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THE INFLUENCE OF PLASMA LEVEL ALTERATIONS OF INFLAMMATORY, ENDOCRINE AND VASCULAR BIOMARKERS FOR THE FORMATION AND PROGNOSIS OF PULMONARY TUBERCULOSIS COMORBID WITH DIABETES MELLITUS TYPE-2

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ანთებითი, ენდოკრინული და ვასკულური ბიომარკერების პლაზმური დონის ცვლილების ზეგავლენა ფილტვის ტუბერკულოზის შაქრიანი დიაბეტი ტიპი-2-თან კომორბიდობის ფორმირებასა და პროგნოზზე

[1] ივანე ჯავახიშვილის სახელმწიფო უნივერსიტეტი, ფარმაკოლოგიის დეპარტამენტი, თბილისი, საქართველო; [2] თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, სამედიცინო ფარმაკოლოგიის დეპარტამენტი, თბილისი, საქართველო; [3] ტუბერკულოზისა და ფილტვების დავადებების ეროვნული ცენტრი, თბილისი, საქართველო; [4] ევროპის უნივერსიტეტის საკვლევი ინსტიტუტი, თბილისი, საქართველო

რეზიუმე

ტუბერკულოზი რჩება ერთ-ერთ ყველაზე დისემინირებულ ინფექციურ დაავადებად, რომელიც ხასიათდება სხვადასხვა გართულებებით და ლეტალური გამოსავლით. ბოლო ათწლეულში ჩატარებული კვლევები ადასტურებს ფილტვის ტუბერკულოზის (ფტ) სიხშირის ზრდას პაციენტებში მეორე ტიპის შაქრიანი დიაბეტით (შდც2).

წარმოდგენილი კვლევის მიზანს წარმოადგენდა ანთებითი ციტოკინების (IL-1B, TNFα), ვაზოაქტიური აგენტების: ეპოქსიეიკოზატრიენოის მჟავების (EETs), ენდოთელინი-1 (E-1), ენდოთელური ზრდის ფაქტორის (VEGF), რეზისტინის (R), ლიპიდური სპექტრის, კატექოლამინების (ნორადრენალინი, ადრენალინი) და ენდოკრინული ფაქტორების (ლეპტინი და ადიპონექტინი) პლაზმური ცვლილების მოდულატორული როლის შესწავლა ფტ-ის ფორმირებასა და მიმდინარეობის პროგნოზზე შდტ2-თან კომორბიდობის დროს. ობსერვაციული კვლევა ჩატარდა 2023-2025 წლების პერიოდში თბილისის ტუბერკულოზის და ფილტვის დაავადებათა ეროვნულ ცენტრში. რეკრუტირებული ორივე სქესის პაციენტები (18 წლის და მეტი ასაკის, n=50) დაყოფილ იქნა 3 ჯგუფად: ა) ჯანმრთელი მოხალისეები (ჯმ), n=10; ბ) სუბიექტები ახლად დადგენილი ფტ-ით, n=20; გ) პაციენტები ფტ-ით შდტ2-თან კომბინაციაში, n=20. ყველა პაციენტი ჩართული იქნა კვლევაში ჩართვის და გამორიცხვის კრიტერიუმების მიხედვით. ტუბერკულოზის მიკობაქტერიის (MTB) არსებობა კლინიკური სიმპტომებისა და რენტგენოლოგიური კვლევის გარდა დასტურდებოდა Gene Xpert MTB/RiF ULTRA ტესტის მეშვეობით. ზემოაღნიშნული აგენტების პლაზმური კონცენტრაციები, ისევე როგორც გლიკემიური კონტროლი უზმოზე გლუკოზის, ინსულინისა და გლიკოლიზირებული ჰემოგლობინის (HbA1c%) პლაზმური დონის განსაზღვრით გაზომილ იქნა ELISA Kits-ის მეთოდით. ინსულინის რეზისტენტობის (ირ) კალკულაციისთვის HOMA-index-ის განსაზღვრით ვიყენებდით ფორმულას: [(გლუკოზა უზმოზე mmol/L X ინსულინი უზმოზე (micromole/L/22,5)]. მიღებული შედეგებიდან გამომდინარე, ფტშდტ2-ით დაავადებულ პაციენტებს აღენიშნებოდათ სტატისტიკურად სარწმუნო პლაზმური დონის მომატება: IL-1 (31,4 (4,2-60,0პგ/მლ, P<0,1534); TNFα (76,2 (3,5-120,0პგ/მლ, P<0,0001), რაც უფრო გამოხატული პოზიტიური კორელაციით ხასიათდებოდა ვაზოაქტიური აგენტის E-1(10,3(3,5-18,4პგ/მლ, P<0,0008), კატექოლამინების, VEGF - 917,44 (400,0-1495პგ/მლ, P<0,00054; R 43,8 (14-259ნგ/მლ, P<0,03846) და ენდოკრინული ფაქტორის ლეპტინის - 2,02 (0,34-5,86გ/მლ, P<0,00001) მიმართ და ავლენდა გამოხატულ ნეგატიურ ურთიერთკავშირს EETs-თან 6,9 (4,8-9,96გ/მლ) და ადიპონექტინთან მიმართებაში (95,47 (18-305პგ/მლ, P<0,00694) ფტ-ის და ჯმ-ების ჯგუფებთან

შედარებით. ეს ცვლილებები ასოცირდებოდა ლიპიდური სპექტრის დარღვევასთან ფტ და ფტშდტ2-ით დაავადებულ პაციენტებში.

კეთდება დასკვნა, რომ ციტოკინები, ვაზოაქტიური და ენდოკრინული აგენტები შეიძლება განხილულ იქნეს როგორც პოტენციური ბიომარკერები ფტ და ფტშდტ2-ის მქონე პაციენტებში დაავადების ადრეული დიაგნოსტიკის, მისი მკურნალობის ეფექტიანობისა და გამოსავლის თვალსაზრისით.

Introduction. Pulmonary tuberculosis (PTB) is one of the most disseminated infectious diseases especially in low-income countries characterized by different complications and fatal outcome [1,2]. According to the World Health Organization (WHO) 2020-year report, 10 million incidences of TB with 1,5 million lethal cases established all over the world [3]. Many authors indicate that production of proinflammatory cytokines [4] such as IL-1B, Il-6, TNF, Il-8 etc. initiate inflammatory reaction as protective mechanism in response to Mycobacterium tuberculosis (MTB). In recent decades, the global burden of PTB comorbid with diabetes mellitus type-2 (DMT2) has risen significantly [5]. Meta-analysis of observational studies [6] showed the increased risk and susceptibility in patients with DMT2 for the development of PTB with unfavorable treatment outcome [7]. PTBDMT2 characterized with more expressed immune alterations and systemic inflammation in comparison with PTB associated to euglycemic state [8]. However, the exact mechanisms of the influence of DMT2 on the formation and progression of PTB is not fully elucidated [9].

A number of evidence suggested that endothelial dysfunction is a common feature for the progression of TB and DMT2, predisposing to poor control of this comorbid pathology [10,11]. Increased plasma level of vasoconstrictive agent endothelin-1 (E-1) in DMT2 may lead to macro- and microvascular complications with proliferative, profibrotic and proinflammatory changes contributing to worsening of associated PTB prognosis, suggesting about implication of vascular mechanisms in MTB infectious [12,13]. Lack of information exists regarding relationship of angiogenic VEGF in progression of PTB or PTBDMT2 as well as the modulatory role of catecholamines and vasodilating agents – EETs (inducing opening of high conductance Ca^{2+}-activated K^+ channels) in the formation and development of PT and PTDMT2 [14].

Experimental and clinical data showed the possible involvement of inflammatory cytokines (IL-1B, TNFα), endocrine factors – adipocytokines including leptin, adiponectin and resistin in glycemic control during PTB and PTBDMT2. Leptin regulates immune, endocrine function and the energy balance [15], while adiponectine being hormonal and homeostatic factor regulates lipid metabolism, glucose level and insulin sensitivity providing anti-inflammatory, antifibrotic and antioxidant effects [16]. In contrast resistin causes increased production of proinflammatory cytokines IL-6 and IL-12 in macrophages involving NF-kB pathway [17]. Increased resistin production may indicate about metabolic and immunological changes in response to altered macrophages function [18]. The exact mechanism concerning influence of abovementioned agents on the development of PTBDMT2 is not precisely established.

The goal of this study was to investigate the influence of cytokines, adipocytokines and vascular biomarkers on the formation and progression of PTB and PTB coincident with DMT2.

Materials and Methods. Observational study was carried out on 50 (30 male, 20 female) adult subjects, aged ≥18 years old, which was conducted in the National Center of Lung Diseases in Tbilisi, Georgia, 2023-2025 years period. Patients were divided into three groups: a) Healthy volunteers (HV), control (HV, n=10); b) Subjects suffered by PTB (n=20); c) Individuals with PTBDMT2 (n=20). Patients were involved in investigation by the following criteria:

Inclusion criteria:

a) Patients 18≥ years old of both sex with bacteriologically verified newly diagnosed PTB;

b) Subjects with coincident DMT2;
c) Healthy volunteers agreed to be involved in this study.

Exclusion criteria requirements:

a) Patients being more than 72 hours under treatment;
b) Individuals that revealed steroid or gestational diabetes;
c) Subjects receiving antiretroviral therapy or having HIV infection;
d) Known allergy to using drugs;
e) Hepatitis B or C;
f) Pregnancy or lactation period.

PTB diagnosis was confirmed on the basis of clinical symptoms including: cough, night sweats, fever, fatigue and weight loss, associated with radiographic control to determine the extent of lung lesion and in necessary cases computer tomography. Bacteriologically PTB was established by using Gene X pert MTB/RIF/Ultra test on the sputum sample [19].

DMT2 diagnosis verified when fasting blood glucose significances according American Diabetes Association criteria [20] attained to ≥ 7,0 mmol and glycated hemoglobin level (HbA1c) - ≥6,5%. In HV and non-diabetic individuals HbA1c value mostly are less then 5,7%. Insulin resistance (IR) was defined by homeostasis Model assessment (HOMA) using for calculation the corresponding formula: [(fasting glucose (mmol/L) x fasting insulin (mcmol/L/22,5)].

For laboratory assays venous blood of patients was taken from cubital vein in fasting condition (9-10a.m) into sterile tubes containing anticoagulant heparin. Obtained samples then centrifuged during 15 minutes at 1000 x g within 30 minutes of plasma collection and were stored at - 20ºC. All above mentioned agents plasma levels: cytokines – IL-1B and TNFα, fasting blood glucose (FBG), glycated hemoglobin (HbA1c%), insulin, lipid spectrum, catecholamines (norepinephrine, epinephrine), adipocitokines – leptin, adiponectin, resistin, vasoconstrictive - endothelin-1, vasodilating epoxyeicosatrienoic acids (EETs) and vascular endothelium growth factor (VEGF) were determined by using ELISA Kits method (Cusabio and My Biosource, USA) based on the quantitative sandwich enzyme immunoassay technique. All steps were performed according manufacturer instruction. The optical density was defined by microplate reader (Rayto RT 2100C, China) set to 450 nm wavelength.

For estimation of hemodynamic parameters such as systolic, diastolic, mean arterial pressure (SBP, DBP, MBP, respectively), and heart rhythm (HR), sphygmomanometer and cardiotachometer were used.

Statistical analysis. To compare receiving data, Student's test or analysis of variance using repeated measures, ANOVA for multiple comparisons using SPS (SPSS Inc, IBM, USA) was performed. Geometric means were used for measurement of central tendency. P<0,05 was considered statistically significant and results are expressed as mean ±SD (Standard deviation). Mann-Whitney U test was used for non-normally distributed data.

Results:

Table 1. Demographic characteristics, hemodynamic parameters and glycemic control indices in healthy volunteers (HV), patients with pulmonary tuberculosis (PTB) and PTB coincident with diabetes mellitus type-2 (DMT2)

Indices	Healthy volunteers (HV), control	PTB,	P value <0,05	PTBDMT2	P value <0,05
Number of patients	n=10	n=20		n=20	
Age, years, median (range)	45 (26-64)	50(38-60)	NS	56(32-71)	NS

Sex, number, male/female, male sex %	7/3 (70,0%)	12/8(60,8%)	NS	11/9(55,0%)	NS
Weight (kg), median range	79(68-82)	66(64-76)	0,0185*	72(65-80)	NS
Body mass index (BMI), kg/m^2, median range	24,2(19,4-28,2)	20,6 (18-31,0)	0,0264*	22,5 (18,9-30,6)	NS
SBP - (mm Hg) Systolic blood pressure	122,1±4,2	130,0±4,5	NS	148,7±5,5	P<0,05**
MBP- (mm Hg) Mean blood pressure	91,3±4,0	99,5±3,4	NS	112,8±4,0	P<0,05**
DBP - (mm Hg) diastolic blood pressure	68,5±2,8	73,6±3,0	NS	84,6±3,6	P<0,05**
HR – (beat/min) Heart rate	72,6±5,0	74,0±3,2	NS	88,5±4,5	P<0,05**
HbA1c, % - Glycated Hemoglobin	5,0±0,2	5,9±0,4	P<0,01*	8,0±0,5	P<0,01**
Fasting blood glucose (FBG), mmol/L	5,4±0,1	6,8±0,2	P<0,01*	10,2±0,6	P<0,01**
Fasting insulin (FI), micromol/L	36,1±4,6	53,5±4,9	P<0,05*	69,5±5,0	P<0,05**
HOMA-index	1,44±0,2	2,69±0,4	P<0,01*	3,5 ±0,2	P<0,05**

Demographic characteristic is shown as geometric means and range (with the exception of age where median and range are represented). P values were calculated by using the Man-Whitney U test.
Hemodynamic and glycemic control values are shown as mean ± SD. *Significant differences between HV and PTB, ** - between PTP and PTBDMT2, P<0,05.

Table 2. Cytokines, adipocytokines, catecholamines and vasoactive agents plasma level alterations in healthy volunteers, pulmonary tuberculosis (PTB) and PTB comorbid with diabetes mellitus type 2 (DMT2)

Indices	Healthy volunteers (HV), control n=10	PTB, n=20	P value, <0,05	PTBDMT2 n=20	P value <0,05
IL-1B, pg/ml	6,5 (2,0-17,4)	19,8(2,8-16,5)	<0,0046	31,4(4,2-60,0)	<0,01534
TNFα- pg/ml	24,2(1,9-48,2)	40,6(3,2-64,0)	<0,0058	76,2(3,5-120,0)	<0,0001
Resistin (R), ng/ml	6,81(2,0-22,2)	28,10(12-210)	<0,00001*	43,8(14-259)	<0,03846**
Adiponectin (A), ng/ml	6745,0 (3800-9672)	143,15 (32-574)	<0,00001*	95,47 (18-305)	<0,00694**
Leptin (L), ng/ml	16,05 (4,21-52,18)	0,73 (0,22-4,5)	<0,00001*	2,02 (0,34-5,8)	<0,00001**
Vascular endothelial growth factor (VEGF), pg/ml	137,12 (45-309)	630,53 (234-945)	<0,00001*	917,44 (400-1495)	<0,00054**
Norepinephrine (NE), pg/ml	136,8±35,4	390,2±48,0	<0,01*	578,6±56,1	<0,05**
Epinephrine (ENE), pg/ml	115,4±22,5	224,6±30,4	<0,05*	318,0±24,2	<0,05**
Endothelin-1 (E-1), pg/ml	3,85(2,0-7,1)	6,1(3,4-10,5)	<0,0236*	10,3(3,5-18,4)	<0,0008**
Epoxyeicosatrienoic acids (EETs), ng/ml	13,45(10,8-15,6)	7,7(4,6-10,0)	P=0,00001*	6,9(4,8-9,9)	<0,2224

Catecholamines (NE, ENE) are shown as mean ±SD. Other values are given as geometric means. P values were calculated by using Mann-Whitney U test.
*-Significant differences between HV and PTB, **- between PTB as compared to PTBDMT2, P<0,05.

Table 3. Comparative plasma lipid profile in healthy volunteers (HV), patients with pulmonary tuberculosis (PTB) and PTB comorbid with diabetes mellitus type-2 (PTBDMT2)

Indices	Healthy volunteers (HV), control n=10	PTB, n=20	P value, <0,05	PTBDMT2 n=20	P value <0,05
TC, mg/dL	163,09±24,2*,**	134,80±21,5	P<0,01	141,71±23,0	P<0,05
HDL, mg/dL	47,21±16,2*,**	35,40±9,81	P<0,05	30,0±6,41	P<0,01
LDL, mg/dL	90,72±18,51*	77,52±15,6	P<0,05	81,65±17,82	NS
VLDL, mg/dL	25,16±7,0	21,34±7,82	NS	29,24±5,61	NS
TG, mg/dL	138,61±22,42*	104,62±19,53	P<0,05	148,5±28,4	NS
AC	2,45±0,6**	3,5±1,0	NS	4,72±1,2	P<0,05

TC (total cholesterol): HDL (high density lipoproteins); LDL- (low density lipoproteins); VLDL (very low density lipoproteins); TG (triglycerides); Atherogenic coefficient (AC)=(TC-HDLc)/HDLc;
*- significant differences between HV and PTB individuals;
**- between HV and PTBDMT2. Values are shown as mean ±SD; P<0,05.

Table 1 demonstrates demographic profile of patients involved in this investigation. Both genders of subjects were participated in this study with prevalence of mail individuals. Median age of recruited patients ranged between 45-56 years. Comparative study of BMI revealed significantly higher value of this parameter in HV-24,2 (19,4-28,2, P<0,0264) as compared to PTB individuals – 20,6 (18,0-31,0) without marked differences with respect to PTBDMT2 subjects – 22,5 (18,9-30,0).

Analysis of hemodynamic indices showed statistically significant elevation of SBP (148,7±5,5 mmHg, P<0,05) and DBP (84,6±3,6 mmHg, P<0,05) in PTBDMT2 group of patients associated with increased HR (88,5±4,5 beat/min., P<0,05) vs. the same values in PTB patients: SBP (130,0±5,4 mmHg) DBP (73,6±4,0mmHg), HR (75,0±5,2 beat/minute), respectively with non-significant differences between this parameters in HV and PTB group of subjects, indicating about increasing sympathetic tone in PTBDMT2 individuals with corresponding alterations in hemodynamic indices in comparison to HV and subjects suffered by PTB without concomitant DMT2.

Glycemic control parameters showed significant increase in HbA1c% value (8,0±0,5%, P<0,01) of PTBDMT2 individuals vs. PTB patients (5,9±0,4%), as well as PTB individuals as compared to HV (5,0±0,2%, P<0,05). This indices in PTBDMT2 subjects were associated with increased plasma level of FBG (10,2±0,6 mmol/L, P<0,01). Such changes in blood HbA1c and FBG levels were accompanied by significant increase in plasma fasting insulin value of PTB group (53,5±4,9 micromol/L, P<0,05) vs HV (36,1±4,6 micromol/L) and PTBDMT2 individuals (69,5±5 micromol/L) as compared to PTB subjects.

Calculations of HOMA index showed pronounced increase of this indices in PTB (2,69±0,4, P<0,01) patients vs HV (1,44±0,2) and PTBDMT2 (3,5±0,2, P<0,05) in comparison to PTB individuals indicating about existence of insulin resistance in late two group of subjects.

Analysis (Table 2) of adipocytokines and vasoactive agents plasma alterations was identified significantly increased level of resistin in PTBDMT2 group of patients 43,8 (14-259) ng/ml as compared to PTB 28,10(12-210 ng/ml, P<0,03846) and HV subjects 6,81 (2-22,2 ng/ml, P<0,0001), respectively in contrast to adiponectin, which plasma levels in HV significantly exceeded 6745,0 (3800-9672 ng/ml) the same value in PTB 143,15 ng/ml (32-574, P<0,0001) and especially PTBDMT2 individuals, 95,47 ng/ml (18-305, P<0,00694), respectively. Leptin plasma levels were significantly decreased in PTB patients – 0,73ng/ml (0,22-4,5, P<0,0001) and PTBDMT2 individuals 2,02 ng/ml (0,31-5,2, P<0,00001).

These values of plasma adipocytokines plasma concentration correlated with marked changes concerning vasoactive substances. VEGF plasma level in PTBDMT2 individuals 917,44 pg/ml (400-1495,

P<0,00054) significantly exceeded the same value regarding PTB – 630,53 pg/ml (234-945) as well as PTB vs. HV 137,12 pg.ml (45-309, P<0,00001).

Catecholamines plasma concentrations also underwent to significant alterations in different group of patients. NE plasma levels significantly increase in PTBDMT2 subjects (578,6±56,1 pg/ml, P<0,05) as compared to PTB individuals (390,2±48,0pg/ml) and PTB vs HV (115,4±22,5 pg/ml, P<0,01). Qualitatively the same alterations were revealed concerning ENE, which plasma concentration like NE was increased in PTBDMT2 subjects (318,0±24,2 pg/ml, P<0,05) as compared to PTB group (224,6±30,4 pg/ml) and PTB individuals concerning HV (115,4±22,5 pg/ml, P<0,05).

Abovementioned changes were accompanied by certain alterations of vasoactive agents plasma concentrations that manifested in significant increase of vasoconstrictive – E-1 plasma level in PTBDMT2 patients – 10,3pg/ml (3,5-18,4) in comparison with PTB group 6,1 (3,4-10,5 pg/ml, P<0,008) and PTB individuals vs. HV - 3,85 (2,0-7,1 pg/ml, P<0,0236). In contrast to E-1, vasodilating EETs plasma level were significantly increased in HV- 13,45 ng/ml (10,8-15,6) as compared to PTB patients – 7,7 (4,6-10,0 ng/ml, P<0,00001) without significant differences between PTB and PTBDMT2 individuals (P<0,2224).

Changes in plasma concentrations of different biomarkers provided influence on lipid profile (Table 3) of involved subjects that was manifested in significantly decreased level of total cholesterol (TC) in PTB group of patients (134,8±21,5mg/dL) in comparison with HV (163,09±24,2mg/dL, P<0,01) with less changes in its concentrations in PTBDMT2 patients. LDL plasma concentrations markedly decreased in PTB patients (77,52±15,6 mg/dL, P<0,05) as compared to HV (90,72±18,51 mg/dL). Significant changes were registered regarding HDL plasma levels that in PTB (35,40±9,81mg/dL, P<0,05) and PTBDMT2 groups (30,0±6,51mg/dL, P<0,01) were reduced markedly as compared to HV (47,21± 16,2 mg/dL, P<0,05), while VLDL plasma level did not undergo to significant changes in PTB (21,34± 7,82 mg/dL) and PTBDMT2 (29,24±5,61mg/dL) individuals vs. HV (25,16±7,0mg/dL) unlike TG plasma levels that significantly decreased in PTB patients (104,62±19,53 mg/dL, P<0,05) and slightly increased non-significantly (148,53±28,4mg/dL) as compared to HV (138,61±22,42mg/dL). Analysis of atherogenic coefficient revealed significant tendency in PTB and especially PTBDMT2 for atherogenic alterations manifested in these group of patients with values – 3,5±1,0 and 4,72±1,2 vs. 2,45±0,6 in HV.

Discussion. Our results concerning demographic profile of recruiting subjects showed that BMI in HV significantly exceeds the same values in PTB group of patients without marked differences PTBDMT2 individuals, which can be explained by chronic infection and inflammation in PTB subjects influencing on their weight [21] while DMT2 comorbidity with PTB (PTBDMT2) can be considered as determinant of metabolic syndrome preventing significant reduction in BMI. Analysis of hemodynamic parameters in our investigation revealed marked increase in SBP, DBP, HR especially in PTBDMT2 individuals that consistent with finding of other authors demonstrating autonomic dysfunction, sympathetic overactivity and inhibition of baroreflex parasympathetic component sensitivity in PTB and DMT2 [22, 23]. Increase plasma level of catecholamines in our study confirmed these data. As it was shown these changes were associated with worsening of glycemic control in PTB and especially in PTBDMT2 individuals vs. HV manifested by increased blood level of HbA1c%, FBG, FI and HOMA-index suggesting about development of insulin resistance in PTB and predominantly PTBDMT2 patients. Our finding consistent with other data indicated about possibility of immune cells aside from inflammation to be involved in metabolic disturbances associated with low intense inflammation [24, 25]. Such process is correlated with production by macrophages cytokines – IL-1B, TNFα, etc. leading to pancreating β-cells dysfunction (Jayashankar, C.A. et al., 2023), which also has been showed in our present investigation with prevalence of their excessive release especially in PTBDMT2 subjects. Inflammatory cytokines production in our study was

associated with increased plasma levels of adipocytokine resistin, as well as VEGF in PTB and PTBDMT2 vs. HV facilitating to vasocontrictive reactions and reduction in plasma concentration of leptin and adiponectin that are in agreement with data receiving by other authors [27, 28] ascribing such plasma alterations of these agents by their possibility to be involved in glycemic control, lipid metabolism, insulin sensitivity, pro- and anti-inflammatory action. Endothelial dysfunction also plays significant role in the formation and progression of PTB and its comorbidity with DMT2, because diabetes induced micro- and macrovascular changes facilitating to severity of PTB [28]. Our results showed increased plasma level of vasodilating EETs confirmed disbalance between these two systems during development of PTB and PTBDMT2 associated with marked decrease TC plasma level in PTB and PTBDMT2 groups vs. HV, decreased HDL and LDL in these groups without significant changes in VLDL with respect to HV and decreased TG in PTB vs. HV with significant increased AC in PTBDMT2 which is in agreement with results of other authors [29, 30, 31, 32, 33, 34, 35, 36].

Conclusion: we can suggest that in the formation and progression of PTB are involved different mechanisms, including inflammatory, endocrine, vasoactive factors system that more expressively are manifested in comorbid cases of PTB with DMT2 leading to more severe currency of this pathology, and can be considered as potential biomarkers for early diagnostic, estimation of treatment effectiveness and outcome of this disease.

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THE INFLUENCE OF PLASMA LEVEL ALTERATIONS OF INFLAMMATORY, ENDOCRINE AND VASCULAR BIOMARKERS FOR THE FORMATION AND PROGNOSIS OF PULMONARY TUBERCULOSIS COMORBID WITH DIABETES MELLITUS TYPE-2

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SUMMARY

Tuberculosis (TB) remains as a most disseminated infectious disease resulting in different complications and lethal outcome. Studies conducted in last decades showed the increase frequency of pulmonary tuberculosis (PTB) in subjects suffered by diabetes mellitus type-2 (DMT2).

The goal of the present investigation was to study the modulatory action of inflammatory cytokines (IL-1B, TNFα), vasoactive agents: epoxyeicosatrienoic acids (EETs), endothelin-1 (E-1), vascular endothelium growth factor (VEGF), resistin (R), lipid spectrum, catecholamines (noradrenaline, epinephrine) and endocrine factors – leptin and adiponectin plasma levels alterations in the formation and prognosis of PTB and PTB comorbid with DMT2. Observational study was carried out in 2023-2025 years period in Tbilisi National Center for Tuberculosis and Lung Diseases (Georgia). Recruiting male and female adult patients (18 and more years old, n=50) were divided into 3 groups: a) Healthy volunteers (HV)-n=10; b) Subjects with newly diagnosed PTB-n=20; c) Patients with PTB coincident with DMT2 (PTBDMT2)-n=20.

All patients were involved in this study according inclusion and exclusion criteria. The existence of MTB along with clinical symptoms and X-rays examinations was confirmed by Gene Xpert MTB/RiF ULTRA Test. Plasma concentrations of abovementioned agents as well as glycemic control of fasting glucose, insulin and glycated hemoglobin - (HbA1C%) levels was performed by ELISA Kits method. Insulin resistance (IR) was calculated by HOMA-index using formula: [(fasting glucose (mmol/L X fasting insulin (micromole/L/22,5)]. Receiving results revealed in subjects suffered by PTBDMT2 significantly higher plasma level of cytokines IL-1 31,4 (4,2-60,0) pg/ml, P<0,1534) and TNFα 76,2 (3,5-120,0) pg/ml, P<0,0001), that more expressively positively correlated with elevated concentrations of vasoactive agents – E-1 10,3 (3,5-18,4) pg/ml, P<0,0008), catecholamines, VEGF 917,44 (400,0-1495) pg/ml, P<0,00054), R 43,8(14-259) pg/ml, P<0,03846) and endocrine factor leptin 2,02 (0,34-5,8) pg/ml, P<0,00001), providing marked negative relationship to EETs 6,9 (4,8-9,9) pg/ml and adiponectin 95,47 (18-305) pg/ml, P<0,00694) as compared to the same values of PTB and especially HV groups of patients. Such events were associated with lipid spectrum disorders in PTB and PTBDMT2 patients.

It is suggesting that cytokines, vasoactive and endocrine agents can be considered as potential biomarkers for early diagnostic and assessment of treatment effectiveness and outcome of PTB and PTBDMT2.

Keywords: Pulmonary tuberculosis, diabetes, cytokines, adipocytokines, lipid spectrum