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A Study of Lipid Parameters in Malarial Patients Attending a Tertiary Health Care Centre in Mangaluru

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The study aims to estimate the lipid parameters among *Plasmodium vivax* and mixed malaria (*P. falciparum and P. vivax*) infected patients.
Study Design: This was a prospective observational and comparative study.
Place and Duration of Study: The present study was undertaken in the Departments of Medicine and Biochemistry at A. J. Institute of Medical Sciences and Research (AJIMS), Mangaluru, Karnataka between Dec 2017 and May 2018.
Methods: It was a prospective observational comparative study. A total of 100 patients (50 *P. vivax* and 50 mixed malaria cases) were consecutively taken in the study. The lipid profiles of the cases

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were compared with that of 100 healthy volunteers (control group). Data was collected and analysed.

Results: Serum total cholesterol, High- Density Lipoprotein (HDL) and Low- Density Lipoprotein (LDL) levels were significantly low(p<0.001) in cases and serum Triglycerides (TG) and Very Low-Density Lipoprotein levels (VLDL) were higher in cases (p<0.001) than in control. There were no significant changes in mean serum lipids profiles between *P. vivax* and Mixed Malaria groups.

Conclusion: The derangement in lipid profiles in falciparum malaria was characteristic and specific for the disease. Characteristic changes were lower HDL, LDL and total cholesterol levels with higher TG and VLDL levels in comparison to control groups. These findings may be of diagnostic and prognostic value.

Keywords: Malaria infection; mixed malaria; lipid profiles.

1. INTRODUCTION

Malaria is an infectious disease that is caused by the mosquito, which is haemoprotozoal organisms belonging to the Apicomplexa phylum and *Plasmodium* genus [1]. Malaria shows high morbidity and mortality rates in the tropical as well as subtropical regions. Among all *Plasmodium* species causing malaria, *Plasmodium falciparum* is the most pathogenic form. The other forms are *Plasmodium vivax*, *P. ovale*, *P. malariae* and *P. knowlesi* [2].

Nearly 698 million people all over the world fall under the high- risk category as per the World Malaria Report of 2017. Among this figure, India alone accounted for 6% of the cases, followed by 6% of mortality rate, and 51% of *P. vivax* cases throughout the world. The 2017 report also stated 1.31 million malaria cases and 23990 deaths in India [2]. Another study by Murray et al. [3] stated that the deaths due to malaria in India were 46, 800 in the studied year (2010). However, the cases of malaria caused by *P. falciparum* accounts for 30–90% of all infectious diseases occurring in the forest areas in case of ethnic tribes; and less than 10% of all cases occur in Indo-Gangetic plains, North and north-western states, as well as south of Tamil Nadu [4]. Unrestrained development of urban areas, drought, migration issues and lax control efforts have been some of the major contributing factors of all malaria cases in India.

The malaria parasite, however, is unable to completely synthesise all of its organic nutrients, including sterols, required for its growth and replication through its biosynthetic pathways, and in order to maintain viability the parasite has to import these nutrients from the host cell through its enveloping membrane, namely the parasitophorous vacuolar membrane (PVM) [5]. Labaied et al. [6] noted that *Plasmodium* could divert and salvage cholesterol from the host cells as it replicates inside the liver cells. Imrie et al. [7] stated that for *in vitro* culturing of *P. falciparum,* the conditions of low HDL concentration with no addition of serum have to be maintained. In the case of high HDL concentrations toxicity towards the growth and development of the parasite within the infected erythrocytes can be seen, which may lead to death or abnormal maturation of trophozoites. The malaria parasite is also able to extract cholesterol directly from the blood via a receptor-mediated endocytosis pathway [8]. These diversions of cholesterol and lipids from the host by the *Plasmodium* parasite, as it rapidly replicates, further contribute to the alterations in the plasma lipid profile. Another contributing mechanism leading to alteration in lipid profile is the fact that the host lipids are required by the malaria parasite for the formation of haemozoin, the malaria pigment. Inside the erythrocytes, the parasite feeds on the intracellular proteins, including haemoglobin, and degrades it, thus releasing free heme. Heme is toxic to the malaria parasite, and it is detoxified by lipid-mediated crystallisation to biologically inert haemozoin. Malaria parasite-induced hepatocellular damage leads to abnormal lipid handling by the liver and hence, unable to maintain homeostasis of lipid and lipoprotein metabolism. This causes derangements in plasma lipid profile [9].

The study was conducted in the Indian city of Mangaluru (formerly known as Mangalore), located on the shores of the Arabian Sea. Due to rapid development in construction activities in the city, this has led to many up surging events such as chloroquine resistance in *P. falciparum* and the city becoming endemic for malaria. Mangaluru has been one of the first cities in India to adopt the artemisinin-based combination treatment for *P. falciparum*. This study aims to evaluate the effects of malarial infection on

serum lipid profile, and also, characterises the pattern of derangements in serum lipid profile induced by malarial infection amongst patients in Mangaluru.

2. MATERIALS AND METHODS

2.1 Selection of Cases and Controls

The Present study was undertaken in the departments of medicine and biochemistry at A.J. Institute of Medical Sciences and Research (AJIMS), Mangaluru, Karnataka between Dec 2017 and May 2018 after approval of institutional ethics committee.

2.2 Study Design

This was a prospective observational and comparative study. This study enrolled 100 confirmed malaria patients (50 confirmed cases of *P.vivax* and 50 confirmed cases of Mixed malaria (*P. vivax* + *P. falciparum*) admitted in Medicine Department of AJIMS.

As the control, age and sex-matched one hundred healthy participants who were without any clinical or laboratory evidence of malarial infection were included as control subjects. Patient's consent was sought through an informed consent form.

Patients excluded from the study were hypertensive, diabetic, suffering from renal diseases, liver disease, obstructive jaundice, bacterial infections, other viral and parasitic infections, cancer, obesity, and alcoholism, H/O drug intake like oral contraceptive pills, steroid, statins and human immunodeficiency virus (HIV) infection.

The age range of participants was between 18 to 50 years. Clinically suspected malaria cases were confirmed using rapid antibody-based diagnostic card tests (Alere Trueline™ Rapid Diagnostic Kit, Bio Standard Diagnostic, Haryana, India) that detect histidine- rich protein 2 (HRP2) or lactate dehydrogenase antigens in finger-pricked blood samples. Confirmation by microscopic detection of malaria parasite was also done.

2.3 Sample Collection

Collection and Processing of Blood Specimen: Following aseptic precautions, five millilitres (5 ml) of fasting venous blood sample was collected from each subject on the second day of visiting the hospital as baseline sample after the patient has been clinically diagnosed for malaria infection.

4 ml of blood sample was collected on a plain vacutainer to assay lipid profile, and 1 ml of blood sample was dispensed into di-potassium ethylenediaminetetracetic acid (K2EDTA) vacutainer bottles for malaria parasite detection on thick blood film.

The blood sample was obtained after a 12 hour fasting period for all controls.

2.4 Microscopic Detection of Malaria Parasite

Thick blood film was made from EDTA blood sample and stained with Giemsa's staining technique for malaria parasite detection; observed under microscopy using x40 and x100 objectives lenses, the procedure was described by Monica Cheesbrough [10]. Standard operational procedures were prepared for identification of malaria species and the detection of malaria parasitemia and smears were examined by a senior medical laboratory scientist. The slide was considered negative when there were no parasites in 100 HPF.

2.5 Biochemical Analysis of Prepared Serum

Biochemical Analysis of Prepared Serum After centrifugation: The serum was decanted and serum HDL, total cholesterol, LDL and triglycerides were estimated using the Beckman Coulter AU chemistry analyser (USA). HDL and LDL were measured by homogenous enzymatic direct assay [11,12]. Serum cholesterol was measured by CHOD-PAP (cholesterol oxidase – phenol and aminophenazone) enzymatic method as described by Allain et al. [13]. Serum triglycerides were measured by GPO/POD (glycerol phosphate oxidase /peroxidase) enzymatic method [14]. LDL concentrations were determined by Friedewald equation [15]. VLDL concentrations were estimated using the assumption that in fasting subjects, the VLDL cholesterol to total plasma triglyceride (TG) ratio is relatively fixed at 1:5 [16].

2.6 Statistical Analysis

Data obtained were analysed using Microsoft Excel for statistical analysis to obtain the

following descriptive statistics: mean, standard deviation (SD), standard error of the mean (SE) and range. The significant test was done by ANOVA Analysis. Statistical significance was considered at p value < 0.05. Bonferroni correction was used to reduce the chances of obtaining false-positive results.

3. RESULTS

This study was concluded on 100 laboratory-confirmed cases of malaria patients of *P. vivax* (50) and Mixed malaria- *P. falciparum*+ *P. vivax* (50). There were 100 healthy volunteers taken as the control group.

Table 1 here shows the mean ages of patients in *P. vivax* group was 29.20±11.90, Mixed Malaria group was 31.82±14.29, and the control group was 38.21±12.07 respectively.

Table 2 shows the sex distribution among cases (males-87% and females 13%) and controls (males-87% males and 13% females).

Table 3 shows the mean value for total cholesterol, HDL and LDL were significantly lower in case group 95.21±22.24 mg/dl, 13.24±7.01 mg/dl and 64.85±16.50 mg/dl respectively than in control group of 182.73±17.14 mg/dl, 44.11±7.30, and 112.38±17.37 mg/dl respectively (p <0.05). But, serum triglyceride and VLDL were significantly higher in case group 146.78±38.59 mg/dl and 29.35±7.27 mg/dl respectively than in control group 132.40±15.51 mg/dl and 24.68±3.68 mg/dl respectively (p <0.05).

The mean values of lipid parameters in the 3 groups (*P. vivax*, mixed malaria and controls) are shown in Graphs 1-5.

Table 1. Age distribution between cases and controls

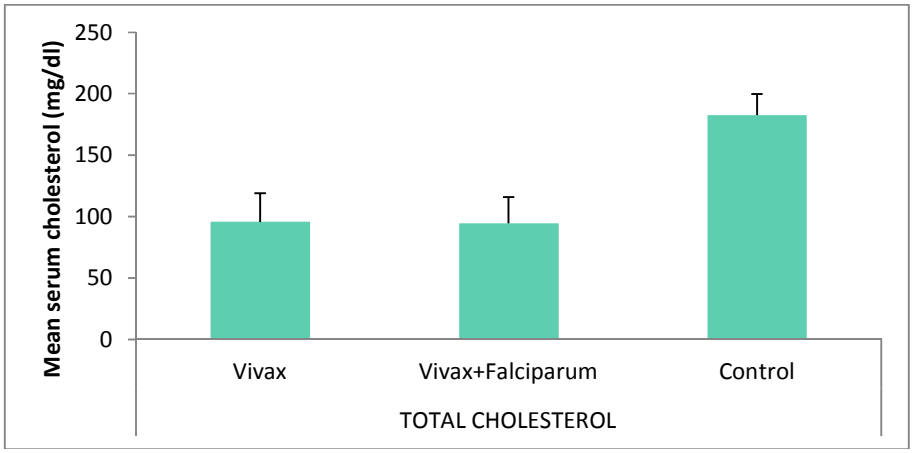
Groups	N	Age (in years)		ANOVA F	P
		Mean	Std. deviation		
Vivax	50	29.20	11.90	11.940	<0.001
Vivax + Falciparum	50	31.82	14.29		HS
Control	100	38.21	9.49		
Total	200	34.36	12.07		

Table 2. Sex distribution between cases and controls

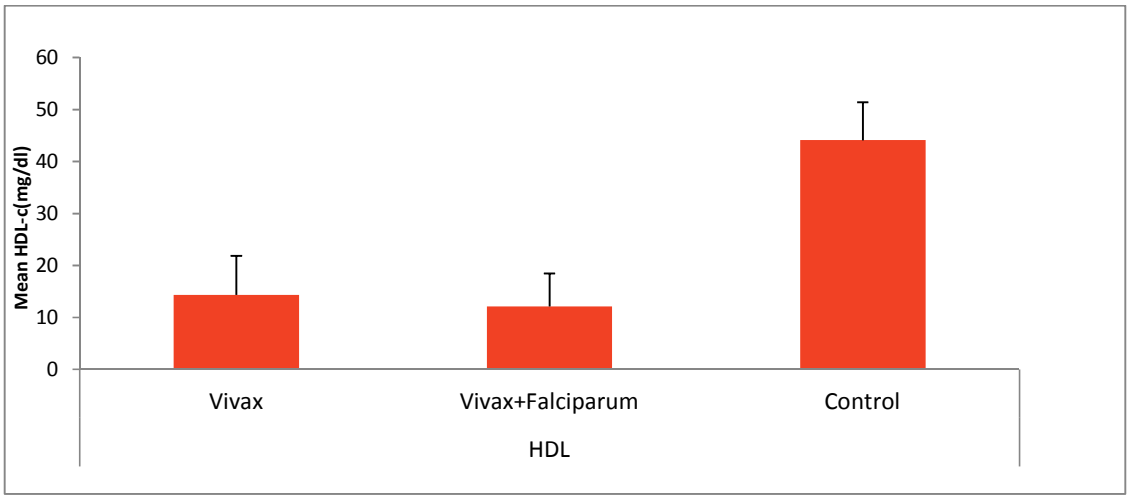
Gender	Group		Total
	Cases	Controls	
Female	13	13	26
	13.0%	13.0%	13.0%
Male	87	87	174
	87.0%	87.0%	87.0%
Total	100	100	200
	100.0%	100.0%	100.0%

Table 3. Comparison of lipid parameters in cases and controls

Parameters		N	Mean	Std. deviation	95% confidence interval for mean		t value	p
					Lower bound	Upper bound		
Total	Cases	100	95.21	22.247	90.80	99.62	31.16	<0.001
cholesterol	Control	100	182.73	17.142	179.33	186.13		HS
Triglycerides	Cases	100	146.78	38.598	139.12	154.44	3.46	0.001
	Control	100	132.40	15.510	129.32	135.48		HS
HDL	Cases	100	13.24	7.014	11.85	14.63	30.49	<0.001
	Control	100	44.11	7.300	42.66	45.56		HS
LDL	Cases	100	64.85	16.503	61.58	68.12	19.84	<0.001
	Control	100	112.38	17.373	108.93	115.83		HS
VLDL	Cases	100	29.35	7.727	27.82	30.88	5.46	<0.001
	Control	100	24.68	3.684	23.95	25.41		HS



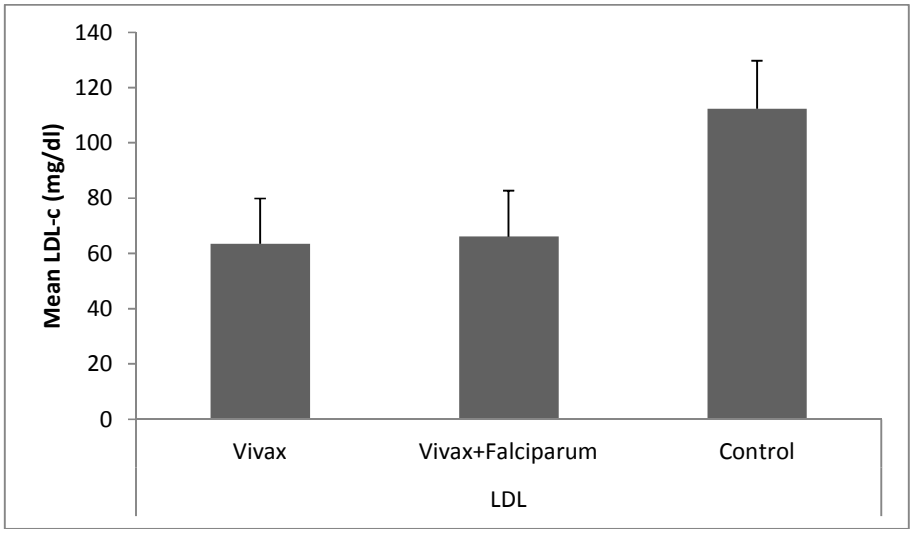
Graph 1. Serum cholesterol levels among the study subjects



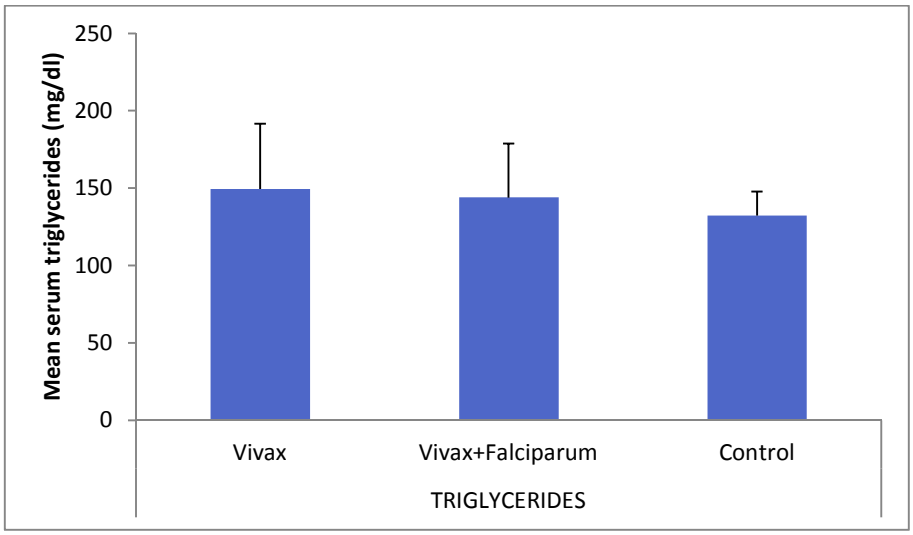
Graph 2. Serum HDL cholesterol levels among the study subjects

Table 4. Comparison of lipid and other biochemical parameters in Vivax and Mixed Malaria

Parameters		N	Mean	Std. deviation	95% Confidence Interval for Mean		t value	p
					Lower bound	Upper bound		
Total cholesterol	*P. vivax*	50	95.84	23.251	89.23	102.45	.282	.779
	P. falciparum+ P. vivax	50	94.58	21.412	88.49	100.67		
Triglycerides	*P. vivax*	50	149.54	42.203	137.55	161.53	.713	.477
	P. falciparum+ P. vivax	50	144.02	34.833	134.12	153.92		
HDL	*P. vivax*	50	14.34	7.515	12.20	16.48	1.580	.117
	P. falciparum+ P. vivax	50	12.14	6.360	10.33	13.95		
LDL	*P. vivax*	50	63.56	16.387	58.90	68.22	-.780	.437
	P. falciparum+ P. vivax	50	66.14	16.683	61.40	70.88		
VLDL	*P. vivax*	50	29.96	8.442	27.56	32.36	.788	.433
	P. falciparum+ P. vivax	50	28.74	6.972	26.76	30.72		



Graph 3. Serum LDL cholesterol levels among the study subjects

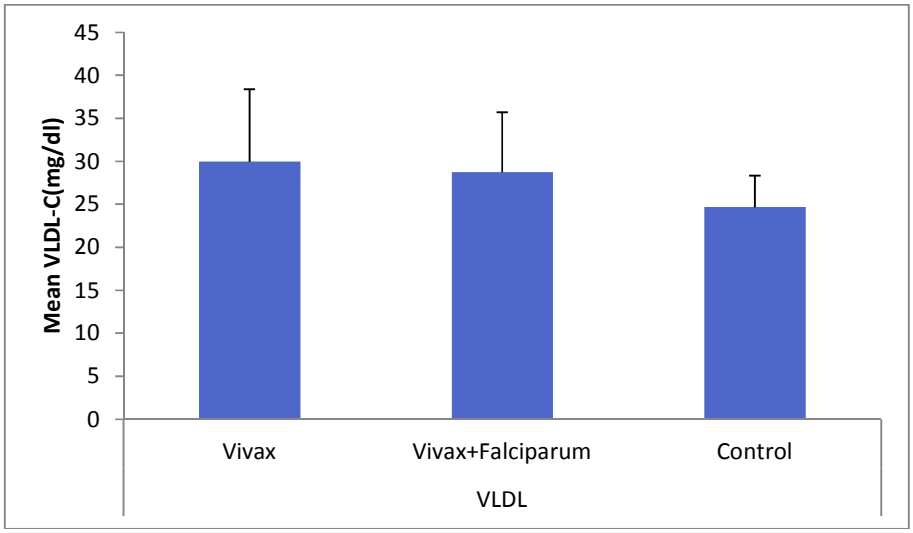


Graph 4. Serum triglycerides levels among the study subjects

4. DISCUSSION

In this study, total cholesterol was significantly lower in *P. vivax* malaria and mixed malaria in comparison with the non-malarial control group. In line with the present findings, a study by Djoumessi [17] carried out a comparative study between the malaria patients with low cholesterol levels with that of the normal healthy control group.

In the current study, HDL, and LDL levels were found to be low, and VLDL and triglycerides levels were found to be high in the case of *P. vivax* malaria and mixed malaria as compared to the healthy group. Visser et al. [18] showed similar statistically significant results regarding the decrease in serum total cholesterol, HDL and LDL in malaria patients as compared to reference values obtained from asymptomatic control subjects. The study also showed increased levels of triglycerides in malaria patients as compared with control values which were in accordance with this study. The current study strengthens the argument that the pattern of derangement of lipid profile seen in malaria is characteristic and specific for the disease.



Graph 5. Serum VLDL cholesterol levels among the study subjects

The serum LDL and HDL levels were found to be low in case of patients with moderate malarial infection as stated by Chikezie and Okpara [19]. The results were suggestive of the fact that low LDL levels, which are oxidised lipoproteins, have a significant effect in determining the pathogenesis of malaria. Also, the results were in line with the present studies. A significant decrease was observed in HDL, VLDL and total cholesterol levels in the malaria- infected group when compared to that of the healthy group [20]. The reduced level of total cholesterol might be due to the reduction in HDL levels, which results in the oxidative modification. This, in turn, increases the intracellular oxidative stress levels in parasitised erythrocytes of patients affected with malaria in addition to extracellular stress resulting out from haemolysed RBCs, which again leads to lipoprotein degradation. Similar results were reported by a few researchers who stated an increase in LDL and HDL levels and a slight increase in TG levels [21,22,23].

Sibmooh et al. [24] stated that in comparison to control, serum VLDL and HDL levels were high in malaria patients. It was also noticed that oxidised LDL was found to increase in the endothelial expression of adhesion molecules. The prevalence of malaria parasite infection in the male is more as considered to females, which was in line with a previous study [25]. This was because the body exposure is more in the case of males in high environmental temperature, and thus, it increases their chances of getting bitten. This study also states better immunity in females, which is due to the genetic and hormonal factors [25].

The current study states that acute malaria case shows decrease in HDL, LDL, TG and total cholesterol levels as compared to control.

The implications of this would include the characteristic pattern of derangement in the lipid profile in malaria may serve as an aid in diagnosing malaria, especially in the absence of positive blood film. In this regard, it is essential to understand that lipid derangements also occur in other infectious diseases. Visser et al. [18] in their meta-analysis and review of studies included comparison between patients with malaria and control group suffering from other febrile diseases, which suggested that the observed changes in total cholesterol, HDL and LDL concentrations were in increased state and found to be statistically significant in the case of malaria as compared to other febrile diseases. The study concluded that these changes were characteristic and specific for malaria.

There is a relation between the extent of lipid derangements and the severity of malaria infection. Al-Omar et al. [26] found an inverse correlation between parasite count and serum cholesterol level. Severe parasitaemia was associated with lower serum cholesterol levels. Parola et al. [27] found that the serum triglyceride levels were higher in falciparum malaria patients as compared to the mild condition. They suggested that hypertriglyceridemia may be

used as an indicator of severity in falciparum malaria.

These findings may have a possible therapeutic implication. Reis et al. [28] found that chloroquine, when combined with lovastatin, prevented cognitive impairment in the murine model of cerebral malaria. Treatment with the statin was found to prevent neurological inflammation and blood- brain barrier dysfunction in case of cerebral malaria in the murine model. Statins might prove to be one of the valuable adjuvant therapeutic agents used in the prevention of cognitive impairment in cerebral malaria patients. This therapeutic effect of statins may, however, be due to their powerful pleiotropic effects that are independent of their cholesterol-lowering properties.

The current study stated that acute malaria infection leads to the production of unique perturbation and modifications in the plasma lipoprotein metabolism and plasma lipid profiles.

Nevertheless, this study was limited by the small sample size. This study only compared malaria patients with asymptomatic healthy controls. Comparing the lipid derangements between malaria patients and symptomatic controls due to other infectious diseases could have enriched the understanding and contribute to the emerging facts. A detailed study needs to be performed on *Plasmodium* biology's core features to understand the disease better. Developing lipidomic, transcriptomic and proteomic profiles of malaria would pave the path towards understanding the metabolism of the casual agents which underlie its molecular aetiology. This will further lead to the development of a novel treatment approach.

5. CONCLUSION

In conclusion, the study further strengthens the findings in other similar studies detailing the characteristic pattern of derangements in lipid profile in malaria patients. Malaria parasites, both *P. vivax* and *P. falciparum* infections, cause derangements in lipid profile that are characterised by low serum total cholesterol, low HDL, low LDL and high triglyceride levels. The decrease in some of the lipids might lead to the onset of severe malarial infection. These derangements may be of diagnostic, prognostic or therapeutic value. Further studies are warranted to fully understand the implications and clinical application of these findings.

CONSENT

All authors declare that written informed consent was obtained from the patient (or other approved parties) for publication of this paper.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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