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EARLY MARKERS OF DIABETIC NEPHROPATHY IN CHILDREN WITH TYPE 1 DIABETES MELLITUS

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The purpose of the study was to reveal the markers for timely detection of diabetic nephropathy in children with type 1 diabetes mellitus. 54 children with type 1 diabetes mellitus were examined (mean age: 13.76±4.5 years; diseases duration: 5.68±3.7 years). Blood glucose, glycohemoglobin, blood urea, general analysis of urine, calcium, creatinine, protein, glucose in the urine and microalbuminuria were determined by laboratory tests. Conditions of kidney and liver were access by abdomen ultrasound. Results showed that in children with type 1 diabetes mellitus there was a positive correlation between microalbuminuria and disease duration ($r=+0.383$, $p=0.036$), urine glucose and the width of the right ($r=+0.82$, $p<0.05$) and left kidney ($r=+0.82$, $p<0.05$), thickening of the parenchyma ($r=+0.84$, $p<0.05$) and microalbuminuria ($r=+0.87$, $p<0.05$). According to the result of our study we recommend systematic monitoring of microalbuminuria and other informative affecting indicators to prevent progression toward diabetic nephropathy in children with type 1 diabetes mellitus.

Key words: type 1 diabetes mellitus, diabetic kidney disease, microalbuminuria, risk factors

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РАННІ МАРКЕРИ ДІАБЕТИЧНОЇ НЕФРОПАТІЇ У ДІТЕЙ ІЗ ЦУКРОВИМ ДІАБЕТОМ 1 ТИПУ

Метою дослідження було визначити маркери для своєчасного виявлення діабетичної нефропатії у дітей із цукровим діабетом 1 типу. Обстежено 54 дитини із цукровим діабетом 1 типу (середній вік 13,76±4,5 року, стаж захворювання 5,68±3,7 року). Лабораторно визначали глюкозу крові, глікогемоглобін, сечовину крові, загальний аналіз сечі, кальцій, креатинін, білок, глюкозу у сечі та мікроальбумінурію. Стан нирок та печінки оцінювали за допомогою ультразвукового дослідження черевної порожнини. Результати показали, що у дітей з цукровим діабетом 1 типу виявлено позитивну кореляцію між мікроальбумінурією та тривалістю захворювання ($r=+0,383$, $p=0,036$), між рівнем глюкози в сечі та товщиною правої ($r=+0,82$, $p<0, 05$) і лівої нирки ($r=+0,82$, $p<0,05$), потовщенням паренхіми ($r=+0,84$, $p<0,05$) та мікроальбумінурією ($r=+0,87$, $p<0,05$). Відповідно до результатів нашого дослідження, ми рекомендуємо систематичний контроль мікроальбумінурії та інших інформативних показників для запобігання прогресу діабетичної нефропатії у дітей з цукровим діабетом 1 типу.

Ключові слова: цукровий діабет 1 типу, діабетична ураження нирок, мікроальбумінурія, фактори ризику.

Diabetic nephropathy (DN) is one of the most severe complications of diabetes mellitus (DM), which can lead to early disability and death due to renal failure [1, 11]. The number of patients with DN, both in patients with type 1 and type 2 diabetes, is constantly increasing [10, 14]. It is known that this complication is 5–6 % in persons under 10 years of age, 20–25 % in persons under 20 years of age, 35–40 % in persons under 30 years of age and 45 % in persons under 40 years of age. The maximum peak of the disease occurs at 15–20 years [6].

There are 2 stages of diabetic nephropathy: microalbuminuria and macroalbuminuria with preservation of kidney function [13]. Currently, DN is diagnosed with the stage of microalbuminuria. It is generally accepted that microalbuminuria is recommended for diagnosis in patients with DM after 5 years of illness [15]. However, studies show that damage to the microvascular endothelium in patients begins earlier [5].

Kidney damage in DM is a progressive multifactorial process associated with metabolic, hemodynamic and genetic causes [8]. The initial provoking factor of all these processes is hyperglycemia, which leads to non-enzymatic glycolysis of proteins, activation of C-protein kinase and a cytotoxic effect [9]. Chronic hyperglycemia and glycemic instability lead to endothelial dysfunction of small vessels (arteries, arterioles, ducts, kidney loops), and, as a result, to micro- and macroangiopathies [3, 7].

Proteins, IgG, immune complexes are deposited in the basement membrane of the renal glomeruli, which leads to thickening of the basement membrane, changes in the structure and function of glomerular collagen, damage to other components of the glomerular matrix, which leads to diabetic nephropathy [11]. Systemic damage to the endothelium leads to an increase in the permeability of the endothelial layer for low molecular weight substances, which leads to capillary occlusion by a thrombus [7]. According to the hemodynamic theory, DM leads to impaired blood circulation in the kidneys, which leads to accelerated filtration [3]. There is a direct relationship between hyperglycemia and hyperperfusion. Thus, when hyperglycemia is high, hyperfiltration is also high. There is also a correlation between hyperfiltration and glycohemoglobin-HbA1c. Prolonged exposure to hydraulic pressure leads to hyperproduction of collagen,

primary sclerotic changes, disruption of glomerular architectonics, and increased basement membrane permeability [11]. All these stages are reversible. Chronic renal failure can be prevented by delay the progression of renal dysfunction to the stage of microalbuminuria [1]. Prevention of the occurrence of DN in type 1 diabetes mellitus (T1DM) was first shown in the DCCT study [4]. All of the above dictates the need to identify criteria for early diagnosis before the development of irreversible changes.

The purpose of the study was to reveal the markers for the timely detection of diabetic nephropathy in children with type 1 diabetes mellitus.

Materials and methods. 54 children with type 1 diabetes mellitus were examined. The diagnosis was confirmed according to the recommendation of the American Diabetes Association (ADA) [2]. The mean age of children was 13.76±4.5 years. The duration of diabetes was 5.68±3.7 years. To access the disturbance of metabolic indicators related to DM and renal function in all children, blood glucose, glycohemoglobin, blood urea, general analysis of urine, calcium, creatinine, protein in the urine and microalbuminuria were determined. Conditions of kidney parenchyma, thickness of kindey, size of the liver lobes were access by abdomen ultrasound. Microalbuminuria, creatinine, calcium, calcium/creatinine ratio in urine were checked using microalbuminuria tests (Teco Diagnostics, USA). Blood glucose was determined by Sapphire plus glucometer (Diab Medical Supplies, UAE), glycohemoglobin Clover A1C (Infopia Co Ltd, Korea), General urine analysis test strips (Teco Diagnostics, USA).

Statistical calculations were performed using the Statistica 14.0 statistical package. Quantitative features were subjected to statistical processing by calculating the arithmetic mean (M) and its standard error (SE). To predict the outcome of a dependent variable multiple linear regression method was used. The differences were considered as significant at $p<0.05$.

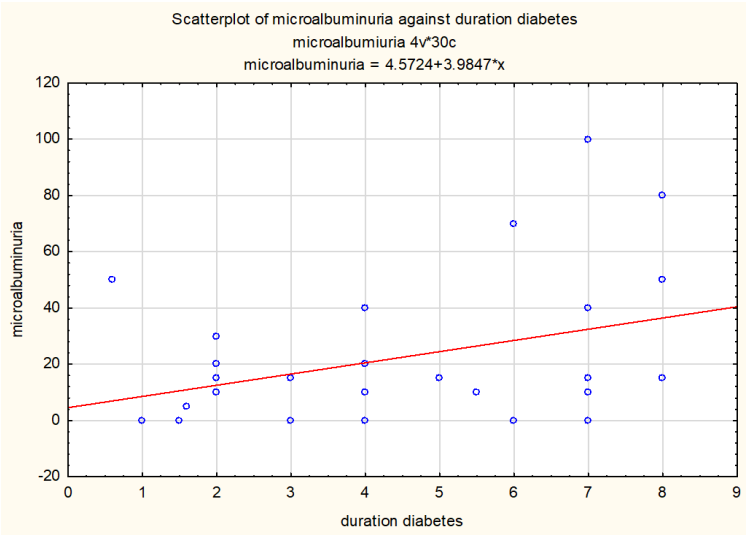

Fig. 1. Linear regression between microalbuminuria and disease duration.

Results of the study and their discussion. In 14.8 % of children (n=8), diabetic nephropathy was detected in the microalbuminuria stage.

Microalbuminuria was recorded at 21.66±25.5 mg/min, proteinuria at 0.005±0.02 %. The regression relationship between microalbuminuria and disease duration in patients was also studied, and this relationship is shown in fig. 1 below.

It was found that there was a positive correlation between microalbuminuria and disease duration ($r=+0.383$, $p=0.036$). Obviously, as the duration of the disease increases, changes in the permeability of the renal filter increase, which is accompanied by an increase in the level of microalbuminuria.

Other indicators of children in this group are given in table 1 below.

Increased glucose in the urine leads to a number of changes. Thus, an increase in urine glucose leads to an increase in the width of the right ($r=+0.82$, $p<0.05$) and left kidney ($r=+0.82$, $p<0.05$), an increase in the thickness of the left kidney ($r=+0.88$, $p<0.05$) and thickening of the parenchyma ($r=+0.84$, $p<0.05$), enlargement of the right lobe of the liver ($r=+0.86$, $p<0.05$), increase in blood pressure ($r=+0.82$, $p<0.05$) and microalbuminuria ($r=+0.87$, $p<0.05$). There is also a correlation between enlargement of the right lobe of the liver ($r=+0.95$, $p<0.05$), thickness of the left kidney ($r=+0.87$, $p<0.05$) and microalbuminuria, and these correlations are positive. As systolic blood pressure rises, microalbuminuria develops ($r=+0.84$, $p<0.05$). As the duration of diabetes increases, systolic blood pressure also increases ($r=+0.90$, $p<0.05$). An increase in protein in the urine also has a negative effect on the left kidney, as the width ($r=+0.81$, $p<0.05$) and thickness ($r=+0.94$, $p<0.05$) of the left kidney increase as the protein in the urine increases. The increase in the right lobe of the liver also occurs against the background of an increase in protein in the urine ($r=+0.86$, $p<0.05$). An increase in glycohemoglobin leads to an increase in calcium/creatinine ratio ($r=+0.88$, $p<0.05$). On the other hand, an increase in the calcium/creatinine ratio leads to a thickening of the parenchyma of the right kidney ($r=+0.88$, $p<0.05$). As the duration of diabetes increases, the above-mentioned changes occur against the background of a decrease in glycohemoglobin ($r=+0.82$, $p<0.05$).

Table 1

Laboratory indicators and indices of abdominal ultrasound examination in children included in the second group

Indices	Mean index and standard inclination
Systolic blood pressure, mm Hg	119.45±13.6
Diastolic blood pressure, mm Hg	76.45±10.38
Puls	91.90±11.5
Blood glucose, mg/dl	321.75±132.4
Glycohemoglobin –HbA1c %	10.76±3.2
Urine in the blood, mg/dl	3.61±2.4
Microalbuminuria, mg/l	8.33±30.8
Creatinine in urine, mg/dl	679.16±526.6
Calcium in the urine, mg/dl	45.83±14.1
Miroalbuminuria/creatinine ratio	0.002±0.005
Calcium/creatinine ratio	0.075±0.13
Urine glucose, mg	427.08±341.6
Acetone in the urine, mg	0.21±0.4
The specific gravity of urine	1021.08±4.8
Protein in the urine, mg	16.66±63.7
Enlargement of the right lobe of the liver, mm	0.90±1.04
The head of the pancreas, mm	20.0±4.8
The body of the pancreas, mm	15.85±2.92
Tail of the pancreas, mm	19.0±3.74
Length of right kidney, mm	99.16±10.7
Width of the right kidney, mm	43.62±6.7
Thickness of right kidney, mm	33.13±7.0
Parenchyma of the right kidney, mm	17.62±3.3
Length of left kidney, mm	102.33±13.2
Width of the left kidney, mm	47.12±10.3
Thickness of left kidney, mm	34.60±7.3
Parenchyma of the left kidney, mm	17.73±3.3

Multiple linear regression between urine glucose and systolic blood pressure, microalbuminuria, right kidney width, left kidney width, thickness, and parenchyma thickness is shown in fig. 2 below.

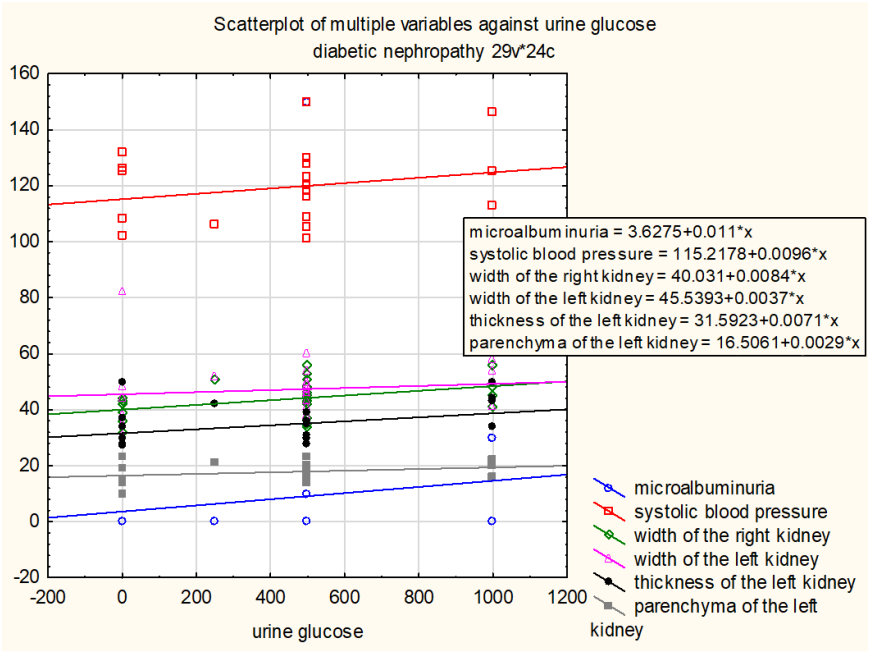

Fig. 2. Multiple linear regression between glucose in urine and a number of indices

The study found that there a number of strong correlation between microalbuminuria and some indicators in T1DM patients and this relationship is positive. Elevated blood glucose leads to an increase in the width of the right and left kidneys, an increase in the thickness of the left kidney and parenchyma, an increase in the right lobe of the liver, an increase in blood pressure and microalbuminuria.

The relationship of factors influencing the course of diabetes mellitus and changes the indicators characterizing diabetic nephropathy is an important task in preventing the early development of renal failure. Therefore, in our study, we focused on identifying the most informative of them, analyzing several indicators. We have confirmed that as the duration of the disease increases, there is an increase in microalbuminuria. Although this fact is indicated in many studies [1, 11, 15], however, there is an opposite point of view.

So, Montgomery KA et al. in their work, reported about the absence of progression of microalbuminuria in patients and even a return to normalbuminuria using repeated random spot urine tests in a single center study. According their results 72 % of type 1 diabetic children had regression to normoalbuminuria [9]. But the study of Montgomery KA et al. had limitations: retrospective nature of study design, and the fact that other affecting factors such as blood pressure, condition of kidney parehchyma, width of kidney etc. were not included as a variable.

In our work, unlike the previous author, we analyzed blood pressure, which gave us additional information about the negative impact of this factor - a positive correlation with microalbuminuria ($r=+0.84$, $p<0.05$).

Son MK et al. observing 109 T1DM patients revealed, that 23 patients had microalbuminuria at baseline, of them 13 (56.5 %) had regression of microalbuminuria, 10 (43.5 %) had persistent microalbuminuria, and 86 patients had no microalbuminuria at baseline, of them 9 (10.5 %) showed progression of microalbuminuria during follow-up period. But they founded lower HbA1c and higher C-peptide at baseline in regression group of T1DM [12]. It means that adequate control of glucose is important in diabetic patients, consistent with previous studies [4, 8, 14].

In this regard, we agree with the authors that elevated urinary microalbumin excretion in a single test does not imply irreversible diabetic nephropathy. Close monitoring and intensive control should be emphasized in children and adolescents with microalbuminuria to prevent or delay the progression of diabetic nephropathy.

In addition, an important factor is a comprehensive assessment of all indicators and the duration of the disease. In our study, this was done using multivariate linear regression, which increases the reliability of the results.

Other studies confirm the importance of glycemic assessment and level for predicting the development of DN. So, Kwon AR in a study of 270 patients with T1DM found that the mean HbA1c for 10 years was significantly higher in the patients with microvascular complications (10.5±2.8 % vs. 8.4±1.4 %). Moreover, the rate of intensive management in the non-complication group was higher than in the microvascular complication group [7].

It suggests the importance of frequent monitoring not only for microalbuminuria in diabetic children and adolescents, but also the other very informative risk indicators, which may lead to adequate intervention and, as a result, prevent progression toward diabetic nephropathy.

Conclusions

1. In children with T1DM there was a positive correlation between microalbuminuria and disease duration ($r=+0.383$, $p=0.036$).

Increased glucose in the urine has a number of correlative links with the some indicies, caracterized diabetic nephropathy: urine glucose and the width of the right ($r=+0.82$, $p<0.05$) and left kidney ($r=+ 0.82$, $p<0.05$); and thickening of the parenchyma ($r=+0.84$, $p<0.05$) and microalbuminuria ($r=+0.87$, $p<0.05$).

2. An increase in glycohemoglobin leads to an increase in calcium/creatinine ratio ($r=+0.88$, $p<0.05$). As the duration of diabetes increases, the above-mentioned changes occur against the background of a decrease in glycohemoglobin ($r=+0.82$, $p<0.05$).

According to the result of our study we recommend systematic monitoring of microalbuminuria and other informative affecting indicators to prevent progression toward diabetic nephropathy in children and adolescents with type 1 diabetes mellitus.

References

1. Alicic RZ, Rooney MT, Tuttle KR. Diabetic Kidney Disease: Challenges, Progress, and Possibilities. Clin J Am Soc Nephrol. 2017 Dec 7;12(12):2032-2045. doi: 10.2215/CJN.11491116.

2. American Diabetes Association Professional Practice Committee. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes–2022. Diabetes Care. 022;45 (Supplement_1):17–38 https://doi.org/10.2337/dc22-S002

3. Chawla A, Chawla R, Jaggi S. Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum? Indian J Endocrinol Metab. 2016 Jul–Aug;20(4):546–51. doi: 10.4103/2230-8210.183480.

4. de Boer IH; DCCT/EDIC Research Group. Kidney disease and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care. 2014;37(1):24–30. doi: 10.2337/dc13-2113.

5. Gil CL, Hooker E, Larrivée B. Diabetic Kidney Disease, Endothelial Damage, and Podocyte-Endothelial Crosstalk. Kidney Med. 2020 Dec 7;3(1):105–115. doi: 10.1016/j.xkme.2020.10.005.

6. Jensen ET, Stafford JM, Saydah S, D'Agostino RB, Dolan LM, Lawrence JM, et al. Increase in Prevalence of Diabetic Ketoacidosis at Diagnosis Among Youth With Type 1 Diabetes: The SEARCH for Diabetes in Youth Study. Diabetes Care. 2021 Jul;44(7):1573–1578. doi: 10.2337/dc20-0389.

7. Kwon AR, Lee S, Chae HW, Kim DH, Kim HS. Frequencies and related factors for microvascular complications in patients with type 1 diabetes. Ann Pediatr Endocrinol. Metab. 2012; 17: 16–26. doi: https://doi.org/10.6065/apem.2012.17.1.16

8. MacIssac RJ, Ekinci EI, Jerums G. Markers of and risk factors for the development of diabetic kidney disease. Am J Kidney Dis. 2014;63(2):39–62. doi: 10.1053/j.ajkd.2013.10.048.
9. Montgomery KA, Ratcliffe SJ, Baluarte HJ, Murphy KM, Willi S, Lipman TH. Implementation of a clinical practice guideline for identification of microalbuminuria in the pediatric patient with type 1 diabetes. Nurs Clin North Am. 2013 Jun;48(2):343–52. doi: 10.1016/j.cnur.2013.01.003
10. Reutens AT. Epidemiology of diabetic kidney disease. 2013 Jan; 97(1):1–18. doi: 10.1016/j.mcna.2012.10.001.
11. Ritz E. Clinical manifestations and natural history of diabetic kidney disease. Med Clin North Am. 2013 Jan;97(1):19–29. doi: 10.1016/j.mcna.2012.10.008.
12. Son MK, Yoo HY, Kwak BO, Park HW, Kim KS, Chung S, Chae HW, Kim HS, Kim DH. Regression and progression of microalbuminuria in adolescents with childhood onset diabetes mellitus. Ann Pediatr Endocrinol Metab. 2015 Mar;20(1):13–20. doi: 10.6065/apem.2015.20.1.13.
13. Sulaiman MK. Diabetic nephropathy: recent advances in pathophysiology and challenges in dietary management. Diabetol Metab Syndr. 2019; 11:7. doi:10.1186/s13098-019-0403-4
14. Tziomalos K, Athyros VG. Diabetic Nephropathy: New Risk Factors and Improvements in Diagnosis. Rev Diabet Stud. 2015 Spring-Summer;12(1–2):110–8. doi: 10.1900/RDS.2015.12.110.
15. Zhang J, Liu J, Qin X. Advances in early biomarkers of diabetic nephropathy. Rev Assoc Med Bras.. 2018 Jan; 64(1):85–92. doi: 10.1590/1806-9282.64.01.85.

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GENERAL DESCRIPTION OF PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA WHO PASSED AN OPEN COMPARATIVE STUDY

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The article provides a general description of the etiology and pathogenesis of patients with community-acquired pneumonia who passed an open comparative study at the Kharkiv Municipal Clinical Hospital No. 25. The most likely causative agents of community-acquired pneumonia in patients of the Therapeutic Department of the Kharkiv Municipal Clinical Hospital No 25 are *Streptococcus pneumoniae* and mixed cultures of bacteria, with an increase in the proportion of *Staphylococcus aureus.* In modern conditions, when choosing the tactics of antimicrobial therapy for community-acquired pneumonia, it is necessary to consider not only the spectrum of the most likely pathogens, but also the trends in the formation of antibiotic resistance in the leading etiological groups. It is impractical to prescribe empirical antibiotic therapy for community-acquired pneumonia without establishing an etiological diagnosis.

Key words: community-acquired pneumonia, etiology, pathogenesis, standard antibacterial therapy.

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ЗАГАЛЬНА ХАРАКТЕРИСТИКА ХВОРИХ ІЗ ПОЗАЛІКАРНЯНОЮ ПНЕВМОНІЄЮ, ЩО ПРОЙШЛИ ВІДКРИТЕ ПОРІВНЯЛЬНЕ ДОСЛІДЖЕННЯ

У статті представлено загальну характеристику з етіології та патогенезу хворих з позалікарняною пневмонією, які пройшли відкрите порівняльне дослідження у міській лікарні № 25 м. Харкова. Встановлено, що найбільш вірогідними збудниками позалікарняної пневмонії у хворих терапевтичного відділення 25-ї Міської клінічної лікарні міста Харкова є *Streptococcus pneumoniae* та мікст-культури бактерій зі збільшенням частки *Staphylococcus aureus*. У сучасних умовах при виборі тактики антимікробної терапії позалікарняної пневмонії необхідно враховувати не лише спектр найімовірніших збудників, а й тенденції формування антибіотикорезистентності провідних етіологічних груп. Абсолютно недоцільним є призначення емпіричної антибактеріальної терапії позалікарняної пневмонії без встановлення точного етіологічного діагнозу.

Ключові слова: позалікарняна пневмонія, етіологія, патогенез, стандартна антибактеріальна терапія.

The study is a fragment of the research project "Mucoactive and herbal medicines for the treatment of cough in acute infectious and inflammatory diseases of the lower respiratory tract", state registration No. 0117U000595.

Community-acquired pneumonia (CAP) is one of the most common diseases of infectious (mainly bacterial) etiology in people of all age groups and is accompanied with high mortality, especially among the elderly and newborns. For the first time, convincing evidence of the infectious nature of pneumonia was obtained in 1882–1883 by Friedlander, who found microbes in the lung tissue of more than 50 deceased patients [5].