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TYPHOID FEVER;
ESTIMATION OF SERUM LIPID LEVELS AND C-REACTIVE PROTEIN

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ABSTRACT… Objectives: The study was planned to see the serum lipid levels and c-reactive proteins in patients with enteric (Typhoid) fever. **Design:** Comparative. **Setting:** Study was conducted at the department of Pharmacology, University of veterinary and animal sciences, and Lahore. **Period:** from April 2014 to October 2014. **Methodology:** A total 100 subjects were included in the study. Amongst them there were 50 patients with typhoid fever and 50 normal individuals. All subjects fulfilled the criteria of inclusion in study and informed consent in written form was taken. Three millimetre venous blood was drawn from each subject, who was centrifuged and serum was preserved for quantitative analysis of Total cholesterol (TC), Triglycerides (TGs), High-density lipoprotein-cholesterol (HDL-C), Low-density lipoprotein-cholesterol (LDL-C) and C-reactive protein (CRP). **Results:** According to this study there was elevation in the levels of TGs and decline was observed in the levels of HDL, LDL, and TC, which is due to lipid peroxidation in typhoid patients. This study highlighted the complexity of lipid variation during Salmonella typhi infection. Elevated level of C-reactive protein reflects the immune response to infection by typhoid patients. **Conclusion:** CRP may play a role in early diagnosis of perforation in patients with typhoid fever. Typhoid fever causes biochemical changes and it should be further investigated to make them helpful for diagnosis.

Key word: Typhoid fever, C-reactive proteins.

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Fever is a medical condition which is characterized by an increase in temperature above the normal range of 36.5–37.5°C (98–100°F) caused by an increase in the regulatory set-point of the body.[1] Altered set point triggers increase in muscle tone and causes shivering. The increase in temperature can be caused by the action of toxic products that affect the temperature regulatory centers.[2]

Fever can be bacterial, viral and parasitic and may be due immune reactions. It can be due to trauma or it may be drug induced. Amongst these fevers there is one important and common fever Typhoid fever (Enteric fever).[3] Enteric fever, also called typhoid fever, is a common disease, caused by bacterium Salmonella enterica, typhi. It is transmitted by the ingestion of contaminated food or water. The causative organism perforates the intestinal wall and is phagocytized by macrophages. It is a Gram-negative motile short bacillus with peritrichous flagella. The bacterium grows best at 37°C / 98.6°F human body temperature. This fever received various names, such as gastric fever, abdominal typhus, infantile remittent fever, nervous fever, and enteric fever.[4] Salmonella species cause a number of infections causing remarkable health threat in various countries. It is prevelant in South East and Central Asia, Africa, America, the Caribbean, and Australlia, but 80% of cases come from India, Nepal, Bangladesh, Indonesia, china, Pakistan, Laos and Vietnam.[5] Within these countries, underdeveloped areas are most effected with typhoid fever.. Around 21.6 million people are infected and almost 200,000 people are killed by

this infection every year.[6] S. typhi–infected bile infects the gall bladder as well, subsequently causing re-entry of the organism into the gastrointestinal tract (GIT) and re-infection of the Payer's patches. Bacteria that do not re-infect the host are typically shed in the stool and are involved in the spread of infection.[7,8]

Intestinal bleeding is the most serious complication of enteric fever, having an incidence of 5% in the infected population. Perforation may develop in the third week of onset of fever. Sudden fall of blood pressure and shock, along with blood in the stool indicates intestinal bleeding. Intestinal perforation causes the leakage of intestinal contents into the abdominal cavity and triggers severe abdominal pain,vomiting, nausea and bloodstream infection (sepsis).

Other less possible complications include pneumonia, inflammation of the heart muscle (myocarditis), renal infections, inflammation of the pancreas (pancreatitis), meningitis, spinal infections (osteomyelitis), and psychiatric problems such as delirium, psychosis and hallucinations.[9]

Different test are performed to diagnose typhoid fever which may include,

Widal test

A slide widal test is most common among diagnostic laboratories as it gives rapid results. One drop of undiluted patients' serum samples for the four antigens is placed on separate slides. One drop of each of the four Salmonella antigens are added to each slide and gently rotated for one minute. After observation under bright lamplight, appearance of agglutination shows that the person is positive for typhoid.[10]

Typhidot

This test consists of a dot ELISA kit which identifies IgM and IgG antibodies against the outer membrane protein (OMP) of the Salmonella typhi. The typhidot test becomes positive within 2–3 days of infection.[11]

Lipid profile

When typhoid fever is at the peak, serum cholesterol level decreases, whereas the normal value of cholesterol is <200mg/L. Similarly HDL-cholesterol and LDL-cholesterol levels also decreases from their normal values that are 45mg/L and <190mg/L respectively but TGs level increases from 200mg/L and causes hypertriglyceridemia. The values of serum lipid levels returned to normal on recovery.[12]

C reactive protein levels in typhoid

C-reactive protein (CRP) is an acute-phase protein with increased concentrations in the blood during infections.[13] CRP belongs to the pentraxin family of proteins, because it has five identical subunits, encoded by a single gene on chromosome 1, which associate to form a stable disc-like pentameric structure.[14]

Bacterial or inflammatory diseases raise the level of CRP. These inflammatory conditions cause the release of interleukin-6 and other cytokines that trigger the synthesis of CRP and fibrinogen by the liver.[15,16] Trauma, inflammation, and infection result in a rapid increase in the level of CRP, which decreases as rapidly with the resolution of these diseased conditions. Hence serum CRP level is commonly used to predict and monitor different inflammatory conditions. It attaches to the damaged tissue, nuclear antigens and to certain pathogenic organisms and plays a role in the subsequent modification of innate immune system. It activates complement system, binds to Fc receptors and acts as an opsonin for several pathogens. These results in the formation of certain cytokines which further enhance the immune response. Unlike IgG, which specifically recognizes specific antigenic molecules, CRP recognizes altered self as well as external agents. It is thought that CRP may have a role as a monitoring tool for altered self and external pathogens. This provides a proinflammatory signal and leads to activation of the humoral, adaptive immune system.[17]

CRP plays a major role in the prediction of early diagnosis of perforation in patients with typhoid

fever. In various previous researches it had been shown that CRP levels in typhoid positive patients are elevated than the normal range of CRP.[18]

The levels of CRP in healthy human serum are 1-5 mg/L. Increased levels are mostly observed in pregnant women during third trimester. Simple inflammation, viral infection (10-40 mg/L), mild bacterial infection (40-200mg/L), severe bacterial infections and burns (> 200 mg/L) result in raised CRP levels.[19]

Typhoid is a bacterial disease due to ingestion of gram-negative bacteria Salmonella Enterica, typhi through contaminated sources. S. typhi is one of the most widespread disease producing bacteria in developing countries and if it is left undiagnosed or untreated, it can result into severe outcome. Newborns and the oldage are at an increased risk of bacterial infections including S.typhi infection. This study was designed to investigate the extent of physiological and biochemical changes in typhoid patients. These changes were assessed through estimation of lipid profile and C-reactive protein. Further research in this area will enable scientists to make new drugs for the treatment of typhoid fever.

METHODOLOGY

A total of 100 subjects were included in the present study. Fifty were typhoid patients, between the ages of 10 to 40. The patients were already diagnosed positive for typhoid through widal and typhoid test, whereas fifty normal individuals of same age group were taken as control. The patients having Hepatitis, Cardiovascular diseases, Lipid disorder, Hypertension, Diabetes and Smoking habits were not included in the study. Formal consent was taken from each subject after the purpose and procedure of the study were clearly explained to them. A questionnaire was made before the study started and it was filled from each subject before blood collection.

Three milliliter of venous blood was drawn from each subject using sterile disposable syringes. A code was used to identify each sample at the time of collection and for preservation of the samples. The blood was transferred to labeled gel vials and centrifuged at 4000-rpm for about 5 minutes at temperature of 37°C in order to separate the serum. The centrifuged samples were then transferred to eppendorf tubes and quantitative analysis of Total cholesterol (TC), Triglycerides (TGs), High-density lipoprotein-cholesterol (HDL-C) Low-density lipoprotein-cholesterol (LDL-C) and C-reactive protein (CRP) was carried out.

RESULTS

In this study, 100 individuals were studied altogether. They were divided into two groups; typhoid infected patients, and normal individuals. Various statistical tests are performed on the data collected and the results of statistical analysis are given below.

Age groups

The entire subjects of the study were divided into three age groups. Frequency of typhoid patients belonging to 10-20 age group was 38%, 42% were of 21-30, while 20% were of 31-40 years of age groups (Table-I & Figure-1).

Age groups	Frequency (N)	Percentage (%)
10-20	38	38
21-30	42	42
31-40	20	20
Total	100	100

Table-I. Age of the entire study subjects.

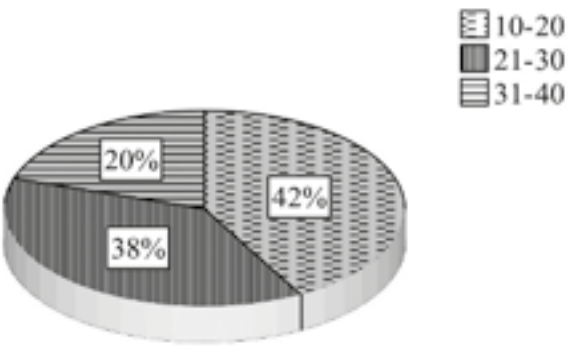

Figure-1. Age of entire study subjects.

Gender

Total 100 subjects were studied out of which 56% were male and 44% were female (Table-II & Figure-2).

Gender	Frequency (N)	Percentage (%)
Male	56	56
Female	44	44
Total	100	100

Table-II. Gender differences of the subjects.

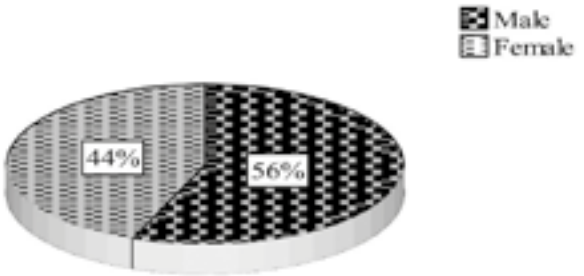

Figure-2. Gender differences of the subjects.

Diagnostic tests

The 50 subjects of typhoid were confirmed by diagnostic tests. Out of those 40% were diagnosed positive for typhoid by Widal test and 60% were diagnosed through Typhidot (Table-III & Figure-3).

Diagnostic tests	Frequency (N)	Percentage (%)
Widal	20	40
Typhidot	30	60
Total	50	100

Table-III. Diagnostic tests of typhoid infected patients.

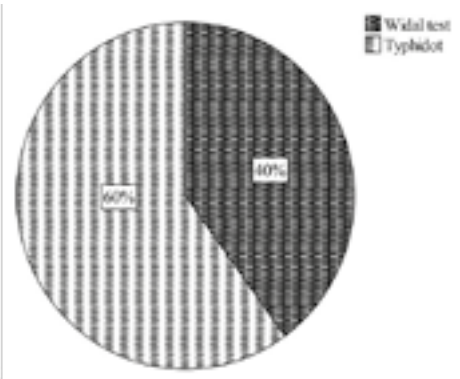

Figure-3. Diagnostic tests of typhoid infected patients.

Anthropometric profiles of normal individuals and typhoid Patients

The results of the study show that the temperature of typhoid patients was comparatively higher as compared to normal individuals. The mean systolic and diastolic blood pressure of typhoid individuals was lower than normal individuals. The blood pressure of typhoid patients was lower because during typhoid patients suffer from bradycardia, which is one of the symptoms of typhoid (Table-4).

Parameters	Frequency (N)	Normal	Typhoid
Temperature	50	98.00 ± .000	99.64 ±. 802
Systolic BP	50	123.68 ± 4.888	106.88 ± 4.663
Diastolic BP	50	80.72 ± 1.703	68.94 ± 3.987

Table-IV. Anthropometric profile of subjects.

Cholesterol level in typhoid and normal individuals

T-test (Independent) was applied and results of the study indicated that the p value 0.000 was significant and the mean score of normal individuals and typhoid patients was M = 173.98 ± 19.403 and M = 148.20 ± 16.326 respectively (Table-V & Figure-5). So, the cholesterol level in normal individuals was higher as compared to typhoid patients.

	Condition	Frequency (N)	Mean	Std. Deviation	P
Choles-terol	Normal	50	174.0	19.403	0.000
	Typhoid	50	148.2	16.326	0.000

Table-V. Cholesterol level in normal individuals and typhoid patients.

Triglycerides level in typhoid and normal individuals

T-test (Independent) was applied and results of the study indicated that the p value 0.000 was significant and the mean score of normal individuals and typhoid patients was M = 114.06 ± 40.754 and M = 168.64 ± 71.965 respectively (Table 6 & Figure 6). So it is concluded that triglycerides level in typhoid patients was higher as compared to normal individuals.

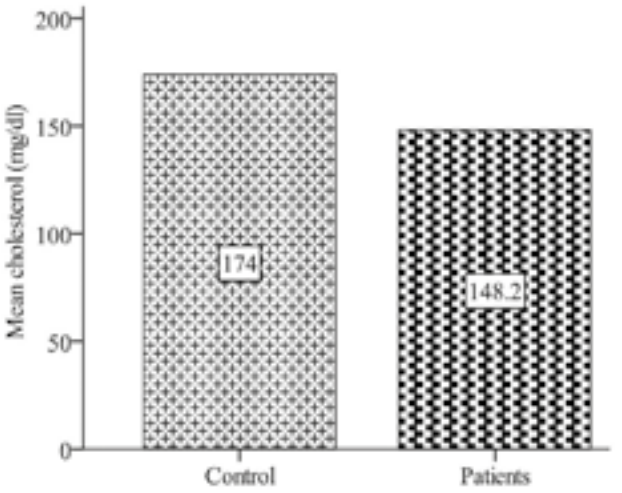

Figure-5. Cholesterol levels in control and typhoid patients.

	Condition	Frequency (N)	Mean	Std. Deviation	P
Trigly-cerides	Normal	50	114.1	40.754	0.000
	Typhoid	50	168.6	71.965	0.000

Table-VI. Triglycerides level in normal individuals and typhoid patients.

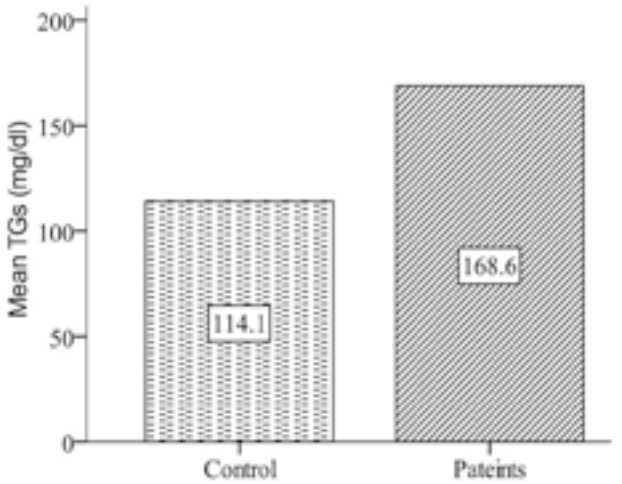

Figure-VI. Triglycerides level in typhoid patients and controls.

HDL level in typhoid and normal individuals

T-test (Independent) was applied and results of the study indicated that the p value 0.000 was significant and the mean score of normal individuals and typhoid patients was M = 46.30 ± 5.93 and M = 34.14 ± 4.389 respectively (Table-VII & Figure-7). So it is concluded that HDL levels in normal individuals was higher as compared to typhoid patients.

	Condition	Frequency (N)	Mean	Std. Deviation	P
HDL	Normal	50	46.30	5.943	0.000
	Typhoid	50	34.14	4.389	0.000

Table-VII. HDL level in normal individuals and typhoid patients.

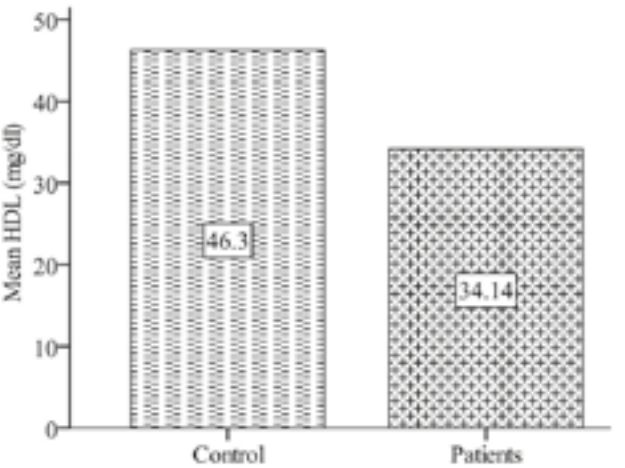

Figure-7. HDL level in typhoid patients and controls.

LDL levels in typhoid and normal individuals

T-test (Independent) was applied and results of the study indicated that the p value 0.000 was significant and the mean score of normal individuals and typhoid patients was M = 108.74 ± 18.421 and M = 81.06 ± 15.001 respectively (Table-VII & Figure-8). So it is concluded that LDL levels in normal individuals are higher as compared to typhoid patients.

	Condition	Frequency (N)	Mean	Std. Deviation	P
LDL	Normal	50	108.7	18.421	0.000
	Typhoid	50	81.1	15.001	0.000

Table-VIII. LDL level in normal individuals and typhoid patients.

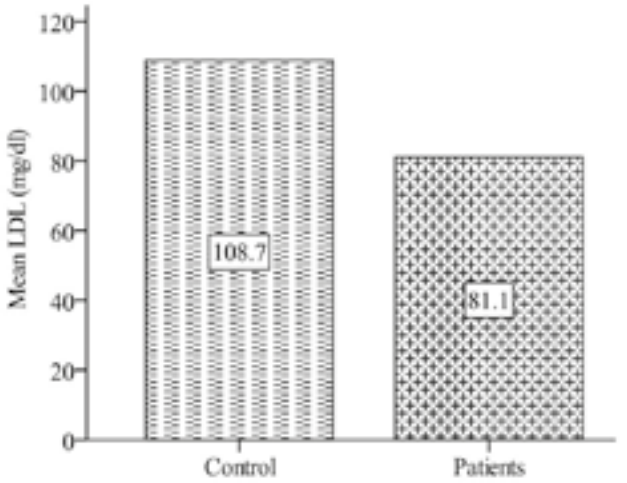

Figure-8. LDL level in typhoid patients and controls.

C reactive protein in typhoid and normal individuals

Almost 42% typhoid patients had high-level of CRP that was greater than 6mg/dl while 8% typhoid patients had CRP levels below 6mg/dl. Normal individuals had CRP levels below 5mg/dl (Table 9 & Figure 9).

CRP	Condition	Frequency (N)	Percentage (%)
Controls	<5mg/dl	50	50
Typhoid	>6mg/dl	42	42
Typhoid	<6mg/dl	8	8
	Total	100	100

Table-IX. Frequency of CRP among normal individuals and typhoid patients

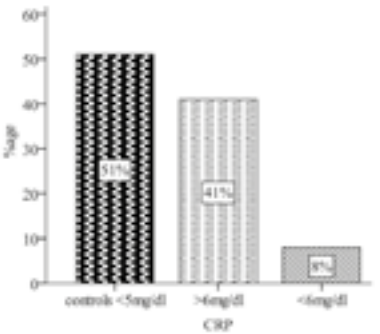

Figure-9. CRP level in typhoid patients and controls.

Statistical analysis

The data obtained from the study was analyzed using the computer software Statistical Package for Social Sciences (SPSS). Quantitative variables were demonstrated as mean standard deviation. Statistical analysis between patients and controls was performed using independent t-test and a p value <0.05 was taken as being statistically significant. The data was then presented in the form of tables and graphs.

DISCUSSION

Typhoid fever is a disease caused by a bacterium, Salmonella Typhi , which is transmitted orally through the ingestion of contaminated food or water.[20] In this study hundred subjects were studied altogether, out of which fifty were typhoid patients and fifty were healthy individuals. Blood samples of typhoid patients already diagnosed through widal and typhidot tests were collected. Then serum lipid and CRP levels were estimated and the data was analyzed through SPSS (version 17.0)

In the present study typhoid patients had lower systolic (106.88 ± 4.66) and diastolic (68.94 ± 3.98) BP when compared to normal individuals' systolic (123.68 ± 4.88) and diastolic (80.72 ± 1.70) BP. The mean body temperature was also high in typhoid patients (99.64 ± 0.802) as compared to normal individuals (98.00 ± 0.000). The main reason of high temperature in typhoid patient is due to immune response against bacterial attack[2] and low systolic and diastolic BP during typhoid is because of decrease heart rate.[21] The results of a previous study also showed lower systolic (106.6 ± 0.71) and diastolic (75.55 ± 2.9) in typhoid BP when compared to normal individuals' systolic (136.38 ± 3.97) and diastolic (87.17 ± 0.6). Temperature of typhoid patients was (98.93 ± 0.33) and (98.6 ± 0.30) of normal individuals. So, the results of the present study are in accord with the results of the previous study.[22]

The clinical symptoms of typhoid patients were mainly fever (100%), headache (52%), abdominal pain (80%), and chills (52%). Toxic substances that affect the temperature regulating centres can cause the increase in temperature. These include bacterial diseases, brain tumours and environmental conditions that may terminate in heat stroke. Typhoid organisms pass through

the pylorus and reach the small intestine after ingestion and multiply rapidly. Abdominal pain is mainly due to disturbance in the bowel function (constipation in adults and diarrhoea in children).[23] The previous studies depicts[24,25] that most common symptoms were fever in 39 (95%), headache in 33 (80%), chills in 20 (45%) and abdominal pain in (95%) patients. All these findings satisfy the previous study.

The mean ± SD total cholesterol level in typhoid patients and control was 148.20 ± 16.326 and 173.98 ± 19.403 respectively. In the present study a significant decrease in cholesterol level was observed in typhoid individuals than normal individuals. Furthermore this decrease in cholesterol level is similar to previous work[26] in which mean ± SD total cholesterol level in typhoid patients was 142.22 ± 29.83 and of healthy individuals was 211.19 ± 22.02. Similarly this decrease in cholesterol level was explained in another previous work[27] that depict that cholesterol is one of the preferential targets of oxidation by free radicals.

Results of the present study shows that mean ± SD level of HDL in typhoid patients (34.14 ± 4.389) were lower than normal individuals, HDL level (46.30 ± 5.93). The decrease in the mean ± SD level of HDL (35.93 ± 2.3) in typhoid patients and (49.3 ± 0.7) in normal individuals was observed in a previous study.[21] Similarly another study reported[28] significant decreases in the level of HDL in typhoid patients. In the present study level of LDL in typhoid patients and normal individuals was 81.1 ± 15.001 and 108.7 ± 18.421 respectively. The previous work done states[22] that mean ± SD LDL level in typhoid patients was 75.05 ± 8.5 and in normal individuals was 110.28 ± 5.50. Another study[29] reported that lipid peroxidation may be attributed to loss of appetite and diarrhoea which are classic in typhoid patients and partially due to the biosynthesis and activation of immune responses like prostaglandins, interleukins, interferon, cytokines etc. The result of the present study coincides with the results of the previous study.

In the present study the mean ± SD level of triglycerides was 168.6 ± 71.96 in typhoid patients and 114.1 ± 40.754 in normal individuals. The level of triglycerides (TGs) was elevated in typhoid patients as compared to that in normal. This increase in TGs was also reported in previous work[22] in which the mean ± SD level of triglycerides was 160.6 ± 5.67 in typhoid patients and 115.1 ± 6.53 in normal individuals, which show a relative increase in the level of triglycerides in typhoid patients. Similarly in another study depicts[28] a severe and protracted hypertriglyceridemia in typhoid patients that return to normal on recovery. The result of the present study shows a positive correlation with the results of the previous study.

The level of CRP was high in 72% patients and normal in 18% patients, whereas all the controls had normal level of CRP. This increase in CRP level is because of the fact that C-reactive protein can recognize the change in self and invasive agents, resulting in provision of early defense by activation of humoral adaptive immune system.[17] The results of a previous study[30] showed that out of 58 cases, 88% children had elevated and 12% children had normal levels of CRP. Hence the results of this study are in accordance with the results of the previous study.

CONCLUSION

This study concludes that by comparing healthy individuals to typhoid patient's elevation in the levels of TGs and decline was observed in the levels of HDL, LDL, and TC, which is due to lipid peroxidation. This study highlighted the complexity of lipid variation during Salmonella typhi infection. Elevated level of C-reactive protein reflects the immune response to infection by typhoid patient. CRP may have a role in the prediction of early diagnosis of perforation in patients with typhoid fever. Typhoid fever cause biochemical changes but these changes can be covered up by antibacterial therapy.

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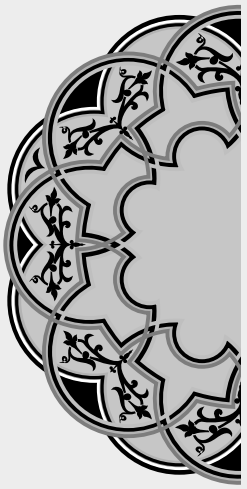

"Even the darkest night will end and the sun will rise."

Vieter Hage

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