Original Research Article

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The lipid profile as a marker for predicting the severity of dengue fever

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ABSTRACT

Background: Dengue fever is a mosquito-borne viral disease. WHO currently estimates 390 million dengue infections annually worldwide. In India between 2015 to 2020, out of 7,08,783 cases about 1,144 deaths have been reported according to National vector borne disease control programme data. This study aims at evaluating the changes in lipid profile among dengue patients with relation to severity and complications.

Methods: It is a cross sectional observational study conducted on 200 patients. The dengue patients were grouped according to WHO classification. The lipid profile was estimated and changes in its parameters were correlated with severity of dengue infection.

Results: The age distribution in our study was between 18 to 65 years with mean age of 28.5 ± 9.2 years. As per WHO 2009 criteria out of 200 patients, 120 (60%) were dengue without warning signs, 68 (34%) were dengue with warning signs and 12 (6%) were severe dengue. There was decreased total cholesterol, LDL-C, HDL-C found in all forms of dengue and statistically significant (p<0.05) lowest levels noted in patients with severe disease according to ANOVA test. Correlation analysis showed a significant negative correlation between LDL-C (r=-0.716), HDL-C (r=-0.657) and total cholesterol(r=-0.621) with relation to severity of dengue (p<0.05).

Conclusions: Results of this study showed serum cholesterol levels are important correlates of dengue pathophysiology and severity and these may be used as a marker for predicting the severity of dengue fever.

Keywords: Dengue fever, Severity, Total cholesterol, LDL-C, HDL-C, Triglycerides

INTRODUCTION

Dengue fever is an acute viral fever with potential fatal complications.¹ Dengue fever was initially called as "water poison" associated with flying insects in a Chinese medical encyclopedia from the Jin Dynasty in 992. It is caused by dengue virus (DENV) which is a positive-sense RNA virus of the family Flaviviridae. There are four serotypes of DENV (DENV 1-4) that are characterized by distinct phylogenetic and antigenic properties and is transmitted by the hematophagous mosquitoes *Aedes aegypti* and *Aedes albopticus*.² Characteristic features of illness are fever, constitutional symptoms and in severe cases shock and bleeding manifestations.³ The revised WHO classification of 2009

categorizes dengue patients according to different levels of severity as dengue without warning signs, dengue with warning signs and severe dengue. The disease is found to be hyper endemic in tropical and sub-tropical regions, most prevalent in South east Asia. Dengue had been restricted to urban areas, but it has now spread to rural regions also. 5

In India, the clinical dengue-like illness as first epidemic was documented in Chennai in 1780. The first virologically evidenced epidemic of dengue fever (DF) was recorded in Kolkata and Eastern Coast of India at around 1963-1964. India experiences cyclic epidemics of dengue infection. The total number of dengue cases has significantly increased in India since 2001 due to

unplanned urbanization, poor water storage, sub-standard sanitary conditions, increasing international travels and changes in environmental factors. For prevention and control of dengue illness in India, National vector borne disease control (NVBDCP) provides guidelines. Between 2015 to 2020 notification of 7,08,783 cases were done according to NVBDCP data.⁷

Treatment for dengue fever has always been supportive, while severe forms of the disease require critical medical management of the patient's body fluid volume. Due to lack of specific antiviral treatment for dengue, early recognition of severity and providing proper medical care reduces case fatality rates to <1%. The ability to make this early predictions of severe dengue in patients who display no warning signs and are at risk of developing severe illnesses like dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) is important and helps in choosing appropriate intensive care therapy thus improving survival.

Early identification of patients at risk of developing severe forms of dengue illness could be possible with the availability of an ideal biomarker. In vitro studies of the pathophysiology of DENV and other flavivirus infections suggest that lipids and lipoproteins may play a role in modifying virus infectivity of target cells.⁸ Thus in the context of patient diagnosed with dengue fever, we aim to assess the changes in serum lipid profile as a potential biomarker in predicting the severity of disease and helping in appropriate management.

Objectives

Objective of current study were to estimate lipid profile in patients with dengue fever and to find its correlation with severity and complications.

METHODS

Study design and setting

A cross sectional observational study was conducted from July 2019 to January 2020 among those patients who gave informed written consent and admitted as confirmed cases of dengue with thrombocytopenia at Victoria hospital, Bangalore medical college and research institute (BMCRI), Bangalore, Karnataka, India.

Inclusion criteria

The study included patients aged ≥18 years of both genders, diagnosed with dengue fever by detecting NS1 antigen or positive Ig M antibodies against dengue virus and with thrombocytopenia (<1,50,000).

Exclusion criteria

The study excluded patients <18 years of age, patients with diabetes mellitus, hypothyroidism, hypertension,

obesity, known dyslipidemic disorders and patients who are on lipid lowering drugs, corticosteroids, oral contraceptives.

Procedure

Detailed history, clinical examination and investigations was done and data was collected using a proforma meeting the objectives of the study. Fasting serum lipid profiles of all patients were measured on the day of admission. Patients were followed up during their hospital stay and assessed for the severity of dengue. Severity was graded according to WHO classification.⁴

Statistical analysis

The quantitative variables were expressed as mean±SD, while categorical variables were expressed in percentage. Data analysis was done by descriptive statistics, one way ANOVA, and the student t test. All statistical analyses were performed using SPSS software (version 16.0, SPSS, Chicago, USA) and p≤0.05 was considered statistically significant with 95% CI.

RESULTS

The sample size in our study was 200 patients. The age distribution was between 18 to 65 years, with mean age of patients being 28.5±9.2 years and most of the patients were in the age group of 18-25 years (Figure 1). The study population included 152(76%) males and 48(24%) females with male to female ratio of 19:6 (Figure 2).

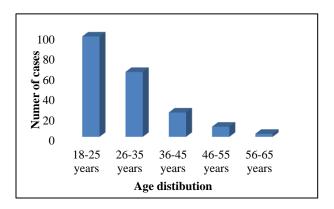


Figure 1: Age distribution of subjects in the study.

Among 200 patients in our study, 120 patients (60%) were dengue without warning signs, 68 (34%) dengue with warning signs and 12 (6%) severe dengue according to WHO 2009 classification. The distribution of patients graded according to severity with majority being in mild illness category is depicted in (Figure 3). The platelet count distribution for each level of dengue disease is depicted in (Table 1). Significantly decreased platelet values were observed in DWWS (dengue with warning signs) and SD (severe dengue) when compared with DNWS (dengue without warning signs).

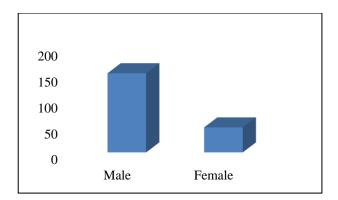


Figure 2: Gender distribution of subjects in the study.

Table 1: Platelet counts in different forms of dengue.

Disease severity	Platelet count (10 ³ /mm ³)
DNWS	76.565±50.28
DWWS	48.36±41.57
SD	26.02±19.26

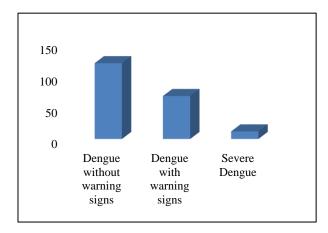


Figure 3: Distribution of patients classified according to severity.

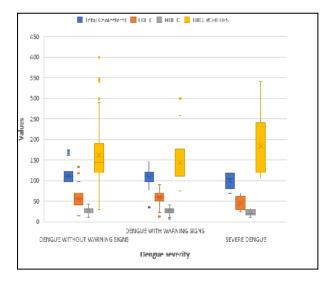


Figure 4: Box plots for comparison between lipid profile and disease severity.

According to ANOVA test, decreased total cholesterol, LDL-C, HDL-C was found in all forms of dengue with lowest levels noted in patients with severe disease. Increased levels of triglycerides are seen as severity of dengue increases. The changes in lipid profile was statistically significant with relation to severity of disease (p<0.05). The lipid profile changes in different severity of dengue are depicted in (Table 2). The box and whisker plot shows the variations of serum lipid profile with different levels of dengue severity which shows decreasing levels of total cholesterol, LDL-C, HDL-C and increasing levels of triglycerides as severity of dengue increases (Figure 4). Correlation analysis showed significant negative correlation between total cholesterol (r=-0.621), LDL-C (r=-0.0.716) and HDL-C (r=-0.656) with relation to severity of dengue. However there was a significant positive correlation between triglycerides and dengue severity (Table 3).

DISCUSSION

Dengue fever is the most prevalent arthropod-borne viral illness. In the past 20 years, the incidence of illness has increased four-fold and this trend appears to be continuing. With no particular antiviral drug or specific therapy available for its treatment, the management of dengue fever is mainly palliative and control of its specific complications. The infection of DENV to humans can lead to asymptomatic, mild or severe disease and the correct classification of severity will enable in selecting the most efficacious therapeutic protocol.

It was observed in current study that dengue fever primarily affects younger population with mean age of 28.5±9.2 years. Similar findings have been reported in studies conducted by Padmaprakash et al and Rabbani et al.10,11 Males (76%) were affected more than females (24%) in current study. An analytical study conducted in Singapore found that predominance of male cases would likely be due to greater male exposures to dengue carrying mosquitoes during daytime hours either at the work place or while travelling to and from work.¹³ A study conducted by Anker et al based on national surveillance data of six Asian countries also showed a male predominance of dengue infection.¹⁴ In present study, 120 (60%) patients were DNWS, 68 (34%) DWWS and 12 (6%) severe dengue. Huy et al in their cross sectional study reported the incidence of 57.3% DNWS, 31.3% DWWS and 11.4% severe dengue. 15 There was a reduction in total cholesterol, LDL-C, HDL-C in all forms of dengue and statistically significant (p<0.05) decrease was seen as severity of dengue increases. Various studies have shown similar relationship between dengue virus infection and circulating lipid alterations in patients with dengue and its severity. 16-18 The inverse relationship between these circulating lipids and dengue severity is mediated by several pathophysiological mechanisms like higher uptake, lowered synthesis, increased degradation from liver.¹⁹

Table 2: Lipid alterations in different levels of dengue severity.

	Dengue severity	Mean	SD	Median	Minimum	Maximum	IQR
TG (mg/dl)	DNWS	137.8	48.7	130	83	400	34.25
	DWWS	180.9	66.8	184	29	348	66.25
	SD	210	68.7	205	103	348	71.5
HDL (mg/dl)	DNWS	29.1	4.9	30	12	40	7
	DWWS	21.3	6.2	20	8	41	7
	SD	14.2	3.6	14	10	20	7.2
LDL (mg/dl)	DNWS	67.1	13.0	66	50	133	12
	DWWS	40.1	14.2	38	12	88	19.2
	SD	29.8	7.5	27.5	23	47	5.2
Total cholesterol (mg/dl)	DNWS	119.6	16.0	118	88	177	16
	DWWS	95.0	17.2	92	69	111	19.5
	SD	83.3	12.9	78	35	133	10.2

Table 3: Correlation analysis between Lipid profile and dengue severity.

Parameter	Total cholesterol	LDL-C	HDL-C	Triglycerides	Platelet counts
Dengue severity	r=-0.621	r=-0.716	r=-0.657	r=0.392	r=-0.333
	p=0.000	p=0.002	p=0.03	p=0.001	p=0.000

DENV is known to modulate lipid signalling pathway, synthesis and metabolism to create an optimum environment to facilitate its replication. Direct effects on the liver include increased expression of LDL receptors and formation of LDL-virus complex which facilitates the viral entry into the cell and increased uptake of LDL into the cell. Analysis by Povoa et al on liver biopsy samples showed hepatic steatosis in severe dengue patients suggesting the increase in lipid uptake.²⁰ The lowered phosphorylation of HMGCo reductase, a rate limiting enzyme in cholesterol synthesis is seen in dengue infection causing reduced synthesis of cholesterol.¹⁹ Dengue infection is known to affect hepatocytes and in severe cases high levels of liver enzymes are seen. Since liver is a major site of cholesterol synthesis, its damage by DENV results in lower circulating lipid levels.

The increase in pro-inflammatory cytokines like TNF- α , IL-6, IL-1 β and activation of oxidative factors due to dengue infection are found to reduce the plasma activity of LCAT (lecithin cholesterol acyltransferase), the enzyme responsible for esterifying free cholesterol in HDL. Furthermore the cytokines are found to increase the LDL receptor mRNA levels and increase the cholesterol catabolism in the cells. Thus pro-inflammatory state due to dengue infection induces degradation and reduces the release of cholesterol from the site of synthesis contributing to lower cholesterol levels.

There was an increase in triglycerides levels as severity of dengue increases (p=0.001). The increase in triglycerides may be due to an increase in lipolysis and de novo fatty acid synthesis in liver and increase in the activity of FASN (fatty acid synthase) a rate limiting enzyme in triglyceride synthesis which is facilitated by NS3 protein of DENV.²³ Gorp et al also found higher

serum triglycerides levels in severe dengue and suggested the use of changes in lipid parameters as prognostic marker to predict clinical outcome.¹⁷ Current study showed a significant negative correlation between total cholesterol (r=-0.621), LDL-C (r=-0.716) and HDL-C (r=-0.657) with relation to severity of dengue. A study done by Duran et al also concluded a similar result of negative correlation between cholesterol, LDL-C, HDL-C with dengue severity.²⁴

Limitations

Limitations of current study were; it's a cross sectional observational study, serum lipid profile is measured only on the day of admission. Thus a larger cohort study with follow ups will be required to ascertain the findings of present study.

CONCLUSION

In current study changes in lipid parameters strongly correlated with disease severity in dengue fever possibly due to mechanisms like altered viral-cell interactions, thrombocytopenia and cytokines involvement. Thus lipid profile should be routinely done as a maker of severity for all dengue patients to identify those at high risk. The decreased lipid parameters associated with dengue severity provide a futuristic approach in lipoprotein infusions as a management to severe dengue patients. The efficacy and safety of this treatment is to be proved in further studies.

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Institutional Ethics Committee

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