

# Dengue and its association with hepatic biomarkers: anti-inflammatory action and utilization of paracetamol as a hepatotoxicity factor

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**Abstract:** Dengue fever is a tropical infectious pathology caused by an arbovirus from the Flaviviridae family, the dengue virus goes through an initial replication in striated and smooth muscle cells. The bioindicators of hepatic functions are enzymes that detect lesions in the hepatocytes. Thrombocytopenia is one of the bioindicators of the key clinical manifestations in dengue patients. Besides the natural process of the platelets in the anti-inflammatory activity, the used drugs act and the auto medication overcharges hepatic functions due to the hepatotoxicity of non-opioid analgesics. Usually, the most used analgesic is paracetamol. The present article aims to associate hepatic biomarkers with the dengue infection and the hepatotoxicity caused by the indiscriminate use of anti-inflammatory drugs like paracetamol. As a research method, the literature review was utilized, with the utilization of scientific articles related to the theme, taken from electronic databases such as Scielo and Google Scholar. Aiming to associate dengue with hepatic biomarkers such as thrombocytopenia and hepatotoxicity caused by the anti-inflammatory drug known as paracetamol. It is important to highlight the relation between thrombocytopenia and dengue's hemorrhage episodes, besides the hepatic overload caused by the indiscriminate use of paracetamol.

**Keywords:** Dengue; Biomarkers; Thrombocytopenia; Hepatotoxicity; Paracetamol.

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## 1. Introduction

A disease similar to dengue was described in the Asian continent more than two thousand years ago, people called it “poisonous water” because of the association to fluvial currents and flying insects [1]. Dengue is a tropical infectious pathology caused by an arbovirus from the *Flaviviridae* family that presents four infecting serotypes: DENV-1, DENV-2, DENV-3 and DENV-4 [1, 2], the severity of the disease is related to the infecting serotype and has a vector named *Aedes Aegypti*, which is a mosquito that disseminates the virus through its sting, the dengue virus goes through an initial replication in smooth and striated muscle cells and fibroblasts, as well as in local lymph nodes [3]. After the replication, the virus begins to circulate through the plasma or are attracted by antigen-presenting cells such as monocytes and macrophages [3,4,5].

Dengue fits in one of the main reemerging diseases since it has increased about 30 times in the last 50 years [4]. The first dengue epidemic in Brazil happened in Roraima in 1981 with DENV-1 e DENV-4, and in 1986 DENV-1 got to Rio de Janeiro (RJ), becoming a public health national problem due to its fast dissemination [5]. DENV-2 also appeared in RJ, when the first fatal cases were registered due to secondary infections [5]. DENV-3 was responsible for a severe summer epidemic in 2001 [5]. Despite the decrease in mortality by dengue in the last years, the co-circulation of 4 serotypes in the country is worrisome, because there is a tendency to the infection of progressively younger people and with even more severe clinical manifestations [4].

According to the Ministry of Health (2016), dengue cases are classified in Dengue (D), Dengue with warning signs and Severe Dengue. Generally, dengue is a viral disease in which the symptomatic manifestations usually cause fever associated with headache, myalgia, arthralgia, prostration and anorexia [4]. Furthermore, in a more advanced stage, the warning signs include abdominal pain, persistent vomit, clinical signs of fluid extravasation (postural hypotension, oliguria), mucosa bleedings, lethargy, hepatomegaly (with liver enhancement above 2 cm) or increase in the hematocrit with rapid decrease of the platelet count. It is worth remembering that even patients that do not present warning signs can evolve to severe dengue [5].

Accordingly, this viral infection can be accompanied by hepatic insufficiency, in which alterations are caused by viral lesions directly to the hepatocytes; besides, there can be an increase in serum transaminase enzymes (intracellular enzymes that catalyze multiple reactions, mainly in the liver, but that also are found in other tissues of the body, when elevated, are an important indicator that a problem exists, most probably in the liver), because of the lack of irrigation in this organ due to the increase of free radicals and capillary leak resulting of the irregular immune response and of the hypoxia, respectively. ALT and AST transaminases are significantly increased in dengue's acute infection and can be used as a predictor of severity of the disease in acute cases [5,6,21].

The liver is notably one of the most important organs in the body, being of vital importance for the organism's good functioning [6]. Still according to Guyton, the liver being the biggest internal organ in the human body, it is responsible for the metabolism and production of numerous substances, acting directly in the synthesis and secretion of bile salts, storage and breaking of hormones, besides promoting the regulation of lipids, proteins and carbohydrates. Its functions can be divided in secretion and excretion functions acting in the bile formation, metabolic functions associated to the other systems in the organism and finally, vascular functions of storing and filtrating blood [6].

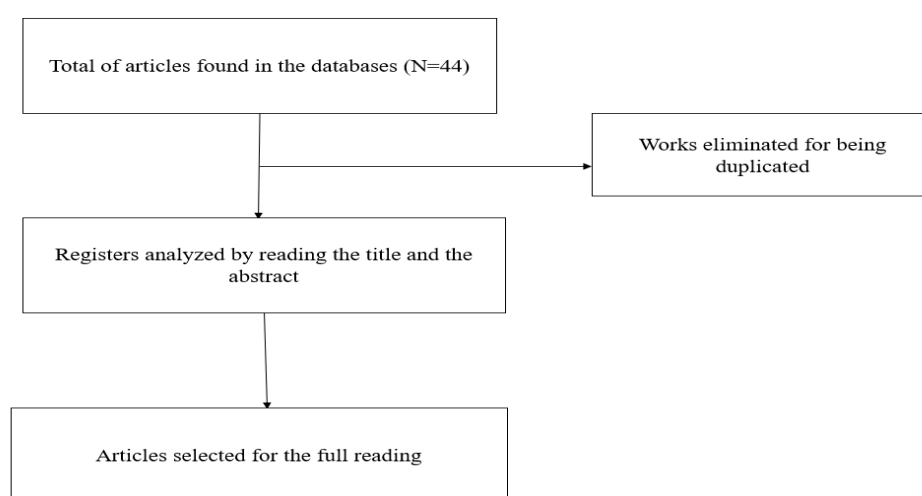
Given the information exposed, considering its extreme importance in the physiology of human systems, techniques were developed along the laboratory history to evaluate the performance and the possible lesions in this organ. In that sense, generally, bioindicators of hepatic functions are enzymes that detect lesions in hepatocytes, enzymes that detect colestasis (delaying in the flow inside the bile ducts) and measurable hepatic metabolites. 1. Enzymes that detect hepatocyte lesions - ALT (alanine aminotransferase); - AST (aspartate aminotransferase); - SDH (sorbitol dehydrogenase); - GLDH (glutamate dehydrogenase). 2 Enzymes that detect colestasis: - GGT (γ-glutamyltransferase); - FA (alkaline phosphatase). 3. Evaluation of hepatic function: - Bilirubin; -Bile acids; -Ammonia; -Urea; -Albumin; -Globulin; -Glucose; -Cholesterol; -Coagulation factors (platelets).

OMS reports that clinical alterations caused mainly in the severe form of dengue are decrease of white cells, platelets, fibrinogen, prothrombin, factor VIII, factor XII and antithrombin III, albumin, increase of hepatic enzymes such as AST (aspartate aminotransferase), ALT (alanine aminotransferase) and other hepatic cofactors [5]. Finally, through a literature review, the aim of this study will be accomplished when evaluating the clinical and laboratorial alterations of hepatic functions in the individuals diagnosed with dengue, through the analysis of their biomarkers.

## 2. Methodology

The present study is a systematic literature review and a review of scientific articles. A literature review was done with articles published in Google Scholar, Scielo, ScienceDirect, U.S. National Library of Medicine (PubMed), between 1997 and 2022. The question that initiated the systematic review was “What is the association between dengue and hepatic biomarkers?”. As inclusion criteria, the studies should only be articles and textbooks of Medical Physiology were utilized as a complement.

Then, articles that were not related to the theme were excluded. Through this systematic analysis 44 articles were identified, being initially excluded 24 articles by the analysis and fitting the keywords criteria, those being: dengue, hepatic biomarkers, thrombocytopenia, hepatotoxicity. Amongst 24 articles, 8 of them were selected according to the evaluation of signs and symptoms and disease definitions.



**Figure 1.** Summary of the utilized method to include the scientific production about the association between dengue and hepatic biomarkers and the utilization of paracetamol as a hepatotoxicity factor.

## 3. Results and Discussion

Dengue represents the second most important disease vector transmitted in the world. Its clinical and epidemiological characteristics awaken the interest of researchers all over the world [9]. The hemogram is a fundamental laboratorial exam in the analysis of different pathologies. The main cell components of the blood analyzed in the hemogram are erythrocytes, leukocytes and platelets composing the erythrogram, leukogram and thrombogram<sup>9</sup>. Hemogram is highlighted with relevant findings such as leukopenia and neutropenia with presence of atypical lymphocytes and thrombocytopenia, with value of platelets below  $100 \times 10^9/112$ . During the evolution of the infection by dengue virus multiple laboratorial methodologies can be performed, despite being a non-specific exam, hemogram is of utmost importance in the patient's follow up and in deciding therapeutic conduct [16].

One of the frequent hematologic findings in dengue is thrombocytopenia that occurs through an immune-mediated process that decreases platelet count. Generally, thrombocytopenia caused by viral infections are secondary and occur due to platelet phagocytosis. More severe forms of dengue affect hepatocytes and lead to the reduction of hepatic activity and hemorrhage episodes and the consequent platelet decrease<sup>10</sup>. The tourniquet test, which analyzes platelet integrity, can diagnose the presence of dengue that presents hemorrhage manifestations [8, 14]. The tourniquet test is performed using the cuff to evaluate the insufflated blood pressure until the medium point of the blood pressure for 5

minutes. Posteriorly to this period, the count of petechia is performed. If twenty or more petechiae appear, the tourniquet test is positive [15].

**Table 1.** Platelet function alterations in dengue are associated with plasma leakage.

Authors	Title	Publishing year
Oliveira DB	Study of the platelets morphological and functional alterations in the infection caused by the dengue virus	2012
Santos FS	Platelet count analysis in the dengue diagnosis	2012
Barreto et al.	Dengue in Brazil: epidemiologic situation and contributions for a research agenda	2008
Barros, TAC	Evaluation of the profile of seric mediators and proteins from the inside of platelets related to thrombocytopenia in patients infected by dengue virus	2015
Faria RJ et al.	Hemogram alteration in dengue patients from the county of São José do Calçado, ES, Brazil.	2016
Torres LV et al.	Paracetamol hepatotoxicity and predisposing factors	2019
Macena TNS et al.	Acetaminophen (paracetamol) hepatotoxicity in dengue	2014
Marques PE	Liver: excessive use of laboratory of paracetamol in dengue	2014

The platelets originate from the megakaryocytes, cytoplasmic fragments with high biochemical activity and medium life of 7 to 10 days [10,11,12]. Before confirming dengue through immune testing, hematologic tests have shown great importance, since according to in vitro studies, there is platelet activation in dengue patients going through the febrile and defervescence phases. The formation on platelet-monocyte aggregates, and the platelet apoptosis, according to this study, seem to be important thrombocytopenia mechanisms during dengue [4]. According to other results, platelets also are important in the context of exacerbated production of cytokines in the blood [13].

Thrombocytopenia is one of the key clinical manifestations in dengue patients. The platelet count can be an indicator of death in patients with platelet count  $<50.000/\mu\text{L}$ . Thrombocytopenia can also be divided in the consummation of platelets during the coagulopathy process, activation of the complement system, increase in the peripheral sequestration<sup>5</sup>. In a study done in São José do Calçado (ES) 656 patients were evaluated, of which 408 presented positive IgM serology for dengue. The hemogram of all symptomatic patients in the initial phase of the disease demonstrated 75,9% of efficiency in the diagnosis of the disease. Amongst the patients with dengue positive IgM serology, leukopenia was

present in 57,7% of them, followed by predominant thrombocytopenia in 32% of the cases, lymphopenia in 21,7%, and increased hematocrit in 14,8% [16].

Although dengue has clinical signs similar to the ones present in other diseases, the importance of hematologic testing is noticed for the indispensable data to prognosis and posterior control of the disease [16, 12]. In another study done in Salvador (BA) the clinical diagnosis of 55 pediatric patients was investigated, of which 89% persisted with dengue's classic fever, 7,27% persisted with hemorrhage fever and 1,8% with dengue shock syndrome. Rapid testing for dengue revealed IgM positivity in 63,8% of the 36 patients in which the study was performed, and IgG positive in 52,2% amongst 44 tested patients. The type 3 of the virus was isolated in 23,6% of the cases, 12,7% did not have the type defined and 63,6% did not go through testing [17].

Regarding these patients' hemograms, leukopenia was observed in 41,8% of the patients, thrombocytopenia in 49% in the first exam, and 50,9% in the second evaluation and in 27,2% of cases in the last measure. The investigated clinic manifestations that could be related to hepatic alterations were abdominal pain, nausea, vomits, jaundice and hepatomegaly. Since 22 children that presented nausea and vomits also presented alteration of the AST hepatic biomarkers and 11 had alterations in ALT. From the 22 which referred to abdominal pain, 19 had AST and 11 had ALT alterations. Whilst the 3 patients with hepatomegaly had ALT and AST alterations [17].

When relating both studies it is noted that there is presence of an alteration in the plaquetary biomarker. Thrombocytopenia through the DENV infection is directly or indirectly related with the virus, through the exposition and mediators secreted because of the infection, has its functionality altered, influencing the coagulation system and the immune response [5]. The platelets actively participate as effectors of the inflammatory response in dengue, either secreting kitocynes on the endothelium, or forming aggregations with monocytes [4].

Dengue serotype determines the severity of the disease: DENV-1: Mild liver aggressions; DENV-2: Aggressive to the liver, can lead to discrete alterations and provoke mild hemorrhage; DENV-3: Very aggressive to the liver, it is characterized by increased alterations in coagulations tests, besides important hemorrhage. DENV-4: Insufficient data about the level of aggression [10]. Besides the natural process of platelets in the anti-inflammatory activity, the pharmacological utilization enters, and the overcharged auto medication damages the hepatic functions due to the hepatotoxicity of non-opioid analgesics that constitute a class of drugs that are persistent in intoxication cases [18]. Generally, in the treatment of patients, depending on the severity of the disease, it is based on the support measures such as antitermic drugs, which include acetaminophen, also known as paracetamol [19].

Paracetamol is an ancient drug with analgesic and antitermic action, to perform its action, the drug, when orally ingested, is converted in the liver, where, after its conversion, starts to act in the nervous system blocking the COX2 cyclooxygenase enzyme, responsible for pain and fever. However, according to Marques et al. [20], the excess of paracetamol leads to the destruction of hepatic cells, that after suffering cellular lysis, releases its mitochondria in the blood circulation, which are recognized by the body as invasors and, in response, it increases the number of neutrophils, that reach the liver and increase hepatic damage. In patients with deficient hepatic activity due to some pathology, such as dengue, the damage can be even more severe, being able to lead to organ loss [20].

#### 4. Conclusions

Returning to the guiding question: Which clinical and laboratorial alterations can be correlated with hepatic alterations produced in the dengue infection? It was observed that the increase in the level of transaminases is directly related with the clinical and laboratorial alterations in patients infected by the dengue virus. As it was observed in the selected

articles, AST and ALT alterations are present in the dengue infection and its increase in the patient's serum are proportional to the evolution of the disease.

It was observed that the decrease in the platelet count is not a good marker of hemorrhage caused by dengue and that the viral serotype is an indicator to the severity of the infection. However, thrombocytopenia is an indicator of the disease's severity, since the viral infection promotes platelet lysis and posterior decrease of platelets in the blood, and because of that, the platelet levels should be paid attention to. Besides, the reduction of hepatocyte activity due to the infection demands a more critical look when it comes to utilizing drugs to attenuate the disease effects. Thus, paracetamol, an effective anti-inflammatory drug against pain and fever can lead to the destruction of the liver cells when in excess, and if associated with the disease, can bring irreversible damages such as possible hepatitis and organ loss.

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