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Medicine

Modulatory Role of Cytokines and Adipocytokines in the Development of Pulmonary Tuberculosis Combined with Diabetes Mellitus

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Abstract. A prospective study was performed in 2022-2024 at the National Center for Tuberculosis and Lung Diseases (Tbilisi, Georgia). A total of 66 patients of both sexes, aged ≥18, were enrolled in this investigation. Recruited subjects were divided into three groups: (1) – healthy, controls (HC, n = 20); (2) – patients with newly diagnosed pulmonary tuberculosis (PTB, n = 22); and (3) – individuals with PTB comorbid with type 2 diabetes mellitus (DMT2, n = 24). In blood, along with glucose, glycated hemoglobin values (HbA1c%) and plasma concentrations of cytokines (IL-1B, IL-6, IL-10, and TNFα), adipocytokines (adiponectin, resistin), and amino acid homocysteine (HCY) levels were also determined. It was shown that HOMA-index expressing insulin resistance in PTBDMT2 subjects was significantly higher (3.0 ± 0.4) as compared to HC (1.1 ± 0.3, $P < 0.05$) and PTB subjects (1.8 ± 0.2, $P < 0.05$), respectively. These alterations were associated with a marked increase in plasma levels of cytokines in PTB and especially PTBDMT2 group of patients vs. HC that positively correlated with significantly increased levels of resistin and HCY vs negative relationship with respect to adiponectin. © *2025 Bull. Georg. Natl. Acad. Sci.*

Keywords: pulmonary tuberculosis, diabetes type-2, cytokines, adipocytokines

Introduction

Tuberculosis (TB) is one of the most widespread infectious diseases worldwide, leading to different complications and fatal outcomes, especially in low-income countries with weak health care systems (Abbas et al. 2022; Bisht et al., 2023). TB predominantly affects lung tissue, being the main target for this disease (Alisjahbana et al., 2021; WHO, 2021). A great number of evidence suggests that inflammation (Kumar et al., 2019; Redford et al., 2011) appeared as a protective reaction in response to Mycobacterium tuberculosis (MTB). In this condition, proinflammatory cytokines – TNFα,

IL-1B, IL-6, and others produced by activated macrophages are involved in inflammatory reactions for attraction of a supplementary number of leukocytes at the site of infection against MTB (Lopez-Gonzalez et al., 2024, Maclean et al., 2019). Among the various non-communicable diseases, DMT2 concerning TB is the most frequent coincident pathology (Bisht et al., 2023), which can compromise defending immunity against MTB, worsening its prognosis (Chen et al., 2022; Critchley et al., 2017, Critchley et al., 2013, Kapur et al., 2016). DMT2 may enhance cytokine responsiveness, indicating that chronic inflammation accompanying DMT2 can be considered as a contributor to poor control of MTB infection (Ecrold et al., 2021; Ji et al., 2020; Kumar et al., 2023; Kumar et al., 2013; Shewade et al., 2017). Experimental and clinical data showed that adipocytokine-resistin (R) may facilitate the development of resistance to insulin, playing an important role between obesity and DMT2 (Abudalo et al., 2023; Al-Rifai et al., 2017; Chen et al., 2009). R causes increased production of proinflammatory cytokines IL-6 and IL-12 in macrophages involving the NF-kB pathway (Abudalo et al., 2023). In contrast to resistin, another adipocytokine – adiponectin regulates glucose level, lipid metabolism, and insulin sensitivity, providing anti-inflammatory, antifibrotic, and antioxidant effects (Abudalo et al., 2023; Kumar et al., 2016; Soh et al., 2021). Meanwhile, its role in TB combined with DMT2 is not precisely established (Abudalo et al., 2023). In recent years, it has been shown that the amino acid homocysteine (HCY) can cause inflammation by activation of certain cytokines, including IL-1B, IL-6, and TNF-α, leading to reactive oxygen species (ROS) accumulation and activation of nuclear factor kappa-B (NF-kB), resulting in oxidative stress (Platt et al., 2017).

The aim of this study was to determine the relationship between inflammatory and endocrine biomarkers as potential risk factors influencing the development and prognosis of PTB combined with DMT2 compared to PTB without DM.

Materials and Methods

A prospective study was performed on 66 adult patients (39 males and 27 females), aged ≥18, in the National Center for Tuberculosis and Lung Diseases, where they were investigated in 2022-2024. Patients were divided into three groups: 1 – healthy, control (HC, n = 20); 2 – individuals with PTB (n = 22); and 3 – individuals with PTB combined with DMT2 (n = 24). Their demographic characteristics included: age, sex, body weight, and height. Body mass index (BMI) was defined by dividing the weight in kilograms by the square of height in meters.

Eligibility criteria. Patients were recruited in the study according to the following inclusion criteria corresponding to:

a) adult patients aged ≥18 with newly diagnosed drug-sensitive bacteriologically confirmed PTB;
b) individuals with concomitant DMT2;
c) healthy subjects who expressed a desire to be involved in the study.

Exclusion criteria was associated with: a) individuals being more than 72 hours under TB treatment; b) weight <45 kg; c) patients suffered with diabetes of steroid or gestational origin; d) confirmed HIV infection or patients undergoing antiretroviral therapy, or suffered with hepatitis B or C; e) history of allergy or any hypersensitivity to ingredients of using drugs or their pharmaceutical formulations; f) pregnancy or lactation period.

PTB diagnostic and laboratory procedures. PTB was proved by clinical signs and symptoms such as: fever, cough, weight loss, night sweats, fatigue, and hemoptysis using six score scale assessment where items ranged from zero (0) – absence of symptoms to six (6) – presence of all symptoms. Individuals with a score significance ≥3 were defined as subjects suffered from a severe form of PTB (WHO,

2021). Radiographic control determined the extent and localization of lung lesions or cavity existence. Additionally, in necessary cases for verification of diagnosis, computer tomography (CT) was used. PTB was confirmed by Gene X pert MTB/RIF/ ULTRA test on the sputum sample (WHO, 2021). Mycobacterial burden in sputum was also investigated using acid-fast bacillus (AFB) smear recommended by WHO (WHO, 2021).

Criteria for diagnosis of DMT2. DMT2 was defined according to the American Diabetes Association criteria (Kumar et al., 2013, 2015) when glycated hemoglobin significance is equal to or exceeds 6.5% (HbA1c ≥6.5%), while FBG value must be ≥7 mmol (12 mg/dL). In non-diabetic subjects, including healthy controls (HC), HbA1c indices are less than 5.7%. Homeostasis model assessment (HOMA) for insulin resistance (HOMA-IR) was obtained by using a formula: [(fasting glycose(mmol/L) x fasting insulin (mcmol/L/22.5)], being a simple and effective index in DMT2.

Blood plasma sample collection and laboratory assays. The blood samples were collected the day after patient admission. Venous blood was drawn from fasting patients between 9-10 a.m. into sterile tubes containing anticoagulant heparin. Samples were centrifuged for 15 minutes at 1000 xg, 2-8ºC, within 30 minutes of plasma collection and were stored at -20ºC.

Cytokines – IL-1B, IL-6, IL-10, TNF, adipocytokines – adiponectin, resistin, amino acid homocysteine, fasting blood glucose (FBG), glycated hemoglobin (HbA1c%) and insulin (INS) levels were measured by ELISA kits (Cusabio and My Biosource, USA) employing the quantitative sandwich enzyme immunoassay technique. All steps have been done according manufacturer's instructions. The optical density was determined using a microplate reader (Rayto RT 210°C, China) set to 450 nm wavelength.

Ethics. The institutional ethical council approved this prospective study. The aim and importance of this investigation was explained to every patient. All participants confirmed their agreement by written consent form. Confidentiality of individuals in compliance with the Helsinki Declaration was maintained.

Statistical analysis. Results are expressed as mean ± SD (standard deviation). To compare receiving data, Student's test or analysis of variance using repeated measures, ANOVA for multiple comparisons using SPSS (SPSS Inc., IBM) was performed. Geometric means were used for the measurement of central tendency. $P<0.05$ was considered statistically significant. Mann-Whitney U test was used for non-normally distributed data, while chi-square tests was used where appropriate.

Results

Patient's demographic profile and clinical characteristics. Comparative demographic and clinical characteristics of patients involved in this study are given in Table 1.

The mean age of HC was 48 years with a median range (28-69) in comparison with PTB subjects, 53 (36-68), and PTBDMT2 50 (34-70), respectively. Male patients prevailed and constituted HC-70%, PTB, 54.5% and PTBDMT2-54.2%, respectively. BMI was markedly higher in HC 23.5 (18.6-31.1) as compared to individuals with PTB 20.8 (17.2-35.2, $P<0.0292$) and exceeded that of the PTB subjects with DMT2, though no significant differences were observed between these groups 21.1(17.6-32.8).

Chest radiographic control showed lungs unilateral and bilateral lesions as well as cavitation without significant distinction between investigated groups related to radiographic severity, including lung lesions or cavitation. In patients suffered with PTB and PTB comorbid with DMT2 was revealed characteristic clinical symptoms, such as:

Table 1. Demographic profile and radiographic characteristics in healthy controls, patients with pulmonary tuberculosis (PTB), and PTB combined with diabetes mellitus type 2 (DMT2)

Characteristic	Healthy controls	PTB	P value <0.05	PTBDMT2	P value <0.05
Number of patients	20	22		24	
Age, years, median (range)	48 (28-69)	53 (36-68)	0.6994	50 (34-70)	0.6132
Gender, number, male/female, male sex %	14/6 (70%)	12/10 (54.5%)	0.4224	13/11(54.2%)	0.5466
Weight (kg), median range	77 (70-85)	64 (60-72)	0.001	68 (62-80)	0.1410
Body mass index (BMI), kg/m^2, median range	23.5(18.6-31.1)	20.8(17.2-35.2)	0.0292	21.1(17.6-32.8)	0.3125
Lung lesion, n %					0.0766
Unilateral		14 (63.6)		9 (37.5)	
Bilateral		8 (36.4)		15 (62.5)	
Cavitation, n%					
Yes		10 (45.45)		16 (66.7)	
No		12 (54.55)		8 (33.3)	

Data on demographic characteristics are presented as geometric means and range (with the exception of age, where median and range are represented). Other results (lung lesion) were compared using the chi-square test.

fever 13 (59%), cough 21 (95%), night sweats 14 (64%), fatigue 15 (68%), hemoptysis 9 (41%) and weight loss 14 (64%) in PTB vs 14 (58%), 24 (100%), 13 (54%), 16 (67%), 6 (25%), 11 (45%) PTBDMT2 individuals without significant difference between them.

Sputum AFB smear grade analysis demonstrated marked differences ($P<0.0172$) between PTB and PTBDMT2 subjects, with significantly higher mycobacterial burden in the case of PTB comorbidity with DMT2 (Table 2), illustrating higher susceptibility of this group of individuals to Mycobacterium tuberculosis.

Table 2. AFB smear grade data in patients with pulmonary tuberculosis (PTB) and PTB with concomitant diabetes mellitus type 2 (DMT2)

Characteristic symptoms	PTB n=22	PTBDMT2 N=24	P value <0.05
AFB smear grade, n (%)			0.0172
0	3 (13.6)	1 (4.2)	
1^+	10 (45.45)	5 (20.8)	
2^+	7 (31.8)	13 (54.2)	
3^+	2 (9.0)	5 (20.8)	

AFB smear grade data were compared by using a chi-square test. Significant difference between the two groups when $P<0.05$.

Glycemic control, insulin resistance and plasma cytokines and adipocytokines alterations in healthy subjects, patients with PTB and PTB combined with DMT2. The analysis of glycemic status on the basis of HbA1c and FBG values (Table 3) revealed the considerable distinction of these indices between PTB and PTBDMT2 groups of patients with marked increase value of HbA1(6.6±0.5%; $P<0.05$) in PTBDMT2 subjects vs PTB individuals (5.1±0.2%) and consequently HC (4.8±0.2%), respectively. FBG level in PTBDMT2 subjects (7.8±0.5 mmol/L, $P<0.05$) significantly exceeded the same value in PTB (5.6±0.3 mmol/L) and HC (5.1±0.4 mmol/L) groups of patients, respectively. Such alterations in HbA1c and FBG in different subjects were accompanied by a pronouncedly increased level of fasting insulin in PTBDMT2 group (61.5±3.2 micromol/L, $P<0.05$) with respect to PTP subjects (49.5±3.3 micromole/L), as well as the later group of patients with HC individuals (34.0±5.1 micromol/L, $P<0.05$). Such changes were associated with statistically significant elevation of Homa-index in PTBDMT2 subjects (3.0±0.4, $P<0.05$) in comparison with HC (1.1±0.3) and PTB patients (1.8±0.2), indicating the develop-

Table 3. Glycemic control, insulin resistance, and plasma cytokines and adipocytokines concentrations in healthy controls, in patients with pulmonary tuberculosis PTB), and PTB combined with diabetes mellitus type 2 (DMT2)

Cytokines (Interleukins) and E-1	Healthy controls n=20	PTB n=22	P value <0.05	PTBDMT2 n=24	P value <0.05
HbA1c, %	4.8±0.2	5.1±0.2	0.83	6.6±0.5**	<0.05
Fasting blood glucose (FBG), mmol/L	5.1±0.4	5.6±0.3	0.78	7.8±0.5**	<0.05
Fasting insulin micromole/L	34.0±5.1	49.5±3.3	0.05*	61.5±3.2**	<0.05
Homa-index	1.1±0.3	1.8±0.2	1.94	3.0±0.4**	<0.05
IL-1B, pg/ml	7.4(1.5-15.0)	17.9(2.0-35.2)	0.0035	28.5(3.0-52.2)	0.01428
IL-6, pg/ml	41.75(2.5-90.0)	68.3(4.0-1205)	0.0129	92.6(4.5-149.0)	0.0081
IL-10, pg/ml	4.3(1.0-8.4)	11.6(2.0-.59.2)	<0.0001	16.9(4.0-35.5)	0.271
TNF-alfa- pg/ml	21.9(1.5-55.4)	36.2(2.0-59.2)	0.0056	73.8(3.0-130.1)	0.0001
Adiponectin, ng/ml	7500 (4505-10100)	136.8(55.4- 480.0)*	P<0.00001	116.5(18.4-552.2)	P=0.0151**
Resistin, ng/ml	9.9 (6.2-13.5)	32.6(10.2-242.6) *	P<0.0001	45.25(10.8-306.2)	P<0.0001**
Homocysteine, micromol/L)	10.3 (6.8-15.6)	12.45(7.1-18.0)	NS	16.3(9.0-24.6)	P=0.0110**

ment of insulin resistance in PTBDMT2 participants. PTB subjects vs HC individuals provided only a tendency for the development of prediabetic condition by a slight increase in Homa-index without attaining its significance to level allowing to consider it as an insulin resistance state.

Changes in glycemic control correlated with alterations in different cytokines plasma concentrations (Table 3).

Glycemic control parameters are shown as mean ±SD. Other values are presented as geometric means. P values were defined using the Mann-Whitney U test, expressing significant differences between: * - HC and PTB groups, ** – PTB and PTBDMT2 groups when P<0.05; NS-not significant.

The plasma levels of proinflammatory (IL-1B, IL-6, TNFα) and anti-inflammatory (IL-10) cytokines in PTB subjects significantly exceeded the values of the same cytokines in HC group: IL-1B (17.9 vs. 7.4 pg/ml, P<0.01), IL-6 (68.3 vs. 41.75 pg/ml, P<0.05); TNFα (36.2 vs. 21.9 pg/ml, P<0.01) and IL-10 (11.6 vs. 4.35 pg/ml, P=0.0001), respectively. In turn, PTBDMT2 participants showed considerably increasing plasma indices of pro- and anti- inflammatory cytokines with respect to PTB except IL-10: IL-1B (28.5 vs. 17.9 pg/ml, P<0.05), IL-6 (92.6 vs. 68.3 pg/ml, P=0.0081), TNFα (73.8 vs 36.2 pg/ml, P<0.0001), IL-10 (16.9 vs. 11.6 pg/ml, P<0.271), respectively. Findings regarding the changes in cytokines plasma concentrations were correlated with certain alterations in plasma levels of adiponectin (An), resistin (R) and homocysteine (HCY) demonstrating in table 3. The baseline levels of An in HC participants were pronouncedly higher than in PTB patients (7500 vs 136.8 ng/ml, P<0.00001) and as compared to PTBDMT2 individuals that revealed significantly lower An plasma content (116.5 ng/ml, P<0.05) vs PTB group of patients. In contrast to An – An-R concentration was markedly increased in PTB as compared to HC group (32.6 vs 9.9 ng/ml, P<0.0001) and especially in PTBDMT2 subjects regarding PTB (45.25 vs 32.6 ng/ml, P<0.0001). Like R, HCY plasma level was significantly elevated in PTBDMT2 individuals as compared to the PTB group (16.3 vs 12.45 ng/ml, P<0.05)

without significant differences in PTB subjects to compare with HC individuals.

Discussion and Results

Our findings concerning glycemic control and insulin resistance showed a marked increase in the value of fasting HbA1c, FBG, insulin, and Homa-index in PTB-DMT2 patients vs PTB and especially HC individuals, which correlated with a marked increase in IL-1B, IL-6, and TNFα plasma levels. Our data are consistent with the results of other authors, demonstrated greater hyperglycemia in PTB coincident with DM than in PTB alone, confirming worsening of glucose metabolism in this group of patients, possibly associated with low-intensity chronic inflammation (Bisht et al., 2023; Kumar et al., 2019, 2020).

Apart from cytokines, adipocytokines – adiponectin (An), resistin (R), and homocysteine (HCY) also provide modulatory action on PTB and PTBDMT2. In different studies (Abudalo et al., 2023), it was shown that in PTBDMT2 subjects increased levels of HbA1c, FBG, and R (Abudalo et al., 2023) are associated with decreased concentration of An in comparison with HC, demonstrating a negative correlation with insulin resistance, in contrast to R, which is in agreement with our results. HCY plasma level increased in DM, which worsened glucose metabolism and, in turn caused hyperglycemia leading to hyperhomocysteinemia (Platt et al., 2017) that is consistent with our results. Impaired endothelium function induced by HCY (Faurholt-Jepsen et al., 2013) can lead to an inflammatory response and monocyte involvement. In contrast to R and HCY, (An) release from adipose tissue is a homeostatic factor regulating glucose and lipid metabolism as well as insulin sensitivity, providing anti-inflammatory and antioxidant effects with negative correlation concerning the development of insulin resistance (Abudalo et al., 2023, Soh et al., 2021). It is suggested that alterations in plasma levels of IL-1B, IL-6, TNFα, and IL-10, as well as adipocytokines and homocysteine, can be considered as potential biomarkers for diagnostic purposes and assessment of treatment efficacy and outcomes in patients with PTP and PTPDMT2.

მედიცინა

ციტოკინებისა და ადიპოციტოკინების როლი ფილტვის ტუბერკულოზისა და მასთან კომბინირებული შაქრიანი დიაბეტის განვითარებაში

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პროსპექტული კვლევა განხორციელდა 2022-2024 წლებში ქ. თბილისის ტუბერკულოზისა და ფილტვის დაავადებების ეროვნულ ცენტრში. ორივე სქესის 66 პაციენტი ასაკით 18≥ წელი, ჩართული იყო კვლევაში, რომლებიც დაყოფილ იქნენ 3 ჯგუფად: I – ჯანმრთელი, საკონტროლო (ჯს, n=20); II – პაციენტები ახლად დადგენილი ფილტვის ტუბერკულოზით (ფტ)-ით (ფტკშდ) (n=22) და III – ინდივიდები, კომბინირებული შაქრიან დიაბეტთან ფილტვის ტუბერკულოზით (n=24). სისხლში გლუკოზისა და გლიკოზირებული ჰემოგლობინის (HbA1C%) მაჩვენებლების გარდა, ვსაზღვრავდით ციტოკინების (IL-1B, IL-6, IL-10 და TNFα) და ადიპოციტოკინების (ადიპონექტინი, რეზისტინი), ასევე ამინომჟავა ჰომოცისტეინის პლაზმური კონცენტრაციების დონეს (HCY). ნაჩვენები იქნა, რომ ინსულინის მიმართ რეზისტენტობის გამომხატველი HOMA ინდექსი ფტკშდ სუბიექტებში სარწმუნოდ აღემატებოდა (3.0±0.4) ჯს ჯგუფის და ფტ-ს მქონე პაციენტების ანალოგიურ მაჩვენებლებს (1.1±0.3, p<0.05) და (1.8±0.2, p<0.05), შესაბამისად. ეს ცვლილებები ასოცირდებოდა პლაზმაში ციტოკინების ოდენობის სარწმუნო მომატებასთან ფტ და, განსაკუთრებით, ფტკშდ-ის მქონე სუბიექტებში ჯს-ის პაციენტებთან შედარებით, რაც დადებით კორელაციურ კავშირში იმყოფებოდა რეზისტინის და HCY-ის მომატებულ დონესთან და ნეგატიურში – ადიპონექტინთან მიმართებაში.

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