

# Role of Oxidative and Nitrosative Stress in Dengue Pathogenesis: A Mini-Review

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## Abstract

Dengue is a mosquito-borne acute viral disease with ubiquitous distribution in tropical and subtropical areas of the world. Dengue virus (DENV) infection is transmitted by the bite of a female *Aedes aegypti* mosquito (the most important vector) infected with DENV. Clinical presentation of this typical arboviral disease varies along a wide spectrum of clinical symptoms. During the course of DENV infection, some individuals develop severe manifestations relates to plasma leakage into tissues caused by increased vascular permeability. The severity of dengue disease may vary considerably according to age, ethnicity, genetic factors, immune status and underlying disease. It may also depend on the co-circulation of DENV serotypes and sequential (secondary) infections with different DENV serotypes. While the exact mechanism of pathogenesis of dengue remains elusive, several lines of evidence demonstrating that DENV infection-derived oxidative stress may trigger the release of proinflammatory cytokines, including TNF-alpha, participating in collective action in dengue disease pathogenesis. In conclusion, we review these findings and discuss about the recent advances that propose a major role of oxidative-nitrosative stress on dengue pathogenesis.

**Keywords:** Dengue; Dengue virus; Severe dengue; Oxidative stress; Nitrosative stress; Endothelial dysfunction

## Introduction

Dengue is a mosquito-borne acute disease with ubiquitous distribution in tropical and subtropical areas of the world. One example of the importance of this viral disease can be seen in the results of a recent multicentric study, which estimates 390 million dengue infections per year (95% credible interval 284-528 million), of which approximately 25% (95% credible interval 67-136 million) manifest clinically (with any severity of disease) [1]. Dengue is caused by Dengue virus (DENV), a single stranded RNA positive-strand virus of the family Flaviviridae. There are four antigenically different serotypes of the virus (DENV-1 to -4) [2,3].

Clinical presentation of this typical arboviral disease varies along a wide spectrum of clinical symptoms. During the course of DENV infection, some individuals develop severe manifestations relates to plasma leakage into tissues caused by increased vascular permeability. The severity of dengue disease may vary considerably according to age, ethnicity, genetic factors, immune status and underlying disease. It may also depend on the co-circulation of DENV serotypes and sequential (secondary) infections with different DENV serotypes [4-8]. In this respect, it has been proposed the involvement of DENV infection-derived oxidative stress on the severity of dengue [9].

By definition, oxidative stress is a disturbance in the balance between the production of reactive oxygen species (ROS) and antioxidants defenses in favour of the pro-oxidants [10,11]. A parallel process is nitrosative stress which is defined as an indiscriminate nitrosilation of biological molecules [12]. Under these stress conditions, the activation of several stress-sensitive intracellular signaling pathways have been reported. This activation involves the production of gene products that can lead to cell death and/or pathophysiological conditions [12-15].

Plasma leakage is the most important characteristic and the best indicator of severity in dengue virus infection. The structural basis of altered vascular permeability is more related to endothelial dysfunction that destruction of endothelial cells (ECs) [16-19]. In this regard,

Yacoub and coworkers [20] have recently reported association between endothelial dysfunction and dengue severity in children and adults.

Many lines of independent empirical evidence explain the relationship between endothelial dysfunction and oxidative stress [21-31]. Endothelial dysfunction can be defined as the partial or complete loss of balance between vasoconstrictor and vasodilators, growth promoting and inhibiting factors, pro-atherogenic and anti-atherogenic factors, and pro-coagulant and anti-coagulant factors. The earliest manifestation of endothelial dysfunction is impaired endothelium-dependent vasodilatation produced by diminished nitric oxide (NO) bioactivity, mainly due to accelerated NO radical degradation by reactive oxygen species (ROS) [32,33]. Consequently, this free radical and messenger molecule is associated with inflammation and oxidative stress [24,28,30].

Multiple studies have established that oxidative stress as a determinant of vascular homeostasis [34-37], and is involved in the pathogenesis of various infectious diseases, such as chronic hepatitis C [38], Japanese encephalitis [39], leptospirosis [40], respiratory syncytial virus-induced acute lung inflammation [41], malaria [42], chagas cardiomyopathy [43], schistosomiasis [44], sepsis [45], acute herpes simplex virus type 1, measles subacute sclerosing panencephalitis [46], and dengue [47].

For the latter example, Soundravally and coworkers suggest that DENV infection-induced oxidative stress can trigger the release

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of proinflammatory cytokines, including TNF-alpha, participating collectively in pathogenesis of severe dengue [9]. This is consistent with studies indicating that DENV virulent strains have a strong influence on gene expression of a variety of proinflammatory cytokines [48-51].

Nwariaku and coworkers have reported that TNF-mediated junctional dissociation and intercellular gap formation are associated with tyrosine phosphorylation of vascular endothelial cadherin (VE-cadherin) [52]. Interestingly, a growing body of evidence demonstrates increased DENV-infected human ECs permeability in conjunction with a downregulation of VE-cadherin by phosphorylation [52-56].

Additionally, there is evidence that an excess circulating angiopoietin-2 (ang-2) may contribute with endothelial barrier disruption caused by intercellular gap formation and downregulation of VE-cadherin [57]. It is important to note that ang-2 has been associated with transient systemic vascular leak in DENV infection [58,59].

Moreover, Thakur et al., [60] reported elevated levels of vascular endothelial growth factor (VEGF) in adults with severe dengue in comparison with patients with non-severe dengue with and without warning signs. Considering that VEGF induces VE-cadherin tyrosine phosphorylation in ECs [61], it is important note that VEGF induction by NADPH oxidase-derived ROS [62,63], and DENV infection-induced intracellular ROS/RNS production have been reported [64,65]. A related study showed that profile of VEGF upregulated expression was associated with DENV infection in human endothelial cells [66].

These data together provide direct evidence for role of oxidative-nitrosative stress in DENV-induced vascular leakage.

Survey of recent studies suggest important role of oxidative-nitrosative stress in pathogenesis of dengue [67,68]. These evidences shows that oxidative/nitrosative stress may be associated with production of dengue pathogenesis-related protein, increased susceptibility of mice to DENV infection with higher replication, hemorrhage development in experimental animal model, and induction of apoptosis in various human and animal cell lines [67]. Also, changes in plasma levels of reactive nitrogen species (nitric oxide radicals), endogenous antioxidants enzymes, lipid peroxidation and protein oxidation markers has been observed in patients with dengue infection [68].

In this context, we are now executing a study evaluating the potential use of plasma levels of protein carbonyls, lipid hydroperoxides and manganese-dependent superoxide dismutase, as prognostics biomarkers for dengue infection severity in pediatric patients, in order to early identification of patients who risk developing severe dengue, and to focus treatment in these group of patients.

## References

1. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, et al. (2013) The global distribution and burden of dengue. *Nature* 496(7446): 504-507.
2. Sadon N, Delers A, Jarman RG, Klungthong C, Nisalak A, et al. (2008) A new quantitative RT-PCR method for sensitive detection of dengue virus in serum samples. *J Virol Methods* 153(1): 1-6.
3. Mangold KA, Reynolds SL (2013) A review of dengue fever: a resurging tropical disease. *Pediatr Emerg Care* 29(5): 665-669.
4. Malavige GN, Fernando S, Fernando DJ, Seneviratne SL (2004) Dengue viral infections. *Postgrad Med J* 80(948): 588-601.
5. Guzmán MG, Kour G (2004) Dengue diagnosis, advances and challenges. *Int J Infect Dis* 8(2): 69-80.
6. Thai KT, Nishiura H, Hoang PL, Tran NTT, Phan GT, et al. (2011) Age-specificity of clinical dengue during primary and secondary infections. *PLoS Negl Trop Dis* 5(6): e1180.
7. Hung NT, Lan NT, Lei HY, Lin YS, Le Bich LIEN, et al. (2005) Association between sex, nutritional status, severity of dengue hemorrhagic fever, and immune status in infants with dengue hemorrhagic fever. *Am J Trop Med Hyg* 72(4): 370-374.
8. Anders KL, Nguyet NM, Chau NVV, Hung NT, Thuy TT, et al. (2011) Epidemiological factors associated with dengue shock syndrome and mortality in hospitalized dengue patients in Ho Chi Minh City, Vietnam. *Am J Trop Med Hyg* 84(1): 127-134.
9. Soundravally R, Hoti SL, Patil SA, Cleetus CC, Zachariah B, et al. (2014) Association between proinflammatory cytokines and lipid peroxidation in patients with severe dengue disease around defervescence. *Int J Infect Dis* 18: 68-72.
10. Halliwell B (2007) Biochemistry of oxidative stress. *Biochem Soc Trans* 35(5): 1147-1150.
11. Giustarini D, Dalle-Donne I, Tsikas D, Rossi R (2009) Oxidative stress and human diseases: origin, link, measurement, mechanisms, and biomarkers. *Crit Rev Clin Lab Sci* 46(5-6): 241-281.
12. Heinrich TA, Silva RS, Miranda KM, Switzer CH, Wink DA, et al. (2013). Biological nitric oxide signalling: chemistry and terminology. *Br J Pharmacol* 169(7): 1417-1429.
13. Evans JL, Goldfine ID, Maddux BA, Grodsky GM (2002) Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes. *Endocr Rev* 23(5): 599-622.
14. Dias AS, Porawski M, Alonso M, Marroni N, Collado PS (2005) Quercetin decreases oxidative stress, NF-κB activation, and iNOS overexpression in liver of streptozotocin-induced diabetic rats. *J Nutr* 135(10): 2299-2304.
15. Orr WC, Sohal RS (1993) Effects of Cu-Zn superoxide dismutase overexpression on life span and resistance to oxidative stress in transgenic *Drosophila melanogaster*. *Arch Biochem Biophys* 301(1): 34-40.
16. Dalrymple NA, Mackow ER (2012) Roles for endothelial cells in dengue virus infection. *Adv Virol* 2012.
17. Srikiatkachorn A (2009) Plasma leakage in dengue haemorrhagic fever. *Thromb Haemost* 102(6): 1042-1049.
18. Basu A, Chaturvedi UC (2008) Vascular endothelium: the battlefield of dengue viruses. *FEMS Immunol Med Microbiol* 53(3): 287-299.
19. Lei HY, Yeh TM, Liu HS, Lin YS, Chen SH, et al. (2001) Immunopathogenesis of dengue virus infection. *J Biomed Sci* 8(5): 377-388.
20. Yacoub S, Wertheim H, Simmons CP, Screaton G, Wills B, et al. (2015) Microvascular and endothelial function for risk prediction in dengue: an observational study. *The Lancet* 385: S102.
21. Silva BR, Pernomian L, Bendhack LM (2012) Contribution of oxidative stress to endothelial dysfunction in hypertension. *Frontiers in physiology* 3: 441.
22. Gori T, Münzel T (2011) Oxidative stress and endothelial dysfunction: Therapeutic implications. *Annals Med* 43(4): 259-272.
23. Rodríguez-Mañas L, El-Assar M, Vallejo S, López-Dóriga P, Solís J, et al. (2009) Endothelial dysfunction in aged humans is related with oxidative stress and vascular inflammation. *Aging cell* 8(3): 226-238.
24. Wadsworth RM (2008) Oxidative stress and the endothelium. *Experimental physiology* 93(1): 155-157.
25. Pereira EC, Ferderbar S, Bertolami MC, Faludi AA, Monte O, et al. (2008) Biomarkers of oxidative stress and endothelial dysfunction in glucose intolerance and diabetes mellitus. *Clin Biochem* 41(18): 1454-1460.
26. Zalba G, Fortuño A, San José G, Moreno MU, Beloqui O, et al. (2007) Oxidative stress, endothelial dysfunction and cerebrovascular disease. *Cerebrovascular Diseases* 24: 24-29.
27. Muller G, Goettsch C, Morawietz H (2007) Oxidative stress and endothelial dysfunction. *Hämostaseologie* 27(1): 5-12.
28. Esper RJ, Nordaby RA, Vilariño JO, Paragano A, Cacharrón JL, et al. (2006) Endothelial dysfunction: A comprehensive appraisal. *Cardiovasc Diabetol* 5(1): 1.
29. Parodi O, De Chiara B, Campolo J, Sedda V, Roubina E (2005) Endothelial dysfunction and oxidative stress in sepsis. *Giornale italiano di nefrologia: organo ufficiale della Società italiana di nefrologia* 23: S69-73.
30. Fayers KE, Cummings MH, Shaw KM, Laight DW (2003) Nitrate tolerance

- and the links with endothelial dysfunction and oxidative stress. *Br J C Pharmacol* 56(6): 620-628.
31. Vallance P, Chan N (2001) Endothelial function and nitric oxide: clinical relevance. *Heart* 85(3): 342-350.
32. Bermudez V, Bermudez F, Acosta G, Acosta A, Anez J, et al. (2008) Molecular mechanisms of endothelial dysfunction: from nitric oxide synthesis to ADMA inhibition. *Am J Ther* 15(4): 326-333.
33. Badimón L, Martínez-González J (2006) Disfunción endotelial. *Revista Española de Cardiología* 6: 21-30
34. Rahman T, Hosen I, Islam MT, Shekhar HU (2012) Oxidative stress and human health. *Adv in Biosci Biotech* 3(7A): 97.
35. Rojas A, Figueroa H, Re L, Morales MA (2006) Oxidative stress at the vascular wall. Mechanistic and pharmacological aspects. *Arch Med Res* 37(4): 436-448.
36. Widlansky ME, Gokce N, Keaney JF, Vita JA (2003) The clinical implications of endothelial dysfunction. *J Am Coll Cardiol* 42(7): 1149-1160.
37. Cai H, Harrison DG (2000) Endothelial dysfunction in cardiovascular diseases: The role of oxidant stress. *Circ Res* 87(10): 840-844.
38. Levent G, Ali A, Ahmet A, Polat EC, Aytaç Ç, et al. (2006) Oxidative stress and antioxidant defense in patients with chronic hepatitis C patients before and after pegylated interferon alfa-2b plus ribavirin therapy. *J Translational Med* 4(1): 1.
39. Yang TC, Lai CC, Shiu SL, Chuang PH, Tzou BC, et al. (2010) Japanese encephalitis virus down-regulates thioredoxin and induces ROS-mediated ASK1-ERK/p38 MAPK activation in human promonocyte cells. *Microbes Infect* 12(8): 643-651.
40. Kalugamage T, Rodrigo C, Vithanage T, Somaratne P, De Silva HJ, et al. (2013) Low serum total nitrite and nitrate levels in severe leptospirosis. *BMC Infect Dis* 13(1): 1.
41. Hosakote YM, Liu T, Castro SM, Garofalo RP, Casola A (2009) Respiratory syncytial virus induces oxidative stress by modulating antioxidant enzymes. *Am J Respir Cell Mol Biol* 41(3): 348-357.
42. Fabbri C, De Cássia Mascarenhas-Netto R, Lalwani P, Melo GC, Magalhães BM, et al. (2013). Lipid peroxidation and antioxidant enzymes activity in *Plasmodium vivax* malaria patients evolving with cholestatic jaundice. *Malar J* 12(1): 1.
43. Machado FS, Tanowitz HB, Ribeiro AL (2013) Pathogenesis of chagas cardiomyopathy: role of inflammation and oxidative stress. *J Am Heart Assoc* 2(5): e000539.
44. Cunha G, Silva V, Bessa K, Bitencourt M, Macêdo U, et al. (2012) Levels of oxidative stress markers: correlation with hepatic function and worm burden patients with schistosomiasis. *Acta Parasitologica* 57(2): 160-166.
45. Macdonald J, Galley HF, Webster NR (2003) Oxidative stress and gene expression in sepsis. *Br J Anaesth* 90(2): 221-232.
46. Valyi-Nagy T, Dermody TS (2005) Role of oxidative damage in the pathogenesis of viral infections of the nervous system. *Histol Histopathol* 20(3): 957-967.
47. Gil L, Martínez G, Tápanes R, Castro O, Gonzalez D, et al. (2004) Oxidative stress in adult dengue patients. *Am J Trop Med Hyg* 71(5): 652-657.
48. Ubol S, Chareonsirisuthigul T, Kasisith J, Klungthong C (2008) Clinical isolates of dengue virus with distinctive susceptibility to nitric oxide radical induce differential gene responses in THP-1 cells. *Virology* 376(2): 290-296.
49. Rababert J, Wasi C, Kinney R, Kasisith J, Pitidhambhorn D, et al. (2007) Attenuating characteristics of DEN-2 PDK53 in flavivirus-naïve peripheral blood mononuclear cells. *Vaccine* 25(19): 3896-3905.
50. Moreno-Altamirano MMB, Romano M, Legorreta-Herrera M, Sánchez-García FJ, Colston MJ (2004) Gene expression in human macrophages infected with dengue virus serotype-2. *Scand J Immunol* 60(6): 631-638.
51. Cologna R, Rico-Hesse R (2003) American genotype structures decrease dengue virus output from human monocytes and dendritic cells. *J Virol* 77(7): 3929-3938.
52. Nwariaku FE, Liu Z, Zhu X, Turnage RH, Sarosi GA, et al. (2002) Tyrosine phosphorylation of vascular endothelial cadherin and the regulation of microvascular permeability. *Surgery* 132(2): 180-185.
53. Corada M, Mariotti M, Thurston G, Smith K, Kunkel R, et al. (1999) Vascular endothelial-cadherin is an important determinant of microvascular integrity in vivo. *Proc Natl Acad Sci* 96(17): 9815-9820.
54. Dewi BE, Takasaki T, Kurane I (2008) Peripheral blood mononuclear cells increase the permeability of dengue virus-infected endothelial cells in association with downregulation of vascular endothelial cadherin. *J Gen Virol* 89(3): 642-652.
55. Kanlaya R, Pattanakitsakul SN, Sinchaikul S, Chen ST, Thongboonkerd V (2009) Alterations in actin cytoskeletal assembly and junctional protein complexes in human endothelial cells induced by dengue virus infection and mimicry of leukocyte transendothelial migration. *J Proteome Res* 8(5): 2551-2562.
56. Luplertlop N, Missé D (2008) MMP cellular responses to dengue virus infection-induced vascular leakage. *Jpn J Infect Dis* 61(4): 298-301.
57. Parikh SM, Mammoto T, Schultz A, Yuan HT, Christiani D, et al. (2006) Excess circulating angiotensin-2 may contribute to pulmonary vascular leak in sepsis in humans. *PLoS Med* 3(3): e46.
58. Van De Weg CA, Pannuti CS, Van Den Ham HJ, De Araújo ES, Boas LS, et al. (2014) Serum angiotensin-2 and soluble VEGF receptor 2 are surrogate markers for plasma leakage in patients with acute dengue virus infection. *J Clin Virol* 60(4): 328-335.
59. Rampengan NH, Warouw S, Ganda IJ (2015) Serum Angiotensin-2 as marker of plasma leakage in Dengue viral infection. *Am J Clin Exp Med* 3: 39-43.
60. Thakur P, Chakravarti A, Aggarwal S, Uppal B, Bhalla P (2016) Elevated levels of vascular endothelial growth factor in adults with severe dengue infection. *Virusdisease* 27(1): 48-54.
61. Esser S, Lampugnani MG, Corada M, Dejana E, Risau W (1998) Vascular endothelial growth factor induces VE-cadherin tyrosine phosphorylation in endothelial cells. *J Cell Sci* 111(13): 1853-1865.
62. Ushio-Fukai M (2007) VEGF signaling through NADPH oxidase-derived ROS. *Antioxid Redox Signal* 9(6): 731-739.
63. Fay J, Varoga D, Wruck CJ, Kurz B, Goldring MB, et al. (2006) Reactive oxygen species induce expression of vascular endothelial growth factor in chondrocytes and human articular cartilage explants. *Arthritis Res Ther* 8(6): 1.
64. Olgarnier D, Peri S, Steel C, Van Montfort N, Chiang C, et al. (2014) Cellular oxidative stress response controls the antiviral and apoptotic programs in dengue virus-infected dendritic cells. *PLoS Pathog* 10(12): e1004566.
65. Yen YT, Chen HC, Lin YD, Shieh CC, Wu-Hsieh BA (2008) Enhancement by tumor necrosis factor alpha of dengue virus-induced endothelial cell production of reactive nitrogen and oxygen species is key to hemorrhage development. *J Virol* 82(24): 12312-12324.
66. Azizan A, Fitzpatrick K, Signarovitz A, Tanner R, Hernandez H, et al. (2009) Profile of time-dependent VEGF upregulation in human pulmonary endothelial cells, HPMEC-ST1.6R infected with DENV-1,-2,-3, and-4 viruses. *Virol J* 6(1): 1.
67. Orozco RC, Pinzón-Redondo HS, Alvis-Guzmán NR (2015) Oxidative-nitrosative stress and dengue disease: A systematic review of in vivo/in vitro studies. *Revista Cubana de Medicina Tropical* 67(2).
68. Castro R, Pinzón HS, Alvis-Guzmán N (2015) A systematic review of observational studies on oxidative/nitrosative stress involvement in dengue pathogenesis. *Colombia Médica* 46(3): 135-143.