Original Article

# Hypertriglyceridemia As A Marker Of Multi-Organ Dysfunction In Leptospirosis

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## Abstract

**Background-** Weil's disease represents the most severe form and can develop after the acute phase as the second phase of a biphasic illness or as a progressive illness. It is characterised by jaundice, renal failure, bleeding disorders and altered mental status

**Objectives-**To find out association between Hypertriglyceridemia and Multi-Organ dysfunction in patients with Leptospirosis.

**Methods-** It was a prospective cross sectional study. Fifty consecutive patients who were diagnosed with Leptospirosis at the Department of Internal Medicine between February 2016 and September 2016 were included in the present study. The diagnosis of Leptospirosis was established by the presence of specific IgM antibodies against L. interrogans as determined by ELISA. No patient was receiving any hypolipidaemic agents or had any evidence of any disease known to affect lipid metabolism. All patients were examined on diagnosis and 4 months after recovery. No change in patients' dietary habits and body weight was recorded during follow-up. Fifty age- and sex-matched healthy volunteers (control population) were also included. SPSS was used for analysis.

**Results-** The patients (49 male and 1 female, mean age 49.5 ± 8.4 years) presented with fever and myalgias, while 4 of them (36%) also presented with jaundice and acute renal failure. Patients with Leptospirosis had decreased levels of TC, HDL-C, LDL-C, Lp(a) and whereas TG and VLDL-C levels as well were elevated compared with 4 months after recovery. Mean LDL particle size was decreased and sdLDL-C levels were increased at baseline compared with 4 months after recovery. Also, sdLDL-C% was markedly elevated at baseline compared with the values after recovery. According to these results, the only parameters significantly affected by creatinine levels were LDL-C and large LDL-C levels (p\0.05 for both). Levels of MODF markers (CRP, IL-1b, IL-6, and TNFa) were increased at baseline compared with 4 months and no difference in the levels of the inflammatory markers was observed between patients 4 months after the resolution of Leptospirosis.

**Conclusion-** Leptospirosis causes impressive alterations in the lipid profile that include markedly elevated TG which is considered as marker for multi-organ dysfunction and sdLDL-C concentration and low HDL-C and LDL-C levels.

**Keywords-** Leptospirosis, Hypertriglyceridemia, Multi-Organ dysfunction, Inflammatory markers, creatinine.

## Introduction-

Leptospirosis is a zoonotic, acute bacterial infection that is spread around the world by spirochetes of the genus Leptospira [1]. Human infection is caused through contact with contaminated urine of carrier mammals, either directly or indirectly through soil or water pollution [1]. The most severe type, Weil's disease, can progress after the acute phase as either the second phase of a biphasic illness or as a chronic condition. Jaundice, renal failure, bleeding issues, and impaired mental status are its defining traits [1].

According to numerous studies, sdLDL particles are more atherogenic than large buoyant ones [3]. Increased levels of sdLDL-C have been linked to periodontitis, HIV infection, as well as Brucella melitensis and EBV infections [4–7]. Lp-PLA2, a vascular disease risk factor [8,] is primarily found on LDL subtypes, with the remainder on HDL (HDL-Lp-PLA2). There are no comprehensive data on the potential changes in the lipid and

lipoprotein profile and related enzymes in leptospirosis patients. In order to assess the potential quantitative and qualitative effects of leptospirosis on serum lipid parameters and related enzymes for multi-Organ dysfunction, we conducted the current study.

## Materials and Methods-

The current study comprised 50 consecutive individuals who received a Leptospirosis diagnosis at the Department of Internal Medicine between February 2016 and September 2016. By using ELISA to detect the presence of certain IgM antibodies against L. interrogans, the diagnosis of leptospirosis was made. There was no evidence of any condition known to impact lipid metabolism, such as neoplasia, hypo- or hyperthyroidism (TSH [5 lU/mL] or TSH 0.01 lU/mL), nor was there any patient using any hypolipidemic medications. Also excluded were participants who had a known history of renal impairment (serum creatinine levels [1.5 mg/dL]). Each patient was assessed at the time of diagnosis and again four months later. During follow-up, no modifications to the patients' food routines or body weight were noted. There were also 50 healthy volunteers (control population) who were age and sex matched. These people were chosen for involvement in the current study based on their age and had previously visited the outpatient clinic of the 2nd Department of Internal Medicine for a routine checkup. All participants signed a document providing their free and informed consent to take part in the current investigation. The institutional ethics committee gave its approval to this work.

## Methodology-

With relation to the subject group and sampling period for each individual, all laboratory parameters were evaluated in the dark. On an Olympus AU600 Clinical Chemistry analyser, TC, HDL-C, and TG values in fasting serum were measured enzymatically (Olympus Diagnostica, Hamburg, Germany). With the exception of one patient whose TG levels were over the cutoff of 400 mg/dL, for whom LDL-C concentration was not determined, LDL-C was estimated using the Friedewald formula. Apo A-I, B, E, and Lp(a) levels were assessed using a Behring Nephelometer BN100 using Date Behring Holding Gmbh's reagents (Liederbach, Germany).

## Statistical Analysis-

SPSS (Version 22.0) was used for analysis and data are expressed as means ± SD. Paired samples t test (or Wilcoxon's rank test, as appropriate) was used for the comparison of study parameters between baseline and 4 months later. Independent samples t test (or the Mann–Whitney U test, as appropriate) was used for the comparison of the study parameters between patients and controls. Analysis of covariance (ANCOVA) was used to assess whether the lipid profile of patients was impaired compared with the lipid profile of controls after adjusting for differences between the two groups regarding renal function as assessed by serum creatinine level. p-value <0.05 is considered statistically significant.

## Results-

**Table 1- Clinical Characteristics and Lipid Profile**

| | Baseline (*n* = 50) | 4 months later (*n* = 50) | *p** | Controls (*n* = 50) | *p*** |
|---|---|---|---|---|---|
| Age | 49.5 ± 8.4 | – | – | 47.5 ± 9.6 | NS |
| Sex (M/F) | 49/1 | – | – | 49/1 | |
| Smokers (Yes/no) | 29/21 | 29/21 | NS | 27/23 | NS |
| TC (mg/dL) | 145 ± 49 | 211 ± 40 | ↘0.01 | 223 ± 29 | NS |
| HDL-C (mg/dL) | 17 ± 7 | 44 ± 11 | ↘0.001 | 57 ± 10 | 0.0 |
| TGs (mg/dL) | 259 (131– | 122 (68–433) | ↘0.01 | 111 (45– | N |

| | | | | | |
|---|---|---|---|---|---|
| | 614) | | | 209) | S |
| Lp(a) (mg/dL) | 2.4 (2.4–34.8) | 7.0 (2.4–78.6) | 0.03 | 8.8 (2.4–70.0) | N S |
| VLDL-C (mg/dL) | 45 (35–93) | 29 (20–52) | 0.03 | 33 (10–63) | N S |
| Large LDL-C (mg/dL) | 79 ± 27 | 116 ± 31 | 0.01 | 124 ± 23 | N S |
| sdLDL-C (mg/dL) | 8 (0–33) | 4 (0–14) | 0.03 | 5 (0–23) | N S |
| sdLDL-C (%) | 22 (0–33) | 3 (0–11) | 0.01 | 3 (0–13) | N S |
| LDL particle size (nm) | 261 ± 5 | 267 ± 6 | 0.03 | 269 ± 3.6 | N S |
| Creatinine (mg/dL) | 2.4 ± 1.4 | 1.1 ± 0.1 | 0.01 | 1.0 ± 0.1 | N S |
| apoA-I (mg/dL) | 59 ± 41 | 128 ± 50 | ↘0.01 | 156 ± 16 | NS |
| apoB (mg/dL) | 118 ± 31 | 95 ± 26 | NS | 101 ± 20 | N S |
| Lp(a) (mg/dL) | 2.4 (2.4–34.8) | 7.0 (2.4–78.6) | 0.03 | 8.8 (2.4–70.0) | N S |
| apoE (mg/L) | 103 (44–153) | 49 (35–68) | 0.01 | 35 (28–66) | N S |

As per table 1 The patients (30 male and 1 female, mean age 49.5 ± 8.4 years) presented with fever and myalgias, while 4 of them (36%) also presented with jaundice and acute renal failure. Patients with Leptospirosis had decreased levels of TC, HDL-C, LDL-C, Lp(a) and whereas TG and VLDL-C levels as well were elevated compared with 4 months after recovery. Mean LDL particle size was decreased and sdLDL-C levels were increased at baseline compared with 4 months after recovery. Also, sdLDL-C% was markedly elevated at baseline compared with the values after recovery. According to these results, the only parameters significantly affected by creatinine levels were LDL-C and large LDL-C levels (p\0.05 for both). Moreover, we divided patients into two subgroups according to serum creatinine levels (\1.5 mg/ dL, n = 7 vs. C1.5 mg/dL, n = 4). We found that the two subgroups differed in HDL-C (23 ± 5 mg/dL vs. 11 ± 2 mg/dL, p\0.01), LDL-C (100 ± 25 mg/dL vs. 52 ± 21 mg/dL, p\0.05) and large LDL-C (88 ± 18 mg/ dL vs. 61 ± 21 mg/dL, p\0.05) levels. However, all three parameters in the subgroup of patients with serum creatinine levels\1.5 mg/dL were still significantly lower compared with the corresponding values of the control population (p\0.03 for all). We also found that the subgroup of Leptospirosis patients with impaired renal function had more severe infection defined as higher cytokine levels [IL-1b: 14.9 (4.6–16.9) pg/mL vs. 4.2 (3.7–5.5) pg/mL, p\0.03 as well as higher CRP levels [150 (38–224) mg/L vs. 31 (29–325) mg/L, p\0.01.

**Table 2- Markers of Multi-Organ Dysfunction in patients with Leptospirosis atbaseline and 4 months**

| | Baseline ($n$ = 50) | 4 months later ($n$ = 50) | $p$* | Controls ($n$ = 50) | $p$** |
|---|---|---|---|---|---|
| CRP (mg/L) | 128 (29–325) | 2 (1–18) | ↘0.001 | 1 (1–2) | NS |
| IL-1*b* (pg/mL) | 6.7 (3.7–16.9) | 3.7 (3.6–5.5) | 0.01 | 3.6 (3.0–35.4) | NS |
| IL-6 (pg/mL) | 8.8 (2.5–58.4) | 2.7 (1.7–4.8) | 0.01 | 1.1 (0.6–64.0) | NS |
| TNF*a* (pg/mL) | 17.3 (10.0–39.0) | 4.2 (1.4–24.0) | 0.03 | 0.2 (0.1–17.5) | 0.01 |
| WBC (1L) | 5,043 ± 432 | 6,440 ± 1,091 | NS | 5,680 ± 1,008 | NS |
| NEUT (%WBC) | 84 ± 6 | 54 ± 7 | ↘0.001 | 59 ± 4 | NS |
| LYMPH (%WBC) | 10 ± 5 | 38 ± 5 | ↘0.001 | 34 ± 4 | NS |
| MONO (%WBC) | 6 ± 1 | 5 ± 2 | NS | 4 ± 2 | NS |

As per table 2 Levels of MODF markers (CRP, IL-1b, IL-6, and TNFa) were increased at baseline compared with 4 months and no difference in the levels of the inflammatory markers was observed between patients 4 months

after the resolution of Leptospirosis and controls, with the exception of the concentration of TNFa, which remained elevated 4 months after recovery compared with the control population.

## Discussion-

In the current investigation, we demonstrated for the first time that leptospirosis is linked to an atherogenic lipid profile, which includes elevated TGs, an increased apoB/apoA-I ratio, higher levels of sdLDL-C, and lower levels of HDL-C, LDL particle size, and HDL-Lp-PLA2 activity. Increases in TG and apoE levels and decreases in LDL-C, HDL-C, apoA-I, apoB, and Lp(a) concentrations are among the lipid profile changes brought on by infection [2]. The effects of the cytokines (IL-1b, IL-6, and TNFa) are mostly responsible for these modifications [9]. LDL receptor expression is stimulated by IL-6 in hepatic cells, which results in higher LDL particle absorption and lower LDL-C levels. In the current investigation, we discovered that baseline LDL-C levels were related to levels of TNFa, CRP, and IL-6 in addition to IL-6 concentration. TNFa may increase LDL receptor activity [2]. Moreover, experimental data show that hepatic cells exposed to TNFa, IL-1b and IL-6 exhibit decreased synthesis of apos (such as apoB), leading to decreased LDL-C levels [10].

When leptospirosis was diagnosed, the TG levels were considerably elevated along with CRP and IL-6 levels, which are indicative of multi-organ failure. Their concentration decreased when the cytokine levels dropped. By promoting hepatic fatty acid synthesis and elevating VLDL production, TNFa, ILs, and interferons can raise blood TG levels [2], which is consistent with our observation of enhanced VLDL-C levels at baseline. We examined apoC-II and apoC-III, which are important regulators of the metabolism of TG-containing lipoproteins, to further clarify this theory[11].

It has been demonstrated that ApoE increases the rate of lipolysis and decreases the effectiveness of the TG-rich lipoproteins' secretion [12]. The observed hypertriglyceridaemia may be caused by the baseline elevated apoE levels, which may be brought on by an increase in apoE production by activated macrophages and/or the liver [13]. This result is consistent with our earlier findings that apoE functions as a positive acute-phase protein in infected patients [13]. Leptospirosis patients reported significantly decreased HDL-C and apoA-I levels at baseline compared to 4 months later. The precise mechanisms causing the drop in HDL-C levels after acute infection are still unknown. Reduced HDL-C levels are a result of EL overexpression, and TNFa and IL-1b may be involved in this effect [14].

In comparison to 4 months later, there was a change in the distribution of LDL subclass toward smaller particles in individuals with leptospirosis. A significant incidence of sdLDL particles has been linked in studies to advanced HIV infection and severe periodontitis [5, 6]. Due to poor lipolysis, increased mobilization of fat from adipose tissue, and altered lipid clearance, ARF is linked to higher TG and lower LDL-C and HDL-C levels [15]. In contrast to the subgroup with normal kidney function, Leptospirosis patients with ARF in our study exhibited decreased HDL-C and LDL-C levels, while no difference in TG levels was seen. But given the higher levels of cytokines in the ARF subgroup compared to those in the control group, this finding might be explained by the more severe infection detected there with normal kidney function.

## Conclusion-

Leptospirosis causes impressive alterations in the lipid profile that include markedly elevated TG which is considered as marker for multi-organ dysfunction and sdLDL-C concentration and low HDL-C and LDL-C levels. Further studies are required for more in depth analysis.

## Conflict of Interest- None declared

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