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Multidrug-resistant tuberculosis and diabetes mellitus as a problem of modern medicine

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Abstract

English:

Aims: *To carry out a comprehensive retrospective assessment of the prevalence, features and course of treatment of patients with multidrug-resistant tuberculosis (MDR-TB) and diabetes mellitus (DM).*
Materials and Methods: *Our study is based on a retrospective analysis of statistical data obtained from 762 current and former MDR-TB patients (74% of patients with resistance only to first-line drugs – isoniazid (H) and rifampin (R); 36% with resistance to H, R and second-line drugs) included in the register of tuberculosis (TB) patients from different regions of Ukraine and the Grodno region of the Republic of Belarus between 2015 and 2019.*
Results and Discussion: *In both groups of the study recurrent TB prevailed: 49 cases (55.7%) of relapse TB compared to 39 cases (44.3%) of primary TB in the main group; 363 cases (53.9%) of relapse TB compared to 311 (46.1%) primary TB in the control group ($P < 0.05$). The rate of successful treatment in the control group is higher than in the main group (64.7% vs. 61.4%; $P < 0.05$). A significant difference between the two groups was observed owing to the difference in frequency of treatment, which in the main group has recorded 27.3%, as against 40.3% in the control group (almost two times lower; $P < 0.05$).*
Conclusions: *The association between TB and DM increases the morbidity, chemoresistance and proportion of recurrences. Pulmonary TB developed significantly more often in middle-aged patients with type 2 DM with moderate and severe states, with subcompensated form and with a complicated course.*

Keywords

multidrug resistance • diabetes mellitus • hydrocarbon metabolism • treatment • epidemiology

Tuberculoza multidrog-rezistentă și diabetul zaharat, o problemă a medicinei moderne

Rezumat

Romanian:

Scopul. *Studiului este o evaluare retrospectivă cuprinzătoare a prevalenței, caracteristicilor, evoluției tratamentului pacienților cu tuberculoză multidrog-rezistentă (TB-MDR) asociată cu diabet zaharat (DZ) tip 2.*
Material și metoda. *Studiul se bazează pe analiza retrospectivă a datelor statistice provenite de la 762 actuali și foști pacienți cu TB-MDR (74% pacienți cu rezistență doar la tuberculostaticele de primă linie – izoniazidă (H) și rifampicină (R); 36% cu rezistență la H, R și tuberculostatice de linia a 2-a) din registrul pacienților cu tuberculoză din diferite regiuni ale Ucrainei și din regiunea Grodno a Republicii Belarus, în perioada 2015–2019.*
Rezultate și discuții. *În ambele grupuri investigate a predominat TB recurentă: 49 cazuri (55.7%) de recidive TB comparativ cu 39 cazuri (44.3%) de TB primară în grupul principal; 363 cazuri (53.9%) de cazuri de recidive TB comparativ cu 311 cazuri (46.1%) de TB primară în grupul control ($P < 0.05$). Rata de succes a tratamentului este mai mare în grupul control comparativ cu grupul principal (64.7% vs. 61.4%; $P < 0.05$). O diferență semnificativă între grupuri este dată de frecvența tratamentului care în grupul principal este de 27.3% vs. 40.3% în grupul control (de aproape 2 ori mai scăzută, $P < 0.05$).*
Concluzii. *Asocierea dintre tuberculoză și diabet zaharat crește morbiditatea, chimiorezistența și rata de recurență. Tuberculoza pulmonară se dezvoltă semnificativ mai mult la pacienții de vârstă mijlocie cu DZ în stadiul moderat și sever, cu formă subcompensată și cu evoluție complicată a bolii.*

Cuvinte-cheie

multidrog-rezistență • diabet zaharat • metabolism al hidrocarburilor • tratament • epidemiologie

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Introduction

Tuberculosis (TB) and diabetes mellitus (DM) are among the significant modern medical problems that have a direct impact on societies' socio-economic indicators. The problem of diabetes, as well as TB, is more acute in countries where TB is epidemic and the burden of diabetes tends to increase linearly (1,2).

The importunity of the problem posed by TB and DM is due on the one hand to the growing number of patients with TB with multiple drug resistance to the pathogen, and on the other to a steady increase in the number of people with various forms of carbohydrate metabolism. Thus, modern objective reality increases the urgency of the problem of this combined pathology, as well as the need for the study and proper understanding of the mechanisms of TB infection in this category of patients (3,4).

A combined pathology should be considered through the course of diabetes, as its proportion in the structure of TB-DM association in recent years has increased significantly and continues to increase rapidly.

It is generally known that diabetes is the background for the development of TB and such comorbidity not only significantly complicates the specific process but also constitutes one of the main risk factors for TB recurrence (level of evidence A) (5).

Diabetes is a serious and usually irreversible state of health that requires control and treatment throughout life. In different countries of the world, the prevalence of diabetes is between 4% and 11% (6). The development of complications from this disease leads to a significant reduction in life's quality, disability, 30% reduction in life expectancy and 2–3 times increase in mortality, as well as the significant financial and economic costs of treatment.

According to the International Diabetes Federation's expertise, approximately 12% of health care costs (>$ 670 billion annually) are included in the treatment of diabetes and its complications. In 2019, 437 million people with diabetes were registered worldwide, and the number of people is projected to increase to 629 million by 2045. Each year, 10 million new people are estimated to develop diabetes, and up to 5 million people may die from complications related to carbohydrate metabolism disorders (7). In total, 12% of deaths in the world are caused by diabetes, of which 43% are under the age of 70 (1,7). This global pandemic remains out of control, tending to increase in every country in the world.

In most WHO regions, diabetes is not necessarily a 'disease of nutritional abundance', as the prevalence of diabetes in some agricultural regions has reached or exceeded the level found in more affluent urban conglomerations (3). Up to 95% of diagnosed cases suffer from type 2 diabetes (1). The increase in type 2 diabetes is associated with globalisation and urbanisation, erosion of traditional food culture, less physical activity and increased consumption of highly refined and more energy-intensive products (3,8).

Diabetes can lead to many serious health complications, especially to microvascular and macrovascular pathologies, as well as to an increased risk of developing infectious diseases, including the SARS-Cov-2 infection, which is probably the basis for reduced resistance to TB infection in the future.

Ukrainian epidemiological studies of diabetes also show a steady increase in the number of patients in the population by 5–6% annually. It is known that diabetes is diagnosed in 50 Ukrainians every day. In total in our country, there are more than 1.5 million patients with diabetes – and about 9000 of them are children. This is about 3.5% of the total population, which is much less than in some other European countries (in Germany – 10.2%, France – 6.2%, Sweden – 7.3% and Spain – 9.9%). However, experts believe that the actual prevalence of diabetes in Ukraine is 2–2.5 times higher due to undiagnosed cases.

DM, as a medical risk factor, most often causes an exacerbation of the TB process and is often the cause of low treatment efficiency (9).

The violation of the intermediate carbohydrates' metabolism oppresses the permeability of all biological membrane changes. These disorders are manifested by their increased permeability and the predominance of exudation, due to unimpeded access to the affected area of inflammatory mediators. Through this mechanism the old foci of TB infection are reactivated.

The metabolic disorders and the glucose tolerance, as well as the self-sensitisation to their tissues, which is characteristic of diabetes, play an important role in the reactivation of post-tuberculous residual changes. Pathophysiological changes that occur in the body in diabetes contribute to the rapid, mainly hematogenous spread of the pathogen, resulting in generalised forms of TB (10).

Some researchers have shown that in diabetes there is a tendency to hypersensitivity, which complicates the course of the disease due to some allergic reactions of varying severity, which leads to significant changes in the treatment and is often a potential threat of chemoresistance in *Mycobacterium tuberculosis*.

According to several studies conducted in recent decades, diabetes significantly worsens the course of TB, prolonging the duration of the disease (±2.2 months) and its severity with a predominance in the pathogen of alteration and exudation (5).

Another feature of such a 'tandem' of these two diseases is the high risk of intolerance to the drugs used for the etiotropic therapy, which inevitably leads to changes in the treatment regimens and tactics contributing to the development of chemoresistance to TB (4).

Some researchers mention that diabetes increases the risk of discontinuation of TB treatment and is the cause of patient loss from irregular follow-up (5).

It is not known whether the poor outcomes of TB treatment described among those with poorer glycemic control are due to existing complications associated with diabetes, or to hyperglycemia itself and metabolic disorders (9).

The risk of TB recurrence in people who have completed TB treatment is also higher among those with diabetes compared to those without carbohydrate metabolism disorders; whether this is due to reactivation of primary *M. tuberculosis* or reinfection with another strain of *M. tuberculosis* remains an unresolved issue (11).

Objective

The objective of the study is a comprehensive retrospective assessment of the prevalence, features and course of treatment of multidrug-resistant tuberculosis (MDR-TB) and DM among patients from certain regions of Ukraine (Chernivtsi, Kharkiv and Ternopil) and the Grodno region of the Republic of Belarus.

Materials and methods

Our study is based on an analysis of statistical data obtained from a retrospective study of 762 cases of MDR-TB from the register of TB patients in the Chernivtsi, Kharkiv and Ternopil regions of Ukraine and the Grodno region of the Republic of Belarus, between 2015 and 2019. We assessed the main epidemiological aspects of the prevalence of diabetes in patients with MDR-TB, the occurrence of adverse reactions of TB therapy (ART) in such patients and the effectiveness of treatment with standard schemes on those comorbidities.

The criteria for inclusion in the study were: patients with pulmonary forms of MDR-TB with a concomitant diagnosis of DM or without it.

We distinguished two groups: the main group consisted of 88 patients with MRD-TB with concomitant DM; the second group (the control one), consisted of 674 patients diagnosed with MRD-TB without concomitant DM. The types of patients in both groups were representative of age and gender.

The patients who were included range from 20 years to 78 years, with a mean age of 41.7 ± 3.4. Most of the surveyed patients were male – 566 (75.6%).

The analysis consists of the assessment of general clinical symptoms, data of ultrasound examination of abdominal organs, X-ray examination of thoracic organs, general and biochemical blood tests (level of total protein, total bilirubin, AST, ALT, urea, creatinine and thymol) and blood sugar. The design of the study corresponded to an open, clinical, selective and prospective observation.

Pearson's correlation coefficient (with a normal sample distribution) and Spearman's correlation coefficient (with a non-normal sample distribution) were used to describe the degree of relationship between the variables.

The primary accounting data of the retrospective analysis were entered by us into a database based on IBM STATISTICA software shell, version 13.0 (serial number AXAR207F394425FA-Q). In the process of statistical processing of research results, the type of data distribution, the probability of the obtained results and other types of analyses were determined. For the data corresponding to the normal distribution, the arithmetic mean sample (M), the value of the standard deviation (s) and the standard error (m), the maximum and minimum values were determined. For the comparison of variables with a normal distribution (parametric), the Student's *t*-test was used, and the statistically significant difference was considered at a value of $P < 0.05$.

Results and discussion

The importance of the chosen syntropy is due to some objective circumstances: the steady increase in the prevalence of carbohydrate metabolism disorders among the population and the persistence of a tense situation with MDR-TB. The epidemiological situation is of strategic importance to the country as a whole, as a further increase in the number of patients with DM and MDR-TB is expected due to the epidemic conditions regarding the prevalence of the Coronavirus.

The analysis of the statistical material shows that over the past 15–20 years there has been a continuous progressive increase in the proportion of combined pathology and MDR-TB in the structure of TB.

In most cases, TB is often combined with human immuno deficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) in 35% of cases, followed by DM in 25% of cases, peptic ulcer disease in 17% of patients with TB, hepatobiliary diseases in 13% and cardiovascular and nervous system pathologies in 6% and 4%, respectively (Figure 1).

Depending on the type of TB cases (primary or relapse TB) in our patients, we found that in both groups of the study the recurrence TB prevailed – 49 cases (55.7%) of relapse TB compared to 39 cases (44.3%) of primary TB in the main group; 363 cases (53.9%) of relapse TB compared to 311 (46.1%) of primary TB in the control group ($P < 0.05$) (Figure 2).

Analysing the prevalence of TB process in the lungs by clinical forms of TB, we found the presence of more severe clinical forms in patients of the main group, with DM.

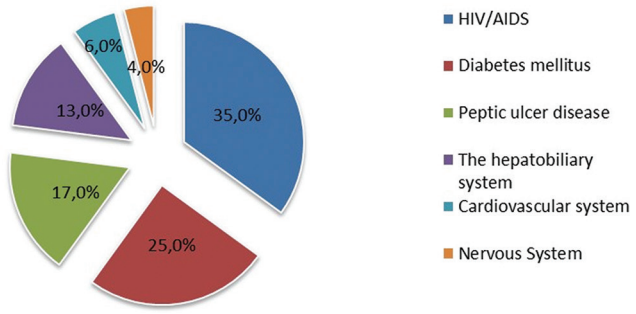


Figure 1. The structure of concomitant pathology in patients with MDR-TB. MDR-TB, multidrug-resistant tuberculosis.

Figure 3 shows that in patients from the main group, heavy, widespread processes were more often registered in the lungs compared with the control group. So, the incidence of disseminated TB is observed two times, caseous pneumonia three times, miliary TB four times and fibro-cavernous TB two times more often than in the control group ($P < 0.05$ in all cases).

The obtained data indicate a more massive lesion of lung tissue in patients with concomitant pathology like diabetes. Another indisputable proof of this is that the prevalence of TB in three or more segments was observed in 72.7% of patients in the main group compared to 51.9% in the control group.

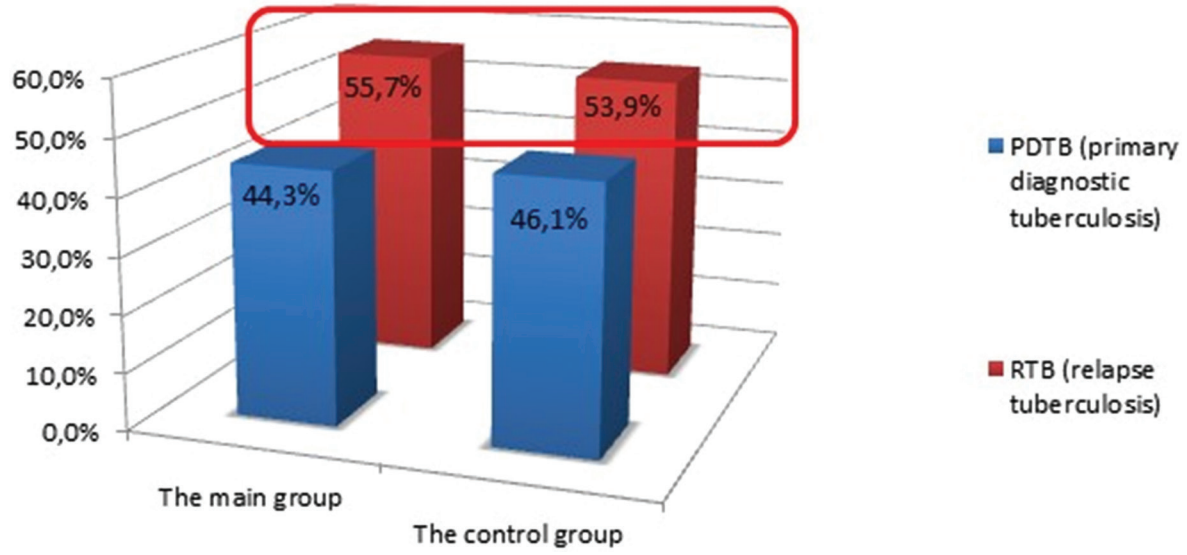


Figure 2. Type of MDR-TB case. MDR-TB, multidrug-resistant tuberculosis; PDTB, primary diagnostic tuberculosis; RTB, release tuberculosis.

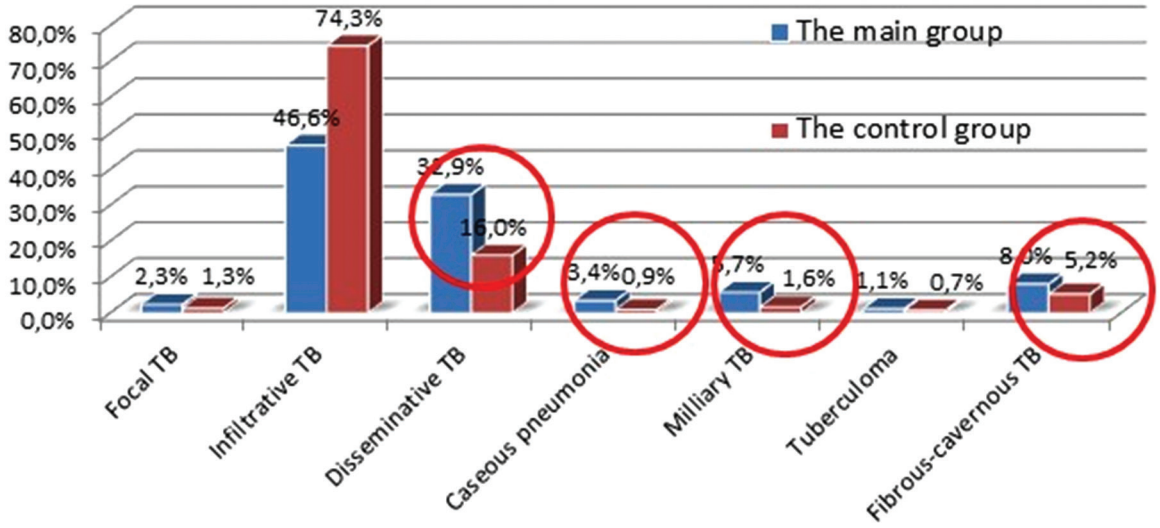


Figure 3. Radiological characteristics of the tuberculous process in the case of DM with MDR-TB. DM, diabetes mellitus; MDR-TB, multidrug-resistant tuberculosis; TB, tuberculosis.

Also, in the main group, the bacterial excretion index was registered in all patients compared to 93.9% of patients in the control group ($P < 0.05$).

The retrospective analysis showed that in patients included in the study, DM was detected in 28 cases (31.2%) simultaneously with pulmonary TB; in 60 cases (68.8%) DM developed before TB and was the background for the manifestation of TB infection, with the average duration of the disease being 6.4 ± 1.2 years (Figure 4).

Most patients had type 2 DM – 64 (72.7%). According to the severity of diabetes, patients were distributed as follows: moderate severity – 48 patients (54.5%), severe – 8 (9.1%) and mild – 30 (36.4%).

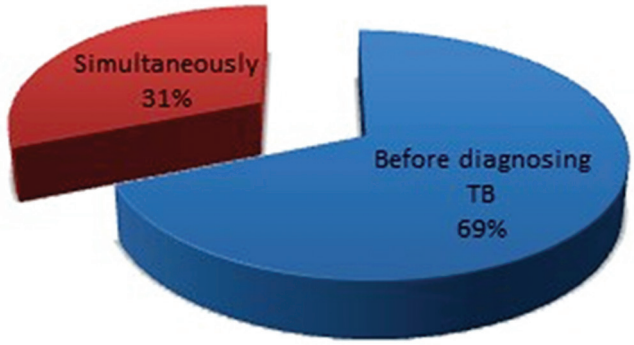


Figure 4. Diagnosis of diabetes in patients with MDR-TB. MDR-TB, multidrug-resistant tuberculosis; TB, tuberculosis.

Depending on the form of diabetes compensation, the distribution was the following: compensated (glycemia ≤ 150 mg/dL) – 27 patients (30.7%), subcompensated (glycemia 150 –400 mg/dL) – 49 patients (55.7%) and decompensated diabetes (glycemia >400 mg/dL) – 12 patients (13.6%) (Figure 5).

According to the anamnesis, we clarified the additional risk factors for the development of TB in patients with diabetes. Depending on existing social factors, the majority of patients belonged to the category of unemployed – 69 patients (78.4%), with secondary education – 34 people (38.6%), secondary special – 36 (40.1%), and higher – 18 (21.3%) education. Most patients rated their living conditions as satisfactory – 80 people (90.1%); and 8 patients (9.9%) as unsatisfactory. Forty-six patients (52.3%) had bad habits, of which 9 patients (10.2%) drank alcohol regularly, 42 patients smoked (47.7%) and 1 patient (1.1%) was addicted to drugs. There were previously three patients (3.4%) with combined pathology in prisons.

At detection of tubercular process in the majority of patients, the clinical symptoms caused by the manifestation of an inflammatory process dominated: intoxication syndrome was noted at 58 (65.9%) patients of the main group as against 317 (47%) patients of the control group; bronchopulmonary – at 25 (28.4%) of the main group as against 124 (18.4%) of the control group; and a combination of these syndromes – in 21 (23.9%) patients with comorbid pathology of MDR-TB and DM compared to 95 (9.6%) patients without concomitant DM. Only 6 (6.8%) patients from the main group compared to

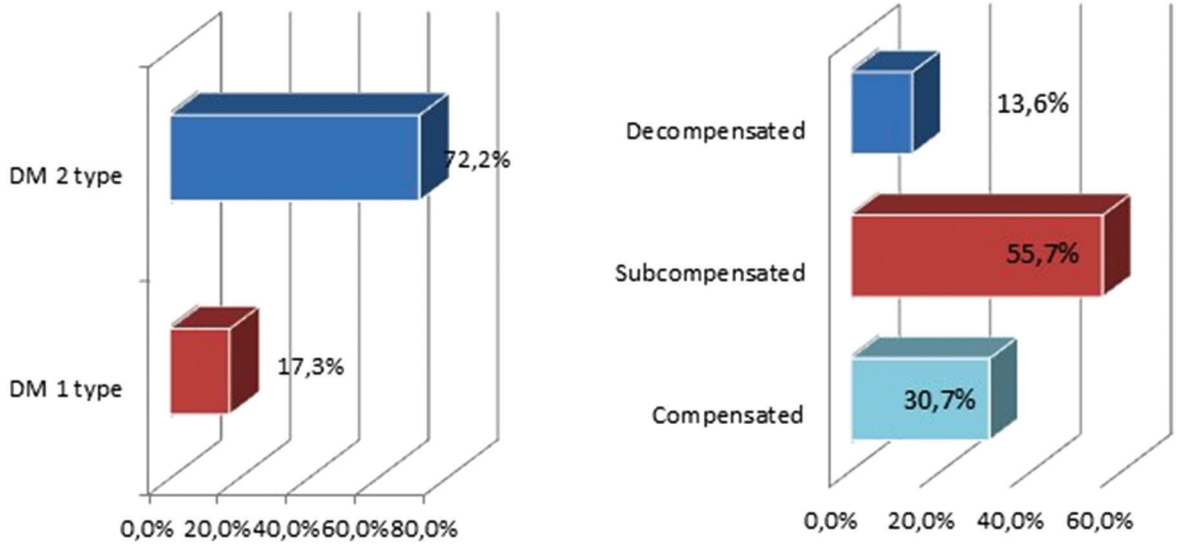


Figure 5. Type and forms of diabetes compensation in patients with MDR-TB (main group). DM, diabetes mellitus; MDR-TB, multidrug-resistant tuberculosis.

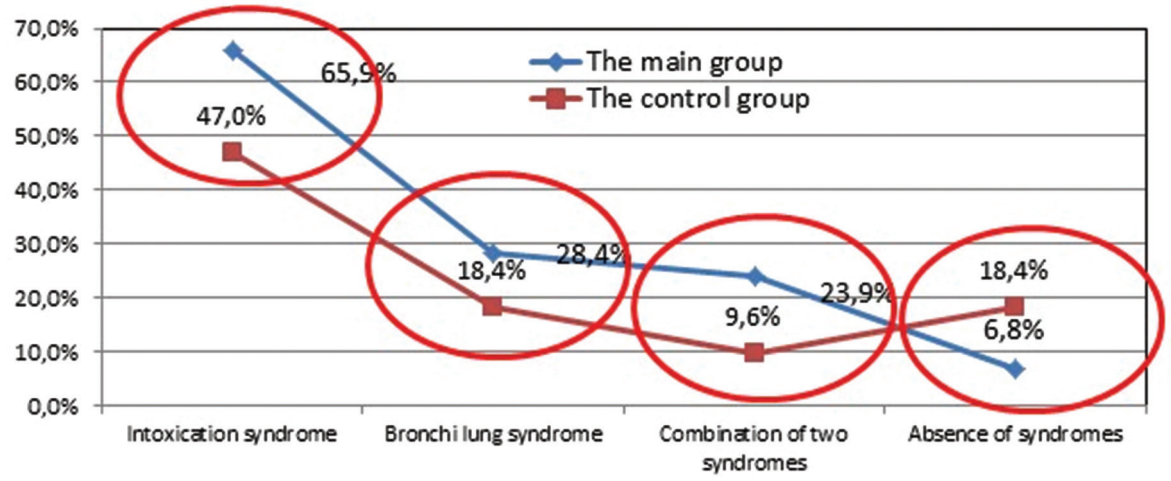


Figure 6. Clinical characteristics of patients in the studied samples with comorbidity of MDR-TB and diabetes. MDR-TB, multidrug-resistant tuberculosis.

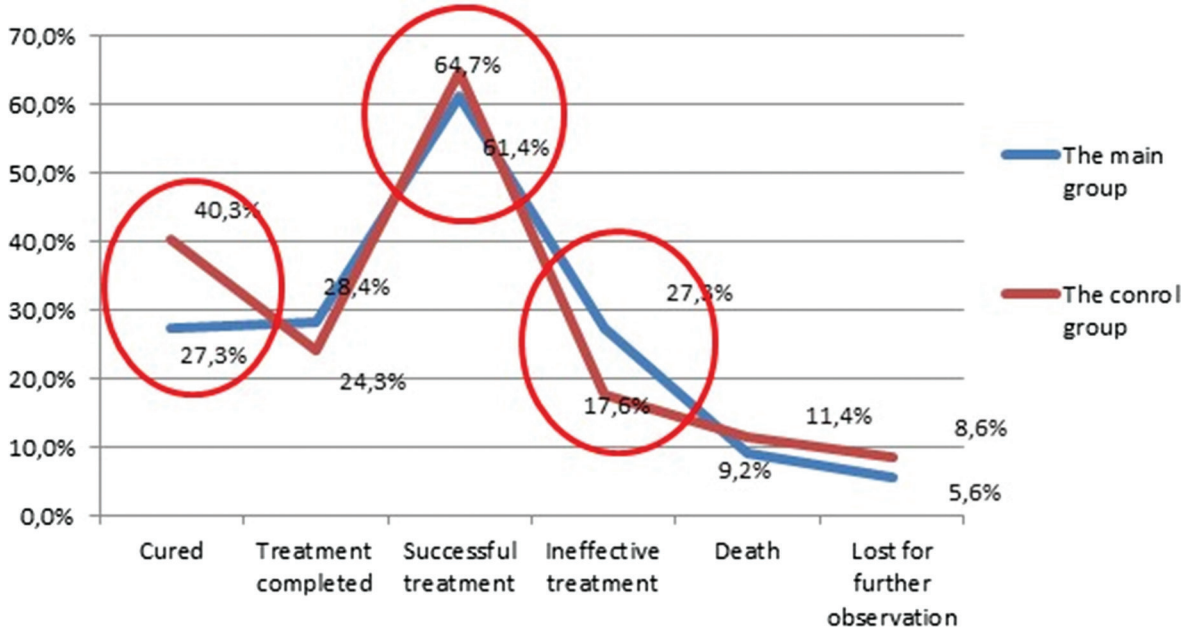


Figure 7. The results of treatment in both groups of the study.

124 (18.4%) patients from the control group had no syndrome (Figure 6).

According to the results of the blood sample analysed, both groups had the same extent of recorded acceleration of erythrocyte sedimentation rate (ESR), anaemia, leukocytosis and lymphopenia. On admission to the hospital, blood sugar averaged 190.9 mg/dL in the main group vs. 66.6 mg/dL in the control groups.

However, the main parameter through which <> <we need to consider this polymorbidity is the effectiveness of TB treatment (Figure 7).

As we can see in Figure 7, the rate of successful treatment in the control group is higher than in the main group (64.7% vs. 61.4%; $P < 0.05$). However, a more significant probable difference is characterised by the treatment rate, which in the main group is 27.3% vs. 40.3% in the control group (almost two times; $P < 0.05$). The rate of ineffective treatment, which in patients with comorbidity was 27.3% (almost every third patient) as against 17.6% in the control group, is also an important statistic for scientists and practitioners to study. Other indicators probably are approximatively the same.

Thus, the combined pathology of MDR-TB and diabetes is a significant cause of ineffective treatment and for a steady increase in the level of disability and mortality of the working population, which entails huge unreasonable costs from the state budget.

It is easy to trace a clear trend towards an increase in the proportion of TB recurrences, the role of combined pathology and chemoresistance in the structure of TB incidence. An even more obvious fact is that these three factors are interrelated and have an undeniable influence on each other.

Thus, with the increasing prevalence of diabetes worldwide and the maintenance of high incidence of MDR-TB, we can expect that the number of people with combined TB and diabetes pathology will increase significantly in the coming decades.

The association between diabetes and TB can be the next challenge in global TB control worldwide, and absence of a timely diagnosis can have a major impact on quality of life and economic productivity. Despite the active participation of states and the world community in the fight against TB, the desired results have not been achieved, primarily due to changes in the structure of the TB disease itself. The combination of MDR-TB/DM significantly worsens the course and prognosis of the latter, as proved by our prospective study.

Conclusions

(1) There is a clear tendency of increasing the combined pathology (MDR-TB/DM) and chemoresistance when we mention the incidence of TB, and also an increasing proportion of recurrences of TB in the presence of DM.

(2) Pulmonary TB developed significantly more often in middle-aged patients ($P < 0.05$) with type 2 DM with moderate and severe states and the subcompensated form, with a complicated course. In patients with diabetes a common tuberculous process in the lungs (79.5% of patients) was registered more often and in all 100% of patients with syntropy, bacterial excretion was registered.

(3) The clinical picture of TB in most patients with diabetes noted manifestations of severe intoxication and bronchopulmonary syndromes, moderate changes in clinical blood tests (accelerated ESR, anaemia and lymphopenia) and high blood sugar.

(4) The rate of successful treatment for the presence of MDR-TB/diabetes syntropy is lower in the main group (61.4% vs. 64.7%; $P < 0.05$). However, a more significant probable difference is characterised by the treatment rate, which in the main group is 27.3% vs. 40.3% in the control group (almost two times; $P < 0.05$). The rate of ineffective treatment in patients with comorbidity was 27.3% (almost every third patient) as against 17.6% in the control group.

Conflicts of Interest

The authors declare no conflict of interest regarding this article.

Compliance with Ethics Requirements

The work was performed according to the requirements that govern researches involving the participation of people – i.e. in compliance with the following statutory provisions and other provisions: Articles 28, 49 and 52 of the Constitution of Ukraine; Articles 6, 7 and 8 of the Law of Ukraine 'On Medicines'; the norms applicable in international practice; ethical standards in the Helsinki Declaration (1964–2013) and those promulgated by the Council of Europe Convention of Human Rights and Biomedicine (1997); EU Directives 2010/63 'On the protection of animals, it is used for scientific purposes'; orders of the Ministry of Health of Ukraine No 249, 01.03.2012; Statute of the Ukrainian Association of Bioethics and Norms GCP (1992); and the requirements and norms of ICH GLP (2002).

Informed consent was obtained from all the patients included in the study.

Authors Contributions

Not applicable

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