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Revisiting pars plana vitrectomy in the primary treatment of diabetic macular edema in the era of pharmacological treatment

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Abstract:

Diabetic macular edema (DME) is the most common cause of moderate visual loss in diabetic patients. The current treatment of choice for center-involved DME is anti-vascular endothelial growth factor (VEGF) treatment. Most patients that undergo pharmacological inhibition with anti-VEGF agents need multiple monitoring visits that include optical coherence tomography imaging and multiple injections. Despite this intensive treatment, up to 60% of eyes will have persistent DME after six consecutive monthly injections of an anti-VEGF. Its sustainability over the long term has been questioned. Pars plana vitrectomy (PPV) by increasing the vitreous cavity oxygenation, relieving vitreomacular traction, and removing cytokines from the vitreous cavity may cause long-term resolution of DME without the aforementioned concerns in selected cases. Eyes with vitreomacular traction clearly benefit from PPV as the primary treatment. The role of PPV for eyes with DME without tractional elements is less clear and needs to be explored further.

Keywords:

Aflibercept, bevacizumab, diabetic macular edema, laser photocoagulation, oxygen, pars plana vitrectomy, ranibizumab, vascular endothelial growth factor, vitreomacular traction

Introduction

The global prevalence of diabetes mellitus (DM) has reached epidemic proportions, and there appears to be no end in sight. According to estimates of the International Diabetes Federation, in 2015, there were anywhere from 340 million to 536 million people affected with DM in the world. By 2040, it is estimated that this number will increase to 521 million to 829 million people. DM is no longer a disease of rich, developed countries. Three-quarters of diabetic patients live in developing countries.[1] All of these individuals will be at risk of developing diabetic retinopathy (DR).

If left untreated, patients with DR can suffer severe visual loss.[2] In developed countries, DR constitutes the leading cause of blindness in the working-age population[3] and has a considerable economic impact on the society, especially on health-care systems.[4-6] Since the introduction of panretinal photocoagulation into routine clinical practice, the rate of severe visual loss has dropped tremendously in developed countries. Diabetic macular edema (DME) remains the most common cause of moderate visual loss in diabetic patients.[7]

Current Treatment

Several recent randomized clinical trials have shown that anti-vascular endothelial growth factor (VEGF) agents outperform macular laser photocoagulation (MLP) in the treatment of center-involved DME.[8-12] Regardless of the anti-VEGF agent chosen,

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up to 40% of eyes treated with these drugs can gain ≥3 lines of best-corrected visual acuity (BCVA).[8,13] These results have changed the treatment algorithm of DME. Currently, anti-VEGF drugs are the preferred first-line treatment of center-involved DME.

To achieve the complete benefits of anti-VEGF therapy, most eyes require multiple monitoring visits and injections over the years.[8] Most patients, in both developed and underdeveloped countries, are undertreated for a variety of different reasons and do not achieve the full potential of anti-VEGF therapy.[14,15] Despite this intensive treatment, up to 60% of eyes will have persistent DME after six consecutive monthly injections of an anti-VEGF.[16] Although relatively safe, intravitreal injections are not without risk. The calculated cumulative risk of endophthalmitis after 20–40 injections has been calculated to be around 1%.[17] There are also economic considerations. Pharmacological treatments are expensive and represent an important economic burden.[18] Smiddy[18] analyzed the economic costs of the different treatments available for DME. Not surprisingly, anti-VEGF therapy is very expensive. The multiple visits and injections impose a burden on the caretakers, health systems, and patients themselves. In many parts of the world, particularly in developing countries, chronic anti-VEGF therapy for DME is not sustainable in the long term. A cost-effective alternative with a less intensive resource use is needed. Pars plana vitrectomy (PPV) has been explored as such an alternative therapy.

The Vitreous and the Pathophysiology of Diabetic Macular Edema

The pathogenesis of DME is complex and multifactorial. DME may be caused or exacerbated by both anteroposterior and tangential tractional forces on the macula.[19-21]

The vitreous has been suggested to play a role in the pathogenesis of DME since the 1980s.[22-24] Prior to the invention of optical coherence tomography (OCT), precise clinical evaluation of the vitreous was difficult due to its transparency. The El Bayadi-Kajiura lens was designed to evaluate the vitreous during slit-lamp biomicroscopy but was not widely employed.[25] Harbour *et al*.[26] noted that even with a fundus contact lens examination, it was very difficult to assess the status of the vitreomacular interface (VMI). In their series of ten eyes that presumably had a thickened and taut posterior hyaloid, during vitrectomy surgery, they discovered that in three eyes, there was no evidence of a thickened and taut posterior hyaloid. In fact, a posterior vitreous detachment (PVD) as well as an epiretinal membrane (ERM) was present. Ghazi *et al*.[27] reported that time-domain OCT was much more sensitive in detecting abnormalities of the vitreoretinal interface than regular biomicroscopic examination. This underscores the valuable contribution of OCT imaging in evaluating the status of the VMI.[20]

Nasrallah *et al*.[23] were the first to suggest that the vitreous may be implicated in the pathogenesis of DME. They used the El Bayadi-Kajiura lens to compare the rate of PVD in the eyes of diabetic patients older than 60 years with DME to those without DME. They found that PVD occurred in 20% of patients with DME as opposed to 55% in those without DME, suggesting that the attached posterior hyaloid might be exerting traction on the macula and contributing to the DME.[23] Gandorfer and Kampik[28] corroborated this finding in their clinical series of 61 eyes that underwent PPV with internal limiting membrane (ILM) peeling. Intraoperatively, they found that 11% of eyes had a PVD compared to 89% where the hyaloid was still attached. Hikichi *et al*.[29] prospectively followed a cohort of eyes with DME for 6 months. In this group of patients, 55% of cases had spontaneous resolution of their DME upon posterior vitreous separation. In contrast, only 25% of cases without PVD had DME resolution.

The VMI is altered in diabetic patients. Chronic hyperglycemia causes nonenzymatic glycation of the vitreous collagen fibrils, which leads to abnormal crosslinking. Breakdown of the blood–retinal barrier allows cytokines to concentrate in the vitreoretinal interface.[21] These cytokines may stimulate the migration of cellular elements with contractile properties into the posterior hyaloid thickening, inducing destabilization of the collagen matrix and leading to tangential traction and macular edema.[26,30-32] Surgical specimens from eyes with a taut and thickened posterior hyaloid have been examined under an electron microscopy and found to be infiltrated with cellular elements of epithelial and glial origin.[33] In addition to the posterior hyaloid, ERMs and the ILM may also cause traction.[34,35] The ILM is composed in part by Müller cell footplates. Histological examination of the ILM in diabetic patients has shown it to be much thicker than that in nondiabetic eyes.[34] Some have proposed that in addition to its tractional mechanical effect on the macula, the ILM serves as a physiologic diffusion barrier that impairs water and cytokine movements, contributing to the formation of DME.[36,37]

Depending on the series examined and the OCT machine used, abnormalities in the VMI can occur in up to 75% of eyes with DME.[38] Vitreomacular traction has been reported to occur anywhere from 4% to 25% of eyes with diffuse DME.[38-40] Extrafoveal traction may be present in up to 34.5% of eyes.[38,40] Up to 22.4% of the eyes may exhibit an ERM.[38] Anywhere from 24.1% to 75% of eyes did not

have any VMI abnormalities.[38,40] In a Taiwanese study,[41] the prevalence of VMI abnormalities was 6.6% and the incidence was 4.42%/year. In this study, they excluded patients with severe DME. Age was the only variable associated with VMI abnormalities. A retrospective, cross-sectional observational study of 198 eyes from the United Kingdom used spectral domain-OCT (SD-OCT) to report that 27% of treatment-naive eyes scheduled for MLP had an ERM or partial vitreomacular separation. Chang *et al*.[42] retrospectively reviewed 201 eyes with DME that did not have any VMI abnormalities at baseline and went on to receive intravitreal anti-VEGF therapy. They found that VMI abnormalities developed in almost 22% of their cohort. They estimated the incidence of VMI abnormalities to be 6.43%/year.

There is a controversy as to whether or not the presence of VMI abnormalities diminish the efficacy of intravitreal drugs in eyes with DME. Some investigators report that the presence of VMI abnormalities did not adversely affect the results of intravitreal anti-VEGF agents.[42,43] In contrast, other investigators have reported a decreased efficacy of anti-VEGF drugs in eyes with DME and concomitant ERM.[44]

PPV eliminates traction by removing the posterior hyaloid, ERMs, and ILM. In addition, PPV may also eliminate DME through nonmechanical means. Hypoxia is a major driver of VEGF secretion, thus alleviation of hypoxia causes VEGF downregulation.[45] Because PPV increases the oxygen concentration in the vitreous cavity,[46] it may also downregulate VEGF secretion. PPV increases the oxygen concentration of the vitreous cavity. In the normal nonvitrectomized rabbit eye, an oxygen gradient exists within the vitreous cavity.[46] Vitrectomy significantly increases the intravitreal oxygen concentration and eliminates the intravitreal oxygen gradient normally found in nonvitrectomized eyes.[46,47] The highest concentration of oxygen is found near the retinal surface, whereas the lowest concentration of oxygen is located in the anterior vitreous just posterior to the center of the lens. The presence of the antioxidant ascorbate in the vitreous cavity and the structure of the vitreous gel contribute in maintaining this relative hypoxic milieu.[48] Normally, oxygen diffuses from the retinal arteries into the adjacent avascular vitreous. The gelatinous structure of the vitreous prevents wide diffusion of oxygen. Diffusion is inversely related to the viscosity of the medium. The vitreous is much more viscous than saline.[49] Before the oxygen gets a chance to diffuse widely, it is consumed by the ascorbate. Removal of the vitreous gel removes ascorbate and decreases its viscosity, allowing mixing and uniform distribution of oxygen in the vitreous cavity fluid.[50] PPV eliminates this oxygen concentration gradient by elevating the oxygen tension in the anterior vitreous.[46] Holekamp *et al*.[47] reported similar findings in humans. A higher concentration of oxygen may also lead to retinal vasoconstriction, which, in turn, decreases the macular thickness.[51] Another mechanism by which PPV may reduce DME involves retinal blood flow. It is well known that chronic hyperglycemia impairs autoregulation of retinal blood flow.[52] In diabetic eyes with clinically significant DME, it has been shown that the perifoveal blood flow velocity was reduced in comparison to diabetic eyes without clinically significant DME and further reduced in nondiabetic eyes.[53] Kadonosono *et al*.[54] calculated the preoperative and postoperative perifoveal capillary blood flow velocity of 11 eyes with DME that were subjected to PPV. Following surgery, they found that the perifoveal capillary blood flow velocity increased, and this increase was correlated with the improvement in visual acuity. Finally, PPV clears the vitreous cavity of cytokines and allows a faster clearance of newly secreted cytokines such as VEGF.[55] In vitrectomized rabbit eyes, the vitreous VEGF's half-life was ten times shorter than that in nonvitrectomized rabbit eyes.

Pars Plana Vitrectomy

Thickened and taut posterior hyaloid

In 1992, Lewis *et al*.[19] reported that in certain diabetic eyes, a taut and thickened posterior hyaloid-exerted macular traction was responsible for DME. They speculated that tangential macular traction could lead to a shallow macular detachment. The DME in these patients did not respond to the conventional MLP. A PPV with stripping of the posterior hyaloid allowed the resolution of the DME with a concomitant improvement of visual acuity in six of ten eyes.[19] Pendergast *et al*.[56] reported on the outcomes of a retrospective case series of 55 eyes with diffuse DME and a taut premacular posterior hyaloid that underwent PPV and posterior hyaloid separation. The mean postoperative visual acuity improved from 20/160 at baseline to 20/80. About half of the eyes in this series attained an improvement of at least two lines of visual acuity; 82% of eyes had a complete resolution of DME at a mean of 4.5 months. They identified macular ischemia and a baseline BCVA of $\leq$20/200 as poor prognostic factors.[56] Upon the introduction of the OCT into clinical practice, Kaiser *et al*.[20] confirmed the presence of a foveal detachment in eyes with a taut and thickened posterior hyaloid. Relief of traction by PPV allowed macular reattachment with an ensuing improvement in visual acuity.[20]

The DRCR.net conducted a prospective observational study of 87 eyes with DME and vitreomacular traction that underwent PPV.[57] Most of the eyes underwent PPV after failing prior therapies for DME. Even though most eyes had an improvement in macular thickness,

this was not reflected in the visual outcomes. They reported that only 38% of the eyes had a gain of ≥10 letters but 22% lost ≥10 letters. There were several weaknesses of the study. The assessment of the presence or absence of vitreomacular traction was made clinically by an individual investigator without any standardized criteria. The surgical technique used was not uniform, reflecting the heterogeneity of the cohort and the surgical preferences of the investigators. ERMs were peeled in 60% of eyes and the ILM in 54%. A variety of visualizing agents, including indocyanine green (ICG), triamcinolone, and trypan blue, were used. A few eyes (5%) received focal or grid MLP intraoperatively. In a third of eyes, panretinal photocoagulation was performed. In two-third of eyes, a corticosteroid was injected at the end of the case. Two-thirds of the cohort had proliferative DR. Macular ischemia was not assessed, so conceivably, this cohort of patients may have had limited potential for visual improvement.[57]

Attached posterior hyaloid without thickening or traction

In 1996, Tachi and Ogino[58] reported that PPV was effective in resolving DME with a concomitant improvement in visual acuity even in the absence of a taut and thickened posterior hyaloid. They reasoned that even without a taut and thickened posterior hyaloid, an attached hyaloid could still exert traction and contribute to DME formation. In their series of 58 eyes, none of the eyes had a PVD. Following vitrectomy and posterior vitreous separation, the DME resolved in 98% of eyes. La Heij *et al*.[59] reported similar results. In their series of 21 eyes with an attached posterior hyaloid, the DME resolved in all the eyes at a mean of 3 months after PPV and posterior hyaloid delamination. In both of these studies, the determination of DME was assessed with biomicroscopy and fluorescein angiography. OCT imaging was not available. La Heij *et al*.[59] noticed that eyes that had prior MLP did not achieve as good visual results as their counterparts that did not have prior MLP. In contrast, Thomas *et al*.[60] concluded that PPV offered little in terms of improved visual acuity or reduction in macular thickness in eyes with DME that had had previous MLP and had an attached posterior hyaloid without evidence of vitreomacular traction. They recommended continuing MLP.

Detached posterior hyaloid and epiretinal membranes

It is unclear how an ERM affects DME. In a small series of thirty eyes, visual acuity and retinal thickness improved regardless of the presence or absence of an ERM or the presence or absence of a PVD, suggesting that ERM plays a small role if at all in the pathogenesis of DME.[61] Ghassemi *et al*.[62] conducted a prospective, noncomparative study of 12 eyes with DME with a concomitant nontractional ERM that were unresponsive to intravitreal bevacizumab and triamcinolone. These eyes underwent PPV, membrane peel, and ILM removal. They reported that despite an improvement in central macular thickness, the BCVA did not improve much. In contrast, the DRCR.net reported that one of the two factors associated with an improvement in visual acuity following PPV was ERM removal.[63]

Detached posterior hyaloid without vitreomacular interface abnormalities

In eyes without any elements of traction, PPV was reported to be beneficial as well. Ikeda *et al*.[64] described five eyes with DME and a detached posterior hyaloid that had a clinical improvement in their condition following PPV. Even in eyes with advanced and severe DME, PPV improved the anatomic outcomes.[65] In contrast, Massin *et al*.[66] reported that in eyes without vitreomacular traction that were unresponsive to MLP, PPV was not beneficial.

Some have proposed that in eyes without obvious vitreomacular traction, the ILM may exert macular traction.[67] Furthermore, the ILM can serve as a scaffold for ERM formation.[68] Because up to 10% of eyes developed recurrent DME and ERM formation after vitrectomy,[56,58] Gandorfer *et al*.[69] recommended ILM removal during PPV. In a retrospective review of 73 eyes, 18 eyes underwent PPV and 55 had PPV plus ILM peeling. Both group of eyes experienced DME resolution, but there was a greater DME resolution in the eyes that had the ILM peeled.[70]

There are only a handful of randomized clinical trials involving PPV for DME. All of these suffer from small numbers and a relatively short follow-up.[60,71-75] All of them were conducted in the MLP era. Most of these studies recruited patients who had persistent or recurrent DME despite prior MLP.[60,72] Several systematic reviews and meta-analyses have been reported over the years.[76-79] Simunovic *et al*.[77] identified 11 studies that met their inclusion criteria. Seven of the studies compared PPV to the natural history of DME,[72,75] MLP,[60,73,74] or intravitreal triamcinolone.[80] The other four studies compared PPV to PPV plus ILM peeling.[37,81-83] Hu *et al*.[78] looked at 14 studies[37,70,82-88] that compared PPV alone to PPV plus ILM peeling. Rinaldi *et al*.[79] performed a similar meta-analysis of four studies.[82,85,89,90] Jackson *et al*.[76] included five randomized clinical trials[60,71-74] in their review. All of these five studies were also included in Simunovic *et al*.'s[77] meta-analysis. According to these reviews, PPV did not offer any visual benefits over MLP or observation despite improvements in retinal thickness.[76,77] It remains unclear if ILM peeling confers a visual benefit over plain PPV.[78,79] The addition of

ILM peeling does appear to cause a better resolution of increased macular thickness than PPV.[78,79] Patel *et al*.[90] raised the issue of possible ultrastructural damage to Müller cells in eyes that undergo ILM peeling. In addition, one cannot rule out intraocular toxicity caused by the ICG used to stain the ILM.

Harbour *et al*.[26] emphasized the importance of prompt surgical treatment because eyes with long-standing DME could develop outer-retinal atrophy. Given the success of pharmacological therapy in the treatment of DME, most physicians will continue injecting for several months before deciding that the eye is not responding appropriately. Repeated injections allow a delay in changing tactics, leading to a long duration of chronic DME prior to PPV consideration. By the time PPV is considered, irreversible photoreceptor damage may already have occurred. Visual improvement would not be expected in these eyes. Currently, it is a common practice to consider PPV when all else have failed.[57]

Michalewska *et al*.[91] performed PPV on 44 consecutive patients with treatment-naive DME. They reported that over half of the patients experienced an improvement of ≥3 lines of BCVA and only 2% lost ≥3 lines of BCVA. They identified the presence of a preoperative ERM, duration of DM, and poor baseline visual acuity as factors associated with a poor postoperative visual acuity. DME recurrence occurred in only 7% of eyes. These results are encouraging and suggest that earlier intervention with PPV may be beneficial, but need to be replicated in larger prospective controlled trials.

Prognostic factors associated with a greater visual gain following PPV include no history of prior MLP,[59] lower hemoglobin A1c,[70] worse baseline visual acuity,[63] and ERM removal during surgery.[63] Factors associated with a greater decrease in macular thickness include ILM peeling, the presence of VMI abnormalities, worse baseline visual acuity, and a greater baseline macular thickness.[63]

Although there is only a moderate correlation between macular thickness and visual acuity,[92] macular thickness has been used as a surrogate marker of success in practically all DME trials. It is time to look beyond plain macular thickness measurements. SD-OCT images permit the identification of the different retinal layers. SD-OCT should be used to screen and select the eyes most likely to benefit from PPV.[93]

SD-OCT may allow better stratification of eyes undergoing PPV for DME. Avci *et al*.[94] noted that eyes with the cystoid subtype of DME as well as the diffuse subtype of DME did not fare. In their series of 21 eyes, only 14% (1/7) of eyes with cystoid DME in comparison to 71% (10/14) of eyes with diffuse DME had an improvement of ≥2 lines of BCVA. Romano *et al*.[95] have warned against ILM peeling in eyes with large intraretinal cysts and an enlarged foveal avascular zone because there is a significant risk of causing subfoveal atrophy and visual loss. In a retrospective case series of 34 eyes, Chhablani *et al*.[93] identified the preoperative damage to the ELM as the strongest predictor for visual improvement. In contrast, baseline central macular thickness was a poor predictor [Figure 1]. Others have identified the presence of subretinal fluid as a favorable biomarker.[96,97]

Some investigators have argued against primary PPV for DME because they believe that intravitreal pharmacokinetics is altered following vitrectomy. Moreover, because some eyes have persistent or recurrent DME following PPV, this could represent a problem. However, our current armamentaria against DME include trans-tenon retrobulbar triamcinolone injections,[98] fluocinolone acetonide implant,[99] and dexamethasone implant,[100] all of which have been shown to be effective in vitrectomized eyes.

Complications reported in the 20G PPV era included retinal tears, rhegmatogenous retinal detachments, neovascular glaucoma, recurrent vitreous hemorrhage, lamellar macular hole, full-thickness macular hole,

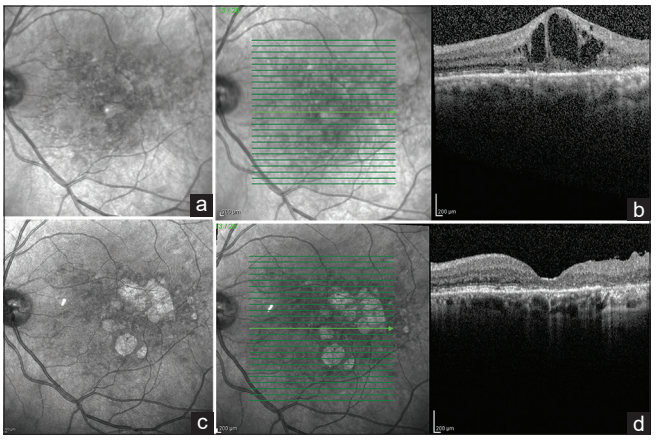

Figure 1: A 56-year-old woman with type 2 diabetes mellitus was diagnosed with center-involved diabetic macular edema in her OS. Her visual acuity at baseline was 20/150. She underwent six consecutive intravitreal injections of 1.25-mg bevacizumab, three intravitreal injections of ranibizumab, macular laser photocoagulation, and two injections of 4 mg of triamcinolone acetonide. Despite these treatments, her diabetic macular edema did not improve. She then underwent pars plana vitrectomy. Her diabetic macular edema resolved, but her visual acuity did not improve. (a) Pre-pars plana vitrectomy infrared reflectance image of the left eye. As this is a confocal image, notice that the image is out of focus. (b) Pre-pars plana vitrectomy spectral domain-optical coherence tomography of the left-eye foveal cut. Notice the intraretinal hyporeflective spaces and the discontinuation of the ellipsoid and external limiting membrane. (c) Post-pars plana vitrectomy infrared reflectance image of the left eye. The diabetic macular edema has resolved. Notice that the image is in focus, and the macular scars from the prior macular laser photocoagulation are clearly in focus. (d) Post-pars plana vitrectomy spectral-domain-optical coherence tomography of the left eye foveal cut. The macula has a normal foveal depression, but the ellipsoid and external limiting membrane are clearly missing

ERM formation, and deposition of hard exudates in the fovea.[51,65,76,101] Over the past two decades, improvements in surgical techniques and instrumentation have made PPV much safer. ILM peeling has been facilitated by chromovitrectomy. Nevertheless, complications may still occur with ILM peeling. Potential retinal toxicity with ICG dye must be taken into account as well.[102] Serious complications such as retinal detachment are estimated to occur in 1% of cases.[103]

Conclusion

In the quarter of a century since the Lewis *et al.*'s[19] initial report on the benefit of PPV in eyes unresponsive to MLP, several changes have occurred in the management of DME and in the general clinical practice of vitreoretinal diseases. OCT has largely replaced fluorescein angiography as the macular imaging modality of choice. Intravitreal anti-VEGF drugs have replaced MLP as the first-line treatment of center-involved DME. Improvements in surgical techniques and instrumentation have made PPV much safer as vitreoretinal surgeons have mostly abandoned 20G PPV and migrated to smaller gauge platforms. The published literature on vitrectomy for DME must be viewed under this context.

PPV could alleviate DME through multiple mechanisms. These mechanisms include elimination of tractional elements, improvement of intravitreal oxygenation, removal of pathological cytokines from the vitreous cavity, and acceleration of the half-life of intravitreal cytokines.[19-21,46,55]

Certain subtypes of DME, namely eyes with vitreomacular traction, clearly benefit from PPV as primary treatment. The role of PPV for eyes with DME without tractional elements is less clear. Most meta-analyses and reviews of the literature suggest that PPV does not offer any additional functional benefit over other treatment modalities. However, these reviews were based on eyes that had previously failed MLP and had had persistent DME for a long time. Eyes with a shorter disease course may fare better with PPV as primary treatment and not as salvage treatment.[91] PPV should not be relegated as a last recourse in the management algorithm of DME. At the very least, a well-designed clinical trial should be performed to test this hypothesis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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