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Dependence of Human-Beta-Defensin-1, Ferritin and Interleukin-6 Levels on the Spectrum of Drug Resistance and Regimens of Anti-Tuberculosis Therapy in Patients with Pulmonary Tuberculosis

Objective — to explore the correlation between the levels of Human-beta-defensin-1, ferritin and Interleukin-6 and the spectrum of drug resistance, as well as the treatment regimens in patients with pulmonary tuberculosis.

Materials and methods. This study included 100 patients with pulmonary tuberculosis, divided into two groups: Group 1 (n = 52) with drug-susceptible tuberculosis and Group 2 (n = 48) with drug-resistant tuberculosis, including patients with multidrug-resistant (MDR-TB) and pre-extensively drug-resistant tuberculosis. Diagnostic assessments included chest X-rays and sputum examinations using microscopic, molecular-genetic and cultural methods. Levels of HBD-1, ferritin and IL-6 were measured using ELISA on fasting blood samples at the onset of treatment and after 60 days. Data analysis was performed using Statistica 8.0 software.

Results and discussion. In patients with drug-susceptible tuberculosis, the initial levels of biomarkers were significantly higher compared to their levels after 60 treatment doses. Specifically, Human-beta-defensin-1 (HBD-1) decreased from (23.38 ± 3.48) pg/mL initially to (11.83 ± 2.30) pg/mL after 60 doses; ferritin decreased from (117.47 ± 12.34) ng/mL to (85.74 ± 13.25) ng/mL; and Interleukin-6 (IL-6) decreased from (87.49 ± 8.43) pg/mL to (51.37 ± 5.15) pg/mL. Conversely, in patients with drug-resistant tuberculosis, while IL-6 levels also showed a significant decrease from (99.78 ± 8.52) pg/mL at the onset to (67.59 ± 8.28) pg/mL after 60 doses, both HBD-1 and ferritin levels increased post-treatment. HBD-1 levels rose from (21.43 ± 4.39) pg/mL to (30.69 ± 5.06) pg/mL, and ferritin levels from (105.13 ± 8.72) ng/mL to (153.43 ± 20.29) ng/mL.

Conclusions. In patients with drug-susceptible tuberculosis, levels of HBD-1, ferritin and IL-6 significantly decrease after 60 days of treatment. This decrease correlates with a reduction in clinical and radiographic symptoms of tuberculosis and the cessation of bacterial excretion. Conversely, in patients with drug-resistant tuberculosis, levels of HBD-1 and ferritin increase after 60 doses of treatment, likely due to a delayed reduction in bacterial load and a prolonged active immune response. However, IL-6 levels significantly decrease, suggesting its primary role in initiating the anti-tuberculosis immune response. The lack of significant differences in these biomarkers between patients with drug-susceptible and drug-resistant tuberculosis at the onset of treatment suggests that drug resistance does not inherently affect the severity of tuberculosis inflammation or the activity of the initial anti-tuberculosis immune response.

Keywords

Human-beta-defebsin-1, ferritin, IL-6, multidrug resistance tuberculosis, pre-extensively drug resistance tuberculosis.

Tuberculosis has posed a deadly threat to humanity since ancient times and continues to be a significant global health issue. The outbreak of TB in 1993 was so severe that the World Health Organization declared it a public health emergency of international concern.

The management of drug-resistant tuberculosis, particularly multi-drug resistant (MDR-TB), pre-extensively drug-resistant (pre-XDR-TB) and extensively drug-resistant tuberculosis (XDR-TB), presents substantial challenges. MDR-TB is defined by resistance to at least the two major first-line bactericidal drugs, isoniazid and rifampicin. Pre-XDR-TB involves resistance to any fluoroquinolone in addition to the multi-drug resistant profile. XDR-TB extends this resistance to include fluoroquinolones and at least one second-line injectable drug from group A (e.g., bedaquiline or linezolid) [4].

To date, 17 chemical compounds have been approved globally for tuberculosis treatment within clinical trials, either as monotherapies or in combination with nine existing anti-tuberculosis drugs [6]. Despite these advancements, *Mycobacterium tuberculosis* (MTB) continues to evolve drug resistance. This resistance is attributed to various factors including the ability of MTB to maintain subpopulations in diverse physiological, metabolic or replicative states and its intrinsic mechanisms that enable drug degradation and modification via cell membrane and metabolic processes [18].

Additional factors contributing to drug resistance include patient non-compliance to treatment regimens, medical errors in prescribing antituberculosis therapy, poor vascularisation of granulomatous lesions which hinders drug delivery to tuberculous areas, formation of non-replicating drug-resistant bacteria within granulomas (phenotypic resistance) and the emergence of genetically resistant bacteria through chromosomal mutations (acquired resistance) [3, 7, 19–21].

Common medical errors that exacerbate resistance spread include adding a single drug to an ineffective regimen, failure to recognise existing drug resistance, lack of therapy supervision, non-adherence to prescribed treatment and suboptimal dosing of second-line drugs [12].

According to WHO estimates, approximately 500,000 new cases of MDR-TB are reported annually. Particularly concerning is the prevalence of latent MDR-TB in Eastern Europe and Central Asia [23]. Factors such as migration, substandard living conditions, poverty and co-existing health conditions like HIV or diabetes exacerbate the spread of drug-resistant tuberculosis [5]. The transmission of resistant TB strains is further compounded by the limited availability of rapid diagnostic laboratory methods for detecting drug resistance and the shortage of effective second-line anti-tuberculosis medications [15].

Resistant tuberculosis, particularly XDR-TB, poses significant treatment challenges. The treatment duration for XDR-TB can extend up to 18 months, yet the prognosis for recovery remains uncertain [1]. Given these difficulties, the need for detailed studies on drug-resistant tuberculosis, including the nature of its progression, treatment outcomes and the host immune response, is increasingly pressing.

Objective — to explore the correlation between the levels of Human-beta-defensin-1, ferritin and Interleukin-6 and the spectrum of drug resistance, as well as the treatment regimens in patients with pulmonary tuberculosis.

Materials and methods

This study enrolled 100 patients with pulmonary tuberculosis, categorised into two groups: Group 1 (n = 52) included patients with drug-susceptible tuberculosis, and Group 2 (n = 48) consisted of patients with drug-resistant tuberculosis, including MDR-TB and pre-XDR-TB. Standard diagnostic assessments comprised chest X-rays and comprehensive sputum analysis using microscopic, molecular-genetic and cultural methods. Additional assessments measured levels of Human-beta-defensin-1 (HBD-1), ferritin and Interleukin-6 (IL-6) via ELISA in fasting blood samples at the onset and after 60 days of treatment. Statistical analysis was conducted using Statistica 8.0 software, employing the Mann-Whitney U test for comparing two independent samples and the Wilcoxon signed-rank test for paired samples, with statistical significance set at $p < 0.05$.

Results

In patients with drug-susceptible tuberculosis, a significant reduction in biomarker levels was observed from the onset of treatment to after 60 doses. Initial HBD-1 levels averaged (23.38 ± ± 3.48) pg/mL (median — 11.41 pg/mL), decreasing by 32.9 % to (11.83 ± 2.30) pg/mL (median — 7.65 pg/mL). Ferritin levels dropped 46.8 %, from an initial (117.47 ± 12.34) ng/mL (median — 115.86 ng/mL) to (85.74 ± 13.25) ng/mL (median — 61.68 ng/mL). IL-6 levels decreased by 44.6 %, from (87.49 ± 8.43) pg/mL (median — 74.51 pg/mL) to (51.37 ± 5.15) pg/mL (median — 41.25 pg/mL), with statistical significance noted at $p < 0.05$ (Fig. 1).

In patients with drug-resistant tuberculosis, initial measurements of IL-6 were significantly higher, averaging (99.78 ± 8.52) pg/mL (median — 104.9 pg/mL) and decreasing by 48.2 % to

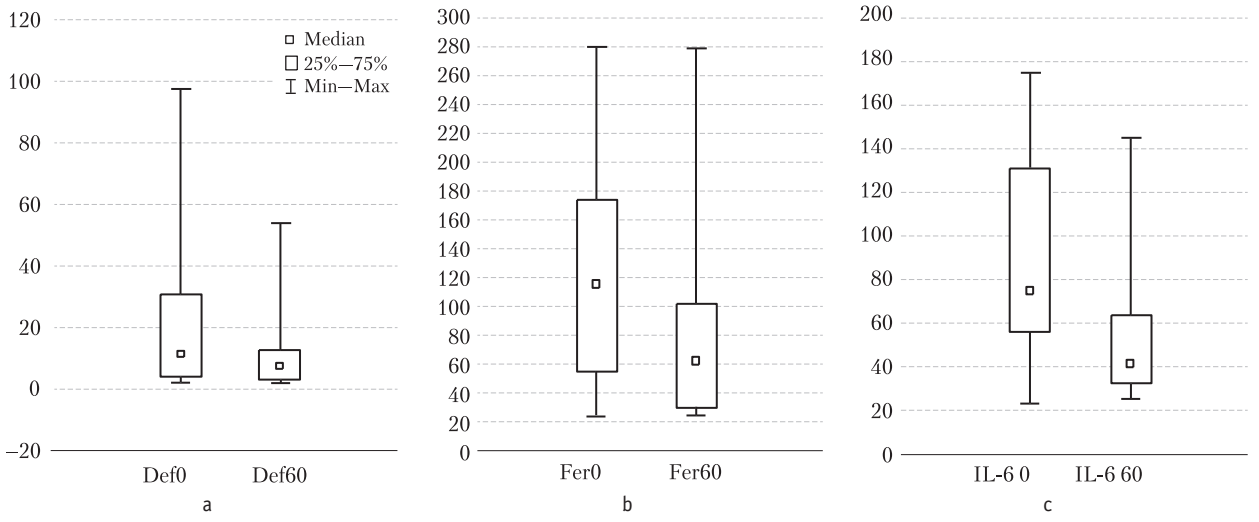

Fig. 1. **Comparison of the level of HBD-1 (a), ferritin (b) and IL-6 (c) at the beginning of treatment and after 60 doses in patients with drug-susceptible tuberculosis**

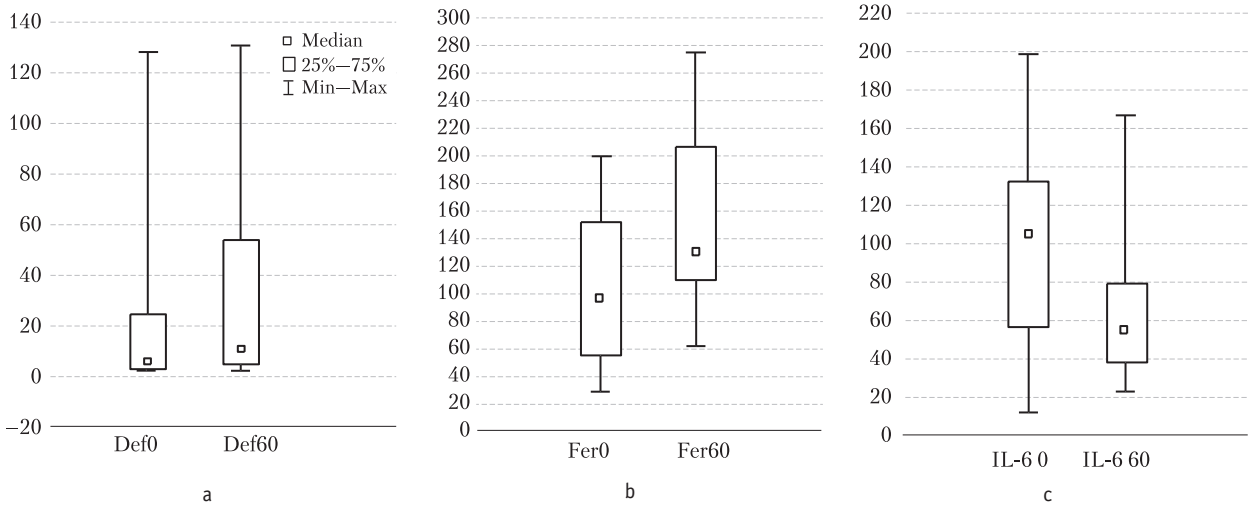

Fig. 2. **Comparison of the level of HBD-1 (a), ferritin (b) and IL-6 (c) at the beginning of treatment and after 60 doses in patients with drug-resistant tuberculosis**

(67.59 ± 8.28) pg/mL (median — 54.35 pg/mL) after 60 doses of treatment ($p < 0.05$). Conversely, levels of HBD-1 and ferritin showed an increase. HBD-1 rose by 93.0 %, from (21.43 ± 4.39) pg/mL (median — 5.58 pg/mL) at the beginning of treatment to (30.69 ± 5.06) pg/mL (median — 10.77 pg/mL) after 60 doses. Similarly, ferritin levels increased by 35.6 %, from (105.13 ± 8.72) ng/mL (median — 95.66 ng/mL) to (153.43 ± 20.29) ng/mL (median — 129.73 ng/mL), also with statistical significance noted ($p < 0.05$) (Fig. 2).

At the initiation of treatment, there were no significant differences in the levels HBD-1, ferritin and IL-6 between patients with drug-susceptible and drug-resistant tuberculosis. However, after 60 doses of treatment, notable differences emerged: HBD-1 levels were nearly threefold higher in patients with drug-resistant tuberculosis compared to those with drug-susceptible tuberculosis. Similarly, ferritin levels in patients with drug-resistant TB were almost double those in patients with drug-susceptible TB. Additionally, IL-6 levels were higher in the drug-resistant group compared to the drug-susceptible group (Fig. 3).

Discussion

Previous studies have explored the relationship between HBD-1, ferritin and IL-6 with the effectiveness of tuberculosis treatment, patient quality of life and respiratory function. However, the dynamics of these biomarkers in relation to the drug resistance profile of MTB and the specific antituberculosis treatment regimen had not been investigated until now [16, 17].

Our findings reveal a significant decrease in the levels of HBD-1, ferritin and IL-6 in patients with drug-susceptible tuberculosis after 60 days of treat-

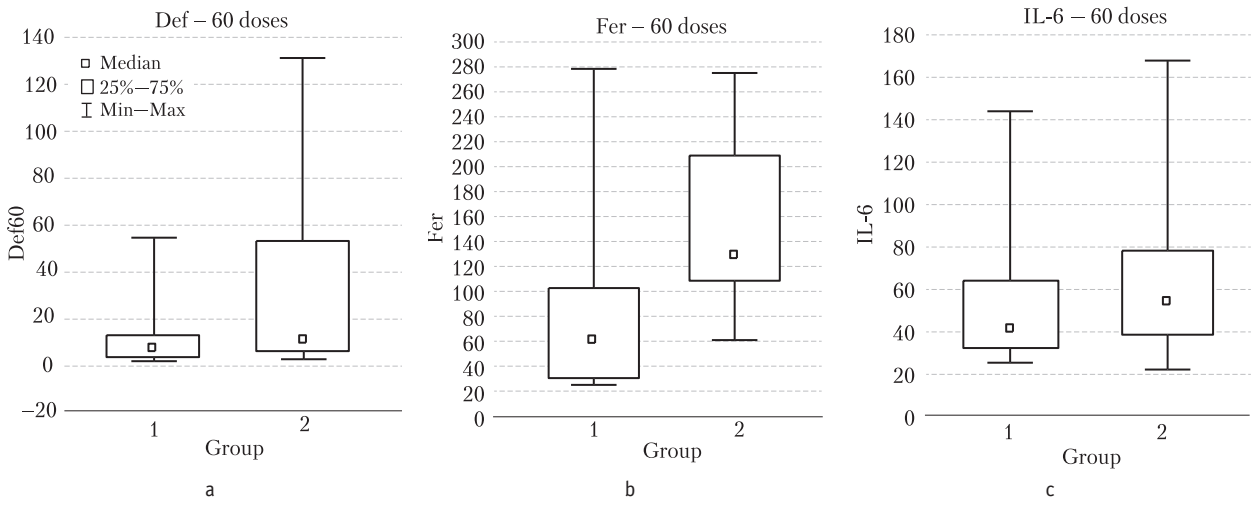

Fig. 3. **Comparison of the level of HBD-1 (a), ferritin (b) and IL-6 (c) in patients with drug-susceptible (1) and drug-resistant (2) tuberculosis after 60 doses of treatment**

ment. Typically, receiving 60 doses of antituberculosis treatment in cases of drug-susceptible tuberculosis is associated with reduced clinical and X-ray manifestations of the disease and cessation of bacterial excretion. These changes often mark the transition of a patient to the supportive phase of antituberculosis therapy. Concurrently, there is a substantial reduction in bacterial load, which diminishes its stimulatory impact on the host's immune system. The observed dynamics in the studied biomarkers further corroborate a decreased intensity of tuberculosis inflammation and a reduction in the activity of the host's anti-tuberculosis immune response.

In patients with drug-resistant tuberculosis, an increase in HBD-1 and ferritin levels was observed after 60 doses of treatment. This phenomenon is likely due to a delayed reduction in bacterial load and a sustained active immune response stimulated by drug-resistant MTB [8]. Additionally, the increase in HBD-1 could be linked to the hepatotoxic effects of second-line antituberculosis drugs, as similar dynamics in defensin production were noted in contexts of increased liver enzymes, such as in patients with liver cirrhosis and those with hemorrhagic fever, according to studies by G. Kaltsa et al. and O. Aksoy et al. [2, 9]. K. Kotoh et al. research further supports this, showing a relationship between hyperferritinemia and liver damage via a macrophage-mediated mechanism [10].

Conversely, the observed decrease in IL-6 levels among these patients suggests its role predominantly in the initial phases of the immune response against tuberculosis [22]. Moreover, as the pronounced symptoms of intoxication and cachexia begin to abate and metabolic normalisation commences around the 60-dose mark, there is a corresponding normalisation in the production of immune system cationic peptides, including HBD-1 and ferritin [13]. This aligns with findings from X. Mao et al., where stimulation of HBD-1 production through dietary supplementation of amino acids and trace elements enhanced microbial resistance in an animal model [11]. Furthermore, D. Sharma et al. have highlighted potential links between iron metabolism, particularly ferritin, and the drug resistance of MTB [14].

The lack of significant differences in the levels of HBD-1, ferritin and IL-6 between patients with drug-susceptible and drug-resistant tuberculosis at the outset of treatment suggests that drug resistance in MTB does not inherently influence the severity of tuberculosis inflammation nor the activity of the anti-tuberculosis immune response initially. However, significantly elevated levels of HBD-1, ferritin and IL-6 observed after 60 doses of treatment in patients with drug-resistant tuberculosis compared to those with drug-susceptible tuberculosis indicate that drug resistance is associated with prolonged bacterial load. This persistent bacterial presence prolongs the engagement of the anti-tuberculosis immune response, leading to sustained higher production of these biomarkers over an extended period.

Conclusions

1. Patients with Drug-Susceptible Tuberculosis: In patients with drug-susceptible tuberculosis, the levels of HBD-1, ferritin and IL-6 decrease significantly after 60 days of treatment. This decline corresponds with a reduction in clinical and radiographic signs of tuberculosis and cessation of bacterial excretion, suggesting effective bacterial clearance and diminishing inflammation.

2. Patients with Drug-Resistant Tuberculosis: Conversely, in patients with drug-resistant tuberculosis, there is an observed increase in the levels of

HBD-1 and ferritin after 60 doses of treatment. This pattern likely reflects a delayed reduction in bacterial load and a prolonged, active immune response due to less effective treatment regimens. Despite this, IL-6 levels significantly decrease, which aligns with its role in stimulating the early phases of the immune response against tuberculosis.

3. Initial Biomarker Comparisons: The initial similarity in levels of HBD-1, ferritin and IL-6 between patients with drug-susceptible and drug-resistant tuberculosis suggests that the presence of drug resistance does not inherently influence the severity of initial tuberculosis inflammation or the activation of the immune response.

No conflict of interests.
Authors participation: research concept and design — O.S. Shevchenko, L.D. Todoriko; data collection — I.A. Ovcharenko; data processing — R.S. Shevchenko; text writing — O.O. Pohorielova; text edition — S.L. Matvyeyeva.

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Залежність рівня β-дефензину-1, феритину та інтерлейкіну-6 від спектра лікарської стійкості й режимів протитуберкульозної терапії у хворих на туберкульоз легень

Мета роботи — встановити залежність рівня β-дефензину-1, феритину та інтерлейкіну-6 від спектра лікарської стійкості і режимів протитуберкульозної терапії у хворих на туберкульоз легень.

Матеріали та методи. У дослідження було залучено 100 хворих на туберкульоз легень, яких розподілили на дві групи: 52 хворі на медикаментозно-чутливий туберкульоз і 48 хворих на лікарсько-стійкий туберкульоз (пацієнти з множинною лікарською стійкістю (до ізоніазиду та рифампіцину) і пре-широкою лікарською стійкістю (до ізоніазиду, рифампіцину та фторхінолонів). Стандартне обстеження хворих передбачало рентгенографію органів грудної клітки, дослідження мокротиння мікроскопічним, молекулярно-генетичним та культуральними методами. Додатково визначали методом імуноферментного аналізу рівень β-дефензину-1, феритину та інтерлейкіну-6 (ІЛ-6) у крові натще на початку лікування та через 60 днів. Статистичну обробку даних виконували за допомогою програмного забезпечення Statistica 8.0.

Результати та обговорення. Дослідження маркерів у хворих на медикаментозно-чутливий туберкульоз виявило статистично значущо вищі показники на початку лікування порівняно з показниками після отримання 60 доз: β-дефензин-1 (0 доз — (23,38 ± 3,48) пг/мл, 60 доз — (11,83 ± 2,30) пг/мл), феритин (0 доз — (117,47 ± 12,34) нг/мл, 60 доз — (85,74 ± 13,25) нг/мл), ІЛ-6 (0 доз — (87,49 ± 8,43) пг/мл, 60 доз — (51,37 ± 5,15) пг/мл). Порівняння рівня ІЛ-6 у хворих на хіміорезистентний туберкульоз виявило статистично значущо вищий показник на початку лікування ((99,78 ± 8,52) і (67,59 ± ± 8,28) пг/мл) відповідно), для β-дефензину-1 і феритину — через 60 доз лікування: β-дефензин-1 (0 доз — (21,43 ± 4,39) пг/мл, 60 доз — (30,69 ± 5,06) пг/мл), феритин (0 доз — (105,13 ± 8,72) нг/мл, 60 доз — (153,43 ± 20,29) нг/мл).

Висновки. Рівні β-дефензину-1, феритину та ІЛ-6 у хворих на медикаментозно-чутливий туберкульоз через 60 днів лікування статистично значущо знижуються, що супроводжується зменшенням клініко-рентгенологічних виявів туберкульозу та припиненням бактеріовиділення. У хворих на лікарсько-стійкий туберкульоз до 60 доз лікування спостерігається підвищення рівнів β-дефензину-1 та феритину, що, імовірно, пов'язано із запізненням зниження бактеріального навантаження у таких хворих та пролонгованою активною імунною відповіддю. Проте вміст ІЛ-6 у цих хворих статистично значущо знижується, що, імовірно, пояснюється тим, що переважна роль ІЛ-6 — це стимуляція початкових фаз протитуберкульозної імунної відповіді. Відсутність статистично значущої різниці за досліджуваними маркерами між пацієнтами з медикаментозно-чутливим та лікарсько-стійким туберкульозом на початку лікування свідчить про те, що наявність лікарської стійкості у мікобактерій сама по собі не впливає на виразність туберкульозного запалення та активність протитуберкульозної імунної відповіді.

Ключові слова: β-дефензин-1, феритин, ІЛ-6, туберкульоз з множинною лікарською стійкістю, туберкульоз з широкою лікарською стійкістю.

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