Topicality of the problem of combined course of multi-drug resistant pulmonary tuberculosis with diabetes mellitus

O. M. Raznatovska¹, Yu. M. Bobrovnych-Dvizova¹, S. B. Norejko², N. A. Gricova³

¹Zaporizhzhia State Medical University, Ukraine, ²Bogomolets National Medical University, Kyiv, Ukraine, ³Shupik National Medical Academy of Postgraduate Education, Kyiv, Ukraine

According to the World Health Organization, today in the world among the infectious chronic diseases one of the leading places and causes of death is multi-drug resistant tuberculosis of the lungs, and chronic non-communicable diseases – diabetes mellitus. The situation is complicated by the fact that the number of patients with combined course of these two heavy separate illnesses that complicate each other increases. It is established that with increasing severity of diabetes mellitus, tuberculosis process in the lungs becomes more complicated and deteriorates, and vice versa, the specific process complicates the course of diabetes mellitus, contributing to the development of diabetic complications. Against this background, the effectiveness of treatment of patients suffering from multi-drug resistant tuberculosis of the lungs in our country remains very low, mainly due to the toxic adverse reactions to antmycobacterial drugs of the reserve line, and in the case of adding diabetes mellitus, it deteriorates even more.

The aim of this study was to review the scientific literature to determine the relevance of the study of combined course of multi-drug resistant tuberculosis of the lungs with diabetes mellitus and perspectives of innovative methods of diagnosis of diabetes mellitus. Early diagnosis of pre-diabetes, and autoimmune diseases will allow the use of timely correction techniques that prevents the development of diabetes mellitus, depending on its type, and in the future the development of serious irreversible processes, allow timely applying appropriate methods of correction of the revealed violations.

Results. Very little amount of work is dedicated to the problem of combined course of multi-drug resistant tuberculosis of the lungs with diabetes mellitus, regardless of its type, the theme is relevant for today, in Ukraine there are no data regarding its study. This combined course of very difficult in the treatment diseases requires not only timely and early diagnosis of autoimmune diseases associated with diabetes mellitus type 1 and pre-diabetes, but also additional complex combined therapy.

Key words: multidrug-resistant tuberculosis, pulmonary tuberculosis, diabetes mellitus.

Огляди

Актуальність проблеми поєднаного перебігу мультирезистентного туберкульозу легень із цукровим діабетом

О. М. Разнатовська, Ю. М. Бобровниччина-Двізова, С. Б. Норейко, Н. А. Грицова

За даними Всесвітньої організації охорони здоров'я (ВООЗ), сьогодні в усьому світі серед інфекційних хронічних захворювань одне з провідних місць і причин смерті посідає мультирезистентний туберкульоз легень, а неінфекційних хронічних захворювань – цукровий діабет. Ситуація ускладнюється тим, що збільшується кількість пацієнтів із поєднанням перебігом цих двох тяжких поєднаних захворювань, які ускладнюють одне одного. Так, встановлено, що під час збільшення ступеня тяжкості цукрового діабету ускладнюється та стає важким перебіг туберкульозного процесу в легенях, і, навпаки, специфічний процес ускладнює перебіг цукрового діабету, сприяючи розвитку діабетичних ускладнень. На цьому тлі ефективність лікування хворих на мультирезистентний туберкульоз легень у нашій країні залишається дуже низькою, переважно внаслідок токсичних побічних реакцій на антимікобактеріальні препарати резервного ряду, а при приєднанні цього діабету вона значно знижується.

Мета роботи – огляд наукової літератури щодо встановлення актуальності вивчення поєднаного перебігу мультирезистентного туберкульозу легень із цукровим діабетом і перспектив інноваційних методів діагностики цукрового діабету.

Встановлено, що рання діагностика предіабету й аутоімунних захворювань дасть можливість застосувати своєчасні методи корекції, що запобігатиме розвитку цукрового діабету залежно від його типу, а надалі – тяжких незворотних процесів, своєчасно застосувати відповідні методи корекції виявлених порушень.

Висновки. Проблеми поєднаного перебігу мультирезистентного туберкульозу легень із цукровим діабетом (незалежно від його типу) присвячено дуже мало робот, тому тема має актуальну сьогодні, а в Україні відсутні дані щодо її вивчення. Такий поєднаний перебіг дуже складних у лікуванні захворювань потребує не тільки своєчасної та ранньої діагностики, але й додаткової складної комплексної терапії.

Key words: мультирезистентний туберкульоз легень, цукровий діабет.
According to the World Health Organization (WHO), today in the world among the infectious chronic diseases one of the leading places and causes of death is multi-drug resistant tuberculosis (MDRTB) of the lungs, and chronic non-communicable diseases – diabetes mellitus (DM) [22,23]. The situation is complicated by the fact that the number of patients with combined course of these two heavy separate illnesses that complicate each other increases. It is established that with increasing severity of diabetes mellitus, tuberculosis process in the lungs becomes more complicated and deteriorates, and vice versa, the specific process complicates the course of diabetes mellitus, contributing to the development of diabetic complications [1–3]. Against this background, the effectiveness of treatment of patients suffering from MDRTB of the lungs in our country remains very low, mainly due to the toxic intoxication. In the patients with both types of DM in the early stage of tuberculous intoxication, a common specific destructive (100 %) infiltrative process in the lungs with the prevalence of cavities up to 2 cm in diameter. In this case the patients were mostly aged from 19 to 29 years. In patients with DM type 2, on the contrary, MRTB of the lungs develops mainly in the first 4 years after the diagnosis of DM, the patients are primarily older than 50 years, and the specific process in the lungs is characterized by a predominance of fibro-cavernous forms with cavities of more 4 cm in diameter on the background of moderately expressed tuberculous intoxication. In the patients with both types of DM in the early antimycobacterial treatment, decompensation of carbohydrate metabolism is defined, correction of which was held with insulin therapy in both groups. The authors additionally used also a variety of pathogenic agents (angioprotectors, heparin and drugs to eliminate side reactions due to the action of antimycobacterial therapy), symptomatic treatment, plasmapheresis, laser- and colapsotherapy. However, against such a massive complex treatment, the authors determine that the effectiveness of therapy in terms of cessation of bacterial excretion was not significantly different depending on the type of DM and accounted for 67–75 %, and according to the healing time, degradation was significantly faster for 1 month in patients with combined course of DM type 1, due to the young age of patients and the nature of the specific process in the lungs.

Thus, in the case of pulmonary tuberculosis with preserved sensitivity, a concomitant DM type 1 has an aggressive character, and DM type 2 has more favourable course due to the following factors. According to the aetiology of the classification of DM by WHO [21], DM type 1 is characterized by the destruction of Β-cells leading to absolute insulin deficiency, and DM type 2 – from predominant insulin resistance with relative insulin deficiency to pre-

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dominant secretory defect with insulin resistance or without it. It means that on the basis of DM type 2 there is insulin resistance on the background of preserved ability of β-cells to secrete insulin. After all, the complex treatment of patients with combined course of MDRTB of the lungs and DM, which includes the correction of carbohydrate metabolism and diversity of additional pathogenetic and symptomatic drugs against the background of antituberculous therapy is more effective in the case of combination with DM type 1, despite its aggressiveness.

As it is known, insulin is a major regulator of carbohydrate, lipid and protein metabolisms in the body. With insufficient insulin, glycogenolysis stimulates in the liver, thereby hyperglycaemia develops. The latter, in turn, causes glycosylation of proteins and lipids with the formation of end products.

According to V. N. Titov and Yu. K. Shyryaeva (2011) [9], one of the negative consequences of hyperglycaemia is the development of systemic inflammatory response syndrome of the organism, which is strongly marked in patients suffering from pulmonary tuberculosis even without concomitant DM.

After the review of the scientific literature on pathophysiological factors of the adverse effects of DM on the course of pulmonary tuberculosis, O. G. Kaminska-ya and R. Yu. Abdullayev (2014) [10] in their scientific article concluded that today established relevance of hyperglycaemia in the development of DM is unquestionable, as it facilitates the launch of a number of the adverse pathophysiological mechanisms which are interrelated and exacerbate each other – it is called oxidative stress, chronic vasculitis, progressive atherogenesis, angiopathy, hypercoagulability syndrome. The majority of these mechanisms are associated with pulmonary tuberculosis.

Today the importance of the definition of prediabetes which involves disorders of carbohydrate metabolism: impaired glucose tolerance (per-oral glucose tolerance test (2 hours after taking 75 g of glucose) ≥7.8 mmol/l), impaired fasting glycaemia (level of glucose in plasma of venous blood ≥6.1 mmol/l and <7 mmol/l) [4,11].

Insulin resistance is one of the links in the genesis of disorders of glucose tolerance and is determined by the disruption of normal transmission of insulin on insulin-dependent cells [10]. It has been proven and substantiated that insulin resistance against the normal insulin level together with periodic hyperglycaemia are factors of stimulation of β-cell function insular apparatus of the pancreas and its depletion [12].

Therefore, the deterioration of insulin secretion and insulin resistance are the trigger mechanisms for the development of DM type 2 and pre-diabetes is the initial stage of it.

T. V. Smurova and S. I. Kovaliova (2007) [13] indicate that violations of all types of metabolism in patients suffering from DM type 2 lead to the accumulation of a large number of substances which stimulate the development of MBT. Ketosis is a cause of infringement of oxidative processes in the body, disruption of phagocytic activity of alveolar macrophages, inhibition of phagocytosis, etc.

It was established experimentally that the progression of tuberculosis correlates with a decrease in the mass of the pancreas and the number of β-cells in its insular apparatus and specific process without DM is accompanied by hyperinsulinemia [10].

Thus, the infectious process in the insolvency of the insular apparatus can provoke disturbance of carbohydrate metabolism, and the more widespread is the infection, the greater are insulin requirements [1]. Therefore, in the case of specific endogenous intoxication in patients with pulmonary tuberculosis, increased need for insulin is one of the first diagnostic signs of the presence of DM.

Combined course of tuberculosis and DM causes profound disruptions of the immune system by stimulating humoral immunity which is the cause of progression of the specific process [13].

G. G. Bayburina (2011) [14] conducted a study of immunological markers of DM in patients on newly diagnosed DM, depending on its type: antibodies to insulin and proinsulin (IAA-insulin autoantibodies, AB-IAA), antibodies to glutamate decarboxylase (GAD-glutamic acid decarboxylase autoantibodies, AB-GAD), antibodies to cytoplasmic antigen of β-cells (ICA-islet-cell antibodies, AB-ICA). These studies were carried out to establish their association with clinical symptoms, indicators of functional activity of β-cells of the pancreas (level of basal C-peptide and fasting insulin) and indicators of lipid profile (total cholesterol, α-cholesterol, triglycerides, calculation of atherogenic coefficient). The researcher found out that among patients with DM type 1, immunopositive were 93.8 % of patients aged to 30 years and 68.6 % – in the age category of 31–50 years. The most significant and reliable indicators among the immunological markers were high titres of AB-GAD and AB-ICA. Thus, against the background of expressed clinical picture of DM, increasing of titre of immunological markers and decreasing in the level of basal C-peptide, indicators of lipid spectrum and body mass index remained in the normal range. DM type 2 was characterized by the following: immunopositive were 47.5 % of patients (due to the growth of titres AB-IAA and AB-GAD) against the background of normal values of indicators of the functional activity of β-cell of the pancreas and elevated levels of the lipid spectrum (total cholesterol and triglycerides). A direct correlation between all indicators of immunological markers with atherogenic coefficient was established; it allowed making conclusion about the dependence of immunological disorders with a state of fat metabolism. For DM type 2 a characteristic feature is the tendency to develop cardiovascular complications.

Thus, diabetes without concomitant TB, depending on the type of the following is true. For type 1: marked clinical manifestations associated with a predominant increase in titres of at-GAD and al-ISA and the decrease in the level of basal C-peptide. For type 2 – the growth of credits at IAA and at-GAD, levels of the lipid spectrum (total cholesterol and triglycerides) and body mass index between which there is a direct correlation, the tendency to develop cardiovascular complications. However, in literature any works have found on similar studies in the case of co-morbid course of MDRTB of the lungs and DM.

The analysis of literary sources showed that researches all around the world regarding the diagnosis and treatment of DM with different types do not tread water. In 2011 innovations in the diagnosis of MD was the fact that WHO adopted the diagnostic levels of glycosylated (glycated) hemoglobin (Hb) to arrive at diagnosis of DM. Thus, the level of HbA1c <5.7 % is a norm, at its level between 5.7–6.4 % – the risk of developing DM and ≥ at its level >6.5 % – they arrive
to diagnosis of DM [15,22]. This approach allows not only the early diagnosis of diabetes, but also to promptly apply preventive measures in high-risk groups, preventing the development of this severe disease.

In levels of glycosylated Hb, blood glucose and glycosuria there are three levels of violation of carbohydrate metabolism [15,23]:

1. Compensated: the level of glycosylated Hb from 6 to 7 %, fasting glucose up to 6 mmol/l and after meals up to 8 mmol/l in the absence of glycosuria.
2. Sub-compensated: the level of glycosylated Hb from 7.1 to 7.5 %, fasting glucose from 6.1 to 6.5 mmol/l and after meals from 8.1 to 9 mmol/l, glycosuria (+).
3. Decompensated: the level of glycosylated Hb above 7.5 %, fasting glucose above 6.5 mmol/l and after meals above 9 mmol/l, glycosuria (+++).

Molecular genetic methods of diagnostics allow timely and quickly detecting different variants of DM that require different kinds of treatment. Thus, V. E. Tytovych et al. (2010) [16] as a result of 11 years of research of contributory and protective gal types (HLA-DRB1, DQ genes) in combination with immunological markers (AB-ICA, AB-AA and AB-GAD) found the risk of developing DM type 1 which suggests that the presence in healthy sibs DQ-2, DQ-8 of gal types predicts a high risk of its development. And among those who have already got sick with DM type 1 in the initial stages, a high titre of all immunological markers revealed. Therefore, the researchers came to the following conclusion that the assessment of the risk of developing DM type 1 on the basis of molecular-genetic and monitoring of immunological markers is a stage in the development of preventive measures aimed at prevention of the development of the disease.

Today it is found out that one-third of cases of DM type 1 is accompanied by other endocrine and not endocrine autoimmune diseases that influence the degree of its compensation [17]. It is established that on the basis of most autoimmune diseases is the violation of T-cell immunity, which leads to destruction of tissue, atrophy of the organ and reduction of hormone production. The leading place among these diseases is autoimmune thyroiditis (up to 30 % of cases), followed by frequency of development by autoimmune gastritis – antibody to parietal cells of the stomach (PCA), autoimmune hepatitis – antipodal Azov AO (AGMA) and at antinuclear (ANA).

It was found out that patients in the initial stages of DM type 1 with the growth of titre AB-GAD, AB TPO are detected [17], while the function of the thyroid gland is not violated. M. Prazny et al. (2005) [25] indicate that excess production of thyroid hormones leads to impairment of glucose uptake and acceleration of gluconeogenesis and glycogenolysis in the liver, and this leads to the development of insulin resistance. K. Vondra et al. (2005) [26] found out that hyperthyrosis in patients with DM type 1 is a cause for the development of ketoadiposis.

V. F. Fadeyev et al. (2006) [19] conducted studies and recommend using determination of the titre rTTH by the method of radio-receptor assay in clinical practice for the diagnosis of autoimmune thyroiditis.

In the literature some works were found devoted to the study of thyroid pathology in patients with pulmonary tuberculosis in Ukraine. Thus, S. L. Matveyeva (2017) [20] in order to diagnose autoimmune thyroiditis was studying the levels of free thyroxin (v. T4), AB rTTH, AB to thyroglobulin (AB TG) and AB TPO. According to the data obtained she established that in patients suffering from pulmonary tuberculosis with concomitant DM in 66.67 % of cases autoimmune thyroiditis with symptoms of subclinical hypothyroidism is diagnosed, which negatively affects both the clinical course of tuberculosis, and the result of antitubercular treatment.

Thus, early diagnosis of pre-diabetes, and autoimmune diseases will allow the use of timely correction techniques that prevents the development of DM, depending on its type, and in the future the development of serious irreversible processes, allow timely applying appropriate methods of correction of the revealed violations.

Conclusions

1. Very little amount of work is dedicated to the problem of combined course of MDRTB of the lungs with DM, regardless of its type, the theme is relevant for today, in Ukraine there are no data regarding its study.

2. This combined course of very difficult in the treatment diseases requires not only timely and early diagnosis of autoimmune diseases associated with DM type 1 and pre-diabetes, but also additional complex combined therapy.

Prospects for further scientific researches. Further study of pathophysiological, biochemical and immunological disorders in the case of co-morbid course of MDRTB of the lungs with DM, improving the corrective therapy, the development of ways to prevent the development of DM in patients suffering from MDRTB of the lungs with the presence of risk factors, etc.

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ISSN 2306-8027 http://pat.zsmu.edu.ua 239


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Griçova N. A., MD, PhD, Associate Professor, Professor of the Department of Phthisiology and Pulmonology, Shupik National Medical Academy of Postgraduate Education, Kyiv, Ukraine.