Update on Gene Therapy for Diabetic Retinopathy

Review Article

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ABSTRACT

Background: Gene therapy has emerged as a promising strategy to alleviate the treatment burden of diabetic retinopathy (DR). The eye is an ideal target for gene therapy due to its immune-privileged status and ease of delivery. Gene therapy relies on the expression of a particular transgene to treat or cure a disease with the fewest possible negative effects. Common gene therapy techniques include gene augmentation, gene-specific targeting, and CRISPR/Cas9-mediated genome editing. Genetic material is typically delivered using viral or non-viral methods. Two gene families have been investigated as possible targets for DR gene therapy: those that address retinal protection and those that target retinal vasculopathy. The first set of genes was chosen with the intention of disrupting the intraocular VEGF pathway in order to reduce neovascularization and increase angiogenesis. Despite significant progress in anti-VEGF therapies, challenges such as the need for frequent intravitreal injections, variable patient response, and failure to address early neurodegeneration in diabetic retinopathy remain unresolved. Gene therapy emerges as a promising alternative by enabling sustained therapeutic effects and targeting multiple pathological pathways. However, clinical translation is hindered by challenges including vector delivery efficiency, immune responses, and off-target effects.

This Review Aims to: Summarize recent advances in gene therapy strategies targeting both angiogenesis and neuroprotection in DR, evaluate key challenges limiting clinical application, and to explore the potential of CRISPR/Cas9 systems in overcoming these barriers.

Key Words: Antiangiogenic therapy, diabetic retinopathy, gene therapy, retinal vasculopathy, VEGF.

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INTRODUCTION

Gene therapy was advanced from early human gene transfer studies to authorized clinical treatments within the last three decades. Due to successful gene therapy trials, a number of gene therapy medicines have received approval from drug regulatory bodies in the USA and Europe[1]. These include the 2012 recombinant adeno-associated virus (rAAV) product Glybera (alipogene tiparvovec), which was used to treat lipoprotein lipase deficiency [2], the 2016 antisense oligonucleotide compound Exondys51 (eteplirsen), which was used to help Duchenne muscular dystrophy patients regain their reading frame [3].

Adeno-associated virus (AAV)-based gene therapy for the inherited retinal condition RPE65-associated Leber's congenital amaurosis (LCA), Luxturna (voretigene neparvovec), was approved by the US Food and Drug Administration (FDA) in 2017 [4], signifying a significant turning point in the field of gene therapy for eye disorders. Since clinical trials have demonstrated the effectiveness and safety of AAV-based gene therapy for hereditary eye diseases, interest in employing gene therapy to treat complex polygenic eye disorders such glaucoma, age-related macular degeneration (AMD), and diabetic retinopathy (DR) has grown [1].

Emerging gene therapies represent a promising frontier in diabetic retinopathy treatment. These approaches aim to correct underlying genetic defects or modulate gene expression to prevent or reverse retinal damage. Techniques such as CRISPR/Cas9-mediated gene editing and adeno-associated virus vector-based gene delivery are being explored for their potential to offer long-lasting solutions with fewer side effects than traditional therapies. Although still in experimental stages, early results suggest these therapies could have a transformative impact on diabetic retinopathy management [5].

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Diabetes Mellitus

Diabetes mellitus is a long-term metabolic disease that is on the rise. Hyperglycemia and microvascular and macrovascular problems brought on by a malfunction in insulin release and/or its biological function are linked to the onset and progression of diabetes mellitus Type 1, Type 2, and gestational DM are the three primary forms of DM[2]. While DM type 2 arises from progressive insensitivity to insulin and a reduction in synthesis of insulin, Type 1 diabetes is brought on by an autoimmune disease that attacks the patient's own insulin-producing beta cells. The pathogenesis of gestational diabetes mellitus is identical to that of type 2 diabetes and is exclusively diagnosed in pregnant women [2].

The incidence of DM is showing a notable increase. There were about 463 million patients had DM worldwide in 2019, according to a prevalence survey, and it was expected that number will rise to 700 million people throughout the next 25 years [3].

Diabetic Retinopathy

The disease's long-term progression impacts the functions of vital organs. Diabetes frequently results in consequences, including diabetic retinopathy (DR). The deep layers of the retina, ciliary vessels, and the central retinal artery can all leak blood due to hyperglycemia, which can harm the blood-retinal barrier and produce ischemic alterations in the surrounding retina [4].

New blood vessels grow because of local retinal ischemia, which can cause tractional retinal detachment and subsequent visual loss. An adequate degree of visual acuity can be maintained with effective general diabetes therapy. But according to ***Semeraro et al.***, almost 10% of DR patients will unavoidably go blind [6].

Proliferative diabetic retinopathy (PDR) and non-proliferative diabetic retinopathy (NPDR) are the two types of diabetic retinopathy. Six phases are now used to classify two types. The three stages of non-proliferative diabetic retinopathy (NPDR) include micro angioma and tiny bleeding sites in stage I, hard exudates in stage II, and cotton wool patches in stage III. Neovascularization and vitreous bleeding are stage IV of proliferative diabetic retinopathy (PDR); fibrovascular proliferation and vitreous organization are stage V; and retinal detachment and resulting stretching-induced blindness is stage VI. Patients with NPDR often do not complain of any visual issues and are asymptomatic. However, NPDR therapy is not very successful when visual impairment occurs. Compared to NPDR, PDR has the potential to result in total blindness and significant vision loss. The length of DM invariably correlates with the prevalence of DR [4].

Gene Therapy

The goal of gene therapy techniques is to alter the pathogenic environment of the retina by controlling the expression of TNF-α and VEGF[7]. As an alternative, these tactics use viral vectors to transfer therapeutic genes to retinal cells [1]. Gene therapy has shown promise in slowing or preventing retinal cell loss and maybe stopping the improvement of diabetic retinopathy. For example, the AAV2-sFLT01 gene therapy, which is presently undergoing clinical trials, aims to prevent retinal edema and VEGF signaling development. The goal of this treatment is to increase the survival of retinal neurons by introducing a gene that codes for this change into the retina [8, 9].

Gene therapy's objective is to provide therapeutic transgenes or replace damaged genes by introducing genetic material into the patient's cells. Achieving sufficient transgene expression at a level that reduces or cures a medical state with few side effects is the aim of gene therapy. Gene augmentation, gene-specific targeting, and, most recently, genome editing are some of the gene therapy techniques [7].

Gene augmentation therapy, which has mostly been used to treat monogenic diseases, involves introducing a novel functioning gene in the host cell to replace a defective gene. Gene-specific targeted therapy aims to supply a healthy copy of a gene for regeneration or protection, or to change the function of an already-existing aberrant gene. Mutant genes can be fundamentally corrected by directly repairing them into functioning genes by genome editing or corrective therapy [10].

Current research on gene therapy for DR uses gene-specific targeted therapy, which is separated into two strategies depending on the disease's pathogenesis: strategies that target vascular hyperpermeability and pre-existing neovascularization, and strategies that try to prevent damage to retinal blood vessels and neurons. Under these headings, a large number of potential targets for DR gene therapy have been studied [10].

- Targeting Retinal Vasculopathy of Diabetes

Hyperglycemia-induced raised permeability of the blood vessels leads to intraretinal fluid collection and associated symptoms, including intraretinal hard exudates and cotton-wool patches, which are the hallmarks of DME. Retinal neovascularization is a characteristic of PDR in late-stage DR brought on by proliferation of endothelial cell and an unbalanced between pro-angiogenic and antiangiogenic elements. Therefore, promoting anti-angiogenesis or preventing endothelial cell proliferation are two strategies for DR gene therapy [11].

Treatment for DME and PDR has changed since intravitreal injections of anti-VEGF medications became available. By binding to VEGF, these substances inhibit the VEGF pathway and neovascularization. Nevertheless, there are drawbacks, such as inconsistent therapeutic response and ineffectiveness in a subset of individuals. For DR gene therapy research, VEGF is a clear therapeutic target. A number of extracellular and intracellular investigations have tried to disrupt the intraocular VEGF pathway. In experimental animal models, sFlt-1, a soluble splice variant of VEGF receptor 1 (VEGFR-1 or Flt-1), has been used to suppress retinal neovascularization. It serves as a decoy VEGF receptor in the extracellular space [11].

The anti-VEGF intraceptor Flt23k is a recombinant construct of the lysine-aspartic acid-glutamic acid-leucine (KDEL) endoplasmic reticulum (ER) retention signal sequence coupled with the VEGF binding domains 2 and 3 of VEGFR-1. Thus, Flt23k has the ability to disrupt VEGF pathways and intracellularly break down VEGF. A study that demonstrated a considerable reduction in choroidal neovascularization in an animal model after injection of AAV-mediated Flt23k offered indirect confirmation of the capacity of AAV-Flt23k to inhibit retinal neovascularization. Inhibiting retinal angiogenesis can also be accomplished by introducing endogenous angiogenesis inhibitors, such as calreticulin antiangiogenic domain (CAD), pigment epithelium-derived factor (PEDF), angiogestin, endostatin, and tissue inhibitor metalloproteinase-3 [12].

- Vascular and Neuronal Protection

Early vascular and neuronal degeneration in DR may be treated with gene therapy prior to obvious clinical abnormalities appear, in addition to suppressing the retina's already-existing aberrant blood vessels. Increased knowledge of the pathophysiology of DR has prompted research into lowering oxidative stress, preventing retinal vascular malfunction, and neuronal death [13, 14].

Early growth response 1 (EGR1) is a key zinc finger transcription factor engaged in many routes. The dramatic increase in EGR1 expression in vascular cells caused by hyperglycemia in diabetes can be among the primary early occurrences in the early stages of DR development. Retinal vascular function may be less negatively impacted by hyperglycemia if EGR1 expression is inhibited. Lysosomal breakdown of malfunctioning proteins or organelles is a hallmark of autophagy, a conserved metabolic process. According to research, microtubule-associated protein 1 light chain 3-II (LC3B-II) is a key molecular biomarker for identifying autophagic activity and is linked to the degree of autophagosome formation [13, 14].

The membrane attack complex is upregulated in DR, which contributes to the death of vascular and brain cells. A membrane-independent inhibitor of the membrane assault complex, soluble CD59 (sCD59) guards against damage to the blood-retinal barrier and retinal neurons. AAV-delivered sCD59 decreased vascular leakage by 60% in a diabetic mouse model generated by STZ in comparison to control animals. Additionally, it has been shown that sCD59 short-term activates retinal glial cells. But there are still questions regarding whether persistent sCD59 expression will lead to reactive gliosis, a harmful mechanism that causes neurodegeneration [15].

DR gene therapy also employs neurotrophic medications as a neuroprotective drug. In rats with STZ-induced diabetes, intravitreal injection of AAV vectors expressing brain-derived neurotrophic factor (BDNF) showed enhanced retinal function and a higher survival rate of retinal ganglion cells than controls. It has also been demonstrated that erythropoietin (EPO), a hematological cytokine, overexpression has a strong neuroprotective impact in DR [16].

Through its downregulation of the EPO receptor, VEGF, and VEGF receptor, one effort demonstrated that in rats with STZ-induced diabetes, intravitreal injection of EPO prevents retinal vascular regression at the early stage of DR. In rats with diabetes caused by STZ, it was demonstrated that subretinal AAV2-mediated expression of EPO effectively prevented retinal neuronal death and breakdown of the blood-retinal barrier. In the early stages of DR, the application of neurotrophic agents may have beneficial benefits, which calls for more research on the necessity of avoiding neurodegeneration [16].

There is increasing evidence that the local renin-angiotensin system (RAS) has a role in oxidative stress and retinal vascular permeability. The advantages of RAS inhibition in individuals with retinopathy who have type 1 or type 2 diabetes have been well demonstrated by clinical research. However, because local angiotensin II (Ang II) is present, existing RAS inhibitors are unable to fully correct neurodegeneration and vascular dysfunction [1].

Furthermore, it is yet unknown how angiotensin-converting enzymes and Ang II type 1 antagonists reduce RAS in the retina. A Vaso protective and counter-regulatory axis including the Mas receptor, angiotensin-converting enzyme 2 (ACE2), and angiotensin-(1–7) (Ang-(1–7)) was examined in one research. In animals with diabetes, injection of AAV vectors expressing ACE2 and Ang-(1–7) led to a significant decrease in oxidative stress, inflammation, acellular capillaries, and retinal vascular leakage. According to these results, ACE2/Ang-(1–7) axis improvement in the RAS may prevent vascular dysfunction and neurodegeneration in diabetic retinas [1].

- CRISPR/Cas-Based Therapies

Gene therapy has advanced beyond gene augmentation to gene editing thanks to the development of the CRISPR/Cas system. CRISPR/Cas uses single-guide RNAs to

identify a particular DNA series, which is then cut by a nuclease like Cas9. Targeting the over-expressed VEGF, this method may be used in gene therapy for DR. Using CRISPR/Cas systems that carry several nucleases, including Cas9 and Cpf1, and short RNA guides that target VEGF and hypoxia involving factor 1a (Hif1a), choroidal neovascularization has been successfully prevented in a mouse model of AMD [17, 18].

In CRISPRi (CRISPR interference) and CRISPRa (CRISPR activation), alternative modified CRISPR/Cas systems were developed to either enhance or suppress gene expression. In these setups, nuclease binds with specific sequences that are directed by sgRNA but loses its ability to cut[19].

Potential DR therapies that either limit the production of angiogenic factors like VEGF or promote the gene expression of antiangiogenic factors like PEDF may make use of these novel CRISPR/Cas systems. In general, research using gene therapy to address pathological alterations in the retina in both initial and final phases stages of DR has not yet produced a medication that is commercially viable. In animal studies for AMD, CRISPR/Cas has shown promise, and it could work as well for DR treatments. A variety of restrictions and difficulties now prevent gene therapy for DR from being translated from laboratory to clinical applications, despite promising experimental results that target either retinal vasculopathy or neurovascular protection [19].

Gene Therapy Challenges

1. Identification of genes that cause disease

The high expense of creating gene-specific treatments and the dependence on precise genetic diagnosis are two of the main issues with both conventional gene therapy and the editing of gene strategy. Since hundreds of mutations in several genes may result in the same clinical symptoms in many hereditary retinal diseases, including RP, the use of a single gene therapy product is limited to people who have a proved genetic diagnosis in that gene. The option of a conventional gene therapy method is eliminated, though, because many patients do not have a genetic identification at all; the gene or genes causing their illness phenotype to were not found [20].

Agnostic Mutation Methods for Gene Therapy

The retinal disease state may be changed by modifier gene therapy even if there is no genetic diagnosis or gene therapy targeted at the mutant gene in one of these individuals [21]. Instead of directly replacing or altering the faulty gene, these treatments impact many networks linked to retinal disease phenotypes and may be able to "reset" these networks to return the retina's equilibrium to normal. Applying this model offers a wider range of treatment options, but careful delivery design is equally important because, like various gene therapies, vector selection and route of administration may affect the therapy's efficacy and transduction efficiency as well as any immune responses [22].

2. Gain-of-Function Mutations

A further challenge is managing harmful gain-of-function mutations, such as those found in autosomal dominant RP and RHO mutations. In the same way, a dominant negative mutation may result in a harmful loss of function. The problem now is to develop a gene variant that is resistant to the silencing treatment. Other gene silencing techniques, such as the use of short hairpin RNAs and allele-specific ribozymes, can be tried in cases of this toxic gain or loss of function, but they would completely silence the gene. The CRISPR/Cas9 systems and other gene editing methods might also be able to correct these mutations [23].

3. Effective Targeting

Ensuring that the product reaches the target tissue or cells is a major challenge in gene therapy. For example, systemically administered gene therapy may not reach the retina due to the blood-retina barrier (BRB). Furthermore, the product of gene therapy must possess the ability to transduce diseased cells. The product's effectiveness can be increased by directly delivering it to the target tissue or by using specific vectors or cell-specific promoters to raise the effectiveness of targeted interactions [22].

Vector Selection and Targeted Engineering

Certain serotypes of adenoviruses and AAVs are desirable for the generation of products of retinal gene therapy due to their tissue-specific tropisms [24, 25]. As mentioned earlier, because of their tissue-specific tropisms, AAV2, AAV4, AAV5, and AAV8 are among the most frequently utilized AAV serotypes for retinal gene therapy[26, 27].

Tissue-specific targeting can be further enhanced by using recombinant or modified vector capsids, which provide more accurate control over the different components of a capsid and vector alterations. The use of promoters unique to particular cell types improved targeting to the impacted cell types [28]. AAV1, AAV4, AAV6, or the designed AAV2-7m8 vector can be used to target RPE cells, whereas serotypes AAV2, AAV5, AAV6, AAV7, AAV8, and AAV9, as well as engineered AAV2-7m8 and AAV8BP2 vectors, target Müller glial cells and photoreceptors [29].

Using a promoter engineering technique, one team recently produced a large library of 230 AAVs, each of which carried a unique synthetic promoter made especially to target particular cell types [28].

Delivery Route

Finding the best way of delivering gene therapy to the tissue remains a difficulty for researchers even after they have chosen the right vector design. Although ocular or systemic routes can be used to deliver gene therapies to the retina, it is usually preferable to utilize a route which will get the treatment as close to the intended tissue as feasible. For example, intravitreal injections for inner retina targets and subretinal injections for outer retina targets[29] Although systemic administration is convenient, the lack of particular targeting may result in nonspecific effects in tissues other than the eyes, decreased target tissue bioavailability, and an increased immunogenicity risk when the medication is administered to more parts of the body [30].

Ocular administration lowers immunogenicity and limits the action of gene therapy to the targeted tissue. Although invasive ocular administration techniques provide more precise distribution and hence boost therapeutic products' bioavailability, they also raise the possibility of adverse effects such infection, detachment of retinal, and bleeding. For these treatments to be administered successfully, trained and experienced surgeons are usually needed [31]. Non-invasive drug delivery techniques are easier to administer and have fewer procedure-related problems, but their bioavailability is lower [30, 32]. Gene therapy represents a challenging shift in managing diabetic retinopathy, offering sustained VEGF suppression and dual targeting of vasculopathy and neurodegeneration. While preclinical studies demonstrate promising results with AAV vectors and CRISPR/Cas9 systems, key challenges such as immune responses, vector delivery efficiency, and high costs remain barriers to clinical translation. Therefore, for effective transduction and a reduced immune response in patients, choosing the best delivery method for a particular gene therapy product is essential.

Future research should develop better retinal-targeting vectors, explore combined therapies, and ensure long-term safety. Integrating gene therapy with current treatments may offer personalized, lasting solutions for diabetic retinopathy.

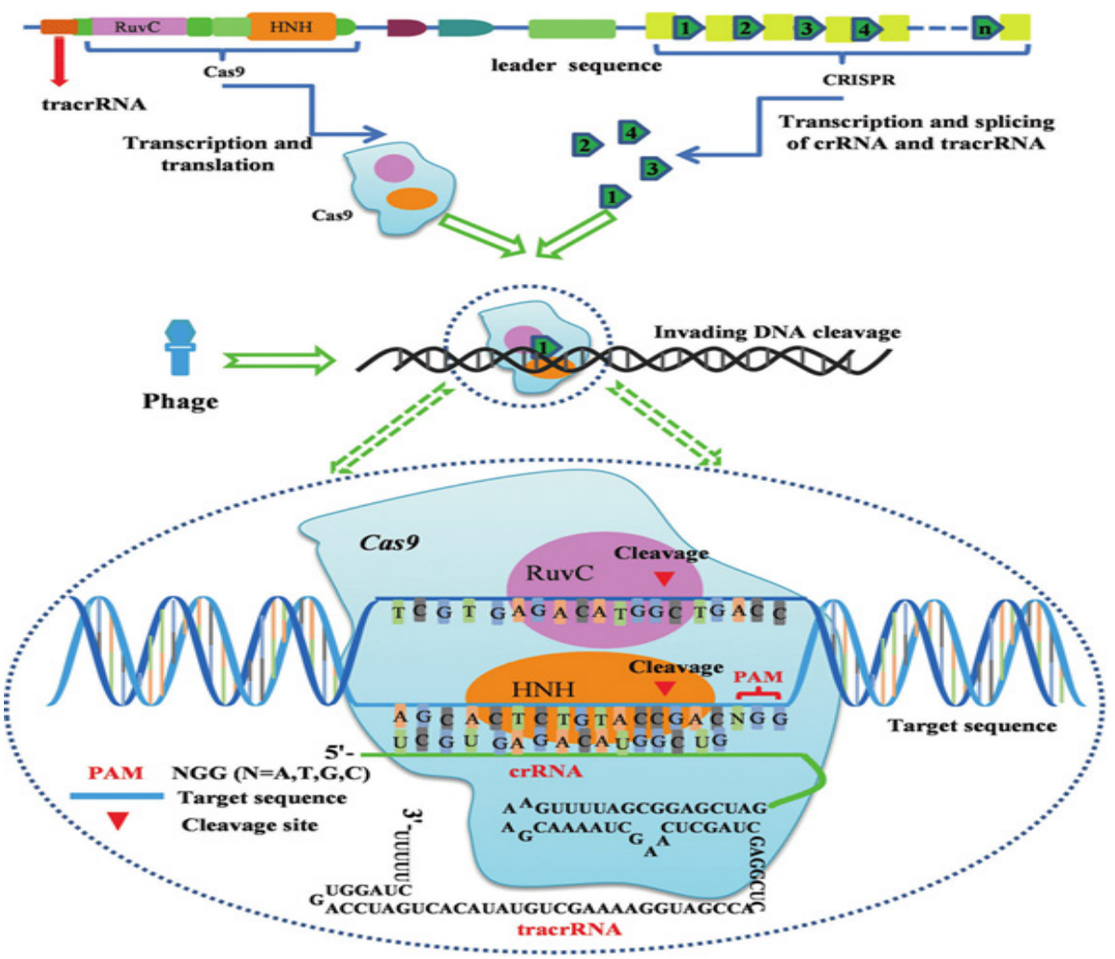

Fig. 1: Molecular mechanism of CRISPR/Cas9-mediated DNA cleavage.

Table 1: Endogenous Angiogenesis Inhibitors in DR Gene Therapy.

Inhibitor	Mechanism of action	Relevance to DR
CAD	Binds VEGF and blocks receptor interaction	Reduces neovascularization in preclinical models
PEDF	Anti-angiogenic and neuroprotective effects	Preserves blood-retinal barrier integrity
Angiostatin	Inhibits endothelial cell proliferation	Suppresses pathological angiogenesis
Endostatin	Targets MMP-2/9 to prevent ECM degradation	Reduces vascular leakage
TIMP-3	Neutralizes matrix metalloproteinases (MMPs)	Mitigates inflammation and vascular remodeling

AUTHORS CONTRIBUTIONS

Sarah Alarifi conducted the literature review, analyzing relevant studies, and drafting the manuscript. Suliman Masuod critically revised the content and contributed to the final version. All authors read and approved the manuscript.

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تحديث حول العلاج الجيني لاعتلال الشبكية السكري

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الخلفية: العلاج الجيني يُعد من المجالات المبتكرة التي قد تساهم في تقليل العبء العلاجي لبعض الأمراض. ونظرًا لكون العين بيئة مناعية مميزة وسهلة نسبياً في إيصال العلاجات إليها، فقد أصبحت هدفًا رئيسيًا لتطبيقات العلاج الجيني. تعتمد هذه التقنية على إدخال جين معين بهدف علاج المرض أو التخفيف من حدته مع تقليل الآثار الجانبية قدر الإمكان. وتشمل الأساليب الشائعة للعلاج الجيني تعزيز الجينات، الاستهداف الجيني، وتعديل الجينوم.

يتم إدخال المادة الوراثية إلى الخلايا المستهدفة باستخدام طرق تعتمد على نواقل فيروسية أو غير فيروسية. وقد تم بحث مجموعتين رئيسيتين من الجينات كأهداف محتملة لعلاج اعتلال الشبكية السكري: الأولى تُعنى بحماية الشبكية، والثانية تهدف إلى تعديل اعتلال الأوعية الدموية في الشبكية. وُجهت المجموعة الأولى من الجينات لتعطيل المسار الداخلي لعامل نمو بطانة الأوعية الدموية داخل العين، مما يسهم في الحد من تكوّن الأوعية الدموية غير الطبيعية وتعزيز نمو الأوعية الدموية السليمة. كما يمكن التصدي لاعتلال الأوعية الشبكية باستخدام عوامل تمتلك خصائص مضادة لتكوّن الأوعية الدموية غير الطبيعية.