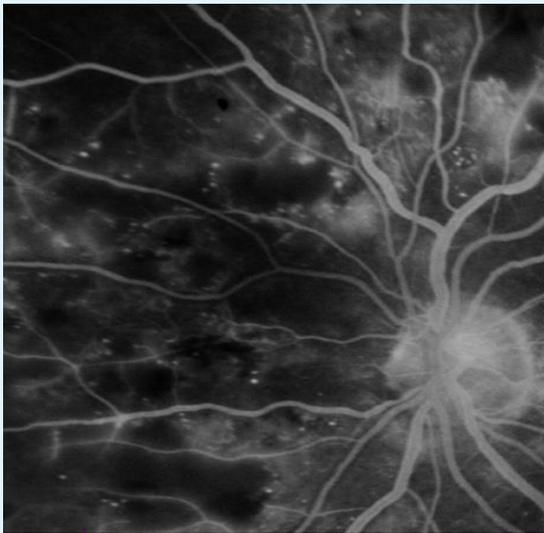


Figure 11: Fluorescein angiogram shows areas of hypo perfusion and capillary dropout.



Figure 12: Retinal Neovascularization with hemorrhage.

**The regression stage:** Neo vessel appears stripped in its early stages as it starts to regress and reduce its diameter (Figure 13),

fibrovascular membrane becomes more visible forming fibrovascular tissue which may contract causing traction retinal detachment in the areas of fibrovascular tissue attachment with posterior hyaloid [16].

Vitreous hemorrhage is one of the most common complications of the proliferative stage and it is induced by contraction of fibrovascular tissue or spontaneous bleeding [17].

Clinically non proliferative diabetic retinopathy is monitored by glycemic control while proliferative diabetic retinopathy requires pan retinal photocoagulation treatment in the absence of diabetic macular edema while in the presence of diabetic macular edema, VEGF blockade agents can be introduced to address both macular edema and proliferation and pan retinal photocoagulation treatment can be deferred to patients who are hard to follow up or treatment failure [18], however surgical management in cases of proliferative diabetic retinopathy is reserved for cases of tractional retinal detachment involving or threatening the macula and in cases of non-clearing vitreous hemorrhage.



Figure 13: Regressed Neovascularization.

## Conclusion

Pathology of diabetic macular edema and retinopathy is multifactorial, understanding the involving factors is important, to individualize the treatment for every patient by targeting the underlying mechanism, sometimes the one or more mechanism is involving and sometimes the pathology changes the mechanism from one form to another. Diabetic macular edema can be caused by vascular element or non-vascular element; however non-proliferative diabetic retinopathy features mainly microaneurysms due to metabolic changes while proliferative diabetic retinopathy is caused by upregulated VEGF triggering the process of angiogenesis.

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