

## ARTICLE

# Serum Lipid Variation in Patients with Dengue Virus Infection and Associated Risks of Cardio Vascular Disorder



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### Competing interests

The authors have declared that no competing interests exist.

## Abstract

**Background:** Dengue virus (DENV) is a most prevalent arbovirus with about 100 million infections worldwide every year. It is endemic in the subtropical and tropical areas in the world, an emerging public health threat. Serum lipidome is a key player in the immune system response of the patient for the period of dengue fever. This study was aimed to assess the lipids deviations in serum of patients with dengue fever.

**Materials and Methods:** Three For this case-control study blood samples of N=65 dengue patients of age  $\geq 18$  year were collected from the Mayo Hospital, Lahore. Whereas samples of 45 healthy individuals were collected from the University of the Punjab, Lahore. Blood samples from subjects were collected to analyze serum lipidome.

**Results:** Significantly ( $P < 0.001$ ) increased serum triglyceride, total cholesterol, low density lipoprotein, and very low-density lipoprotein while a significant ( $P < 0.001$ ) reduction in high density lipoprotein was observed in the dengue patient's serum in contrast to the control.

**Conclusion:** We can conclude that DENV infection can contribute to dyslipidemia with subsequent cardiovascular disorder symptoms. Therefore, patients infected with DENV should monitor their serum lipid profiles to deal with DENV induced effects to the cardiovascular physiology.

**Key words:** Atherosclerosis, Cardiovascular disorders, Dengue fever, Dyslipidemia, Lipids

## Introduction

Dengue fever is an acute viral infection having potential for serious complications, caused by the Dengue virus (DENV; Ravi et al., 2021). Currently, dengue fever is the most quickly spreading viral disease all over the world (Torres et al., 3032). With a few major outbreaks, its prevalence is recorded in over hundred countries. Approximately 390 million individuals are infected by DENV each year, of which about 24.62% gets hospitalized for treatment (WHO, 2022). In Pakistan, the first dengue fever outbreaks occurred in 2010, and it's continued since then (WHO, 2011). In the recent outbreak of 2021 and 16580 cases, with 257 losses in Lahore alone have been recorded (WHO, 2022).

DENV is a Flavivirus, and it belongs to the family Flaviviridae. There are four different serotypes of this virus, each has a unique antigenic and phylogenetic characteristic. At first, every serotype was localized to a specific geographical region. However, due to globalization, different serotypes have spread globally which can all be found in the same geographical region (Ravi et al., 2021). Despite of several potential vectors of this virus, *Aedes aegypti* seems to be the most prevalent (Higa, 2011) and globally it is responsible for transmission of DENV (Soria et al., 2014).

Little is known about lipidemia and DENV infection. Changes in the serum lipid profile has been shown related with the viral infections (Durán et al., 2015). DENV enters in the cell through with low-density lipoprotein (LDL) receptors and subsequently reduces the uptake of viruses by the cells, which indicates an interaction of the DENV with the lipoproteins during infection cycle

(Thejaswini et al., 2021). Such DNEV induced changes in serum lipid profile may lead to lipid related complications like cardiovascular complications, in the DENV infected patients (Ramos et al., 2018).

The aim of this work was to find out the variations in serum triglycerides (TG), Total Cholesterol (TC), High-density lipoproteins (HDL-C), low-density lipoprotein (LDL-C), and very low-density lipoprotein (VLDL-C), as a risk prognosticator in cardiovascular patients infected with DENV virus and developed dengue fever.

## Materials and Methods

The case-control study was approved by the Ethical Review Committee of the Institute of Zoology, University of the Punjab, Lahore, Pakistan. Our investigation comprised N=110 subjects of age  $\geq 18$  years. Among them, N=65 were RT-PCR-positive DENV patients from the Mayo Hospital Lahore. Whereas N=45 individuals were control for this study from the Institute of Zoology, University of the Punjab.

Enrolment for this study of all eligible individuals was based on written informed consent and all samples were anonymized. Patients with chronic liver disease, subjects taking statin medication, and those with co-infections including malaria, leptospirosis, scrub typhus, and typhoid was excluded from the study. The study recorded the subjects' history and relevant general physical and systemic examinations. On the day of hospitalization, venous blood samples were obtained in order to measure lipid profile parameters i.e., triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), very low-density lipoprotein (VLDL-C).

Since our investigation involved human participants, we made sure to follow all safety protocols while taking and recording samples. Venous blood specimens were taken from the study participants with the help of a registered technician in clot activators vacutainers used for serum separation. After clotting, samples were centrifuged at 3000 rpm for 10-15 minutes to separate the serum, and then serum was stored at  $-80^{\circ}\text{C}$ , until further use.

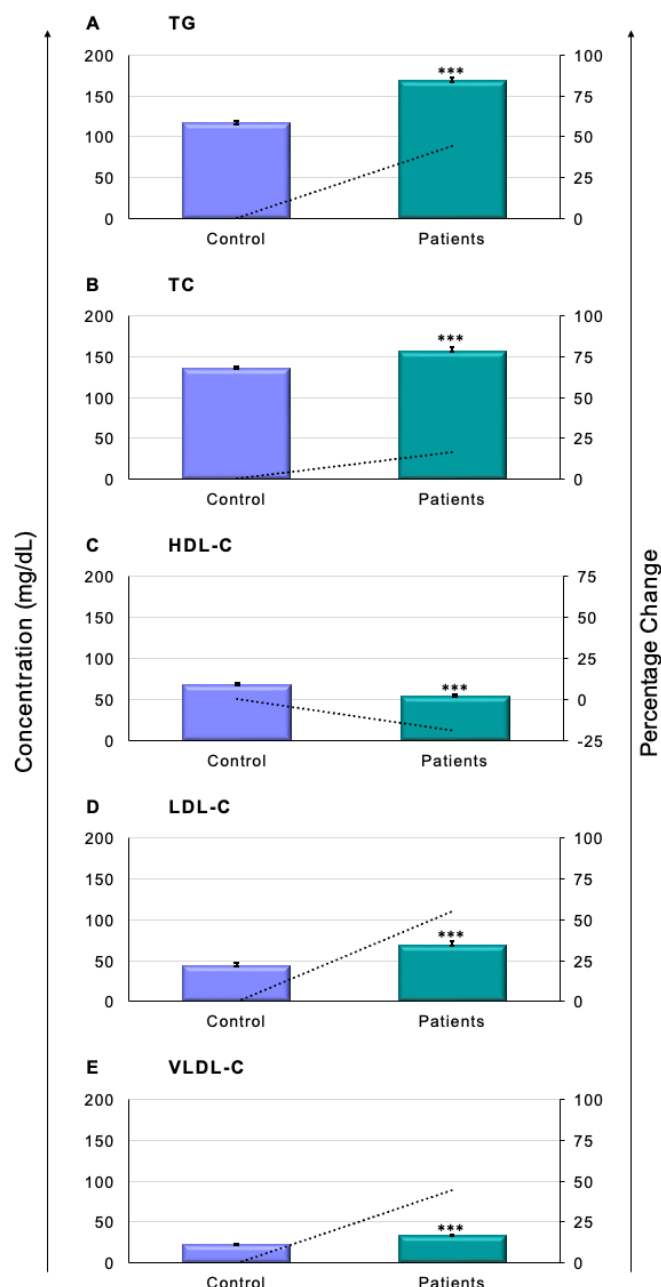
Serum lipid profiling was done using commercially available kits from Monlab, Spain through chemistry analyzer (Robert Riele Photometer 5010). While very low-density lipoprotein (VLDL) level was calculated by the method of Friedewald et al. (1972).

Statistical analysis was done with GraphPad Prism 4.00 software. The significance of the difference was assessed by student's t-test (independent sample) with significance at  $P < 0.05$ . The results are presented as Mean  $\pm$  SEM along primary y-axis and percentage changes are presented along secondary y-axis.

## Results

Significant differences in serum lipids profile were found in the DENV infection cases when compared with normal healthy control group (Table 1). A significant ( $P < 0.001$ ) increase of 44.47% in serum TG level was found in patients as compared with controls (Figure 1A). Similarly, the total cholesterol demonstrated a significant ( $P < 0.001$ ) increase of 16.15% in

patients when compared with controls (Figure 1B). However, in HDL-C levels a significant ( $P < 0.001$ ) decline of 19.26% was observed in patients when compared with controls (Figure 1C). LDL-C levels in serum of patients was significantly ( $P < 0.001$ )



**Figure 1:** Lipid profile comparison of patients suffering from dengue virus infection with the normal healthy control. Triglyceride (TG, 44.47%; A), Total Cholesterol (TC, 16.15%; B), Low Density Lipoproteins (LDL, 55.37%; D), very low-density lipoproteins (VLDL, 44.41%; E) increased in infection condition whereas High Density Lipoproteins (HDL, 19.26%; C) was decreased in infection condition. The data was analyzed using student's t-test, and significance is reported at  $P < 0.001^{***}$ .

elevated with 55.37% as compared to controls (Figure: 1D). Serum VLDL-C of patients was also significantly ( $P < 0.001$ ) increased with 44.41% in contrast to controls (Figure: 1E) (Table: 1).

**Table 1: Overall comparison of serum lipid parameters in the control group and patients infected with DENV through independent sample t-test.**

Parameters (mg/dL)	Mean $\pm$ SEM		t- value	P- value	Percentage difference
	Controls (N=45)	Patients (N=65)			
TG	116.70 $\pm$ 2.90	168.60 $\pm$ 4.45	8.82	<0.001	44.47 $\uparrow$ ***
TC	135.60 $\pm$ 2.96	157.50 $\pm$ 4.42	3.74	<0.001	16.15 $\uparrow$ ***
HDL-C	67.76 $\pm$ 1.85	54.71 $\pm$ 1.25	6.06	<0.001	19.26 $\downarrow$ ***
LDL-C	44.45 $\pm$ 2.91	69.06 $\pm$ 5.01	3.78	<0.001	55.37 $\uparrow$ ***
VLDL-C	23.35 $\pm$ 0.58	33.72 $\pm$ 0.89	8.82	<0.001	44.41 $\uparrow$ ***

TG: Triglycerides, TC: Total cholesterol, LDL: Low-density lipoprotein, HDL: High-density lipoprotein and VLDL: Very low-density lipoprotein  
 $\uparrow$ : Increase,  $\downarrow$ : Decrease; \*\*\* indicate significance at  $P < 0.001$ .

## Discussion

In our study a marked increase in the serum TG levels in DENV patients indicates a disturbed lipid metabolism in the cells that may include decline in lipolysis, increased de novo synthesis in the liver, or viral NS3 protein mediated increase in the fatty acid synthase (FASN) activity, which is a rate limiting enzyme of TG production pathway. Furthermore, the DENV controlled lipid processing in the target cell leads to the formation of lipid vesicles for viral replication that increases the mobilization of lipids vesicles, containing of triglyceride. Therefore, the serum level of the TG is increased (Melo et al., 2018). High triglycerides level is a risk factor for cardiovascular disorders as it is one of the major causes for atherosclerosis and found to be associated with coronary heart diseases, ischemic stroke, myocardial infarction, and atherosclerosis which may lead to death (Nordestgaard & Varbo, 2014).

Serum TC was found elevated in DENV patients when compared to healthy controls. The cause for this change can be the enhanced hepatic cholesterol synthesis or reduced lipolysis or cellular uptake. This increase in TC may be attributed to increase in TG levels. As the cells break TG from triglycerides and cholesterol containing droplets that leads to increase in cholesterol level (Nordestgaard & Varbo, 2014).

Hypercholesterolemia can result in several cardiac complications such as stroke, ischemia, and peripheral artery diseases. A 1% increase in plasma TC doubles the chances of coronary heart disease (Castelli, 1998; Félix-Redondo et al., 2013). DENV infected patients aged above 65 years are more likely to develop coronary heart disease (CHD) because of hypercholesterolemia (Manolio et al., 1992).

Serum HDL-C level was decreased to 19.26% in DENV infected patients as compared to controls and this decrease can be attributed to reduced activity of lecithin cholesterol acyltransferase enzyme, the enzyme responsible for esterification of free cholesterol to HDL-C, leading to decrease in HDL-C level (Ravi et al., 2021). NS1, the catalytic protein of DENV decreases the activity of the APOA-1, in DENV infected patients. APOA-1 translates the apolipoprotein-1 (ApoA-1), which is a major part of HDL-C (Coelho et al., 2021). HDL-C is

vital for cardiovascular health due to its antiatherogenic function, due to its like antioxidation, anti-inflammation, reverse transfer of cholesterol, anticoagulation, vasodilation, and antiapoptotic properties. Therefore, low HDL-C may be a contributing factor to the development of cardiac disorders like myocardial infarction, coronary heart disease and atherosclerosis etc. (Bruckert & Hansel, 2007; Mahdy Ali et al., 2012)

The Ludwigshafen, Risk and Cardiovascular Health (LURIC) study has reported that a high level of LDL increase the risk of cardiovascular fatalities (Hoogeveen & Ballantyne, 2021). LDL, a major contributor to CVDs gets deposited in arteries, undergoes oxidation, and attracts the inflammatory cells to the deposition site leading to development of atherosclerotic plaque (McCormack et al., 2016; Sakellarios et al., 2013).

The increased VLDL-C plays an essential role in pathophysiology of the dengue fever manifestations (Ramos et al., 2018), as it increases the risk for development of thrombosis. Serum levels of LDL and VLDL are correlated as a higher VLDL concentration raises the LDL. This lipoprotein boosts the synthesis of prothrombin and consequently causes the coagulation of blood in the vessels that leads to chronic problem (Kullet, 2003).

Serum TC is a major prognosticator of the risk of CVDs. With a higher triglycerides and low-density lipoproteins concentrations while a low concentration of high-density lipoproteins, the CVDs risk may increase (Castelli, 1988).

## Conclusion

Dyslipidemia in the dengue fever patients prognosticate the severity of infection with potential of CVDs risks. Dengue fever patients with prior history of CVDs needs to be closely monitored for their lipid profile during the DENV infection period due to DENV influenced dyslipidemia with potential to cause critical changes in the patient's CVDs.

## Author contributions

The authors confirm contribution to the paper as follows: study conception and design: NR, SA; sample, data collection and analysis: SA, MA, HA, interpretation of results: NR, KM, MAI; draft manuscript preparation: KM, HA, MAI. All authors reviewed the results and approved the final version of the manuscript.

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