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THE IMPACT OF X-RAY SEVERITY AND MICOBACTERIA EXCRETION ON GLUCOSE METABOLISM DISORDERS IN NEWLY DIAGNOSED PULMONARY TUBERCULOSIS PATIENTS

Abstract. *Aim. The present study was performed to detect the glucose metabolism disorders in newly diagnosed pulmonary tuberculosis patients and to evaluate the relation of the disorders to the X-ray severity and the presence of mycobacteria excretion. Materials and methods. We examined 78 patients with newly diagnosed pulmonary tuberculosis. Oral glucose tolerance test, fasting insulin level were measured, the insulin resistance index (HOMA-IR) and the body mass index were calculated. For statistical data processing, the general-purpose data processing software package Statistica for Windows version 13.2 was used. Results. Our study found an increase in glycosylated hemoglobin level, which correlated positively with the volume of pulmonary lesion. Oral glucose tolerance test demonstrated statistically significant increase of the median of 2 hour blood glucose level in the group of patients with mycobacteria excretion. The median of the fasting plasma insulin level was 3.8 times higher in patients with newly diagnosed pulmonary tuberculosis, compared to the control group. Conclusions. Our findings suggest that pulmonary tuberculosis is associated with glucose metabolism disorders. Mycobacteria excretion and bilateral pulmonary lesions were accompanied by the impaired glucose tolerance and increase of glycosylated hemoglobin levels, that allows consider these indicators as markers of unfavorable course of pulmonary tuberculosis.*

Key words: *pulmonary tuberculosis, oral glucose tolerance test, insulin, Homeostatic Model Assessment of Insulin Resistance.*

Introduction. About 1.7 billion people, 23% of the world's population, are estimated to have a latent tuberculosis (TB) infection, and are thus at risk of developing active TB disease during their lifetime [1]. The lifetime risk of active TB is significantly increased among those who have predisposing factors like comorbid diseases or pathological conditions that can lead to immune defense weakness. According to WHO experts, the top five most significant risk factors for TB are poor nutrition, Human Immunodeficiency Virus (HIV) infection, Diabetes Mellitus (DM) and harmful habits (tobacco and alcohol abuse). Individual risk of TB in patients with DM is significantly lower than the risk of HIV-positive patients, but in countries with high TB-DM burden, it plays a key role in TB morbidity control [2].

TB-DM comorbidity has become a major public health problem in Ukraine. According to the Public Health Center of the Ministry of Health of Ukraine, in 2016, the incidence of TB-DM comorbidity in Ukraine reached 2.5 per 100 thousand population (1044 cases were detected), this is about 3.1% of the total TB cases. For comparison: in 2015 this indicator was 2.7%. The percentage of comorbidities among patients with multidrug-resistant tuberculosis (MDR-TB) also had raise from 3.7% in 2015 to 4.2% in 2016.

It is known, that clinical course of patients with TB-DM tends to be more severe due to immunosuppression and interaction of anti-TB and DM drugs. TB-DM patients have higher treatment failure rate, compared to non-diabetic TB patients (4.8% vs. 1.5%). In addition, the number of TB relapses is statistically significantly higher among DM patients if to compare with non-DM (20% vs. 5.3%).

Recent studies have shown a high prevalence of newly diagnosed type 2 diabetes and pre-diabetes among TB patients [3-5].

Aim. The present study was performed to detect the glucose metabolism disorders in newly diagnosed pulmonary tuberculosis patients and to

evaluate the relation of the disorders to the X-ray severity and the presence of mycobacteria excretion.

Material and methods. We examined 78 newly diagnosed pulmonary TB patients. All of them were treated in Kharkiv Regional TB Dispensary No. 1 from 2016 to 2017. We excluded from the study patients who had HIV/TB co-infection, TB/DM comorbidity, pregnant women, children and elderly patients. Depending on the mycobacteria excretion, which was confirmed by culture, microscopic smear and molecular methods of diagnosis of tuberculosis, patients were divided into groups. The control group included 20 healthy persons, which were correlated with the comparison groups by gender and age. All patients were examined according to the order of the Ministry of Health of Ukraine No. 620 of 14. 09. 2014. Additionally oral glucose tolerance test (OGTT) was performed and fasting insulin level was measured. HOMA-IR and Body Mass Index were calculated.

Statistical processing of the obtained results was carried out by analyzing the contingency tables using the StatisticaBasicAcademic 13 for Windows software package. We used the median (Me) interquartile range (Lower - lower quartile, Upper - upper quartile) and sample size (min - minimum, max - maximum value). The difference between groups was determined by non-parametric statistics using the Kolmogorov-Smirnov test and Mann-Whitney (CMW) test criteria. To study the independent variables, we used the non-parametric Kruskal-Wallis (CKW) test criteria and the median test.

The work was performed according to the requirements for researches with the participation of people: Statute of the Ukrainian Association for Bioethics and the GCP norms (1992), requirements and norms of ICH GLP (2002), typical ethics provisions of the Ministry of Public Health of Ukraine 66 dated February 13, 2006.

Results. Group I consisted of 19 newly diagnosed pulmonary TB patients who had no mycobacteria excretion (24.4 %). Group II included 59 newly diagnosed pulmonary TB patients who had mycobacteria excretion (75.6 %). Age and sex distribution were nearly the same in both groups. Age ranged from 20 to 57. Men prevailed in both groups: 10 (52.6 %) and 44 (7.6 %) respectively. The overwhelming majority of Group I patients were hospitalized to the TB hospital in satisfactory condition. Clinical course of the Group II patients was aggravated. They were often complained of fatigue - (44.1%), fever - (37.3%), night sweats - (16.9%) and coughing that lasts three or more weeks - (50.8%).

In most patients of both groups the BMI was within normal ranges, though 6 patients from Group II (10.2%) had expressed underweight (BMI < 16.0).

When comparing medians of the carbohydrate profile indicators of TB patients and healthy controls, we found statistically significant difference ($p<0.01$, CMW) in fasting insulin levels (16.15 mcU/ml vs. 4. 78 mcU/ml) and 2-hour glucose levels (4.95 mmol/L vs 3.92 mmol/L). HOMA-IR was statistically significantly higher among TB patients (3.19 vs. 0.82). But we didn't find statistically significant differences in fasting blood glucose levels (4.28 mmol/L vs.3.92) and glycosylated hemoglobin levels (5.67% vs. 5.77%) between groups respectively ($p>0.01$, CMW).

X-ray examination reviled that in most cases patients of both groups had infiltrative changes in their lungs (Group I – 94.8%, Group II – 96.6 %). For Group I patients, there were mainly pathologic changes within one lobe (63.2%), while in Group II we observed huge infiltrative changes in both lungs (79.7%). Cavitation was present in 31.6% patients in Group I and in 77.9% of Group II patients. It should be noted, that in Group I patients prevailed single cavities up to 1.0 cm in diameter (83.3%), on the contrary, in Group II, multiple decay cavities of various sizes were prevailed (63%).

Depending on the increase in the volume of infiltrative changes, there was a monotonous statistically significant ($p=0.0409$, CKW) increase in the median level of glycosylated hemoglobin from 4.8% (pathological changes within the lobe of the lung) to 6% (total lesion of one lung) with a maximum of 7.1% with bilateral lung injury. Thus, when both lungs were involved in the pathological process, the level of glycosylated hemoglobin was increased by almost one and a half times as compared with limited lung changes. The OGTT showed a statistically significant ($p= 0.023384$, CMW) increase in the median of 2-hour glucose level in pulmonary TB patients who had mycobacteria excretion 5.8 mmol/L compared to those, who had no mycobacteria excretion (4.7 mmol/L).

Discussion. *Mycobacterium tuberculosis*, the etiological agent of Tuberculosis can induce

Reactive Oxygen Species (ROS) production by activating phagocytes which are important part of host defense mechanism against Mycobacterium. ROS production is enhanced by the host cells to clear out mycobacterial infection. However, this can become damaging to the host cell itself. Such damage is controlled by the induction of antioxidant defense mechanisms. Excessive ROS production may promote tissue injury and inflammation in affected individuals. Imbalance between the free ROS and the antioxidant mechanisms usually leads to oxidative stress (OS) [6]. In the lung, there is a higher risk of OS compared to other organs. Many studies demonstrated that increased oxidative stress is associated with insulin resistance pathogenesis by insulin signals inhibition and adipokines dysregulation. Research in this area has revealed that there is a strong correlation between the state of oxidative stress in the body and the incidence of insulin resistance and even late stage diabetes cases [7,8].

In our study we found the presence of insulin resistance in patients with newly diagnosed pulmonary tuberculosis that is confirm the results of previous researchers. We did not find statistically significant differences between glycosylated hemoglobin levels and fasting blood glucose levels in pulmonary tuberculosis patients compared to healthy controls. It allows us to suppose, that such routine research methods like glycosylated hemoglobin and fasting blood glucose test have low sensitivity when detecting carbohydrate metabolism disorders in patients with pulmonary tuberculosis.

But, we found a statistically significant increase in glycosylated hemoglobin level of pulmonary tuberculosis patients that positively correlated with the volume of pathological changes in the lungs which is indicate to deeper glucose metabolism disorders in tuberculosis patients who had bilateral injury of pulmonary tissue, compared to those, who had limited pathological changes. We also identified, at a statistically significant level, glucose metabolism disorders in the form of impaired glucose tolerance in patients with newly diagnosed pulmonary tuberculosis who had mycobacteria excretion.

Conclusions. According to our results, patients with newly diagnosed pulmonary tuberculosis develop insulin resistance - condition that is a precursor to developing of type 2 diabetes. Mycobacteria excretion and bilateral injury of lung tissue leads to expressed carbohydrate metabolism disorders. Fasting blood glucose level is low sensitivity index when detecting carbohydrate metabolism disorders, while glycosylated hemoglobin and oral glucose tolerance test can be considered as markers of impaired glucose metabolism in patients with pulmonary tuberculosis.

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