The association of obesity and severe dengue: possible pathophysiological mechanisms

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Key Learning Points:

- Obesity seems to increase the risk of developing severe dengue and as the two epidemics converge, it is important to understand why.
- Obesity has been shown to reduce AMPK activity and cause cellular stress, which could allow for enhanced viral replication and additional pathology
- In obese patients, the chronic elevation of pro-inflammatory adipokines leads to chronic inflammation and thus may contribute to dengue pathophysiology
- Obesity causes additional stress and dysfunction to endothelium. This in combination with dengue induce dysfunction and degradation of the glycocalyx could lead to great vascular leakage.
- Obesity alters immunomodulation, polarising the immune system to a more pro-inflammatory response while also impairing adaptive and innate cellular responses, reducing the immune systems ability to clear the virus and contributing to pathology.

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Abstract

Dengue virus (DENV) is a medically important flavivirus and the aetiological agent of Dengue, a normally self-resolving febrile illness that, in some individuals, can progress into Severe Dengue (SD), a life-threatening disorder that manifests as organ impairment, bleeding and shock. Many different risk factors have been associated with the development of SD, one of which is obesity. In many countries where DENV is endemic, obesity is becoming more prevalent, therefore SD is becoming an increased public health concern. However, there is a paucity of research on the mechanistic links between obesity and SD. This is a narrative review based on original research and reviews sourced from PubMed and Google Scholar. Four key areas could possibly explain how obesity can promote viral pathogenesis. Firstly, obesity downregulates AMP-Protein Kinase (AMPK), which leads to an accumulation of lipids in the endoplasmic reticulum (ER) that facilitates viral replication. Secondly, the long-term production of pro-inflammatory adipokines found in obese individuals can cause endothelial and platelet dysfunction and can facilitate SD. Thirdly, obesity could also cause endothelial dysfunction in addition to chronic inflammation, through the production of reactive oxygen species (ROS) and possible damage to the glycocalyx found in the endothelium. Finally, obesity has several effects on immunomodulation that reduces NK cell function, B and T cell response and increased pre-disposition to stronger pro-inflammatory cytokine responses after viral infection. Together, these effects can lead to greater viral proliferation and greater tissue damage both of which could contribute to SD. The four mechanisms outlined in this review can be taken as reference starting points for investigating the link between obesity and SD, and to discover potential therapeutic strategies that can potentially reduce disease severity.

Background

Dengue virus (DENV) is one of the most important arboviruses that results in significant morbidity and mortality globally. An estimated 100 million clinically apparent (total 400 million) infections occur annually leading to an estimated 50,000 deaths per year (1). With geographical expansion of the *Aedes* mosquito vector, the burden of the disease is expected to increase with time. DENV is a Flavivirus and has 4 distinct serotypes (DENV1-4) Dengue usually presents as a febrile illness, accompanied by headaches, nausea, vomiting, joint pain, muscle pain, and minor bleeding. A small proportion of cases however, progress into Severe Dengue (SD) which manifests as organ impairment, bleeding and plasma leakage leading to shock which can be life-threatening (2). Several different risk factors have been identified for the development of severe dengue, including age, gender, secondary infections, host and viral genetics, and presence of co-morbidities such as hypertension and diabetes (2).

Recently, obesity has been proposed as a potential risk factor for SD. A systematic review and meta-analysis of paediatric patients published in 2018 found that obesity produced an odds ratio for SD of 1.38 (1.10-1.73, 95% Confidence interval)(3)(image 1). In addition, another recent study conducted in Kerala, India on the outcomes of pregnant dengue patients has also highlighted overweight patients having a significantly higher rate of adverse outcomes(4). The plausible association between obesity and SD is particularly concerning as while DENV mainly affect low- and middle-income countries (LMICs) (1), many of these countries are currently experiencing a large obesity epidemic(5). There has also been a marked increase in the rates of obesity in all areas of the globe between 1990-2010 with some of the largest increases being in Latin America, the Caribbean, East Asia, and the Pacific(6). The main drivers behind this recent increase in prevalence include (i) changes in nutritional availability with traditional diets being replaced with processed food high in fat, salt, and sugar, (ii) reduced prices that promote habits like frequent snacking and (iii) reduction in physical activity as jobs have shifted form manual labour to sedentary positions(6). This trend is further compounded by differences in obesity prevalence between rural and urban areas, with urban areas seeing higher rates of both obesity and Dengue, facilitating the convergence of these two epidemics (2, 7).

Given the potential increased risk of developing SD associated with obesity, it seems likely that as the obesity epidemic continues, a greater burden will be placed on healthcare in dengue-endemic countries. Thus, it is vital to understand the pathophysiological mechanisms behind the association between the two. Dissecting the mechanisms involved will also allow for identification of novel therapeutic targets that can reduce the burden or severity of SD. Investigating the pathological mechanisms of dengue and the pathways leading to severe disease remains challenging, due to the lack of a suitable animal model which accurately recreates the transient increased capillary permeability syndrome that is seen in humans (2). . Despite this, several different pathophysiological mechanisms have been characterised and are increasingly understood. DENV pathogenesis primarily acts through DENV's effect on the innate and adaptive immune system, through the disruption of the glycocalyx and by directly causing endothelial dysfunction. The glycocalyx layer is a semi-permeable membrane that can actively regulate the permeability of the endothelium and can regulate the diffusion of water and small solutes while also preventing large macromolecules for diffusing across the endothelium (8). Severe manifestations in dengue patients usually occur when the viremia begins to decline, during which time, peak endothelial leakage and viral control coincide with a cytokine storm (high circulating levels of pro-inflammatory cytokines and Tumour-necrosis factors (TNFs)) which likely contribute to endothelial dysfunction (9). Another explanation for plasma leakage is the binding of viral protein NS1 to the glycocalyx layer of the endothelium, where the glycocalyx layer is subsequently degraded by NS1 through the shedding of heparan sulphate proteoglycans(10), increasing endothelial permeability that ultimately leads to plasma leakage(10). Recently, the bioavailability of nitric oxide (NO) during the early stages of infection have been found to correlate with SD outcome. Though the mechanisms behind the loss of NO bioavailability are not yet fully understood, the reduction of NO caused by DENV infection may also restrict vasomotor function, and glycocalyx loss resulting in plasma leakage (11). Finally, secondary infection (where an infected patient has been previously infected with a different DENV serotype) is associated with increased risk of SD. Cohort studies now support the role of antibody-dependent enhancement (ADE) in SD outcome (12),where sub-neutralizing concentrations of cross-reactive antibodies can opsonize DENV infection into Fc-receptor expressing myeloid cells, resulting in increased viral replication and inflammatory responses that exacerbates dengue disease. In addition, the secondary T-cell response in secondary infections is often dysfunctional due to the activation of cross-reactive T-cells generated during the primary DENV infection. This results in the generation of T cells with low avidity towards the DENV serotype responsible of the secondary infection which delays viral clearance and allows for an increased viral load(9).

With our current knowledge of the molecular processes that can lead to dengue pathogenesis, there are a number of possible ways obesity could affect these processes that can increase their susceptibility to the development of SD. This review will focus on four possible mechanisms through which obesity acts as a risk factor in the development of SD. These mechanisms include altered AMPK expression and activity, the production of pro-inflammatory adipokines, increased oxidative stress that leads to endothelial dysfunction and the effects on immunomodulation.

The potential role of AMPK dysregulation

Adenosine Monophosphate (AMP)-Activated Protein Kinase (AMPK) is a major regulator of cellular energy homeostasis with a diverse range of functions including regulating lipid metabolism, protein synthesis, glucose metabolism, autophagy, redox regulation, and has been linked to anti-aging and anti-inflammatory properties (13). AMPK activity and expression is controlled and influenced by a number of external factors including nutrition, caloric intake, exercise, aging, and obesity/inflammation (13).

In obesity, AMPK is often downregulated, contributing to insulin resistance, leptin (a satiety and anti-obesity hormone released by adipocytes to prevent over-nutrition by primarily acting on the hypothalamus) resistance, and other metabolic disorders (13, 14). There are two possible mechanisms that cause AMPK to be downregulated in obesity. The first is the effect of overnutrition, where the accumulation of glucose, fatty acids and amino acids leads to the suppression of AMPK via a variety of mechanisms, including phosphorylation of specific amino acid residues, ubiquitination of specific amino acid residues and sub-cellular protein localisation (13). The second way is through the chronic inflammation that is often induced in obesity. The mechanism of action is thought to be the increased induction of pro-inflammatory cytokines such as TNF-α and IL-6 which in turn increase the activity of SOSC3 and PP2C, leading to both decreased AMPK phosphorylation and AMPK protein expression (13, 15)

The role of AMPK in DENV infection is still being investigated. Several studies have shown that DENV downregulates AMPK activity in order to prevent lipid metabolism and increase lipid quantities available to form the lipid envelope during viral replication. This view is supported by a series of papers where the induction of AMPK activity through pharmacological means, severely impacted viral activity and replication (16, 17). The main mechanism used by DENV to downregulate AMPK is through the prevention of AMPK Thr-172 phosphorylation, inhibiting the phosphorylation of HMGCR which increases its activity. The increase in HMGCR activity subsequently resulted in the accumulation of cholesterol within the ER, allowing for enhanced viral replication (16). This evidence is further supported by papers detailing molecules that increase the activity of AMPK, by phosphorylating the Thr-172 residue they have antiviral properties against DENV (17). However, there is also some recent evidence suggesting that the inhibition of AMPK activity could also lead to a reduction in viral replication. Interestingly, DENV can also induce AMPK signalling while supressing mTOR signalling in order to induce lipophagy which is required for viral replication (18, 19). This process involves the recruitment of autophagosomes to lipid-droplet bound protein AUP1. The process of lipophagy then occurs, releasing fatty acids which are then processed in the mitochondria via β-oxidation to release ATP(19).

While the exact role of AMPK in DENV infection is not fully understood, obesity could play a role in enhancing DENV infection. Obese individuals already have a low AMPK activity, which is further downregulated by DENV in order boost ER cholesterol levels (16), thus facilitating viral replication that could lead to more severe disease. However, this mechanism relies on the downregulation of AMPK not being detrimental to viral replication by inhibiting lipophagy and thus reducing the rate of replication (fig 1). Another possibility is that the suppressed AMPK expression and function may result in reduced capacity to cope with cellular stress caused by DENV infection, inducing maladaptive ER stress and inflammatory responses that may promote SD outcome (20, 21).

Role of pro-inflammatory adipokines

One of the major roles of adipocytes is to link metabolism with immunity and vice versa. This is achieved through the release of adipokines, a complex network of soluble factors (22). Many of these adipokines have pro-inflammatory properties, with two of the most important being Leptin and Resistin (22).

Leptin is an adipokine with distinct central (acting in the hypothalamus) and peripheral (acting outside the hypothalamus) roles. Its role within the immune system is the increased secretion of pro-inflammatory cytokines including TNF-α, IL-6 and IL-12(23). The expression of leptin mRNA in adipose tissue can be further upregulated by pro-inflammatory cytokines such as TNF-α and IL-1β(23). In obese individuals, serum levels of leptin can remain chronically elevated which in turn can then contribute to chronic inflammation(23).

Similarly, resistin is a pro-inflammatory cytokine which induces the secretion of TNF-α, IL-6 and IL-1β(24). Unlike leptin however, resistin is produced by a wide variety of cells in humans with expression

being higher in peripheral-blood mononuclear cells (PBMCs) than in adipocytes(22). Endothelial cells have also been shown to be resistin sensitive, upregulating the expression of VCAM1 and ICAM1 allowing for additional transendothelial migration(22). In obese patients, both of these adipokines are found to be at elevated levels and this gives rise to low-grade chronic inflammation(22). This low-grade ongoing form of inflammation been linked to many different disorders, including metabolic disorder, insulin-resistance disorders, various cancers, immunity disorders and endothelial dysfunction(22).

The increased levels of inflammation caused by both leptin and resistin could modify DENV infection through two possible mechanisms. First, increased inflammation causes higher levels of C-Reactive Protein (CRP) to be present in serum(25). CRP is a major marker for inflammation, with CRP levels increasing 1000-fold during certain bacterial infections. CRP has also been associated with more severe clinical outcomes in dengue infections (Vuong et al BMC medicine in press). As well as being a marker of inflammation, CRP can also play a role in the pathogenesis, as it processes key functions that may leave a patient more vulnerable to severe dengue. The increased CRP levels caused by DENV infection can lead to the downregulation of endothelial Nitric Oxide Synthase (eNOS) expression, attenuating NO production, loss of vasomotor function (25), and early endothelial dysfunction that is associated with severe plasma leakage in dengue (11). With the elevated levels of CRP associated with obesity, the effects of CRP on eNOS and NO production is likely to be further amplified, thus exacerbating disease severity.

Secondly, the elevated levels of leptin and resistin encourage the production of pro-inflammatory cytokines, while other adipokines can lead to an increased production of anti-inflammatory cytokines, particularly IL-10(22). Thus, obesity could lead to an imbalance of pro- and anti-inflammatory cytokines with both groups of cytokines being produced in excess(22). In dengue patients, this imbalance has been associated with the development of haemorrhagic manifestations. That elevated levels of these cytokines are found in obese patients could thus prime these individuals to more severe manifestations (26).

Endothelial dysfunction

One of the key factors in determining DENV pathology is the process of endothelial dysfunction and increased capillary permeability, causing plasma leakage and coagulopathy (11). One of the ways DENV can cause endothelial dysfunction is through oxidative stress and the associated tissue damage. During the febrile stage of infection, key markers of oxidative stress include Hydroxyeicosatetraenoic acids (HETEs) in plasma and F2-isoprotanes (F2-IsoPs) in urine(27). Other studies have also indicated elevated lipid peroxidation products such as protein carbonyls and malondialdehydes to be associated with SD (28). While it is not certain whether the effects of these reactive oxygen species (ROS) released during DENV infection are advantageous or deleterious for DENV pathogenesis. Oxidative stress has however been shown to cause damage to endothelial cells and has been previously linked with cardiovascular events such as atherosclerosis(29). Another proposed mechanism of DENV induced capillary leak involves disruption to the glycocalyx layer. During DENV infection, both whole virus and DENV NS1 protein have been shown to bind to heparan sulphate, a key structural element of glycocalyx(10). This disruption to the glycocalyx layer results in leakage of plasma and key serum proteins including albumin, with smaller proteins seeing more severe leakage than large proteins(30). In patients who develop shock as a result of SD, high levels of heparan sulphate can be found in the patient's urine, and high levels of syndecan1 (31) (Yacoub S PhD thesis), further suggesting the extent of damage to the glycocalyx is a major contributor to the development of SD (10). The third way DENV can cause endothelial dysfunction is through the disruption of endothelial-dependent vasodilation. In particular, levels of NO availability are reduced during the febrile stages of DENV infection, along with the NO-precursor l-arginine(11). Another way of endothelial dysfunction could involve the CRP disrupting the activity of eNOS and thus decreasing the production of NO(22).

In obese individuals, chronic inflammation caused by adipokines can result in the downregulation of eNOS, thereby reducing the production of NO and diminishing the capacity for vasomotor function (22). Additionally, the decoupling of eNOS has also been shown to increase production of reactive oxygen species (ROS) including H_2O_2, OH^- and $ONOO^-$, all of which can cause oxidative damage, resulting in further endothelial dysfunction(32). While damage to the glycocalyx layer has not been directly investigated in obese individuals, the disrupted glycocalyx layer integrity is often seen in patients with diabetes and metabolic syndrome. While the precise mechanisms still remains unclear, it is thought that an increase in Transforming Growth Factor-β (TGF-β) can alter the synthesis of matrix proteins and thus affecting glycocalyx integrity (33). Interestingly, TGF-β has been observed to correlate with the body-mass index (BMI), which provides support that obesity may also impact glycocalyx integrity by altering TGF-β expression (34).

Immunomodulation

With the defined biological links between adipocytes and the immune system, it is perhaps not surprising that obesity has been found to alter the immune system, and specifically immunomodulation in several different ways. These changes can include altered antibody repertoires, changes to NK cell activation, altered CD8+ T memory cell formation, and altered T cell metabolism(35-37).

It has been found that obesity has a similar level of antibody response attenuation as aging does, with a few key markers defining the difference (35). Firstly, obese individuals have a decreased subset of anti-inflammatory B-cells, while also having increased levels of pro-inflammatory B-cells. Total B-cell function is also impaired with reduced AID activity. The reason for this seems to be because of increased production of pro-inflammatory cytokines, particularly intracellular TNF-α, which all negatively associate with AID activity in stimulated B-cells due to the upstream inhibition of AMPK (35). This fact may impact DENV infection in two important ways. The production of more pro-inflammatory antibodies seems likely to cause tissue damage and endothelial dysfunction as previously discussed. And, perhaps a more interesting way, is that this process may affect antibody-dependent enhancement and as a result cause more severe disease(12). It is possible that the reduced activity of B-cells found in obese individuals, could result in a reduced protective antibody-titre and thus augment the risk of antibody-dependent enhancement and a greater risk of SD development.

Obesity also leads to an increase in inflammatory monocytes, as evidenced by increased CD16+ circulating monocytes in humans (38, 39), and increased accumulation of M1 activated macrophages in adipose tissues (40). Monocytes and macrophages are known to be the primary target cells for DENV. However, inflammatory monocyte and macrophage subsets have been shown to be more susceptible to DENV infection and induce greater proinflammatory responses such as IL-1β, TNF-a, IL-6, IL-18, CCL2, 3 and 4 that may potentially exacerbate disease severity (41, 42). Thus, the systemic low-grade chronic inflammatory state in obesity may promote progression to SD by amplifying proinflammatory responses to DENV.

Obesity has also been shown to severely impact T-cell repertoire, function and metabolism(36). Obese patients have been observed to have a reduced number of γδ T cells, with those present also exhibiting reduced functionality with impaired IL-2 receptor expression and INF-γ production(36). In addition, the function of regulatory T cells (Tregs) is also significantly inhibited and elevated leptin levels produce more pro-inflammatory T cell subtypes including: Th1, Th17 and cytotoxic T lymphocytes (CTLs)(36). These processes could exacerbate an already heightened T cell response observed during severe dengue leading to T cell apoptosis of dengue-specific T cells and inability to eliminate virus-infected cells(43).

Obesity alters T cell metabolism and T cell differentiation. Metabolism is a key driver of T cell differentiation, function and cytokine production and metabolic pathways influence the development of various T cell subsets during infection (44). After the peak of the effector response the contraction

of antigen-specific T cell populations and the generation of stable memory T cells is also supported by changes in metabolism (45). Thus, the metabolic dysregulation that occurs in the obese is likely to affect the anti-viral functions of the T cell response during dengue infection as well as the long-term survival of memory T cells. Obese children and adults display altered T cell and antibody responses to influenza vaccination (46). Similarly, obese mice display an impaired T cell response towards secondary influenza infection virus compared to their lean counterparts, with increased risks of infection (47). Studies also show evidence of impaired immune responses to vaccines such as hepatitis B, hepatitis A, rabies and tetanus in obese individuals (48). This leads to the attenuated proliferation of T cells during infection and thus an attenuated immune response(36). This could mean that a more prolonged and pro-inflammatory response is produced in obese patients during DENV leading to exacerbated activation of T cells with poor effector function while lacking key anti-viral T cell subtypes including γδ T cells, meaning that more damage is done to the sites of infection over longer periods of time, as it takes longer to clear the virus and contract the immune response.

Finally, obesity is also known to impact the function of NK cells, key components of any anti-viral response during the early stages of infection. While short-term exposure to leptin has been shown to improve conjugation between NK cells and tumour cells as well as higher expression of TNF-related apoptosis inducing ligand(37); chronic exposure to leptin (which occurs in obese individuals) has been shown to impair NK cell immune functions as well as NK cell proliferation(37). NK cells from obese children were shown to be metabolically stressed and impaired in their cytotoxic capabilities compared to those from their non-obese counterparts [(49)]. A recent study shows that NK cells from obese individuals are impaired in their cytotoxic abilities due to the uptake of lipids from the environment which induces a metabolic paralysis of the cells (50). As a result, in obese individuals the function of NK cells is heavily attenuated and thus the immune system's ability to prevent the proliferation of DENV during early infection would be severely impaired. Furthermore, in Hepatitis B infection NK cell impairment was shown to associate with an exacerbated CD8+ T cell response, suggesting that NK cells play an immunomodulatory role on CD8+ T cells either through the elimination of virus-infected cells or through direct killing of anti-viral CD8+ T (51). Studies in mice also propose NK cells as rheostats modulating the anti-viral T cell response (52).

Collectively, these different effects that obesity has on immunomodulation ultimately mean that DENV could proliferate with less resistance, may benefit from ADE, and that the immune system could ultimately cause far more tissue damage when compared to a non-obese patient.

Conclusions

As the incidence of obese individuals continues to grow in DENV endemic areas, it will become increasingly important to understand the mechanistic relationship behind the elevated risk of developing SD found in obese patients. It is important to piece together the information on the pathology of DENV and pair it with the information on how obesity can affect immunity, metabolism and endothelial function; in order to identify plausible mechanisms for further investigation. In this paper, a series of possible mechanisms have been identified focusing on a few key aspects, including altered cellular metabolism, endothelial dysfunction, chronic inflammation and immune modulation (table 1).

Given the highly integrated nature of the immune system and adipose tissue, it seems likely that a combination of these different factors is responsible for the increased risk associated with being obese. However, it remains important to investigate each of these possible links to establish a correlation, and where possible, mechanistic models (fig 2) (table 1). A systems biology approach that employs and integrates various biological parameters such as transcriptomics, proteomics, metabolomics, flux analyses and epigenetics could thus be useful in deciphering the precise mechanisms involved in SD pathogenesis. The possible mechanisms detailed in this paper would thus provide a solid starting point for future investigations and studies.

Methods

This review is a non-systematic narrative review. PubMed (PM) was used as the primary search tool for both original research and review articles published between 2000-2019, with Google Scholar being used for supplementary information. The key search terms used and the number of hits for each database were: “Dengue”(PM=18,899), “Obesity and Dengue”(PM=25), “Obesity and Severe Dengue”(PM=14), “Obesity and LMICs” (PM=86), “Dengue Pathology”(PM=1919), “Obesity and AMPK”(PM=2,514), “Dengue and AMPK”(PM=6), “Obesity and Inflammation”(PM=23,645), “Obesity and Adipokines”(PM=18,057), “Inflammation and Dengue” (PM=595), “Inflammation and Endothelial Dysfunction”(PM=13,876), “Dengue and Endothelial Dysfunction”(PM=96), “Obesity and Endothelial Dysfunction”(PM=3,694), “Obesity and Immunomodulation”(PM=4,228), “Obesity and the Immune System”(PM=7,702), “Immune Response to Dengue”(PM=1,808). From these searches, the returns where organised by each database based on the relevance to the search term and the first 50 (where possible) were selected for review. The abstract and title for each of these papers was then checked for relevance to the topic being reviewed. Those that were found to be relevant were included in the review. Other papers were also included after expert consultation at the discretion of the author.

Tables and Figures

Image 1: An obese paediatric patient suffering from severe dengue.

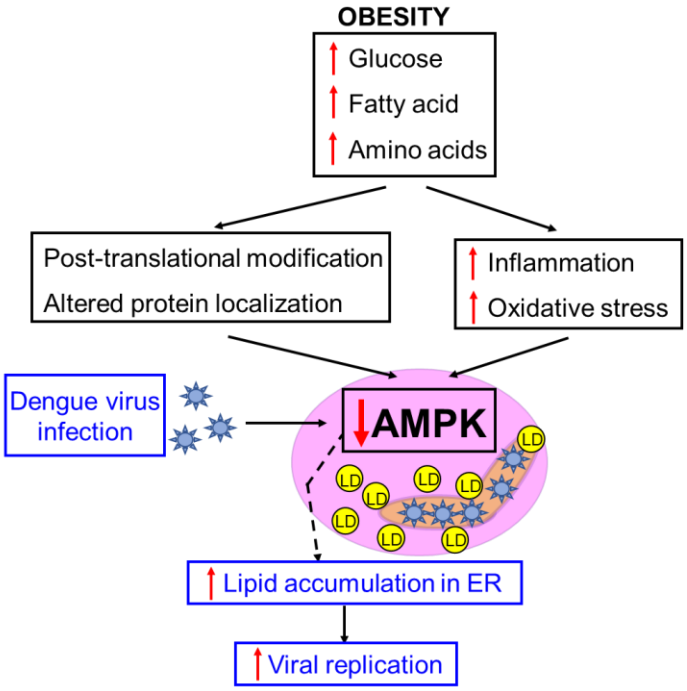

Figure 1: Schematic showing how obesity can downregulate AMPK levels and AMPK phosphorylation, and mechanisms of how reduced AMPK levels may predispose individuals to more severe dengue disease

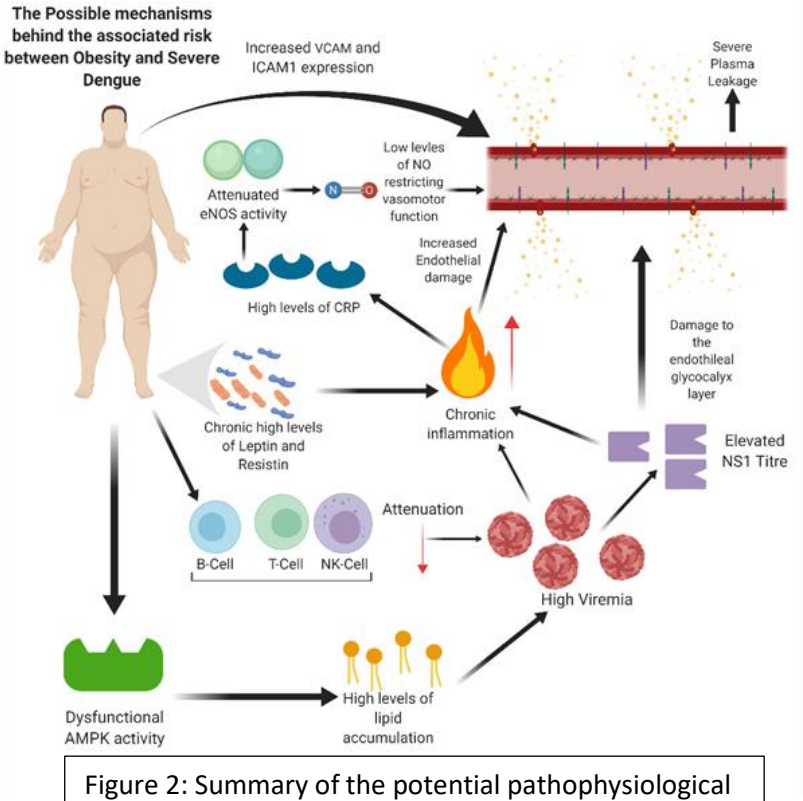

Figure 2: Summary of the potential pathophysiological mechanisms driving the increased risk f severe dengue in obese patients

Pathway	Conditions of interest	Alterations to biomarkers of interest	Supporting papers
Metabolism	Obesity	AMPK↓	Jeon, 2016., Xu et al, 2012., Steinberg et al, 2006
	DENV infection	AMPK↓(Effect of DENV on AMPK activity remains controversial)	Jimenez de Oya et al, 2018 (DENV decreases AMPK activity)., Soto-Acosta et al, 2017(DENV decreases AMPK activity)., Jordan & Randell, 2017(DENV increases AMPK activity)., Randell, 2018(DENV increases AMPK activity)
	Reduced AMPK activity	ER Stress↑, Mitchondrial stress↑	Chan et al, 2019., Herzig & Shaw, 2018
Inflammation	Obesity/Chronic Inflammation	Leptin↑, resistin↑, TNF-α↑,IL-6↑, CRP↑, IL-1β↑, IL-12↑, VCAM-1↑, ICAM-1↑, IL-10↑, eNOS↓, NO↓	Tilg & Moschen, 2006., Iikuni et al, 2008., Bokarewa et al, 2005., Sproston & Ashworth, 2018
Endothelial Function	DENV infection	HETEs↑, F2-IsoPs↑, ROS↑, endothelial dysfunction↑, NS1↑, Heperan Sulphate Proteoglycans↑, EGL dysfunction↑, Albinum leakage↑, transferrin leakage↑, urinary heperan sulphate↑	Seet et al, 2009., Heitzer et al, 2001., Puetra-Guardo et al, 2016., Wills et al, 2004
	Severe Dengue	NO↓, arginase-1↑, L-arginine↓, RHI↓, plasma leakage↑, loss of coordination:IL-6~ IL-8~ IL-10	Yacoub et al, 2017., Iani et al, 2016
	Obesity	eNOS↓, Glycocalyx intergrity↓, TGF-β↑, BMI↑	Avogaro & de Kreutzenburg, 2005., Bakker et al, 2009., Torun et al, 2007
Immunomodulation	Obesity	B-cell Response: AID↓, TNF-α↑, AMPK↓, B-cell response↓, IgG reponse↑, 12 month-post vaccination Antibody titre↓	Frasca et al, 2017., Sheridan et al, 2012.,
		Macrophage Response: Circulating CD16+ Monocytes↑, M1 Macrophages↑, M2 Macrophages↓	Jordan et al, 2019., Poitou et al, 2011., Lumeng et al, 2007.,
		T-cell Resposne: γδT-cells↓, IL-2R↓, IFN-γ↓, Th1 cells↑, Th17 cells↑, CTLs↑, CD8+ T-cell activation↓, T-cell response to Influenza Vaccine↓,Vaccine Response↓	Green & Beck, 2017., Pearce & Pearce, 2013., Pearce et al, 2009., Sheridan et al, 2012., Rebeles et al, 2019., Tagliabue et al, 2016.,
		NK cell Response: NK cell immune functions↓, Peripheral NK cell frequency↑, NK cell activation↑, NK metabolic stress↑, NK cell metabolic paralysis↑, envirnomental lipid uptake↑, CD8+ T-cell death ligand↑, NK mediated CD8+ T-cell deletion↑, NK cells act as Rheostats for CD8+ T-cell	Wrann et al, 2012., Tobin et al, 2017., Michelet et al, 2018., Peppa et al, 2013., Waggoner et al, 2011
	DENV infection	Antibody titre (within a specific range), ADE↑, M1 Macrophage Produced Cytokines↑, GM-Macrophage Susceptibility↑	Katzelnick et al, 2017., Wong et al, 2012., Wu et al, 2013

Table 1: Summary of review findings and relevant supporting literature

List of Abbreviations:

DENV: Dengue Virus

SD: Severe Dengue

LMICs: Low- Middle-Income Countries

TNF: Tumour Necrosis Factor

NO: Nictric Oxide

ADE: Antibody Dependent Enhancement

AMP: Adenosine Monophosphate

AMPK: AMP-Activated Protein Kinase

IL: Interleukin

PBMCs: Peripheral-Blood Mononuclear Cells

CRP: C-Reactive Protein

eNOS: endothelial Nitric Oxide Synthase

HETEs: Hydroxyeicosatetraenoic acids

F2-IsoPs: F2-isoprotanes

ROS: Reactive Oxygen Species

TGF: Transforming Growth Factor

BMI: Body-Mass Index

NK: Natural Killer

Tregs: Regulatory T-cells

CTLs: Cytotoxic T-Lymphocytes

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