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Impact of diabetes comorbidity on outcome of pulmonary tuberculosis

Objective – to assess the impact of diabetes mellitus on anti-tuberculosis treatment outcome in patients with pulmonary tuberculosis.

Materials and methods. A retrospective, selective, descriptive study which included 119 adults with pulmonary tuberculosis confirmed by the microbiological assay GeneXpert MTB/Rif was performed. The general group was distributed in the study group (SG) which included which 34 patients were diagnosed with 2nd type DM and control group (CG) which included 85 patients never diagnosed with DM or disturbances of glucose metabolism or DM. In 15 (44%) patients of the SG the DM was diagnosed at the same time as TB and 19 (56%) were diagnosed before tuberculosis with DM. The patients were registered in the period 2014–2016 in the Municipal Hospital of Pneumophthisiology of Chişinău in the Republic of Moldova. The investigational schedule included information about anamnesis, clinical examination, results of the radiological and microbiological investigations performed according to the National Clinical Protocol. Statistical methods used were comparative, synthesis and discriminated analysis.

Results and discussion. Tuberculosis and diabetes represents an epidemiological challenge. In the Republic of Moldova 12.3% of the population suffers from diabetes or reduced tolerance to glucose and almost 5% of cases with pulmonary tuberculosis are diagnosed with diabetes. Starting with 2018 the patients with diabetes are actively annually screened for tuberculosis and the rate of patients detected by that way achieved 65%. The research demonstrated that diabetes mellitus with disease related complications being more than 45 years old are at high risk for tuberculosis. Poor treatment outcome (death 17%, treatment default 15% and failure 9%) could be explained by the comorbidity-related complications.

Conclusions. Risk factor for acquiring tuberculosis in patients with diabetes mellitus is the disease itself and the related complications, as well the age more than 45 years old. More frequently the patients with diabetes were detected by active screening and had unfavorable disease outcome.

Key words

Tuberculosis, risk factors, diabetes mellitus.

Diabetes mellitus (DM) is an important public health, one of four priority non-communicable diseases targeted by the development goals, leading to a high rate of complications and premature death [7, 8]. In the Republic of Moldova (RM) every 10th citizen suffers from disturbances of glucose metabolism [6]. The mortality by DM was 11.5/100,000 in 2015 in RM [5]. Patients with both types DM represent one of the high risk for tuberculosis and should be screened annually in RM [1]. The evolution of tuberculosis in DM is unfavorable

due to disturbances of glucose metabolism [4]. Late detection and late onset of the therapy, dietary errors and inadequate treatment represent the cause of the worsening of TB process under the specific treatment [3]. The antidiabetic therapy in TB patients should be individualized and depends on the patient's state, the disease extensibility and the severity of DM. Each patient with DM should be hospitalized for the anti-TB treatment. First of all, it is necessary to compensate the metabolic disorders with a physiological diet and optimal dose of anti-TB drugs. The anti-TB treatment should be administrated with caution due to high rate of adverse drug reaction and the treatment

Table 1. Distribution in groups according to the sex, age and demographic characteristics

Groups	Indices	PTB&DM	PTB	p
		n = 34	n = 85	
Sex	Men	21 (62.0%)	61 (71.1%)	> 0.05
	Women	13 (38.2%)	24 (28.3%)	> 0.05
Age	18–44 y.o.	6 (18.0%)	52 (62.0%)	< 0.001
	> 44 y.o.	28 (82.0%)	25 (29.0%)	< 0.001
Demographic	Urban	17 (50.0%)	41 (48.0%)	> 0.05
	Rural	17 (50.0%)	38 (45.0%)	> 0.05
	Homeless	0	6 (7.0%)	> 0.05

should be strictly monitored [2]. The aim was to establish the impact of DM on acquiring TB and the final outcome.

Materials and methods

Was performed a retrospective, selective, descriptive study which included 119 adults with pulmonary tuberculosis confirmed by the microbiological assay GeneXpert MTB/Rif. The general group was distributed in the study group (SG) which included which 34 patients were diagnosed with 2nd type DM and control group (CG) which included 85 patients never diagnosed with DM or disturbances of glucose metabolism or DM. In 15 (44%) patients of the SG the DM was diagnosed at the same time as TB and 19 (56%) were diagnosed before tuberculosis with DM. In all patients with diabetes were diagnosed different types of diabetes-related complications. The patients were registered in the period 2014–2016 in the Municipal Hospital of Pneumophtisiology of Chişinău, Republic of Moldova. The investigational schedule included information about anamnesis, clinical examination, results of the radiological and microbiological investigations performed according to the National Clinical Protocol. Statistical methods used were comparative, synthesis and discriminated analysis. The research was approved by the bioethical university committee nr. 14, 15/10/2015. The predictability value of the involved factors was calculated using two by two tables.

Results and discussion

Assessing general, social and economical peculiarities it was established the statistical predominance of male vs female in both groups: 21 (61.8%) vs 13 (38.2%) in SG group and 61 (71%) vs 24 (28%) in CG, male/female ratio = 1.6/1 in SG and 2.5/1 in CG (table 1). Young patients, less than 44 years old, predominated in the CG 52 (62%) vs 6 (18%) in SG and older than 45 years in the SG 28 (82%) vs 25 (29%) patients in the CG. So age

45 years old and more was a high risk factor for TB in patients with diabetes mellitus (OR = 11.2; CI 95%: 5.8–60). A similar distribution in subgroups according to the demographic characteristics was identified in both groups, however homeless patients were established only in the CG.

Distribution by economic groups established that employed patients predominated in the SG 14 (41%) vs 21 (24%) in the CG, unemployed predominated in the CG 56 (61%) vs 8 (23%) in the SG, retired persons predominated in the SG 8 (23%) vs 8 (9%) in the CG, as well persons with disabilities: 4 (12%) in the SG vs 7 (8%) in the CG. By studying the civil status it was identified a statistical higher rate of married persons in the SG 16 (47%) vs 15 (18%) in the CG, as well of the divorced and widowed 10 (29%) in the SG vs 22 (7%) in the CG. Single patients predominated in the CG due to the young age 58 (57%) vs 8 (23%) in the SG. When assessing the educational level it was established that one half of both groups graduated general school. The incomplete general educational level was more frequently identified in the CG 24 (28%) vs 6 (18%) cases in the SG. Higher educational level was established in a limited number of cases in both groups (table 2).

The risk groups with epidemiological impact were: migrants 6 (18%) in the SG vs 16 (19%) in the CG, persons previously incarcerated were 13 (15%) in the CG (table 3). Exposure to a source of the TB infection predominated in the SG 11 (53%) vs 25 (29%) in the CG and was established as a low risk factor (OR = 1.1; CI 95% 0.5–2.7). All cases from the SG and 36 (41%) in the CG had associated diseases, which were a high risk factor (OR = 45; CI 95% 42–48) for TB in diabetic patients. Active tobacco smoking and alcohol drinking prevailed in the CG: 63 (74%) vs 13 (39%) in the SG, and respectively 38 (45%) in the CG vs 7 (21%) in the SG.

The most of the patients from SG were detected by high risk groups screening, as recommended by

Table 2. Distribution in groups according to the economic, marital and educational level

Groups	Indices	PTB&DM	PTB	p
		n = 34	n = 85	
Economic	Employed	14 (41.0%)	21 (25.0%)	< 0.001
	Unemployed	8 (23.0%)	52 (62.0%)	< 0.001
	Retired	8 (23.0%)	8 (9.0%)	> 0.05
	Students	0	5 (6.0%)	> 0.05
	Disease disability	4 (12.0%)	7 (8.0%)	> 0.05
Marital	Single	8 (23.0%)	48 (57.0%)	< 0.001
	Married	16 (47.0%)	15 (18.0%)	< 0.001
	Divorced/widowed	10 (29.0%)	22 (7.0%)	< 0.001
Educational	Primary/illiteracy	2 (6.0%)	8 (9.0%)	> 0.05
	Incomplete secondary	6 (18.0%)	24 (28.0%)	> 0.05
	General	16 (47.0%)	34 (40.0%)	> 0.05
	Professional	6 (17.0%)	17 (20.0%)	> 0.05
	Superior	4 (12.0%)	2 (2.0%)	> 0.05

Table 3. Distribution in high risk groups

Groups	Indices	PTB&DM	PTB	p
		n = 34	n = 85	
High risk groups	Migrants	6 (18.0%)	16 (19.0%)	> 0.05
	Previously detained	0	13 (15.0%)	< 0.01
	Close TB contact	11 (35.0%)	25 (29.0%)	> 0.05
	HIV infection	1 (3.0%)	2 (3.0%)	> 0.05
	Associated disease	34 (100.0%)	36 (42.0%)	> 0.05
	Psychiatric disorders	1 (3.0%)	8 (9.0%)	> 0.05
Harmful habits	Tobacco smoking	13 (39.0%)	63 (74.0%)	< 0.001
	Alcohol abusers	7 (21.0%)	38 (45.0%)	< 0.001

Table 4. Distribution in high risk groups depending on Case-finding and Microbiological characteristics

Groups	Indices	PTB&DM	PTB	p
		n = 34	n = 85	
Case-finding	Passive case finding	12 (35.0%)	60 (71.0%)	< 0.001
	Active screening	22 (65.0%)	13 (15.0%)	< 0.001
	Directly addressed to the hospital	0	12 (14.0%)	< 0.01
Microbiological characteristics	Positive AFB microscopy	22 (64.0%)	61 (72.0%)	> 0.05
	Positive culture for MBT	24 (71.0%)	64 (75.0%)	> 0.05
	Xpert MTB/Rif	26 (77.0%)	76 (89.0%)	> 0.05

the national standard: 22 (64%) *vs* 13 (15%). As symptomatic cases were detected more often patients from the CG 60 (70%) *vs* 12 (14%). By direct addressing to the specialized hospital were detected only patients from the CG 12 (14%) (table 4). Microscopic AFB smear positive assays were identified in more than 2/3 of both groups: 22 (64%) *vs* 61 (71%). Positive culture results at conventional media (Lowenstein Jensen or BACTEC)

were established in 25 (71%) patients from the SG and 76 (89%) in the CG.

When identifying the clinical radiological characteristics of tuberculosis it was established that infiltrative forms was diagnosed in 28 (82%) cases in the SG compared with 76 (89%) in the CG. Disseminated forms of tuberculosis were identified in 4 (12%) cases of the SG and 8 (9%) cases of the CG. Fibro-cavernous TB was diagnosed in 2 (6.0%)

Table 5. Clinical and radiological characteristics and anti-tuberculosis outcome

Groups	Indices	PTB&DM	PTB	p
		n = 34	n = 85	
Case-finding	Infiltrative	28 (82.0%)	76 (89.0%)	> 0.05
	Dissemination	4 (12.0%)	8 (9.0%)	> 0.05
	Fibro-cavernous	2 (6.0%)	1 (1.0%)	> 0.05
Microbiological characteristics	Successfully treated	20 (59.0%)	66 (78.0%)	> 0.05
	Died	6 (17.0%)	3 (4.0%)	< 0.05
	Lost to follow-up/interruption	5 (15.0%)	8 (9.0%)	> 0.05
	Treatment failure	3 (9.0%)	5 (6.0%)	> 0.05

Table 6. Clinical characteristics and anti-tuberculosis outcome

Groups	Indices	Fisher exact	Indices			AR
		p	LR	RR	OR	%
Medical characteristics	Diabetes and complications	0	43	2,36 (1.84–3.02)	NA	58
	Age > 45 y.o.	0	28	8.81 (2.6–12.9)	11.2 (4.13–30.4)	28
Case management and outcome	Detected by screening	0	27	4.4 (2.46–7.87)	10.1 (4.1–25.4)	76
	Death	0.008	6	2.62 (1.49–4/59)	5.85 (1.37–24.9)	40

cases in the SG and 1 (1.3%) case in the CG. Anti-tuberculosis treatment outcome was statistically lower in the SG compared with the CG (table 5).

The rate of healed patients were lower in the SG 20 (59%) than in the CG 66 (77%) cases. Died more frequently patients from the SG 6 (17%) compared with 3 (3%) from the CG. Interrupted the anti-tuberculosis treatment more frequently patients from the SG 5 (15%) compared with 8 (9%) in the CG and failed the treatment 3 (8%) in the SG compared to 5 (5%) in the CG (table 6).

An important outcome of the research was the calculation of the likelihood ratio, odds ratio, relative risk and the attributable risk (AR). They were used for identifying the persons with diabetes which have the highest risk to develop tuberculosis. The hierarchy of risk factors according to the probability (likelihood ratio) to develop tuberculosis was the diabetes comorbidity and its complications and age more than 45 years old. Both characteristics were assessed as high risk factors, through the value of the relative risk and odds ratio. The patients with diabetes were more frequently detected by active screening and the statistical indices demonstrated that they are accessible for the primary healthcare providers. Even if the social and epidemiological risk factors predominated in the control group the risk for death in patients with diabetes.

At the end synthesis we can affirm that tuberculosis and diabetes represents an epidemiological challenge and important problem for the healthcare

system. In the Republic of Moldova, 12.3% of the population suffers from diabetes or reduced tolerance to glucose [6]. Nowadays, in the Republic of Moldova the rate of patients with pulmonary tuberculosis diagnosed with diabetes encounters almost 5.0% [6]. Starting with 2018 the patients with diabetes are included in the list of the high risk groups, which should perform the annual chest X ray in the frame of the active screening by the primary health care level. There are several risk factors which increase the risk for developing tuberculosis in diabetic patients: older age, HIV infection, male sex, smoking, alcohol addiction or substances abuse [3, 7]. If tuberculosis is detected earlier a more favorable outcome could be achieved. Our study demonstrated that diabetes mellitus has a strong influence on the tuberculosis outcome. Obtained results were similar with other studies, which identified a high rate of death. Poor treatment outcome could be explained by the comorbidity and related complications, as well due to the social determinants (unemployment, low income).

Conclusions

Risk factor for acquiring tuberculosis in patients with diabetes mellitus is the disease itself and the related complications, as well the age more than 45 years old. More frequently the patients with diabetes were detected by active screening and had unfavorable disease outcome (died, defaulted or failed the treatment).

No conflicts of interest.

Participation of authors: concept and research design — E. Lesnic, L. Todoriko; collection of material — O. Tafuni, A. Malic; collect of material — E. Lesnic; writing the text — E. Lesnic; statistical processing of data — O. Tafuni, A. Malic; editing text — E. Lesnic, L. Todoriko.

Bioethical committee acceptance was obtained on 28.02.2016, N 14, of Nicolae Testemitsanu State University of Medicine and Pharmacy Chisinau, Republic of Moldova.

The research was performed through an individual grant offered in the frame of the PhD study of Nicolae Testemitsanu State University of Medicine and Pharmacy Chisinau, Republic of Moldova.

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Вплив супутньої патології цукрового діабету на результати лікування туберкульозу легень

Мета роботи — оцінити вплив цукрового діабету (ЦД) на ефективність лікування у хворих на туберкульоз (ТБ) легень.

Матеріали та методи. Проведено ретроспективне, вибіркоче, описове дослідження, в яке було залучено 119 дорослих з активним ТБ легень, підтвердженим мікробіологічним аналізом GeneXpert MTB/Rif, які були зареєстровані в 2014–2016 рр. у муніципальній лікарні пневмофізіології м. Кишинева (Республіка Молдова). Пацієнтів розподілили на дві групи: дослідну — 34 пацієнти з ТБ легень і ЦД 2 типу та контрольну — 85 пацієнтів з ТБ легень, у яких ніколи не діагностували порушення метаболізму глюкози або ЦД. У 15 (44 %) пацієнтів ЦД діагностовано одночасно з ТБ, у решти — до верифікації діагнозу ТБ. Дизайн дослідження передбачав збір анамнезу, клінічне обстеження, рентгенологічні та мікробіологічні дослідження згідно із Національним клінічним протоколом. Статистичну обробку результатів проводили за допомогою програмного пакета Statistica 13 з використанням χ^2 -критерію і тесту Манна–Уїтні, а також порівняльних, синтезованих та дискретних методів.

Результати та обговорення. У Республіці Молдова відзначено епідемію ТБ і діабету: 12,3 % населення страждає на ЦД або має знижену толерантність до глюкози, майже у 5 % випадків ТБ легень діагностують ЦД. Починаючи з 2018 р., пацієнтів з ЦД, які належать до групи ризику, щорічно перевіряють на ТБ, кількість виявлених таким чином пацієнтів становить 65 %. Дослідження продемонстрували, що пацієнти з ЦД, який супроводжується ускладненнями в осіб віком понад 45 років, мають підвищений ризик захворювання на ТБ. Низьку ефективність лікування (смертність — 17 %, перерване лікування — 15 % та невдача лікування — 9 % випадків) можна пояснити ускладненнями перебігу коморбідної патології.

Висновки. Чинниками ризику виникнення ТБ у хворих на ЦД є захворювання та пов'язані з ним ускладнення, а також вік понад 45 років. Найчастіше пацієнтів із ТБ та супутнім діабетом виявляють за допомогою активного скринінгу. Відзначено низьку ефективність лікування і несприятливий прогноз перебігу туберкульозу при коморбідності з цукровим діабетом.

Ключові слова: туберкульоз, чинники ризику, цукровий діабет.

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Влияние сопутствующей патологии сахарного диабета на результаты лечения туберкулеза легких

Цель работы — оценить влияние сахарного диабета (СД) на эффективность лечения у больных туберкулезом (ТБ) легких.

Материалы и методы. Проведено ретроспективное, выборочное, описательное исследование, в которое были включены 119 взрослых с активным ТБ легких, подтвержденным микробиологическим анализом GeneXpert MTB/Rif, зарегистрированных в 2014–2016 гг. в муниципальной больнице пневмофтизиологии г. Кишинёва (Республика Молдова). Пациентов разделили на две группы: опытную — 34 пациента с ТБ легких и СД 2 типа и контрольную — 85 пациентов с ТБ легких, у которых никогда не диагностировали нарушение метаболизма глюкозы или СД. У 15 (44 %) пациентов СД диагностирован одновременно с ТБ, у остальных — до верификации диагноза ТБ. Дизайн исследования предусматривал сбор анамнеза, клиническое обследование, рентгенологические и микробиологические исследования согласно Национальному клиническому протоколу. Статистическую обработку результатов проводили с помощью пакета программ Statistica 13 с использованием χ^2 -критерия и теста Манна–Уитни, а также сравнительных, синтезированных и дискретных методов.

Результаты и обсуждение. В Республике Молдова отмечена эпидемия ТБ и диабета: 12,3 % населения страдает СД или имеет сниженную толерантность к глюкозе, примерно в 5 % случаев ТБ легких диагностируют СД. Начиная с 2018 г., пациентов с СД, относящихся к группе риска, ежегодно проверяют на ТБ, количество выявленных таким образом пациентов составляет 65 %. Исследования показали, что пациенты с СД, который сопровождается осложнениями у лиц старше 45 лет, имеют повышенный риск заболевания ТБ. Низкую эффективность лечения (смертность — 17 %, прерванное лечение — 15 % и неудача лечения — 9 % случаев) можно объяснить осложнениями течения коморбидной патологии.

Выводы. Факторами риска возникновения ТБ у больных СД являются заболевания и связанные с ним осложнения, а также возраст старше 45 лет. Чаще всего пациентов с ТБ и сопутствующим диабетом выявляют с помощью активного скрининга. Отмечена низкая эффективность лечения и неблагоприятный прогноз течения туберкулеза при коморбидности с сахарным диабетом.

Ключевые слова: туберкулез, факторы риска, сахарный диабет.

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Стаття надійшла до редакції 17 квітня 2019 р.