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## Assessment of some immune markers in typhoid-patients: A case control study

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**Abstract**---A case-control study was carried out in the General Teaching Hospital in Balad City, Iraq. Eighty-eight male and female were included in this study; 58 typhoid-patients infected with *S.typhi* and 30 healthy individuals as controls. Acute typhoid-patients have been diagnosed according to positive blood culture and IgM and chronic typhoid-patients have been diagnosed according to positive stool culture and IgG. Four immunological markers have been measured in all individuals' serum; interleukin 4 (IL-4), interleukin 17 (IL-17), cluster of differentiation 8 (CD 8) and cluster of differentiation 22 (CD 22) using an Enzyme-Linked Immunosorbent Assay (ELISA). We diagnosed 32 and 26 patients infected with acute and chronic infection respectively, the results proved a significant increase (P-value=<0.05) in all markers in acute and chronic infections as compare with control. A significant differences P-value (0.0003 and <0.0001) has been proved between acute and chronic infection in IL-4 and IL-17 respectively. While, there was no significant differences P-value ( 0.13and 0.32) between acute and chronic infection in CD8 and CD22 respectively. **Conclusions:** IL-4, IL-17, CD8 and CD22 serum levels increase in typhoid-patients caused by *S.typhi* in humans. IL4 and IL-17 increase dependently on the duration and severity of the disease, while CD8 and CD22 increase in both acute and chronic infection without significantly increasing between them.

**Keywords**---*Salmonella typhi*, Immune response, IL-4, IL-17, CD8, CD22.

## Introduction

The motile enteropathogenic intracellular bacterium *S.typhi* causes most cases of typhoid fever, also called enteric fever, and kills more than 180,000 people each year (Mohammed and Aljanaby, 2020; Iwasaki et al., 2021). The other bacterium is *Salmonella enterica* serovars Paratyphi A and B (*S. paratyphi*) (Männe et al., 2019). *Salmonella typhi* is a gram-negative bacterium and a facultative intracellular pathogen that causes an acute and chronic generalized infection of the reticulum-endothelial system, intestinal lymphoid tissue, and gallbladder in humans (Bula-Rudas et al., 2015; Sharma et al., 2021). The severity of infection caused by this bacterium is dependent on two factors: the type of strain and the immunological status of the host (Dougan and Baker, 2014; Johnson et al., 2018). It is known that humans are the only reservoirs of *S.typhi* and *S.paratyphi* since typhoid fever spreads by the oral route due to food and water contaminated by these bacteria (Afzal et al., 2019; Das et al., 2019). Therefore, these pathogens have been considered a major public health problem worldwide, especially in developing countries where about 27 million new infections of typhoid fever occur each year and about 90% of these typhoid deaths occur in Asia (DeRoeck et al., 2007; Kumalo et al., 2021). The innate and cell mediated immunity (CMI) have an important protection role against *S.typhi* (Sztejn et al., 2014). CMI, especially interleukins and CD markers have vital role in host defense against acute and chronic *S.typhi* infection (Sztejn et al., 2014; Takaya et al., 2020). Interleukin-4 is a cytokine produced by mast cells, T-helper 2, basophil and eosinophil has a potent regulatory role in immunity due to its role in leukocyte survival under bacterial infection conditions, B-cell growth factors and stimulating B-cell differentiation (Sachin et al., 2012). Interleukin-17 has an important role in patients infected with *S.typhi* due to recruiting neutrophils to the mucosa in the intestine to prevent invasion of this pathogen (Noto et al., 2017). On the other hand, IL-17 causes excessive inflammation, contributing to colitis (Huang, 2021; Sheikh et al., 2022). The Cluster of Differentiation 8 (Cytotoxic T-cell) is generated in the thymus and expresses the T-cell receptor and a co-receptor and is usually composed of one CD8 $\alpha$  and one CD8 $\beta$  chain (Schäfer and Zerneck, 2021). CD8+ T cells recognize peptides presented by MHC Class I molecules, found on all nucleated cells (Raskov et al., 2021). Cluster of differentiation 22 is a B cell-specific glycoprotein of the sialic acid binding lectin family expressed on the surface of maturing B cells (Qin et al., 2018; Lanza et al., 2020). Cluster of differentiation 22 functions as an inhibitory receptor for B cell receptor signaling (Haas et al., 2018; Fry et al., 2018). Despite many published articles about the immune response in laboratory animals infected with *Salmonella*, there was no adequate information about the role of IL-4, IL-17, CD8 and CD22 in human models. Therefore, this work aims to assess these immune markers in acute and chronic typhoid patients caused by *S.typhi*.

## Methods

### Study design and patients

A case-control study was performed in the General Teaching Hospital in Balad City, Iraq. Eighty-eight males and females were included in this study; 58

typhoid-patients infected with *S.typhi* and 30 healthy individuals were used as controls.

### **Ethical considerations**

All ethics approvals have been obtained from all typhoid-patients, including the collection of samples such as blood, stool, and all personal information.

### **Blood and stool collection and culture**

Ten ml of blood has been collected from all individuals by sterile syringe distributed as follow; 5 ml were collected in a sterile tube and left at room temperature to clot and centrifuged at 3000 rpm for 5 min, and 5 ml of blood was mixed with brain heart infusion broth and incubated for seven days at 37°C (Aljanaby and Medhat, 2017; 2017; Aljanaby et al., 2022). Ten grams of stool was collected from the same individuals in a sterile container mixed with 10 ml of sterile distilled water and incubated aerobically with brain heart infusion broth at 37°C for 24 h. After the end of the incubation period, blood and stool were cultured by sterile swab onto blood agar and SS-agar plates and incubated aerobically at 37°C for 24 h (Adam et al., 2019; Majeed and Aljanaby, 2019).

### **Diagnosis of *S.typhi***

*S.typhi* isolates were diagnosed according to all standard microbiological tests and Vitek2® system test (Aljanaby and Aljanaby, 2018; Alhasnawi and Aljanaby, 2022).

### **Acute and chronic infection**

According to the manufacturing company, the IgG/IgM Combo rapid test has been used to diagnose acute and chronic infections (CTK Biotech, USA) (Abd-Aljabar and Aljanaby, 2021). All typhoid patients with positive blood culture and IgM have been considered acute infections. Those with positive stool culture and IgG have had chronic infections (Mawazo et al., 2019; Voysey et al., 2020).

### **ELISA**

The four immunological markers were measured according to manufacturer's company instructions (Bioassay Technology Laboratory, Shanghai, China) (Rashad and Aljanaby, 2021).

### **Statically analysis**

Graphpad-prism V.10 computer software was used in this study. Each marker's mean  $\pm$  SE value has been measured using the T-test, unpaired, one-tailed, and significant digits at 0.05. p values less than 0.05 were considered statistically significant (Aljanaby and Alhasnawi, 2017; Hasan et al., 2021; Aljanaby et al., 2022; Hadi and Aljanaby, 2022; Medhat and Aljanabay, 2022).

## Results

Out of a total of 58 patients infected with *S.typhi*, we recorded 32 patients with acute infections (positive blood culture and IgM positive) and 26 patients with chronic infections (positive stool culture and IgG positive). The statistical analysis in Fig.1 shows a significant increase (P-value = 0.002) in the IL-4 serum concentration of total typhoid-patients ( $339.61 \pm 31.35$  pg/ml) when compared to the control ( $209.88 \pm 19.34$  pg/ml), and significant differences (P-value = 0.0003) between acute ( $246.82 \pm 10.72$  pg/ml) and chronic infection ( $453.81 \pm 62.27$  pg/ml). Fig. 2 indicated a highly significant increase (P-value= $<0.0001$ ) in IL-17 in total typhoid-patients ( $253.12 \pm 16.12$  pg/ml) as compared with control ( $52.096 \pm 1.69$  pg/ml) and a similar significant increase has been recorded between acute ( $201.78 \pm 20.23$  pg/ml) and chronic infection ( $316.30 \pm 20.19$  pg/ml). CD8 concentration of total typhoid-patients ( $24.351 \pm 1.22$  pg/ml) was significantly increased (P-value= $<0.0001$ ) as compared with control ( $7.7820 \pm 1.33$  pg/ml) while, there was no significant differences (P-value= 0.13) between acute ( $23.136 \pm 1.29$  pg/ml) and chronic infection ( $25.846 \pm 2.22$  pg/ml) (Fig. 3). Also, the CD22 concentration in the serum of total typhoid-patients ( $1029.3 \pm 93.35$  pg/ml) was highly significantly increased (P-value= 0.0008) as compared with control ( $581.94 \pm 61.42$  pg/ml) while, there were no significant differences (P-value= 0.32) between acute ( $1076.0 \pm 150.67$  pg/ml) and chronic infection ( $1372.2 \pm 162.54$  pg/ml) (Fig. 4).

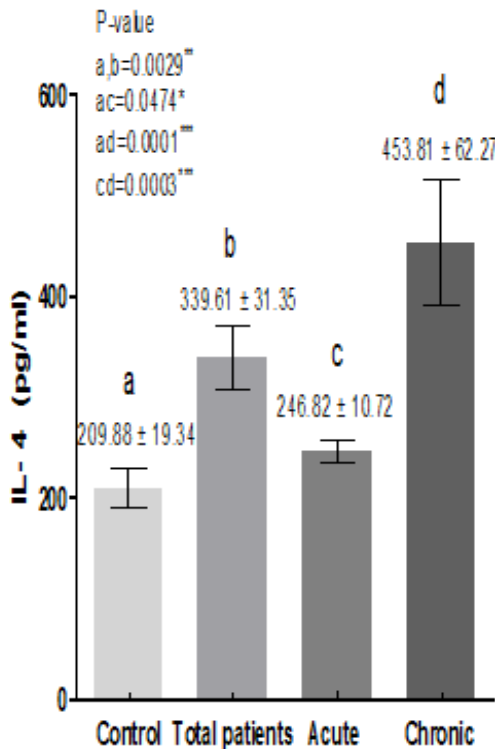


Fig. 1 IL-4 serum concentration in *S.typhi*- patients and control

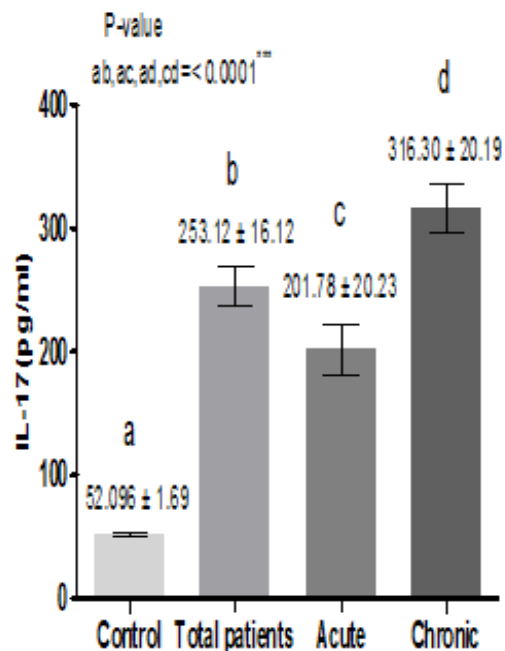


Fig. 2 IL-17 serum concentration in *S.typhi*-patients and control

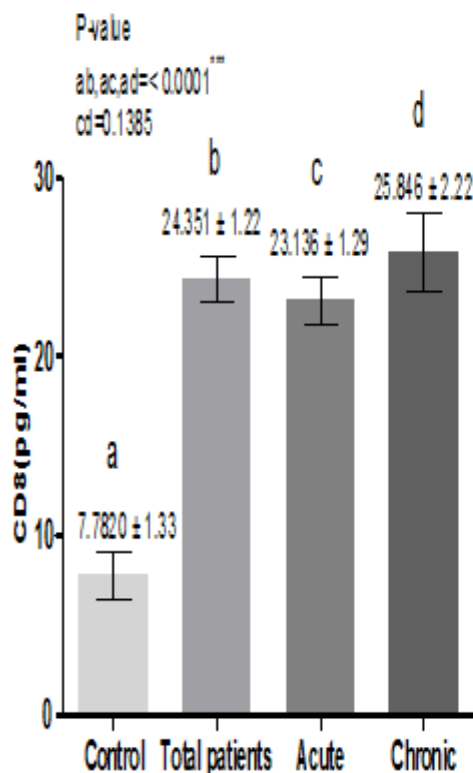


Fig. 3 CD8 serum concentration in *S.typhi* patients and control

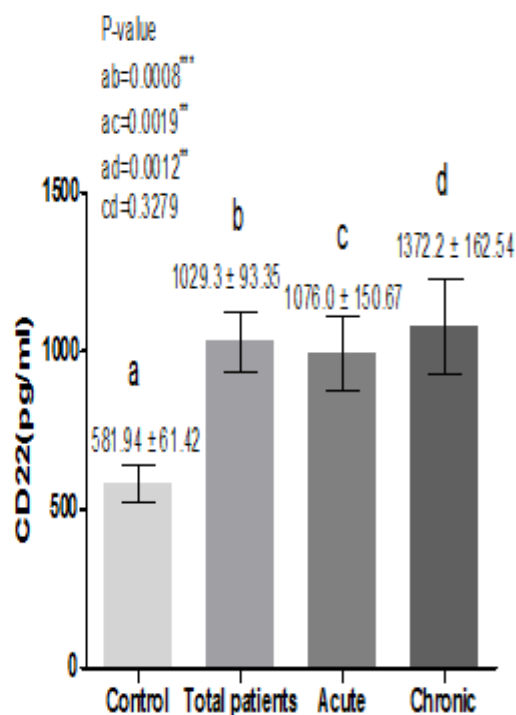


Fig. 4 CD22 serum concentration in *S.typhi* patients and control

## Discussion

Innate and adaptive immunity play a key role in the response to bacterial infections (Sun et al., 2020). Innate immunity is the first line of defense against different types of bacteria, such as *S.typhi*. After *S.typhi* infection, the innate immune system has many mechanisms in the early stages of infection that lead to host survival, including: increasing macrophages, neutrophils, and dendritic cells in number, preventing bacterial replication, and cytokine production, leading to the release of a signal that activates and recruits inflammatory cells to the site of infection (Marino et al., 2007; Vidlak and Kielian, 2012; Ingram et al., 2017). The current study aims to evaluate IL-4, IL-17, CD8 and CD22 levels in patients infected with acute and chronic *S.typhi* infection. Our results (Fig.1) demonstrated a significant increase in IL-4 levels in patients infected with acute and chronic *S.typhi* infections as compared with control. Interleukin 4 is a cytokine produced from many cells such as mast cell, basophil, eosinophil and T-helper 2 and assistance in the prevention of apoptosis of macrophages, lymphocytes, endothelial cells and help in the regulation of cell division (Ul-Haq et

al., 2016; Eini et al., 2020). Recently, IL-4 receptor signalling showed an essential role in immune response type 2 due to increased neutrophil response against bacterial infection, inhibiting the formation of neutrophils outside traps and antagonising the effects of granulocyte colony-stimulating factor on neutrophils in humans. Therefore, the positive relationship between IL-4R signalling and neutrophils protects the body from neutrophil-inflicted harm and bacterial infection (Ilkka, 2018; Egholm et al., 2019; Deimel et al., 2021). Fig. 2 proved a significant increase in IL-17 concentration in acute and chronic *S.typhi*-patients compared with control. Interleukin 17 produced from cells that are located in epithelial barriers, therefore, play an essential defence role in the host against extracellular and intracellular bacterial infection in both acute and chronic infection (Valeri et al., 2016; De Morales et al., 2020). Interleukin 17 has two essential mechanisms against infection; the production of antibacterial peptides, which depends on the corporation action between IL-17 and IL-22 on epithelial cells and inducing gut and lung epithelial cells to express chemokines that attract neutrophils to the site of infection (Nogales et al., 2008; Feng et al., 2009). Our findings proved a significant increase in CD8 and CD22 levels in patients infected with acute and chronic *S.typhi*, while there was no significant difference between the two types of infection (Fig. 3 and Fig. 4). Many studies suggested that CMI, particularly CD8 T-cytotoxic cells, constitute a significant component in controlling typhoid fever (Salerno-Goncalves et al., 2002; Fresnay et al., 2016). Some researchers suggested that CD8 may play a role in destroying infected host cells due to the production of some cytokines such as IL-17 that lead to limited infection (McArthur et al., 2012). Experiments involving the adoptive transfer of CD4 T-cells from TCR-transgenic mice into Salmonella-infected mice showed the bacteria induce a progressive culling of newly activated, high-avidity, antigen-specific CD4+ T cells that express higher levels of programmed death-ligand 1 in an SPI-2 dependent manner, this mechanism reshapes the repertoire of antigen-specific T cells after Salmonella infection (Ertelt et al., 2011; Lopez-Medina et al., 2014; Mei et al., 2017). The cluster of differentiation 22, also known as CD22, is an inhibitory receptor due to the four immune receptor tyrosine-based activation motifs within its cytoplasmic tail. Yet to classify it simply as a receptor that inhibits B cell functions would mean ignoring data that reveals a more nuanced story (Otipoby et al., 2001; Clark and Giltiay, 2018). A recent study discovered that CD22, a member of the sialic acid-binding Ig-like Siglec family of lectins, is essential in the innate immune response against bacterial infection (Fernandes et al., 2020). CD22 is a new inflammatory mediator produced in the bloodstream post-infection; this soluble biomarker can help diagnose Gram-negative bacterial infection, with diagnostic accuracy comparable to other cytokines such as IL-6. Furthermore, CD22 is more valuable than IL-6 in predicting outcomes in patients with a bacterial infection (Jiang et al., 2015; Shah et al., 2020). IL-4 and IL-17 may be higher in chronic inflammation than in acute, and there is no significant difference in CD8 and CD22 levels because IL-4 and IL-17 are secreted and controlled by mature T-helper cells, essential in the adaptive immune response (Stott et al., 2013; Reinhart and Kaufmann, 2018). The results concluded that IL-4, IL-17, CD8 and CD22 serum levels increase in typhoid-patients caused by *S.typhi* in humans. IL4 and IL-17 increase dependently on the duration and severity of the disease, while CD8 and CD22 increase in both acute and chronic infection without significantly increasing between them.

## Conclusions

IL4 and IL-17 serum levels increase dependently on the duration and severity of the disease in a patient infected with *S.typhi*. While the levels of CD8 and CD22 increase in acute infection and chronic infection without significantly increasing between them, this indicates the critical role of these cytokines against *S.typhi* infection.

**Declaration of competing interest:** This work has no conflicts of interest.

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