

REVIEW

Systemic Risk Factors in Branch Retinal Vein Occlusion: a Comprehensive Review

Christina GARNAVOU-XIROU^{a, b}, Georgios BONTZOS^a,
Georgios SMOUSTOPOULOS^a, Stavros VELISSARIS^a, Alexandros PAPADOPOULOS^a,
Efsthios GEORGOPOULOS^a, Panagiotis STAVRAKAS^b,
Constantinos GEORGAKOPOULOS^b, Tina XIROU^a, Vasileios KOZOBOLIS^b

^aDepartment of Ophthalmology, Korgialenio-Benakio General Hospital, Athens, Greece

^bDepartment of Ophthalmology, University Hospital of Patras, Patras, Greece



ABSTRACT

Background: Retinal vein occlusion (RVO) is a major cause of vision impairment globally. Obstruction in the retinal venous system is often due to thrombus formation at arteriovenous crossing points, leading to symptoms localized to the affected retinal area. Systemic conditions like hypertension, diabetes mellitus, dyslipidemia and heart disease are recognized risk factors for RVO, influencing the components of Virchow's triad.

Objective: This work aims to provide an updated overview of systemic risk factors associated with branch retinal vein occlusion (BRVO) development and to explore management options for the prevention or modification of associated risks.

Methods: Review of the literature concerning the pathogenesis and risk factors of BRVO, including diabetes mellitus, hyperlipidemia, hematologic conditions, hormonal factors, thyroid disease, and the impact of COVID-19 and related vaccines on BRVO incidence.

Results: Diabetes mellitus contributes to BRVO through mechanisms like endothelial dysfunction and thrombogenesis. Hyperlipidemia – through lipid-mediated vascular changes – and hematologic conditions – by predisposing to hypercoagulability – significantly increase BRVO risk. Hormonal imbalances and thyroid diseases also influence BRVO development through their effects on vascular and hemostatic systems. Furthermore, COVID-19 has been identified as a potential risk factor for BRVO, possibly due to its pro-thrombotic effects.

Conclusion: Branch retinal vein occlusion represents a complex interplay of systemic and local vascular factors, necessitating comprehensive management strategies. Early detection and modification of risk factors is crucial for preventing vision impairment associated with BRVO. The ongoing pandemic and its systemic implications underscore the importance of continued research into the multifactorial etiology of BRVO and optimization of management strategies to improve patient outcomes.

Keywords: BRVO, vein occlusion, risk factors, diabetes, hypertension.

Address for correspondence:

Georgios Bontzos, MD, PhD

Postal address: Korgialenio – Benakio General Hospital, Atanasaki 11, 11526, Athens, Greece

Tel: +2132068754; email: gbontzos@hotmail.gr

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ABBREVIATIONS

RVO: retinal vein occlusion

BRVO: branch retinal vein occlusion

CRVO: central retinal vein occlusion

COVID-19: coronavirus disease 2019

INTRODUCTION

Branch retinal vein occlusion (BRVO) is a significant cause of vision impairment worldwide, ranking as the second leading cause of blindness resulting from retinal vascular diseases (1). Globally, over 20 million individuals suffer from BRVO, a figure expected to rise due to population aging (1, 2). Advancing age is a recognized risk factor for BRVO, suggesting an inevitable increase in the incidence of this condition (3, 4). The impact of BRVO extends beyond the individual, affecting the quality of life and imposing significant economic burdens on society.

Retinal occlusion encompasses two primary forms: BRVO and central retinal vein occlusion (CRVO), with BRVO showing a prevalence between 0.5% and 2.0%, while CRVO is less common, with a prevalence ranging from 0.1% to 0.2% (5). The obstruction in the retinal venous system, which is the hallmark of RVO, can be attributed to thrombus formation. This blockage might occur in the central, hemi-central, or branch retinal vein, often resulting from compression by adjacent sclerotic retinal arteries, external forces, or diseases affecting the vein wall such as vasculitis (6).

Virchow's triad, which includes endothelial injury, abnormal blood flow and hypercoagulability, has been instrumental in understanding the predisposition to thrombosis, including RVO. Conditions such as hypertension, diabetes mellitus, dyslipidemia and heart disease, which influence the components of Virchow's triad, have been linked to an increased risk of RVO in various studies (7-10). However, the role of hypercoagulability as a risk factor for RVO, especially its differential impact on BRVO *versus* CRVO, remains a topic of ongoing research and debate (11-14).

The management and understanding of RVO requires a comprehensive approach that considers the various risk factors, including systemic conditions that may predispose individuals to

this vascular occlusion. As the prevalence of BRVO is notably higher than that of CRVO and given the aging global population, the need for effective screening, prevention and treatment strategies is more critical than ever (15). Such efforts are essential not only for mitigating the immediate effects of RVO on vision but also for addressing the broader social and economic implications of this condition. The purpose of the present work is to provide a comprehensive update on the systemic risk factors associated with BRVO development and explore management options associated with the prevention or modification of associated risks. □

METHODS

We looked through PubMed and Google Scholar databases for articles published between January 2010 and January 2024, using the following query terms: (retinal vein occlusion) OR (BRVO) AND (risk factors). We found 620 articles. After abstract screening, all articles that were not available in English, all studies on animals, *in vitro* models were excluded. For the purpose of the review, we also included systematic reviews and meta-analyses. In total, 157 articles focusing on the systemic risk factors for BRVO were further considered for analysis. □

RESULTS

Several risk factors were found, as described below.

Hypertension

The role of hypertension as a primary factor in the pathogenesis of BRVO is complex and multifaceted, implicating various mechanistic pathways that contribute to vascular compromise within the retinal circulation. The retinal vasculature is uniquely susceptible to systemic blood pressure alterations due to its autoregulatory capacity designed to maintain constant blood flow despite fluctuations in the systemic arterial pressure (16, 17). Chronic hypertension challenges this autoregulation, leading to structural and functional changes in the retinal arterioles, including wall thickening, luminal narrowing and increased vascular tone. These alterations exacerbate the vascular shear stress and contribute

to endothelial dysfunction, a pivotal early event in the pathogenesis of BRVO (18, 19).

Endothelial cells, lining the interior surface of blood vessels, play a critical role in maintaining vascular homeostasis by regulating blood flow, thrombosis and inflammatory responses. Hypertension-induced endothelial dysfunction is characterized by a diminished production of nitric oxide (NO), a potent vasodilator, and an increased expression of endothelial adhesion molecules, promoting leukocyte adhesion and migration. This dysfunctional state favors a pro-thrombotic and pro-inflammatory milieu, conducive to the formation of venous thrombi at arteriovenous crossing sites where the retinal vein is compressed by a sclerotic arteriole (16).

Furthermore, hypertension accelerates the process of arteriolosclerosis, leading to the thickening of arteriolar walls and contributing to the mechanical compression of the adjacent veins. This compression, particularly at arteriovenous crossings where the shared adventitial sheath is present, is a critical mechanical factor in the development of BRVO. The resulting venous stasis, coupled with endothelial injury and a hypercoagulable state, fulfills the criteria of Virchow's triad for thrombus formation (20). Although there is not a direct correlation between arterial pressure values and risk for BRVO development, research has shown that the severity of hypertension has a significant impact on the associated risk. Complicated hypertension has a three-fold increased risk for BRVO development compared to uncomplicated cases (20).

Diabetes mellitus

A large meta-analysis has previously revealed that there was no significant association between diabetes mellitus (DM) and BRVO, as opposed to CRVO (21, 22). However, there is gathering evidence that DM has a significant role in BRVO pathogenesis (23). Hyperglycemia, which is at the core of diabetes-related vascular complications, instigates a cascade of biochemical disruptions leading to endothelial dysfunction and microvascular damage. Persistent elevation of blood glucose levels promotes the non-enzymatic glycation of proteins and lipids, forming advanced glycation end products (AGEs) which engage with their receptor (RAGE) on endothelial cells, activating intracellular signaling pathways that foster vascular inflammation, increased per-

meability and thrombogenesis. These processes are instrumental in the pathophysiological progression toward BRVO, as they exacerbate endothelial cell injury and disrupt normal blood flow within the retinal venous system (24-26). Similarly to hypertension, the severity of diabetes is important. Patients with diabetes and systematic complications have an increased risk of developing BRVO (20).

Diabetes induces hemodynamic changes characterized by increased blood viscosity and altered blood flow dynamics, contributing to the venous stasis component of Virchow's triad. The hyperglycemia-induced upregulation of inflammatory mediators and pro-coagulant factors further predisposes individuals with diabetes to thrombosis within the retinal veins (27). Concurrently, oxidative stress plays a critical role in diabetic vascular disease. Similarly to hypertension, excessive production of reactive oxygen species (ROS) in DM impairs NO bioavailability, a crucial vasodilator, compounding endothelial dysfunction and promoting a pro-thrombotic state conducive to BRVO (28).

The intersection of diabetes and BRVO is further illuminated by the inflammatory pathways that underlie diabetic retinopathy, a common microvascular complication of diabetes. Pro-inflammatory cytokines, such as tumor necrosis factor- α (TNF- α) and interleukin-1 beta (IL-1 β), are elevated in the diabetic state, fostering an environment of vascular inflammation that can precipitate venous occlusive events (29). These cytokines, along with VEGF-driven vascular permeability, create a retinal milieu prone to the development of BRVO (30, 31).

Hyperlipidemia

Hyperlipidemia, characterized by elevated levels of lipids in the bloodstream, including cholesterol and triglycerides, has been implicated as a significant risk factor for BRVO (7, 32, 33). Unlike the mechanisms associated with hypertension and diabetes, which predominantly involve direct vascular and endothelial alterations, hyperlipidemia contributes to BRVO through lipid-mediated vascular changes and indirect effects on blood rheology and inflammatory pathways (34).

Hyperlipidemia facilitates the development of atherosclerotic plaques within the vasculature, including the retinal arterioles. Atherosclerosis in

the context of BRVO involves the accumulation of lipids within the vascular wall, leading to increased rigidity and narrowed lumen diameter (35, 36). These changes can exacerbate the mechanical compression at arteriovenous crossing points, a critical site for BRVO pathogenesis. The accumulation of lipids, particularly low-density lipoprotein (LDL) cholesterol and its oxidized forms (oxLDL), can directly injure the vascular endothelium, promoting an inflammatory response and contributing to the thrombogenic environment conducive to vein occlusion (37).

Hyperlipidemia impacts blood viscosity and platelet function, both of which playing crucial roles in the development of BRVO. Additionally, hyperlipidemia is known to enhance platelet aggregation and activation, further increasing the risk of thrombus formation within the retinal venous system (38). The interaction between lipids and the coagulation cascade, including the up-regulation of procoagulant factors and downregulation of fibrinolytic activity, accentuates the hypercoagulable state (39).

The role of inflammation in the pathogenesis of BRVO under hyperlipidemic conditions cannot be overstated. Lipids, especially oxLDL, are potent mediators of vascular inflammation, capable of activating macrophages and endothelial cells to release inflammatory cytokines and chemokines. This inflammatory milieu not only damages the vascular endothelium but also promotes the recruitment and adhesion of leukocytes to the vascular wall, exacerbating endothelial dysfunction and contributing to the sequence of events leading to venous occlusion (40).

Hematologic conditions

Hematologic conditions that predispose to hypercoagulability play a critical role in the pathogenesis of BRVO, presenting a complex interplay between clotting mechanisms and vascular integrity. These conditions, ranging from inherited thrombophilias to acquired disorders, contribute to an increased risk of thrombus formation within the retinal venous system.

Inherited conditions such as Factor V Leiden mutation, prothrombin G20210A mutation and deficiencies in natural anticoagulants like protein C, protein S and antithrombin III have all been identified as significant contributors to hypercoagulability and, by extension, to BRVO. These genetic variations alter the coagulation cascade,

tipping the balance toward thrombogenesis (41). Factor V Leiden, for instance, renders Factor V resistant to inactivation by activated protein C, leading to unchecked thrombin generation and fibrin clot formation. Such mutations can significantly increase the risk of venous thromboembolism in the systemic circulation and are implicated in the occlusion of retinal veins (42).

Acquired conditions such as antiphospholipid syndrome (APS), characterized by the presence of antiphospholipid antibodies like lupus anticoagulant, anti-cardiolipin and anti- β_2 glycoprotein I, also predispose individuals to thrombotic events, including BRVO. These antibodies promote thrombosis by interfering with the phospholipid-dependent steps of coagulation, activating endothelial cells and impairing the function of natural anticoagulants. The role of APS in retinal vascular occlusions highlights the complex interactions between autoimmune responses and coagulation pathways (43, 44).

The pathophysiological impact of hypercoagulable states on the retinal venous system involves both direct and indirect mechanisms. Directly, the propensity for clot formation within the retinal veins leads to venous occlusion and subsequent retinal ischemia. Indirectly, hypercoagulability can cause a secondary inflammatory response, further damaging the vascular endothelium and exacerbating the conditions conducive to BRVO. The resultant hypoxia and ischemia trigger compensatory mechanisms, including neovascularization, which can worsen the prognosis by leading to complications such as vitreous hemorrhage and tractional retinal detachment (45-47).

Hormonal factors

Estrogens and other sex hormones exert significant effects on vascular endothelial function. Estrogens, for example, have been shown to promote vasodilation through the enhancement of endothelial nitric oxide synthase (eNOS) activity, leading to increased production of NO, a potent vasodilator. However, the imbalance of hormones, either through natural menopause or other endocrine disorders, can lead to endothelial dysfunction, characterized by reduced NO availability and increased production of vasoconstrictors such as endothelin-1. This dysfunction predisposes to vascular occlusive diseases, including BRVO, by promoting a state of in-

creased vascular tone and susceptibility to thrombosis (48, 49).

The use of hormone replacement therapy (HRT), particularly estrogen-alone or estrogen-plus-progestin regimens, has been associated with an increased risk of thromboembolic events, including deep vein thrombosis and pulmonary embolism (49). The pro-thrombotic effects of HRT are attributed to alterations in coagulation factors, leading to increased levels of procoagulant factors (such as Factors VII and VIII, and fibrinogen) and decreased anticoagulant activity (e.g., protein S levels). These alterations may similarly contribute to the pathogenesis of BRVO by enhancing the propensity for thrombus formation within the retinal venous circulation (50, 51).

Oral contraceptives, which typically contain combinations of estrogen and progestin, have been implicated in altering the hemostatic balance and endothelial function, thereby contributing to thrombotic risks. Oral contraceptives induce a prothrombotic state through several hemostatic changes, including increased levels of coagulation factors (Factor VII, VIII, and X), reduced anticoagulant protein S levels, and enhanced platelet aggregability. These modifications contribute to a hypercoagulable state, predisposing to thrombus formation (52, 53). Estrogen components in oral contraceptives are known to affect endothelial health directly. While physiological estrogen levels support endothelial function and NO production, the pharmacological doses in contraceptives can have variable effects on endothelial integrity and vasomotor function, potentially leading to vascular constriction and increased vascular resistance (54). Hormones in oral contraceptives impact the renin-angiotensin system and endothelin-1 levels, both of which play critical roles in vascular tone regulation. Alterations in these systems can lead to vasoconstriction and impaired venous outflow, contributing to conditions favorable for BRVO development (55).

Thyroid disease

The relationship between thyroid disease and the development of BRVO encapsulates a nuanced interplay of metabolic, vascular and hemostatic factors inherent to thyroid dysfunction. Both hypothyroidism and hyperthyroidism exert profound effects on the cardiovascular system

and hemostasis, potentially influencing the risk of thrombotic events within the retinal circulation.

Hypothyroidism is associated with atherosclerotic changes, increased cholesterol levels and altered coagulation, all of which can contribute to vascular occlusive diseases. The hypothyroid state leads to increased levels of total cholesterol, LDL and possibly, lipoprotein (a), which are known risk factors for atherosclerosis. Additionally, hypothyroidism can induce a hypercoagulable state characterized by elevated fibrinogen levels and increased platelet aggregability, enhancing the propensity for thrombus formation. These changes, coupled with endothelial dysfunction, may contribute to the pathogenesis of BRVO by promoting venous occlusion in the retinal circulation (56, 57).

Conversely, hyperthyroidism is characterized by a state of enhanced metabolic rate leading to weight loss, increased blood pressure and a heightened risk of atrial fibrillation. The increased cardiac output and elevated systolic blood pressure in hyperthyroidism can exacerbate endothelial damage and contribute to vascular remodeling (58). Moreover, hyperthyroidism has been linked to alterations in coagulation parameters, including reduced levels of protein C and protein S as well as increased levels of von Willebrand factor, potentially contributing to a prothrombotic state. These hemodynamic and hemostatic changes may increase the risk of developing BRVO by promoting conditions conducive to venous stasis and thrombosis in the retina (59).

COVID-19

The emergence of COVID-19 as a global pandemic in 2020 has prompted extensive research into its systemic implications, including its association with the development of BRVO. Recent studies have elucidated the role of SARS-CoV-2, the virus responsible for COVID-19, in precipitating a pro-thrombotic state, attributable to direct viral effects and secondary inflammatory responses. The precise mechanisms remain under active investigation, but evidence suggests that COVID-19 facilitates thrombogenesis through the elevation of pro-thrombotic and inflammatory biomarkers such as von Willebrand factor, fibrinogen, ferritin and interleukin-6 (IL-6), alongside the augmentation of both innate

(e.g., complement system activation) and adaptive immune responses, and disturbances in the renin-angiotensin system. The hypercoagulable state associated with COVID-19 is characterized by increased D-dimer levels, prolonged prothrombin time, activated partial thromboplastin time and elevated fibrinogen and cytokine levels, collectively fostering the conditions conducive to RVO development, independent of traditional systemic risk factors.

Anecdotal evidence and case reports have begun to highlight a potential correlation between COVID-19 and BRVO. In 2023, Kapsis *et al* (60) reported a case involving a 65-year-old male who developed BRVO two days post-recovery from COVID-19, in the absence of other risk factors. Similarly, Duff *et al* (61) described the development of BRVO in a 74-year-old female, otherwise in good health, concurrent with a COVID-19 infection. Furthermore, a significant cohort study by Modjtahedi *et al* (62) revealed an uptick in the incidence of post-COVID retinal vein occlusions compared to the pre-pandemic era. The authors suggested that these findings might be attributable to secondary factors related to the pandemic, such as increased sedentary lifestyles, diminished management of systemic comorbidities like diabetes and hypertension and delays in seeking medical attention.

Parallel to the implications of SARS-CoV-2 itself, there has been speculative evidence regarding the potential role of COVID-19 vaccines in BRVO onset. Case reports include an instance published by Pur *et al* (63), detailing a 34-year-old healthy male who experienced BRVO two days following administration of the BNT162b2 mRNA vaccine. In a subsequent report, Gironi *et al* (64) documented a case of a 50-year-old male, with moderate risk factors, developing bilateral BRVO within 24 hours post-immunization with the mRNA-1273 vaccine. Efforts to establish a comprehensive understanding of the relationship between COVID-19 vaccines and BRVO have been undertaken by researchers such as Singh *et al* (65) and Feltgen *et al* (66), with the former identifying a weak temporal association and the latter finding no substantive link between vaccination and BRVO incidence. Recent evidence suggested that vaccines may induce thrombosis with thrombocytopenia in susceptible individuals. This novel syndrome, which has been termed 'vaccine induced thrombotic thrombo-

cytopenia' (VITT) by experts, leads to the formation of thrombi in sites such as arteries, cerebral sinuses and splanchnic veins, in persons carrying the anti-PF4 antibody (67). In addition to VITT, other proposed pathophysiological mechanisms of vaccine-induced BRVOs include the triggering of thrombi in individuals with retinal vasculitis and in those with a background of homocysteinemia (68). Despite the above evidence, the scarcity of available data in combination with the heterogenous nature of the various studies means that more research regarding the side-effect profile of COVID-19 vaccines is required, as it is vital to establish the risk-benefit profile, especially in susceptible individuals. ■

CONCLUSIONS

The profound impact of BRVO on global vision health cannot be overstated (5, 69). As a leading cause of vision impairment and the second most common retinal vascular disease leading to blindness, BRVO represents a significant public health challenge (1). The condition's prevalence, influenced by demographic trends such as an aging population, underscores an urgent need for comprehensive strategies encompassing early detection, risk factor modification and targeted treatment to mitigate its consequences.

The pathogenesis of BRVO is multifaceted, involving mechanical compression at arteriovenous crossings, endothelial dysfunction and a hypercoagulable state as delineated by Virchow's triad. These mechanisms highlight the critical role of systemic conditions such as hypertension, diabetes mellitus, hyperlipidemia and hematologic disorders in predisposing individuals to this occlusive vascular event (26, 33, 37, 38).

Emerging evidence also points to the contribution of less conventional risk factors, including hormonal imbalances, thyroid diseases and even the global pandemic of COVID-19, further complicating the BRVO risk landscape (60, 66). The early identification of BRVO is paramount for several reasons. Firstly, it allows for the initiation of timely and appropriate treatment strategies aimed at preserving or restoring visual function. Secondly, it provides an opportunity for the modification of underlying risk factors, potentially preventing the occurrence of BRVO in the contralateral eye or the development of other

vascular complications. Thirdly, early detection enables prompt referral to low vision services, ensuring patients receive the necessary support for lifestyle adjustments and minimizing the risk of secondary complications such as falls (70).

Given the potential for BRVO to lead to severe complications like retinal neovascularization, vitreous hemorrhage and tractional retinal detachment, the role of early intervention cannot be overstated. The evolving landscape of BRVO management, characterized by the integration of systemic and ocular treatment approaches, highlights the need for ongoing research to refine our understanding of its pathophysiology and optimize therapeutic strategies.

In conclusion, BRVO presents a complex clinical challenge that requires a proactive management approach. The interconnection between systemic health and ocular pathology in BRVO emphasizes the need for interdisciplinary collaboration in patient care. As we advance our understanding of BRVO's multifactorial etiology and harness the potential of innovative diagnostic and therapeutic modalities, the prospect of improving visual outcomes and quality of life for affected individuals remains promising. ■

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