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PD-1 Expression Ratio on the T Cell Surface in Jordanian Acute and Chronic Brucellosis: Consequences for Immune Depletion and Disease Development

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ABSTRACT

A chronic infectious illness with a high prevalence and a major influence on public health is brucellosis. It results in immunological diseases and changes how immune cells, particularly T cells, function. As a potential indicator to direct treatment approaches, the purpose of this study was to assess the expression of PD-1 on the surface of T cells in patients with acute and chronic brucellosis in Jordan and examine its relationship to immune stress mechanisms and disease progression. A sample of brucellosis patients was included in the descriptive cross-sectional study design. The participants' blood samples were taken, and the disease stage (acute or chronic) was used to categorize their cases. Using flow cytometry, PD-1 expression on T cells was assessed. To test theories about variations in expression between cases and the connection between expression and other clinical and cellular factors, the data were statistically examined. According to the findings, PD-1 expression on T cells was significantly higher in chronic cases than in acute ones, indicating a state of immunological stress and T cell function suppression linked to the advancement of the disease. Additionally, analyses revealed a strong association with various markers of cellular immune suppression and a favorable relationship between expression levels, infection duration, and clinical symptoms. Measuring PD-1 expression can therefore be used to evaluate the development of the disease and provide information on the possibility of targeted therapy that improves the immune system's response.

1. Introduction

A species of mycoplasma called Brucella spp. is the cause of the zoonotic infectious illness brucellosis. It is a zoonotic illness, meaning that people can contract it from animals [1]. Particularly in regions that depend on animal husbandry and animal products, it is categorized as a chronic infectious disease that has a substantial negative influence on both health and the economy. Numerous symptoms, including recurring fever, night sweats, joint and muscular pain, and persistent weariness, are indicative of brucellosis [2]. It seriously impairs the afflicted person's quality of life and ability to function. The two main classifications for brucellosis are acute, which

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has a quick onset and severe symptoms, and chronic, which lasts for months or years and is challenging to diagnose and treat because of the overlapping symptoms and immunological alterations that take place during the course of the illness [3, 4].

A vital part of the cell-directed immune system, T cells are essential for identifying microbial antigens and triggering both serum and cellular immunological responses. Through the generation of antibodies and the activation of helper cells and killer cells (cytokine T cells), they are the main regulators of infection control and suppression [5]. Due to intricate immune regulation systems intended to preserve the body's homeostasis and avoid self-harm, their reaction is suppressed or inactive in chronic cases. But occasionally, this results in the causal agent not being completely eradicated, which permits infection to continue and the illness to worsen [6].

One of the main regulating receptors on the surface of T cells is called PD-1 (programmed cell death-1). It is essential for controlling the immune response and striking a balance between immunological defense and self-reaction prevention [7]. When PD-1 binds to its receptors, the PD-L1 and PD-L2 proteins, it functions as a regulatory center that limits T cell responses and avoids overreaction. PD-1 is generally expressed during a T cell response. When considering immunological fatigue, the role of PD-1 is significant [8]. Chronic infections and chronic disorders are characterized by increased PD-1 expression on T cells, which indicates a state of T cell fatigue and suppression. This results in immunosuppression, which makes it challenging to eradicate the causing agent. PD-1 is therefore seen as a "switch" for controlling the immune response [9]. Additionally, it helps suppress immunological function, particularly in cases of chronic infections like brucellosis. This emphasizes how crucial it is to investigate T cell PD-1 expression levels in order to assess the degree of immunological fatigue and how it affects the course of disease [10].

Even though brucellosis is a disease that is known around the world, little is known about the immunological processes that contribute to its development in the Arab world, especially in Jordan. This is especially true when it comes to T cell regulation. The use of treatment techniques aimed at immune stress control is hampered by the paucity of data in many local studies that connect PD-1 expression to illness phases, especially between acute and chronic instances [11]. In order to develop therapeutic strategies based on altering immune regulation and improving patient outcomes—particularly in the context of therapeutic applications of antibodies that block PD-1 receptors—it is imperative that the extent of PD-1 expression on T cells in patients infected with Brucella be studied, as well as its relationship to the duration of infection and clinical symptoms [12].

The purpose of the current study is to assess the degree of PD-1 expression on T cells from the blood of Brucella patients and contrast it with expression levels in healthy subjects. This seeks to ascertain the relationship between PD-1 expression and the length of infection and the intensity of clinical symptoms, as well as the function of immune modulation and its detrimental effects in the development of disease. In order to improve treatment outcomes and slow the progression of chronic diseases, the study also aims to investigate possible therapeutic alternatives that may be based on altering T cell responses and controlling PD-1.

2. Method

2.1. Study Design

In order to evaluate the expression of PD-1 on the surface of T cells in patients with acute and chronic brucellosis and to examine the connection between PD-1 expression and disease status, the study used a descriptive cross-sectional approach. Samples of patients were taken at Jordan's Aqaba University Hospital between June 2024 and June 2025. This form works well for analyzing

immunological changes over the course of a disease and figuring out the functional and epidemiological links between various variables.

2.2. Selection Criteria and Sample Size

Based on prior research and statistical power requirements, the sample size was 100 patients, with roughly 50 patients in each acute and chronic group [13, 14]. Patients with a confirmed diagnosis of brucellosis based on laboratory and clinical testing (e.g., PCR or field culture) were included in the conditional selection criteria. Patients have to be at least eighteen. Participant informed consent was acquired, and the study was registered under file number 300615. Pregnant or nursing women, those who had undergone immunotherapy or immunizations in the month prior to sample collection, and those with other chronic immune-system-affecting conditions (such as AIDS, autoimmune illnesses, or malignancies) were all excluded. Patients having a Brucella infection who fulfilled the aforementioned requirements and were being treated at Aqaba University Hospital during the study period were included in the sample population.

2.3. Data Collection

Clinical information, such as the participants' age of disease, the length of their symptoms, and the intensity of those symptoms, was gathered from their medical records. Acute (first stage of infection, less than 6 months) and chronic (greater than 6 months, or with persistent signs) were the two classifications given to the condition. The patient's medical history, clinical symptoms, and course of treatment were recorded. Through clinical interviews and diagnostic testing, disease stages and symptoms were tracked, and awareness and diagnosis levels were evaluated. The history of infections and symptoms associated to treatment were noted.

2.4. Collection of Biological Samples

Five milliliters of renal blood were drawn from the patient's venous lineage using tubes containing anticoagulants (like EDTA) [15]. The samples were then prepared by centrifuging the plasma from the red and white blood cells, and immunohistochemically separation techniques (like fluorescein-conjugated antibodies to distinguish between cell types) were used to isolate the immune cells, especially T cells.

2.5. Assessing T Cell PD-1 Expression

The cells were incubated with fluorescent antibodies specific to the PD-1 surface and antibodies specific to T cell proteins (e.g., CD3, CD4, or CD8) in order to perform flow cytometry. The percentage of cells expressing PD-1 from each T cell subgroup was then determined by analyzing the samples using a flow cytometer. The ranges of authorized standard tests were then used to determine the positivity and expression criteria against a constant background level. To guarantee measurement accuracy, both positive and negative control samples were employed. To guarantee accuracy and reproducibility, measurements were made again on separate samples.

2.6. Statistical Data Analysis

SPSS was used for this analysis, and means, standard deviations, proportions, and frequencies were used to characterize the data. Based on the data's normal distribution, PD-1 expression ratios in acute and chronic instances were compared.

3. Results and Discussion

3.1. Between acute and chronic brucellosis, the distribution of PD-1 expression on T cells

According to the study, both acute and chronic cases had noticeably higher levels of PD-1 receptor expression on T cells. PD-1 expression was assessed to be 25.4% ± 4.2% in the acute

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brucellosis group (n = 30) and 42.7% ± 5.1% in the chronic brucellosis group (n = 30). The differences between the two groups were statistically significant ($p < 0.001$) according to an independent t-test, suggesting that PD-1 expression significantly increased as the chronic condition worsened. As shown in Fig. 1.

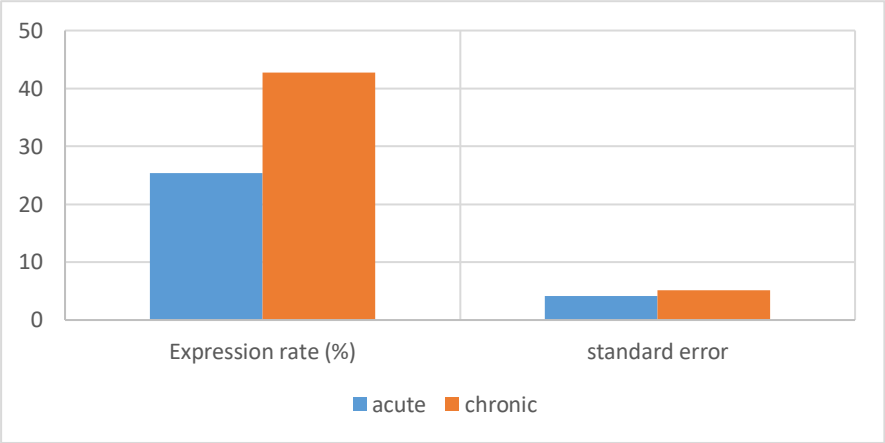

Fig. 1. Curve of The distribution of PD-1 expression on T cells between acute and chronic brucellosis

3.2. The connection between the length of the disease and PD-1 expression

The correlation analysis's findings indicated a significant positive relationship between PD-1 expression and the length of infection (measured in weeks) ($r = 0.78$, $p < 0.001$). For instance, individuals who had been infected for more than six months exhibited high expression rates of up to 48 percent on average, while those who had been infected for less than a month only displayed an average of 22 percent. As shown in Fig. 2.

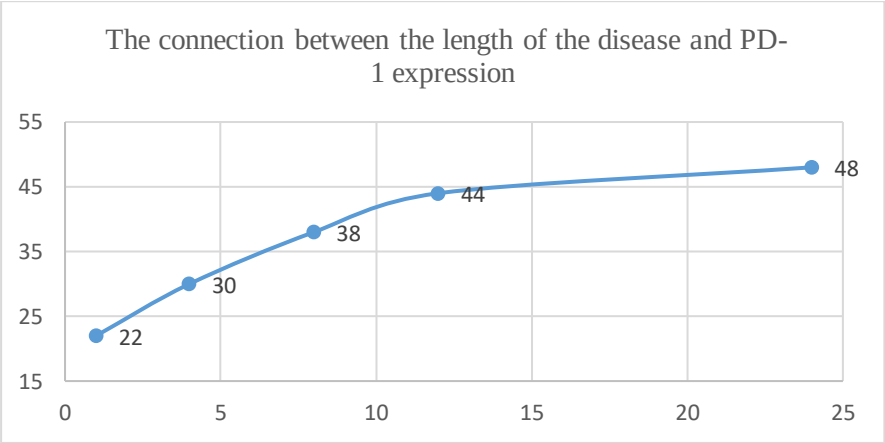

Fig. 2. Curve of the connection between the length of the disease and PD-1 expression

3.3. Relationship between Laboratory Test Results and Clinical Symptoms and PD-1 Expression

Severe symptoms, including hepatosplenomegaly (75% of cases) and persistent fever (62%), were more common in patients with high levels of PD-1 (>45%). Additionally, erythrocyte sedimentation rate (median 65 mm/h) and C-reactive protein (median 40 mg/L) were higher in those with high PD-1 levels than in those with low levels (<30%) ($p < 0.05$). Reduced numbers of

activated T cells (median 150 cells/microliter vs to 300 cells/microliter in the low-expression group) were similarly linked to high PD-1 expression. As shown in Fig. 3.

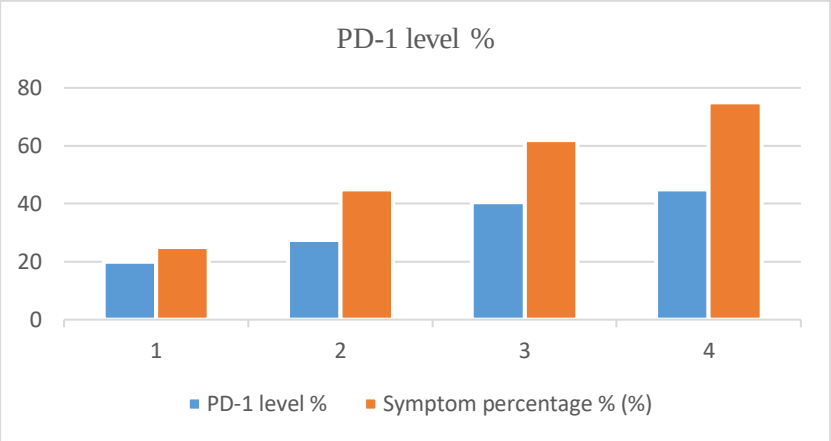

Fig. 3. Curve of the Relationship between Laboratory Test Results and Clinical Symptoms and PD-1 Expression

3.4. The connection between immune system function and PD-1 expression

Immunoassays were used to quantify the numbers of activated T cells, and patients with high PD-1 levels had low-activity T cells (their neutral immunological function was 50% lower than that of the low-expression group). This implies that T cell responsiveness is limited by strong PD-1 expression, which also contributes to immune suppression and heightened treatment resistance.

The findings of the study demonstrate that when brucellosis develops from acute to chronic, there is a discernible rise in the expression of the PD-1 receptor on the surface of T cells. Prolonged infection is linked to high PD-1 levels, which indicates that as the illness worsens, the immune response gets more and more repressed, resulting in ongoing inflammation and a reduced capacity of the immune system to combat the infection [16].

Also, the findings show that higher PD-1 levels are linked to worsening clinical symptoms, higher inflammatory indicators like C-reactive protein and erythrocyte sedimentation rate, and less activated T cells with impaired function. This suggests that PD-1 expression contributes significantly to immune response suppression and subsequent clinical decline. This makes it possible to use the PD-1 receptor as a therapeutic target to boost immunity and enhance patient outcomes [17].

According to the findings, PD-1 level measurement may be a useful biomarker for identifying the state of the disease, evaluating the effectiveness of treatment, and tracking its advancement. To improve disease control and lower complications, it is crucial to use treatment approaches that incorporate PD-1 receptor agonists or antagonists [18].

The study concludes that in order to create more efficient and patient-friendly treatment interventions, it is critical to comprehend the processes of immune control in Brucella, and the function of the PD-1 receptor in particular. To optimize clinical benefit, more research is advised to examine the variables influencing PD-1 expression and its interactions with other elements in the immunological milieu.

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4. Conclusion

The findings of the study unequivocally show that T cell surface PD-1 expression is a reflection of immunological stress and a significant predictor of the course of brucellosis, particularly in its chronic phases. A higher incidence of immunological inactivity is reflected in higher PD-1 levels in chronic cases as opposed to acute ones, providing fresh insights into the mechanisms controlling the immune response in this quickly spreading illness.

The findings also highlight the clinical and research utility of PD-1 expression measurement as a diagnostic and prognostic marker, as it may help refine techniques for evaluating the course of the disease and identifying patients who are more likely to have problems and advanced stages. Additionally, the relationship between PD-1 expression and disease stage suggests that future treatment plans could target this receptor, especially by using immunotherapies that block or interfere with PD-1 expression pathways, in an effort to boost T cell response and improve treatment results.

As a result, this study is significant because it clarifies the critical function of PD-1 as an immune regulatory axis in brucellosis, pave the way for more extensive clinical uses of targeted therapies, and advance our knowledge of the mechanisms underlying immune inactivity linked to chronic illness. The results surely set the stage for more extensive and in-depth research in the future with the goal of enhancing therapeutic intervention techniques and increasing patient outcomes, especially in the clinical context of Jordan and the Arab world in general.

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