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NARRATIVE REVIEW

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Dengue fever in hyperglycemic patients: an emerging public health concern demanding eyes on the effective management strategies

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Abstract

Background and aims: Hyperglycemia, also known as diabetes, is a metabolic disorder characterized by elevated levels of glucose in the bloodstream. It can lead to the prolonged dysfunction, injury, and deterioration of several organs. In addition, dengue is a viral illness transmitted by mosquitoes that has reached epidemic proportions worldwide. In this article, we focused on the severity of comorbidities, difficulties in managing them, and preventive measures meant to lessen the risks associated with comorbidities in diabetic patients with dengue infection.

Methods: We explored a number of databases, including PubMed, Scopus, Embase, Web of Science, Google Scholar, and the Cochrane Library, for this review article using various related keywords.

Results: The findings of this review article indicate that elderly dengue patients with diabetes should be admitted to the hospital for close observation and early management using fluid therapy. An observed association exists between dengue hemorrhagic fever (DHF) and diabetes, indicating a possible consequence in this specific group. Additionally, patients with diabetes who contract dengue show elevated levels of inflammatory markers. Diabetes mellitus deteriorates the immune system, which exacerbates the progression of dengue fever. Cutting-edge technology and scientific research may assist in addressing the challenges that diabetes and dengue viruses pose in low- and middle-income countries. Implementing innovative diabetic care management is essential to ensuring consistency of care, improving a healthy lifestyle, and lowering patient risk factors and comorbidities.

Conclusion: Dengue fever has spread to epidemic levels throughout the world. Inflammatory markers increase and the prevalence of DHF is greater in diabetes individuals with dengue infection. Given the continued growth of dengue in Asian nations, it is imperative that we concentrate our efforts and resources on providing more precise and effective treatment for this emerging issue.

KEYWORDS
co-morbidity, dengue, dengue in diabetes patients, diabetes, healthcare strategy

1 | BACKGROUND

The dengue virus (DENV) is highly diverse genetically and is frequently encountered alongside five different serotypes (DENV1, DENV2, DENV3, DENV4, and DENV5).[1] This co-circulation increases the likelihood of severe dengue infection due to the antibody-dependent enhancement effect.[2] The transmission of DENV occurs when infected female *Aedes* mosquitoes, mostly *Aedes aegypti* and, to a lesser extent, *Aedes albopictus*, bite humans, resulting in a human-mosquito-human cycle.[3] Globally, the World Health Organization (WHO) documented a tenfold surge in reported cases between 2000 and 2019, with the number jumping from 500,000 to 5.2 million. In 2019, there was an unprecedented surge, with documented occurrences expanding to 129 countries.[4]

Diabetes is a group of metabolic illnesses characterized by high levels of glucose in the blood due to abnormalities in the synthesis or efficiency of insulin, or both.[5] Diabetes is a condition marked by persistently high blood sugar levels, known as chronic hyperglycemia. This condition is associated with the gradual decline, dysfunction, and damage of various organs, notably the eyes, kidneys, nerves, heart, and blood vessels.[6] With the majority living in low- and middle-income countries, diabetes affects around 422 million people worldwide. Additionally, diabetes is directly responsible for causing 1.5 million deaths annually.[7]

Comorbidity associations arise when two or more diseases are found together in an individual more frequently than would be expected by mere chance.[8] Due to compromised immunity, delicate blood vessels, and an increased susceptibility to bleeding, individuals with diabetes experience exacerbated symptoms of dengue fever. In light of the increasing prevalence of both diseases, it is crucial to understand the post-effect and management of the severe dengue and diabetes mellitus comorbidity. This article centers on the gravity of comorbidities, the challenges faced, approaches to their management, and preventive interventions intended to mitigate the potential risks associated with comorbidities in diabetes patients with dengue infection.

2 | METHOD

For this review paper, we used a variety of related keywords to search a number of databases, including PubMed, Scopus, Embase, Web of Science, Google Scholar, and the Cochrane Library. “Diabetes”, “hyperglycemia”, “dengue fever”, “infection”, “management difficulties”, “diabetic patients”, “co-morbidity”, “healthcare strategy”, and “dengue in diabetic patients” were among the terms that were looked up. This effort did not include any data collecting or data analysis, but examined and compared the findings of various linked notable scientific studies with the mentioned illness comorbidities.

3 | DENGUE

Dengue infection occurs when an individual is bitten by a mosquito that is carrying the virus. The virus is then transmitted into the person's body when the mosquito is feeding on their blood, which is necessary for the mosquito to produce eggs. The virus is injected into the epidermis along with saliva, and there is evidence to suggest that it may also be deposited in the outer layer of the skin, potentially enabling it to circulate throughout the bloodstream directly.[9] The fully developed dengue virus particle is composed of a single-stranded RNA genetic material enclosed within a 30 nm-diameter icosahedral or isometric protein shell called a nucleocapsid. The nucleocapsid is encased by a lipid sheath. The envelope proteins, responsible for the virus's attachment to host cell receptors, perform various vital functions for the virus, such as transporting the viral genome into the host cell, causing clumping of red blood cells, triggering the production of neutralizing antibodies, and eliciting protective immunological responses.[10] The main age groups affected by dengue fever are adults and older kids. It occurs in both the early and the latter stages of infections. In most cases, the symptoms manifest with an abrupt and swift rise in body temperature, often known as a high fever. This fever may occur in two phases, lasting generally from 3 to 7 days.[11] *Aedes* mosquito eggs have the ability to endure desiccation, allowing them to survive for extended periods. The large concentrations of mosquitoes are caused by inadvertent disposal of garbage and poor sewerage drainage facilities. Significant increases in the numbers of mosquito larvae have been observed both during and after the period of prolonged rainfall. This leads to outbreaks of dengue fever in the countries of South and Southeast Asia during the monsoon season.[12] The prevalence of dengue has had a substantial surge in the past few decades, escalating from 8.14 cases per 100,000 individuals in 2000 to 67.16 cases per 100,000 individuals in 2019. Each year, an estimated 50 to 100 million infections are recorded in more than 100 nations where the disease is prevalent, posing a risk to nearly half of the global population.[13]

4 | DENGUE INFECTION

Dengue infection presents with a broad spectrum of clinical manifestations, spanning from a mild, insignificant fever to serious physiological complications. Dengue fever (DF) is a relatively mild subtype of the disease that occurs during primary infection. The condition is marked by a mild headache, muscle discomfort, fever, joint pain, abdominal pain, body pain, and pain behind the eyes, as well as immune system dysfunction in the form of a low platelet count, swollen lymph nodes, and a low white blood cell count.[14] In the case of hemorrhagic DF, there is a malfunction in the hemostasis process, which is of high grade. Furthermore, the occurrence of significant

vascular leakage frequently leads to dengue shock syndrome (DSS), causing greater injury to patients. During DSS, patients experience hypovolemic shock, characterized by decreased blood volume and reduced blood flow to the peripheral tissues. This can lead to tissue damage and, in extreme situations, may cause multiorgan failure.[15] Secondary heterologous dengue infection is the most widely recognized risk factor for severe dengue. The etiology of this phenomenon is thought to be antibody-dependent enhancement (ADE) of infection. ADE develops when viruses, which are bound to antibodies that do not completely destroy them, are identified and engulfed by immune cells, including dendritic cells and monocytes/macrophages, via a receptor known as the Fc receptor. This process ultimately leads to an increase in virus production. Furthermore, the presence of non-neutralizing heterotypic antibodies that exhibit cross-reactivity might lead to an elevation in antibody-dependent cellular cytotoxicity (ADCC) and an intensified activation of mast cells. Consequently, the synthesis of vasoactive mediators occurs, which have been empirically shown to play a role in the progression of dengue vascular pathology. In addition, host characteristics such as pre-existing metabolic abnormalities (hyperglycemia), age, gender, and human leukocyte antigen (HLA) type are considered potential risk factors. Viral factors, such as viral load and nonstructural protein 1 (NS1) antigenemia, may also contribute to the risk.[16]

4.1 | Dengue pathogenesis in nondiabetic individuals

DENV modulates the host-cellular machinery involved in producing its offspring. Nevertheless, this process of cellular acquisition is accompanied by several challenges in the form of immune defense responses to viral offspring during various phases of the lifespan: entry of the virus, replication, and discharge. The dengue virus, however, deliberately evades immune system detection and often targets intracellular signals that inhibit viral activity. To activate innate immunity, pattern recognition receptors attach to pathogen-associated molecular patterns (PAMPs). During the early stage of innate immunity, some signals trigger the production of interferons (IFNs) and interleukins by infected host cells, including dendritic cells (DC). Similarly, natural killer (NK) cells also stimulate IFNs to rapidly eliminate viral loads from the host organism.[17] The identification of foreign DENV sensors and the coordination of immune responses across various immune cells are essential functions of toll-like receptors (TLRs), which play a vital role in nonspecific innate immunity. TLRs are a group of pattern recognition receptors present in several cells of the immune system, including dendritic cells, macrophages, and natural killer cells. These receptors have a vital function in innate immunity by detecting and reacting to PAMPs found on the outer layer of invading bacteria.[18]

TLRs have been associated with the response of the innate immune system to dengue virus infection. The TLR3, TLR7, and TLR8 receptors are involved in the recognition of viral ribonucleic Acid (RNA), a crucial component of the dengue virus. TLRs are only found within endosomes and possess the capacity to engage with viral RNA. TLR3 identifies double-stranded RNA, a commonly generated outcome of viral replication. The cross-linking of TLR3 to viral RNA triggers subsequent signaling pathways that produce pro-inflammatory cytokines and type I interferons. They play a crucial role in combating viruses. Research has demonstrated that the activation of TLR3 can trigger an antiviral condition that restricts the multiplication of the dengue virus in infected cells.[19] Upon receiving signals from released chemicals, multiple cellular signaling networks are activated. These pathways include the stimulation of nuclear factor kappa B (NF-κB), the phosphorylation of interferon regulatory factor 3 by IkappaB kinase1, the participation of myeloid differentiation primary response protein 88 and mitogen-activated protein kinases, and the activation of IFN-α/β and interferon-stimulating genes. These chemicals collectively induce widespread activation and secretion of IFNs and numerous types of cytokines in the cellular environment.[20] The cytoplasmic helicases, specifically retinoic acid-inducible gene I (RIG-I) and MDA5, are important biological components that play a substantial role in the development of innate responses against DENV. The activation of the Janus kinase (JAK)/signal transducer of activation (STAT) signaling network by IFN-α/β is essential for the inhibition of viral infection caused by DENV. Significant roles are played by adapter molecules, namely tyrosine kinase 2 (TYK2), JAK1, STAT1 to 3, and STAT5, in activating other networks, such as the mitogen-activated protein kinase p38 cascade and the phosphatidylinositol-3-kinase (PI3K) cascade. Subsequently, these signaling networks initiate the synthesis of many antiviral proteins, pro-inflammatory cytokines, leukocytes, chemokines, and other antiviral substances within the host cell.[17,19,21]

DENV employs various mechanisms to disrupt and prevent the host's antiviral defenses. It induces a significant reorganization of cellular membranes, accompanied by alterations to the host's metabolism to facilitate the creation of offspring. It infiltrates cellular vesicles without being detected by the host cell lysosomes and prevents the activation of endoplasmic reticulum stress-induced reactions.[22] The main mechanism employed by DENV to duplicate its genome is autophagy. Furthermore, it induces inhibitory reactions towards various signaling cascades, RNA interference (RNAi) pathways, and interferon (IFN)-linked networks. Currently, multiple studies are examining DENV-specific proteins such as nonstructural protein 4B (NS4B), NS2B-NS3 protease, and subgenomic flavivirus RNA (sfRNA) to comprehend their essential function in suppressing host antiviral responses through different mechanisms.[23] Furthermore, DENV often mimics the cellular mRNA of host cells, enabling it to evade recognition by the innate immune system, including signaling cascades and the production of IFNs. The viral proteins NS2A, NS4A, and NS4B have a significant impact on the suppression of JAK/STAT network activation and the transcription of several genes involved in host defense. DENV evades innate immune responses in host cells by directly ubiquitinating and degrading critical cellular components, rather than triggering innate immune system reactions towards viral levels. These avoided reactions additionally lead to variations in the adaptive immune response and overall disease results.[20,24]

Following ineffectual and unidentified innate immune responses, the adaptive immune system establishes a defensive mechanism in which both cellular and humoral responses are produced about 6-7 days after the first viral infection.[23] Antibody production occurs when DENV antigens are detected on the surface of antigen-presenting cells (APCs), particularly clusters of differentiation (CD) 4 + T lymphocytes. Specificity of the antibodies is shown towards the envelope protein E and PrM glycoproteins of the DENV, which are found on its surface. Research has demonstrated that CD8+ and CD4 + T lymphocytes identify nonstructural and structural proteins in distinct ways.[21,22] This phase initiates the activation of adaptive immunity by engaging effector and helper T cells. These cells then generate humoral immune responses by T helper (Th) 1- and Th2-mediated mechanisms in cells infected with the virus. Through the secretion of IL-2, IFN-γ, and tumor necrosis factor (TNF)-β, Th1 cells preferentially induce inflammatory responses and tissue damage. Th2 induces T-cell activation and proliferation by releasing cytokines such as interleukin (IL)−4, IL-5, IL-6, IL-10, IL-13, and other interleukins.[25] B-cells particularly control the generation of antibodies that target viral proteins, including the NS1 protein. These antibodies lyse cells infected with DENV by utilizing the complement mechanism of adaptive immunity. The DENV NS1 protein engages in several cellular interactions with macrophages, PBMCs, TLR4, platelets, apoptotic molecules, NF-κB, and other signaling molecules to facilitate adaptive responses against DENV.[24]

Understanding the imbalanced production of cytokines, chemokines, and interleukins is crucial since they play a significant role in both the development and resolution of dengue hemorrhagic fever (DHF) in an infected person.[18] Finally, the viral epitopes interact with memory T cells, which subsequently produce pro-inflammatory cytokines and release these cytokines through the vascular endothelium. The discharged material exhibits heightened concentrations of cytokines, chemokines, and interleukins, as well as soluble CD4 and CD8 cells, which stimulate the development of DHF and DSS in the bodies of hosts.[17]

4.2 | Dengue pathogenesis in diabetic patients

There is a significant connection between the severity of dengue in diabetic patients and various factors such as inflammation, oxidative stress, elevated levels of advanced glycation end products (AGEs), high blood sugar levels (hyperglycemia), inadequate control of blood sugar levels (poor glycemic control), the presence of other medical conditions (coexisting comorbidities), high levels of C-reactive protein (CRP), elevated IL-8 levels, and increased perfusion index.[26] Ultimately, these elements result in inflammation, facilitate the spread of the virus, and worsen the symptoms of dengue. Dengue predominantly invades the myeloid cells of the host, including monocytes, macrophages, and dendritic cells, by selectively binding to receptors that are distinct to each cell type. These receptors include dendritic-cell-specific ICAM (Intercellular Adhesion Molecules)3-grabbing non-integrin (DC-SIGN), liver or lymph-node-specific ICAM3-grabbing integrin (L-SIGN), glycosaminoglycans (CD14), C-type lectins, and mannose receptors (CD206).[27] Viral RNA is detected by pathogen recognition receptors, including RIG-I, melanoma differentiation-associated protein 5 (MDA5), and TLR 3 and 7. This identification leads to the activation of various downstream factors, such as Stimulator of interferon genes, Interferon regulatory transcription factors 3 and 7, TIR domain-containing adapter inducing IFN-β, and nuclear factor kappa B (NF-κB).[28] These transcription factors are essential in the innate immune system as they inhibit the migration of type I interferon responses to additional monocytes following viral infection. The high Th1/Th2 ratio[29] and elevated levels of pro-inflammatory markers such as TNF-α, IFN-γ, IL-2,[30] and IL-6[31] are defining characteristics of diabetes. The levels of Th1 cytokines IFN-γ and TNF-α are elevated in individuals with diabetes and are also linked to catastrophic outcomes in dengue hemorrhagic fever.[32] By activating PI3K via the nitric oxide and peroxy-nitrite pathways,[33] neutrophil activation and the formation of neutrophil extracellular traps (NETs)[34] are stimulated, hence further enhancing immunopathogenesis. Studies conducted on human neutrophils in a laboratory setting have demonstrated that elevated blood sugar levels in individuals with diabetes cause neutrophils to become highly prone to a process called NETosis. This process has detrimental effects on the balance and stability of tissues.[35] Clinical investigations have found that levels of NETs are higher in patients with dengue, which can worsen the damage caused by existing diabetes.[36] In diabetes, the impaired condition of the endothelium barrier, when coupled with dengue infection, further amplifies the consequences of vascular damage. In addition to these effects, diabetes can lead to a notable increase in mean platelet volume and reticulated platelets, which become hyperreactive to stimuli.[27] Elevated platelet activation in diabetic patients could be a possible factor contributing to the significant reduction in platelet count seen in dengue-infected persons with diabetes. A study has demonstrated a significant association between diabetes, severe dengue, death, high levels of glutamic-pyruvate transaminase, and thrombocytopenia.[37]

Individuals with complications associated with type 2 diabetes (T2D) exhibit lower levels of the immunosuppressive regulatory T cell (T_{reg}) population and the anti-inflammatory IL-10 cytokine in their peripheral system.[38] If the T_{reg} to T-effector cell ratio is higher, it has been observed to restrict acute dengue.[39] However, a decrease in the T_{reg} population among diabetic individuals with dengue could potentially result in serious consequences of dengue infection in these individuals. The involvement of the eukaryotic initiation factor 5A (eIF5a) in the modulation of T-cell activity, particularly in the context of the pancreatic β-cell environment, has been documented. Through the reduction of anti-glutamic acid decarboxylase 65-kilodalton isoform antibody levels, inhibiting this factor has been demonstrated to promote remission in a humanized mouse model of type 1 diabetes (T1D).[40] It is noteworthy because recent evidence has shown that eIF5a is likewise pro-viral for the replication of DENV serotype 2. The former undergoes post-translational alteration caused by the latter to acquire its active state.[41] The protease-activated receptor-1 (PAR-1) protein regulates the function of

CD8 + T-cells. The inhibition of PAR-1 leads to a reduction in the secretion of effector proteins by interference with the transport of actin at the immunological synapse.[42] This is noteworthy since recent studies have shown that increased levels of PAR-1 act as a biomarker for systemic inflammation linked to T2D. These elevated levels are strongly correlated with increased levels of pro-inflammatory cytokines such as IL-6 and CRP in the serum.[43] Additionally, studies have shown a strong positive correlation between the severity of dengue fever and the levels of PAR-1 in the serum.[44] Obese patients with diabetes experience significant activation of several B-cells, resulting in heightened synthesis of pro-inflammatory cytokines IL-6 and TNF-α, as well as reduced levels of IL-10. However, their response to new antigen stimulation is diminished. This is harmful because patients may experience heightened vulnerability to acquiring viral infections without producing robust humoral immune responses.[45]

5 | DENGUE IN DIABETIC PATIENTS

Comorbidities were found to exacerbate the severity of dengue sickness, indicating that certain characteristics of the host operate as risk factors in the development of DHF/DSS/severe dengue. Diabetes mellitus, specifically type 2 diabetes mellitus (DM2), is a widely prevalent disease worldwide. It is considered one of the significant host risk factors for the development of severe dengue, including DHF and dengue shock syndrome DSS.[46,47] An association has been observed between hypoalbuminemia, hypertriglyceridemia, advanced age, and the severity of thrombocytopenia in persons who have been diagnosed with dengue infection.[37] Diabetic individuals have a greater occurrence of increased inflammatory markers and decreased platelet counts, suggesting that diabetes may operate as a predisposing factor for increased vulnerability to severe dengue infection.[48] Diabetic individuals with inadequate control of glucose and comorbidities are more vulnerable to developing severe instances of dengue fever.[26]

Diabetes is characterized by hyperglycemia resulting from reduced tissue responsiveness to insulin, which triggers an elevated secretion of insulin from pancreatic beta cells. The ongoing release of substances eventually leads to pancreatic exhaustion and permanent damage.[49] The impaired insulin action and secretion, leading to increased blood glucose levels, can disturb the equilibrium between nitric oxide and reactive oxygen species in endothelial cells. The substantial role of nitric oxide in maintaining vascular homeostasis and inducing vasodilation is crucial.[50] Oxidative stress and reactive oxygen species can deactivate nitric oxide by generating endothelin 1, resulting in vasoconstriction and platelet aggregation.[51] Furthermore, these components possess the capacity to stimulate immune pathways associated with inflammation, which are defined by the increased synthesis of monocyte chemoattractant protein-1, selectins, vascular cell adhesion molecule-1, and ICAM-1. This sequence delineates the mechanism by which monocytes adhere to the endothelium, followed by the activation of macrophages and an increased secretion of IL-1 and TNF-alpha. These mechanisms function to enhance the inflammatory reaction. Vasoconstrictive drugs are also generated via an intensified cyclooxygenase-2 pathway, which is marked by elevated levels of thromboxane A2 and reduced synthesis of prostacyclin. Furthermore, this intensifies the disruption of vascular control and leads to the degradation of endothelial function. This intricate series of events forms the foundation for the typical vascular events seen in people with diabetes. Given that pro-inflammatory substances promote vasoconstriction and a prothrombotic condition, it is reasonable to anticipate the occurrence of vascular events due to endothelial dysfunction.[34,52–54] Type 2 diabetes mellitus (T2DM) can be considered as a dysfunction of the endothelium, which results in a complex vascular condition. This condition ultimately leads to a multitude of difficulties affecting small and large blood vessels, which in turn impact important organs like the heart, brain, kidneys, and eyes. Diabetes has been identified as a potential risk factor that exacerbates severe forms of dengue.[49]

Dengue is characterized by increased levels of inflammatory markers, including CRP, endocan, and IL-8. Therefore, individuals who have concurrent inflammatory diseases, such as diabetes, may experience a more intense and even fatal manifestation of dengue. Multiple studies over the years have consistently shown a strong correlation between diabetes and inflammation. Hyperglycemia disrupts the structure and function of the endothelium, resulting in a long-lasting inflammatory condition caused by the activation of T-lymphocytes and the release of pro-inflammatory cytokines, including gamma IFN and TNF.[55] One of the primary signs of complicated dengue fever is greatly influenced by these cytokines. In addition, it has been found that DM has detrimental impacts on the immune system, including decreased chemotaxis, leukocyte adhesion, and infection phagocytosis, which increase an individual's vulnerability to infections.[56,57]

There are several case-studies found to date. A 13-year-old boy was first hospitalized with dengue fever but later developed diabetic ketoacidosis (DKA) during the critical phase of dengue hemorrhagic fever.[58] A 26-year-old Sinhalese male patient infected with dengue shock received a diagnosis of transient diabetic ketoacidosis. The patient manifested first signs of postural dizziness, nausea, and vomiting. Furthermore, the patient has indicated a heightened frequency of urination during the first day. The patient, who had previously undiagnosed diabetic mellitus, experienced DKA due to DHF acting as a trigger factor. There were a limited number of case reports documenting the occurrence of dengue virus-causing diabetic ketoacidosis.[59] Supradish et al. documented a case involving a 16-year-old Thai girl who had dengue shock, characterized by severe dehydration and ascites.[60] Additionally, another research paper indicated that those with diabetes had a 2.5-fold increased risk of developing dengue hemorrhagic fever.[61] Dengue fever in individuals who have diabetes may pose a serious threat and result in complex therapeutic management. Therefore, further investigation is required to mitigate the incidence of comorbidities between dengue and diabetes.

6 | THERAPEUTICS AND TREATMENTS

The urgent requirement to prevent and/or combat potential future dengue outbreaks necessitates the advancement of effective, preventative, or curative comorbidity management (Table 1).

TABLE 1 An overview of the therapeutic development of dengue in patients with diabetes.

Drugs	Mechanism of action	References
Metformin	Antidiabetic that reduces the risk of acquiring severe dengue fever by 33% reducing the effects of diabetes: restricted pan-serotype efficacy of dengue.	[Cheang et al.][62]
Ivermectin	An antiparasitic medication that decreases cholesterol and blood sugar in db/db mice: NS3 helicase activity is inhibited.	[Palanichamy Kala et al.][16]
Niclosamide ethanolamine	Increases serum insulin levels in T1D patients and prevents pancreatic β cells by blocking NS3, which stops the early phases of viral replication.	[Han et al.][63]
Demethylasterriquinone B1 (DMAQ-B1)	Activates viral RNAi and antiviral responses in *Aedes aegypti* by insulin mimicry through the JAK/STAT pathway.	[Trammell et al.][64]
Lycorine	Antidiabetic that prevents viral multiplication and endocytosis; reduces diabetic peripheral neuropathy.	[Yuan et al.][65]

Nevertheless, it is imperative to persist in the development or modification of existing medications or therapies to properly tackle the prevalent and occasionally overlooked issues associated with type 1 and type 2 diabetes mellitus. Despite occasional fragments of data suggesting that certain antiviral vaccines may cause hyperglycemic reactions, particularly in individuals with a genetic predisposition to diabetes, vaccinations remain the most effective means of preventing viral infections.[66]

There are several categories of vaccinations that have been developed, such as live attenuated vaccines, recombinant subunit vaccines, inactivated virus vaccines, viral vectored vaccines, DNA vaccines, and mRNA vaccines (Table 2). These methods mostly perform by enhancing resistance to either the DENV virions or the envelope proteins identified on the virus's surface causative of the illness. Furthermore, scientists are investigating innovative methods for vaccine development that combine sophisticated vaccination concepts such as NS1-based, mRNA-based, and mosquito-based immunization alongside traditional vaccines. Their objective is to prevent infection by disrupting the DENV life cycle within mosquitoes.[72]

7 | DISCUSSION AND RECOMMENDATIONS

Diabetes and dengue are becoming increasingly prevalent worldwide. However, it is crucial to assess the possibility of having concurrent medical conditions between dengue and diabetes mellitus. Dengue patients who have both pre-existing diabetes and cardiovascular disorders have an eightfold increase in the possibility of serious organ involvement compared to dengue patients without these conditions. Furthermore, dengue patients who have both diabetes and hypertension, or both diabetes and hyperlipidemia, or both cardiac diseases and hyperlipidemia, are at a significantly higher risk compared to dengue patients who have only one of these comorbidities or none at all.[73,74]

The clinical features of dengue undergo dynamic changes over time. It is crucial to identify predictors that can assess the possibility of dengue progressing from its early clinical stage to severe dengue. DM2 is a multifaceted disorder characterized by chronic metabolic dysfunction and compromised immune systems. It is commonly suggested to be a major contributor to the potential clinical development of dengue, leading to various consequences. When comparing DM2 patients to individuals without DM, it is shown that DM2 patients have a comparable leukocyte count. However, there may be functional alterations in the leukocytes of DM2 patients.[26] A research investigation discovered a molecular mechanism by which excessive hyperglycemia (HG) facilitates DENV infection. Based on their research, it was found that HG therapy did not have any impact on viral attachment or entrance, as well as antiviral IFN responses. However, treatment with HG increased the amount of viral titer and the generation of viral proteins via stimulating the host translational factor PABP (P100 and poly(A)-binding protein). Additional treatment approaches that aim to prevent the effects of HG-induced PABP by blocking the PI3K/AKT signaling pathway and directly suppressing PABP through decreasing glucose uptake and disrupting translational complex formation have the potential to decrease DENV replication. The mice developed with DM also exhibited increased mortality, viral protein expression, and brain viral burdens. The findings suggest that increased blood sugar levels enhance the ability of the DENV virus to infect cells by fostering the process of viral translation.[75]

The involvement of inflammatory cytokines is essential in the manifestation of clinical symptoms associated with DHF, particularly the third space fluid shift. Endothelial dysfunction is responsible for this shift, which results in hemoconcentration, hypotension, and shock. The typical physiological mechanism by which allergies and diabetes elevate the risk of developing DHF is by inducing endothelial dysfunction. This dysfunction increases the intrinsic permeability of the endothelial surface in individuals who have previously been infected by another serotype, allowing fluid shift to occur.[61] Dengue hemorrhagic fever is characterized by an increased immune response triggered by the presence of heterotypic antibodies targeting a particular serotype of the dengue virus as a result of a fresh infection. Autoimmunity is often associated with type 1 diabetes mellitus, leading to chronic activation of the immune system. By activating this process, inflammation occurs in tissues and capillaries, therefore enhancing the probability of inflammation and the secretion of pro-inflammatory cytokines in tissues, particularly in the

TABLE 2 Current status of dengue vaccine development: licensed or under development.

Name	Adjuvanted	Type of Valence	Manufacturer	Evaluation	References
DENVax/ TAK-003	No	Tetravalent	Takeda	Phase III trial in vivo	[Hou et al.][67]
Dengvaxia/CYD-TDV	No	Tetravalent	Sanofi Pasteur	Licensed	
TV003/ TV005	No	Tetravalent	NIAID[a]	In vivo (phase IIIB)	
TDEN	No	Tetravalent	WRAIR[b] and GlaxoSmithKline	In vivo (phase I-II)	[Bauer et al.][68]
DPIV	Yes	Tetravalent	WRAIR[b] and GlaxoSmithKline	In vivo (phase I)	[Diaz et al.][69]
TVDV	Yes	Tetravalent	U.S. Army Medical Research and Development Command, WRAIR,[b] NMRC and Vical	In vivo (animal and phase I)	[Pintado Silva and Fernandez-Sesma][70]
V180	Yes	Tetravalent	Merck & Co	In vivo (phase I)	
DSV4	No	Tetravalent	International Centre for Genetic Engineering and Biotechnology	In vivo (animal)	
mRNA vaccines (prME-mRNA, E80-mRNA, and NS1-mRNA)	No	Tetravalent	CAS Laboratory of Molecular Virology and Immunology, Institute Pasteur of Shanghai	In vivo (animal)	[Zhang et al.][71]

[a]National Institute of Allergy and Infectious Diseases, National Institutes of Health.
[b]Walter Reed Army Institute of Research.

endothelium. This explains the elevated risk of plasma leakage in dengue fever.[76]

The standard methods employed for DENV diagnosis comprise the enzyme-linked immunosorbent assay and the reverse transcription-polymerase chain reaction technique.[77] Early identification of NS1 can be a highly successful method for diagnosing DENV infection soon after the onset of fever, as NS1 appears in the early stages of the infection.[78] Diagnosing diabetes entails measuring blood glucose levels either while fasting or during an oral glucose tolerance test. HbA1c readings are now suggested for diagnosing diabetes and pre-diabetes.[79]

A retrospective investigation of confirmed dengue patients with diabetes found that metformin use reduced the incidence of severe dengue and had a dose-dependent inverse relationship with dengue severity.[80] This study does not indicate if metformin affects diabetes management or DENV replication. An open-label, two-phase dose escalation experiment (NCT04377451) of metformin in dengue patients with obesity is underway in Vietnam to determine its acute illness efficacy.[81] Currently, phase III efficacy trials are evaluating the tetravalent dengue vaccine candidate TV005. This dengue vaccination induces immune responses against all four serotypes. Based on these findings, more research is needed to speed up vaccination availability.[2] An adjuvant in a vaccine can decrease or remove undesirable side effects while boosting the effectiveness, immune response, and duration of the vaccination.[82] A research study demonstrated that individuals who had both dengue and type 2 diabetes and maintained well-controlled blood sugar levels were unlikely to have a greater probability of experiencing severe dengue or its sequelae, irrespective of any other pre-existing health issues. These findings emphasize the significance of optimizing blood sugar levels by maintaining a HbA1c level below 7%, as suggested by the American Diabetes Association for patients with diabetes.[26]

A study conducted in Singapore revealed that adult patients who had both diabetes and hypertension had a higher likelihood of developing DHF compared to those without these disorders. The result was drawn from a case–control analysis of individuals with DHF and dengue. The cause of this connection is not apparent, although diabetes mellitus leads to immune system malfunction along with simultaneous immunosenescence. Elderly dengue patients with diabetes should be hospitalized for close observation and early management with fluid therapy, since it can be lifesaving.[83] Close monitoring of crucial clinical indications is necessary, along with recognizing metabolic abnormalities such as diabetes, which can indicate a more rapid clinical progression. Diabetes mellitus is marked by the generation of pro-inflammatory cytokines and endothelial dysfunction, which could potentially worsen the cytokine storm observed in DHF.[84] Furthermore, numerous instances of comorbidities remain unidentified and unknown. Epidemiological data for each disease, whether particular or associated with comorbidities, is crucial for managing disease severity and planning and evaluating prevention measures in low and middle-income countries.[85] A research study by Menaka et al.[86] demonstrated that a 56-year-old male patient was hospitalized due to symptoms of excessive urination, excessive thirst, and dizziness. To verify the diagnosis of diabetic ketoacidosis, the capillary blood glucose level was measured and determined to be above 600 mg/dl. Furthermore, the presence of metabolic acidosis was noted, evident by a pH level of 7.28 and the detection of urine ketone bodies. The patient disclosed a prior episode of dengue

hemorrhagic fever. The initiation of goal-directed fluid therapy followed the confirmation of the diagnosis of DHF. To restore the intravascular volume, fluid was given based on the observed changes in the packed cell volume (PCV). Dextran was administered in accordance with the given instructions. Continuous monitoring was performed to measure blood pressure, pulse pressure, urine output, and PCV. At regular intervals, measures of arterial blood gas, capillary blood glucose, and serum electrolytes were collected, and the insulin infusion was modified as needed. Additionally, potassium replacement was performed as necessary. To effectively manage the dengue leaking phase, it is crucial to prevent excessive fluid accumulation by refraining from overly aggressive intravenous fluid therapy. Simultaneously, it is crucial to administer sufficient fluids throughout the management of DKA (Diabetic Ketoacidosis) to prevent prolonged acidosis, which might result in additional difficulties. Managing fluid balance becomes a therapeutic difficulty when these two conditions are present simultaneously.[86] Intensive monitoring and careful management of fluids are effective in addressing this difficulty.

Elderly individuals diagnosed with diabetes should strive for an ideal dietary pattern and protein consumption. All elderly persons with diabetes who are able to do so safely are advised to participate in consistent physical activity, including aerobic exercise, weight-bearing exercise, and/or resistance training. Elderly people diagnosed with type 2 diabetes who are overweight or obese and have the capacity to engage in safe physical activity might consider implementing a comprehensive lifestyle modification. The primary objective of this strategy is to introduce dietary modifications, enhance physical activity, and attain a moderate weight reduction of 5–7%. Enhancements in quality of life, mobility and physical functioning, and management of cardiometabolic risk factors are among the advantages of this strategy. For elderly individuals with diabetes, it is advisable to decrease the dosage of drugs that have the potential to induce hypoglycemia (such as insulin, sulfonylureas, or meglitinides) or switch to an alternative prescription that carries a reduced risk of causing hypoglycemia. This therapy should be implemented for persons who have a high susceptibility to hypoglycemia, while considering their particular glycemic goals. It is advisable to simplify intricate treatment plans, particularly those requiring insulin, to minimize the chances of experiencing low blood sugar levels (hypoglycemia) and taking many medications (polypharmacy). This simplification can also alleviate the burden of therapy, provided that it aligns with personalized glycemic targets.[87]

The predominant containers used as breeding grounds for *Aedes* mosquitoes included tires, plastic buckets, plastic drums, and coconut shells. Breeding of *Aedes* larvae occurs in stagnant water. Governments must effectively manage the proper handling, elimination, and recycling of containers. The residents should also take responsibility to prevent water accumulation on rooftops, in courtyards, and in flowerpots. Using drones to identify stagnant water and potential mosquito breeding sites on rooftops is strongly suggested.[2] To reduce the occurrence of dengue, conventional methods such as the extensive application of durable insecticide-treated nets (LLINs), indoor residual spraying (IRS), spraying in peridomestic spaces, and mosquito repellents are being employed. After conducting thorough study, it is now feasible to employ Green Synthesized Plant-Based Metallic Nanoparticles as an effective approach for the treatment of dengue. There are several approaches that can be used to efficiently control dengue in areas where it is widespread. These include the release of genetically modified mosquito species, bacteria such as Wolbachia spp. and Asaia spp., protozoans like *Chilodonella uncinata*, bacterial agents like Bacillus thuringiensis subspecies israelensis, predatory fish such as *Gambusia affinnis* and *Poecilia reticulata*, fungi like *Beauveria bassiana*, insect growth regulators, biopesticide spinosad, and mechanical control techniques like eave tubes and attractive sugar baits. These strategies have been extensively researched and proven to be effective.[88]

Cutting-edge technology and scientific research can assist in addressing the challenges posed by diabetes and dengue viruses in low- and middle-income nations, which are characterized by lack of awareness, inadequate healthcare infrastructure, and insufficient preventive measures. This includes using artificial intelligence (AI) for population screening and medical support, the internet of things (IoT) for monitoring *Aedes* mosquito outbreaks, and the surface acoustic wave technique for identifying female *Aedes* mosquitoes based on frequency to eliminate them promptly.[89,90] Identifying metabolic risk variables for DHF might help clinicians prioritize dengue patients upon admission, ensuring appropriate level of treatment. This would assist healthcare personnel in dengue-endemic regions of developing countries to identify individuals at higher risk and optimize the utilization of the limited healthcare resources at their disposal. Lifestyle management involves meal planning, scheduled physical activity, blood glucose monitoring, taking diabetic medications, and managing episodes of illness and fluctuations in blood glucose levels. Developing novel diabetic care management is crucial to ensuring consistent care, enhancing healthy habits, and decreasing patient risk factors and comorbidities. Diabetes technology can empower individuals with diabetes and enhance their self-care.[91] There is a lack of evidence-based data about the clinical presentation, prognosis, and impact of antidiabetic therapy on dengue fever. Consequently, additional research is necessary to fill this knowledge vacuum in the field. This will help provide a fundamental framework for future endeavors in research.

8 | CONCLUSION

The worldwide occurrence of dengue disease has escalated to epidemic levels. People with diabetes have a higher incidence of DHF, suggesting a potential complication in this population. Diabetes patients with dengue infection demonstrate an increase in inflammatory markers. Diabetes mellitus suppresses the immune system, making the evolution of dengue fever worse. With the ongoing dengue spread in Asian countries, it is crucial that we focus our attention and resources on treating this issue more accurately and efficiently.

AUTHOR CONTRIBUTIONS

Shandipon Roy Shawon: Conceptualization; writing—original draft. **Mohammad Khaled Iqbal Hamid:** Conceptualization; writing—original

draft. **Hossain Ahmed:** Conceptualization; writing—original draft. **Sakif Ahamed Khan:** writing—review and editing; conceptualization. **Syed Masudur Rahman Dewan:** Conceptualization; writing—review and editing; supervision.

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CONFLICT OF INTEREST STATEMENT

None.

GUARANTOR

All authors have read and approved the final version of the manuscript. SMRD, the corresponding author, had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

TRANSPARENCY STATEMENT

The lead author Syed Masudur Rahman Dewan affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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