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Current understanding of the pathogenesis of Dengue virus infection and therapeutic diet for controlling associated symptoms

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Abstract
In modern decades, Dengue virus is very much serious concern in both developing and developed countries. In tropical areas, 75% occurrence of Dengue are present, among them most of the infestations are lenient to immunosuppressed besides 5% occasion of Dengue infections are chronic. Persistent Dengue infections have many serotypes of Dengue virus. The seriousness of Dengue is hanged on various mechanism of immunopathogenic including host and viral agents. Pathophysiology of Dengue virus can be depended on alteration of T cells, immunopathology of antibody, cytokine storm. Manifestations of Dengue are agony in bones, muscles, joints, headache, temperature of fever is 40 °C, macular skin infestations, small haemorrhagic infections including purpura, malaise, petechiae, ecchymosis, epistaxis, haematuria, gums bleeding, aches. Dengue virus infections are present about 3 to 7 days approximately. Dietary modification is very much needed to balance the manifestation of Dengue. The therapy of macrophages must be started through modifying the concentration of butyrate along with specifically manage the ratio of *Bacteroidetes* and *Firmicutes* which lesions the activity of proinflammatory mediators for instance NO, IL-6, IL-12 with the help of suitable dietary pattern. Noteworthy, adequate amino acids, dietary fibre, Poly Unsaturated Fatty Acid (PUFA), Mono Unsaturated Fatty Acid (MUFA), vitamins, polyphenols and other bioactive components are very much closely associated in monitoring the homeostasis of macrophages in intestine. This review is the sum up of pathophysiology, symptoms along with dietary strategy of Dengue virus.

Keywords: Bacteroidetes, Dengue haemorrhagic fever, Dengue shock syndrome, dietary fibre, virus

Introduction
The aetiology of dengue is the dengue virus (DENV). This is very much widespread as a serious disorder, influence 400 million of people around the globe per year [1]. Authors have asserted that, the manifestations of Dengue may be prevented as an asymptomatic or moderate flu like disease, some of this generate chronic disorder like Dengue haemorrhagic fever (DHF), Dengue shock syndrome (DSS), which is expressed with the help of coagulator dysfunctions, dripping of capillaries as well as escalated vascular frailty [2]. Furthermore, secondary DENV infestation is very much interconnected with infections of chronic dengue [3]. The symptoms of dengue are nausea, fever, muscle cramp, joint pain, and headache apart from that skin infections are very much prominent [4]. According to literature review, DENV is a linear stranded RNA flavivirus attached along with the capsid and circled through a binding protein consists E (Envelope) and prM/M (premembrane/ membrane) structural protein contents. Some non-structural protein (NS) elements are NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5. Included NS have multiple functions such as NS1 coordinates along with NS4A/B to establish the viral replication proceedings. On the other hand, NS3 execute helicase and protease enzyme [5]. NS4A initiates autophagy as well as NS4B formulate disconnection of NS3 helicase from viral RNA [6]. NS5B is regarded as DENV protein which is the applicable as RNA dependent RNA polymerase that reproduces viral RNA and RNA methyl-transferase which save the viral genome through the capping of RNA as well as smoothing the translation of polyprotein [7]. Furthermore, NS5 is very much pronounced for

replicating the virus, which is selected for cytotoxic T cells retaliations [8]. DENV may supress the signal of receptors as well as type I interferon feedback through the retinoic acid inducible gene- I (RIG-I) such receptors (RLR), Nucleotide adhering oligomerisation domain (NOD), such as receptors or toll like receptors (TLRs) [9]. Noteworthy, the procedure of methylation of NS5 2'-O of 5' stop the virus infestation is discerned through RIG-I on the other hand NS3 is very much associated in suppressing the translocation of RIG-1 up to mitochondria through adhering along with mitochondrial chaperon protein 14-3-3€. NS4A is linked along with suppressing the RIG-1 communication along with Mitochondrial antiviral signalling protein (MAVS) through attaching to the MAVS-CARD looks like domain and also the dominion of the transmembrane [10]. Noteworthy, NS2A and NS4B are very much interconnected in supressing the RIG-I/MAVS signalling avenue though stopping the phosphorylation of TANK binding kinase 1 (TBK1) interferon regulating factors (IRFs) besides lesion the concentration of IFNβ introduction [11]. Moreover, NS2B/3 stop interferon formation through breaking the activator of interferon gene protein compounds [12]. DENV has serotypes with four variants like DENV-1, 2, 3, 4 [13]. Precisely, DENV is established after morsel of female Aedes mosquitoes. Primarily, infection along with serotypes of DENV promote inadequate security opposed to all four serotypes because of only cross reactions. This sensitized immunological cognition as well as security may be grabbed if dengue affected patients are more prone to reinfections along with same serotyped factors [14].

Pathophysiology

The pathophysiology of DENV infection is intricate among the virus, genes of host and immune responsibility of the hosts, these are very much adhered to DENV pathogenesis. Authors have noted that, phagocytes the combination of virus-antibody through the cells by Fcγ (Fragment-γ) receptors therefore enhancing viremia [15].

Pathophysiology of T cells in case of DENV

The aetiology of DENV infection is involved to various serotypes [16]. CD8 T cells have essential potentiality for lesions the activity of pathogenic microbes. Many dengue complications arise 10-20-fold severe in sick person along with peripheral DENV infestations so that, prime construction of the adaptive immunity to one kind serotype of DENV increases the chronic complications in time of secondary contamination which are expressed by lots of serotypes [17]. Initial DENV infestations like triggering the vernacular CD8 T cells to discriminate into effector T cells [18]. The HLA confined T cell epitopes on various protein molecule are observed to each person who are unsusceptible to DENV infestation. The recognition of DENV is constructional or non-constructional proteins are arbitrated [19]. T cells may acknowledge to subordinate infestations which is be caused of various DENV serovar [20]. Usually, vigorous immunity emerges in each person who have similar serovar as well as cross active serotype T cells retaliation appears in post condition of secondary infestation. Enhanced frequency of DENV particular T cells have shown in primary DENV infestation and these cells acts for triggered phenotypic matters [21]. In post condition of inflammation, particular T cells have shown triggered marking points CD69 after that, another stimulator like CD38, CD71, HLA-DR [22]. Noteworthy, CD8 T cells have produced in time of IFN γ activation along with many peptides which are caused of the downregulation in TCR signalling component. In case of acute DENV inflammation, homotypic T cells are gathered opposed to inflamed DENV that is interlinked along with defence contrary to serotype. Subordinate DENV infestations are caused of various serotype that promote endangered T cells. Therefore, unsuccessfully regulating the infection at the time of subordinate heterologous infestation besides keep up chronic dengue inflammation through introduction & imprudent cytokine generation [21]. Authors have reviewed that, cytokine storm is the most pronounced in chronic manifestation of dengue besides increased the parameter of proinflammatory cytokines like TNF, soluble TNF receptors 1(sTNFR1), sTNFR2, IFN-γ and chemokines like CXCL8, CXCL9, CXCL10, CXCL11 and CCL5 and anti-inflammatory cytokine like Interleukin 10(IL-10) are very much prominent [23]. Newly the interconnection among DENV and T cells have investigated in case of dengue vernacular $CD4^+$T and $CD8^+$ T cells are liberal for dengue infestations [24]. These couple cells assist in replication of virus and excrete the components of virus. DENV may contaminate $CD4^+$T and $CD8^+$T cells in case of acute illness. DENV is inflamed and reproduced in $CD4^+$T cells and $CD8^+$T cells by interconnection along with heparan sulphate moiety [25]. Baring of DENV to heparin- an obstructor of host heparin sulphate viral communication restricted the virus infection in $CD4^+$T cells and $CD8^+$T cells along with heparinase III which is the heparin sulphate degrading enzyme that ameliorate DENV infections affirmed that, heparin-sulphate moiety is included into DENV attaching to T cells. Authors have addressed that, apoptosis into monocytes and dendritic cells which affect the immunity and infestation when apoptosis of parenchymal cells in liver and endothelial cells effects to hepatic inflammation and complication of haemorrhage in chronic dengue. Furthermore, apoptosis into leukocytes and the cells of micro-vascular endothelium into pulmonary and intestinal tissue is very much prominent and interlinked along with the leak of vascular plasma [26].

Immunopathology of Antibody

Antibody of DENV plays a wide role. Neutralised antibody generally focuses enveloped (E) protein and manage opposed to all epitopes [27]. Monocytes and macrophages show the receptors of immunoglobulin. DENV tropism for receptors express promoting antibody to the expression of virus defined as Antibody Dependent Enhancement (ADE) of infestation. The phenomena of ADE express complicated form of distress and it may be categorised as immunopathology. In case of ADE, preceding antibody is generated from previous infestation of DENV adheres to other DENV harmful component in ensuing infestation along with another serotype of DENV [28]. According to literature review, ADE is classified as extraneous and inherent [29]. The occurrence of extrinsic ADE due to presence of mononuclear phagocytes and enhanced the interconnection of receptors and incarnate the virus immune association. External elements are involved into bad consequences of dengue ADE correlated pathophysiology. On the other hand, internal ADE uplift the generation of viral community through suppressing the type-1 interferon and triggered the IL-10 biosynthesis and advocate Th-2 immune response [30]. Monocyte, Macrophages and

Dendritic cells indicate FCγ receptors upon the exterior. Pathophysiology to downregulate the Antibody Dependent Enhancement (ADE) into the host and furnish the Antibody dependent cellular cytotoxicity (ADCC) antibody is in there into similar serum that is caused of ADE. ADCC antibodies are present in stimulating the natural killer (NK) cells opposed to ADE [31]. Authors have also revealed that, the defeatist selector like TAF class linked NF-κB stimulator (TANK) and Sterile-alpha armadillo motif (SARM) express the lesion activity of TLR indicating compound and reveal TLR-3,4,7 in DENV viable cells, outcome is stop the generation of IRF1 and IRF3 [32]. The appearance of ADE arbitrate virus in initial macrophages persuade the activity of combination so that replication and translation of viral properties are escalated [33].

Pathophysiology of cytokine storm

Dendritic cells generate T-1 interferon however it may excrete proinflammatory cytokine. DENV infested Dendritic cells excrete matrix metalloproteinase (MMP)-2 and (MMP)-9 to enhance the accessibility of endothelial monolayer [34]. Various DENV proteins like NS4B and NS5 activate the formation of IL-8 through the macrophages and cells of endothelium. In post DENV infestation, the secretion of IL-6, CXCL10, CXCL11 and RANTES from cells of endothelium which increases the infestations and absorptivity of vascular membrane leads to leaking of plasma membrane. Initial infestation of DENV changes the pronouncement of cell surface receptors in endothelium and reactive to vascular endothelium growth factor-A (VEGF-A) [35]. In chronic dengue, the cascade of immune cells conciliates through effectors of immunity resulting chronic infection. At the time of DENV infestation, immune cells such as monocytes, macrophages, NK cells, DENV specified CD4 and CD8 T cells excrete TNF-α which express the infestation besides increasing the susceptibility of vascular membrane [36]. Furthermore, TNF-α promotes the absorptivity of vascular membrane besides cheer for cell death. The foremost functions of TNF-α in pathophysiology of DENV the siege of TNF-α may be accurate for ameliorating DENV infestations [37]. Another investigations have revealed that, parameters of cytokine oscillate extremely also after the fever. IL-10 is the strongest distinctive marking point for Dengue and CD121b is regarded as an anticipating highlighter for chronic dengue. In continuation of DENV, the formation of inflammatory cytokines such as TNF-α, IL-6 and IL-10 from the DENV infested cells, introduces the proclamation of some components like CD62E, CD106, CD62P that promote infestations, leakage the endothelial membrane and leaking the plasma membrane. Adherence the components like CD54, CD106, CD62E, CD62L, CD62P and CD154 are wavered. On the other hand, IL-2, IL-6, IL-8 are present in escalated level in chronic condition of dengue [38]. In chronic stages of DHF infected patients, enhances the parameters of IL-4, IL-6, IL-10 besides IFN-γ and IL-2 are raised in time of DENV infection especially in fever however these are present in decreasing quantity into Chronic dengue haemorrhagic fever (DHF). Furthermore, IL-2, IL-6, IFN-γ, TNF-α are present in increasingly at the case of acute infestation on the other hand, IL-4 and IL-10 are grown up at 4-8 days of sickness [39].

Symptoms of Dengue

Manifestations of Dengue are agony in bones, muscles, joints, headache, fever (temperature is 40 ^{o}C), macular skin infections, as well as small haemorrhagic infections are purpura, malaise, petechiae, ecchymosis, epistaxis, haematuria, gums bleeding, aches and also affliction. Authors have asserted that, DENV infection are present about 3 to 7 days [40].

1. Anticipated dengue but no symptoms included headache, arthralgia, myalgia, leucopenia [41].
2. Deterrent symptoms of Dengue are agony in abdomen, continuous vomiting, outflow of pleural membrane, ascites, thickening of the gallbladder wall. Bleeding of mucus membrane for instance epistaxis, haematuria, sluggishness and so on [42].
3. Chronic DENV infestations can hamper the functions of central nervous system therefore dementia or cognition and other mental illness is observed [43]. Authors have reviewed that, DENV2 serotypes affect host very much rather that DENV1 serotypes. DENV3 express musculoskeletal manifestations [44]. Moreover, trauma, gathering of fluid is caused of dyspnea, excessive bleeding, damage transaminitis like aspartate aminotransferase and alanine aminotransferase and also collapse the body organs.
4. NS1, NS3, NS5 can ameliorate this inflamed DENV infections. Moreover, chronic complications like vascular disorder, coagulopathy, cytokine storm is observed when decreased viremia [45].

Dietary strategy of Dengue fever

Western diet is very much interrelated along with proinflammatory pathological avenue. Activation of proinflammatory macrophages introduce non filtrate into adipose tissues so that resulting generate insulin resistance and low-grade inflammation [46]. An experiment has revealed that, HFD (High fat diet) intake escalation of capase-1 stimulation and IL-18 appearance in macrophages which establish insulin resistance [47]. High salt diet (HSD) has proinflammatory activation on macrophages [48]. High salt increases the proinflammatory contents of western diet model through the stimulation of proliferation of proinflammation phenotype (M1) macrophages and stop the autophagic capability of macrophages [49]. Furthermore, HSD trigger the inflammasome by reactive oxygen species (ROS) of mitochondrial cells at hypertonic state and elevated the release of IL-1β by capase-1 stimulation into macrophages [50]. HSD activate antimicrobial functions. Noteworthy, HSD establishes the generation of interferon by p38MAPK/ATF2/AP1 signalling communication and elevates antiviral capacity [51]. Limited proteins have ability to decrease the proliferation of macrophages. The cramped quantity of protein or amino acid decreases the addition of protumour M2 macrophagesb [52]. So that, western dietary model provides gloomy effects on health. On the other hand, Mediterranean diet decreases in the macrophage proinflammatory cytokine release [53]. This type of diet is very much discriminated by combined oleic acid anthocyanin therefore programmed in decreasing the proinflammatory macrophages such as MCP-1, TNF-α, IL-6 and escalated the inflammatory highlighters [54]. Another important diet is Nordic diet that lesions the inflammation [55], stop the stimulation of platelet [56]. In general berries which are foremost subject for this type of diet [57]. This diet fallen down the concentration of TNF-α [58], stop the NF-κB as well as MAPK cascades, limited the formation of nitric oxide (NO).

according to literature study, the impact of various dietary strategies is very much pertinent to macrophages of intestine. Dietary patterns alter the intestinal macrophages function and influence the homeostasis in gut [59]. HFD triggers MCP-1/CCR2 into macrophages of intestine in host have cancer in colon on the other hand, CD163 is the highlighter of macrophages have defined [60]. Increased levels of TGF-B, TNF-α, IL-1β have observed in macrophages of intestine [61]. Furthermore, short chain fatty acids promote immunomodulatory activity upon intestinal macrophages. The therapy of macrophages has proceeded through adequate butyrate production that is the key metabolic compound of gut microflora especially, proportion of *Bacteroidetes* and *Firmicutes* that lesions the activity of proinflammatory mediators for example NO, IL-6, IL-12 etc. [62]. Noteworthy, amino acids, dietary fibre, PUFA, MUFA, vitamins, polyphenols and other bioactive components are very much closely associated in monitoring the homeostasis of macrophages in intestine [63].

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