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CLINICAL FEATURES OF PULMONARY ARTERIAL HYPERTENSION IN PATIENTS WITH CHRONIC DESTRUCTIVE LUNG TUBERCULOSIS COMBINED WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstract. ***Aim.*** To examine the role of NT-pro brain natriuretic peptide (NT-proBNP) interleykin 6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) as predictors for identification and severity of PAH in patients with CDLT+COPD. ***Material and methods***. Using diagnostic-based approaches included immunochemistry, high-resolution

computed tomography (HR-CT) Doppler echocardiography (Doppler-Eco) we characterized the biomarkers directly identifying the risk for development of PAH in patients with chronic lung tuberculosis, detection of cellular immune response. The risk for development of PAH in patients was learned by assessing of proinflammatory cytokines (IL-6, TNF-α) and proinflammatory peptides (CRP, NT-pro BNP). Depends on volume of irreversible morphological changes related lung tuberculosis all patients were divided in two groups: 1) 26 patients with CDLT+COPD and with PAH, 2) 25 patients with CDLT+COPD without PAH, 12 practically healthy individuals served as controls. All patients have been admitted to the Departments of Medical University. ***Results and discussion.*** Our data reveal that proinflammatory cytokines (IL-6, TNF-α) and proinflammatory peptides (CRP, NT-pro BNP) may play role as predictors for assessment of development severity of PAH in patients with CDTL and COPD. Our study also shown that the high level of proinflammatory cytokines and peptides were associated with more severe PAH in patients. In CDLT+COPD, lung parenchyma, bronchi vessels is involved in complex processes coupling the bronchopulmonary and cardiovascular systems. ***Conclusions***. Chronic lung inflammation with elevation of the level proinflammatory cytokines and peptides have critical contribution of lung parenchyma, bronchi and vessels remodeling and the fringe of nonreversible morphological changes in the lung at PAH in CDLT+COPD.
Key words: chronic obstructive pulmonary disease, chronic destructive lung tuberculosis, pulmonary arterial hypertension, cellular immune response, diaskintest, proinflammatory cytokines and peptides.
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КЛИНИЧЕСКИЕ ОСОБЕННОСТИ ЛЕГОЧНОЙ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ У БОЛЬНЫХ С ХРОНИЧЕСКИМ ДЕСТРУКТИВНЫМ ТУБЕРКУЛЕЗОМ ЛЕГКИХ В СОЧЕТАНИИ С ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНЬЮ ЛЕГКИХ

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Реферат. ***Цель*** – изучить роль N-терминального участка мозгового натрийуретического пептида (NT-proBNP), интерлейкина 6 (IL-6), фактора некроза опухоли-α (TNF-α) и С-реактивного белка (CRP) в качестве предикторов тяжести легочной артериальной гипертензии у пациентов с хроническим деструктивным туберкулезом легких и хронической обструктивной болезнью легких. ***Материал и методы***. Были обследованы пациенты с хроническим деструктивным туберкулезом легких и хронической обструктивной болезнью легких (*n*=51). В зависимости от морфологических изменений все пациенты были разделены на две группы: 1-я группа – 26 пациентов с хроническим деструктивным туберкулезом легких и хронической обструктивной болезнью легких и легочной артериальной гипертензией, 2-я группа – 25 пациентов с хроническим деструктивным туберкулезом легких и хронической обструктивной болезнью легких без легочной артериальной гипертензии. 12 практически здоровых людей составили группу контроля. С помощью иммунохимических методов были определены уровни провоспалительных цитокинов (IL-6, TNF-α) и провоспалительных пептидов (CRP, NT-pro BNP). Обследованным проводилась компьютерная томография высокого разрешения (HR-CT) и допплер-эхокардиография (Doppler-Echo) для оценки состояния паренхимы легких и степени легочной артериальной гипертензии. Для сравнения и определения значимости количественных различий в парных группах использовался непараметрический критерий Уилкоксона (Манна – Уитни), а между несколькими группами – критерий Крускала – Уоллиса. Корреляции между исследуемыми параметрами определены по критерию Спирмена. Расчеты были выполнены с использованием программного пакета SPSS 20. ***Результаты и их обсуждение.*** Наши данные показывают, что провоспалительные цитокины (IL-6, TNF-α) и провоспалительные пептиды (CRP, NT-pro BNP) могут играть роль предикторов оценки тяжести легочной артериальной гипертензии у пациентов с хроническим деструктивным туберкулезом легких и хронической обструктивной болезнью легких, так как коррелируют с более тяжелой легочной артериальной гипертензией. При хроническом деструктивном туберкулезе легких и хронической обструктивной болезни легких паренхима легкого, сосуды бронхов участвуют в сложных процессах взаимодействия бронхолегочной и сердечно-сосудистой систем. ***Выводы.*** Хроническое

воспаление легких с повышенными уровнями провоспалительных цитокинов и пептидов играет решающую роль в ремоделировании бронхов и сосудов, а также необратимых морфологических изменениях в легких при легочной артериальной гипертензии на фоне хронического деструктивного туберкулеза легких и хронической обструктивной болезни легких.
Ключевые слова: хроническая обструктивная болезнь легких, хронический деструктивный туберкулез легких, легочная артериальная гипертензия, клеточный иммунный ответ, Диаскинтест, провоспалительные цитокины и пептиды**.**

Для ссылки: Клинические особенности легочной артериальной гипертензии у больных с хроническим деструктивным туберкулезом легких в сочетании с хронической обструктивной болезнью легких / Д.М. Исмаилзаде, Р.И. Байрамов, З.Т. Гурбанова [и др.] // Вестник современной клинической медицины. – 2019. – Т. 12, вып. 6. – С.22–28. ***DOI:*** 10.20969/VSKM.2019.12(6).22-28.

Chronic destructive lung tuberculosis (CDLT) is one of the forms of pulmonary tuberculosis in clinical forms, is characterized by progressive course. Chronic obstructive pulmonary disease (COPD), regardless of the degree of severity, is manifested by a chronic inflammatory process with a predominant lesion of the distal respiratory tract and pulmonary parenchyma. For patients with COPD, a decrease in the maximum expiratory flow rate and a slow deterioration in the gas exchange function of the lungs are characteristic, which reflects the irreversible nature of airway obstruction. The etiology of COPD is directly related to the risk factors that cause the disease. COPD is a clinical example of a polygenic disease in which the effect of external risk factors is realized when there is a certain genetic predisposition. Certain diagnostic difficulties arise when a combination of pulmonary tuberculosis especially its chronic destructive forms, and COPD because of similar clinical manifestations of both diseases. In the presence of such a combination on the 1st place always exposed tuberculosis and assigns the appropriate chemotherapy for TB doctors (phthisiatricians) often forget this is no less urgent than pulmonary tuberculosis, another important disease – chronic obstructive pulmonary disease. As a result of inadequate treatment of COPD, frequent exacerbations of the disease occur, which are often perceived as exacerbations of a specific process and, correspondingly, accompanied by an intensification of the chemotherapy regimen. As a result of frequent exacerbation and constant progression of COPD, this category of patients often has complications of a combined pathology, one of which is pulmonary hypertension, often leading to the death of patients.

Annually 8,6 million new cases and 1,3 million deaths are attributed to tuberculosis [1]. The traditionally recognized clinical presentation of chronic lung tuberculosis is fibrocavitary disease [2]. During pulmonary tuberculosis (TB), proinflammatory cytokines (IL-6, TNF-α) rich to the inflamed lung [3]. T-cells regulation of immune response in lung tuberculosis is associated with accumulation of cytokines included IL-1, IL-6, IL-8, GC-SF, and monocyte chemoattractant factor (MCF-1), whereas production of granulocyte macrophage colony-stimulating factor and macrophage inflammatory protein-1 was reduced [4]. The implications of this are that local immune dysregulation can be responsible for disease manifestations.

One of most common symptoms of chronic and persistent lung tuberculosis is dyspnea [5]. In such patients, together with irreversible morphological changes in lung tissue (parenchyma) these changes may affect also lung vascularity and may developed vascular remodeling in pulmonary arteries [6]. This mechanism together with hypoxic vasoconstriction may play important role for development in of PAH in such patients [7, 8]. PAH is an established complication of CDLT and COPD [9, 10] and they have been demonstrated to be an independent risk factors for death [11]. Its prevalence depends on severity of irreversible morphological changes in lung parenchyma, and PAH typically occurs in a subpopulation of patients with CDLT and COPD with significantly morphological changes, when ventilation perfusion mismatching is severe and associated with hypoxia [12, 13]. During reference analysis we identified limited data related with some biomarkers which may play role as predictor for development and severity of PAH in patients with CDLT+COPD.

The **aim** of the present study was to describe the clinical, biomarkers and computed tomography (CT) characteristics of patients with CDLT+COPD with or without PAH.

Material and methods. Data were retrieved from all consecutive patients with CDLT+COPD older than 40 years of age who were referred to the tertiary unit of our university between January 2012 and May 2017 for complete examination of chronic respiratory failure and treatment. The study was performed in accordance with the ethical standards of the bioethical committee, developed in accordance with the Helsinki Declaration of the World Medical Association «Ethical Principles of Medical Research Involving Human Subjects» with the amendments of 2013 and the «Rules of Ethical Conduct of Medical Workers» approved by the Order (№ 137) of the Ministry of Health of the Republic of Azerbaijan dated 29.12.2011. The patients and persons of control group had to undergo a standardized panel of investigations, including carefully assembled histories, physical examinations, X-ray examination, explored the peripheral blood (complete blood count) and sputum examination on the presence of AFB. Detection of cellular immune response carried out using Diaskintest based on an evaluation of delayed-type hypersensitivity. We used the interdermal injection of Diaskintest at a dose of 2 mkg in 0,1 ml, containing ESAT6-CFP10 (Leceo, Russia) present in virulent strains of MBT. The reactions were evaluated visually after 72h and measured the size of induration in millimeters. The result were considered negative in the absence of infiltration, doubtful if hyperemia without infiltration, positive if there is infiltration (papules) of any size, hyperegic when the diameter of infiltration 15 mm and more, formation vesicle and necrosis and (or) the presence of lymphangitis, lymphadenitis. pulmonary

function test a (PFTs), arterial blood gas analysis, 6-minute walk test, blood tests (IL-6, TNF-α, CRP, NT-pro-BNP), transthoracic Doppler echocardiography, computed tomography, and right heart catheterization (RHC) for the purpose of our study, the inclusion criterion was a diagnosis of chronic lung tuberculosis based on characteristic symptoms (e.g. sputum smear and culture for mycobacterium tuberculosis, dyspnea, cough) associated with nonreversible morphological changes in lung tissue on HR-CT PFTs were assessed by using bodyplethysmography (Body Box, Hyp Air Compact). PH was defined as PAPm≥25 mmHg assessed by RHC. The diagnosis of COPD was established according to the recommendations of GOLD (2016) on diagnosis, treatment, the presence of risk factors for COPD and post bronchodilator FEV1 to FVC ratio of <70%. Spirometry with bronchodilator test (inhalation sympathomimetic with short-acting β2-agonist Ventolin «Glaxo Smith Kline») (gsk) – 2 doses = 20 μg) was used with measurement of bronchodilation response after 15 minutes. The spirometry study was performed using the Bodytest device (Erich Jaeger, Germany) and SPM – 300 (Bionet, South Korea) in accordance with the criteria proposed by the joint group of experts of the American Thoracic and European Respiratory Society (ATS/ERS).The actual values of the spirographic indexes, the registration of the P-FEV curve were compared with the predicted values developed by the experts of the European Community of Coal and Steel (1983) and evaluated the changes in indicators according to the GOLD recommendations. Proinflammatory cytokines (IL-6, TNF-α) and proinflammatory peptides (CRP, NT-pro BNP), high resolution computed tomography (HR-CT), Doppler echocardiography (Doppler Echo) and right heart catheterization (RHC), examination methods have been used in an effort to fulfill the assigned tasks.

Echocardiography (ECHO) examination was carried out with Aloka-1700 scanner (using 3mhz ultrasound transducer).

The concentration of IL-6 and TNF-α in blood serums is determined using a standard reagent kit produced by Human (Germany), by means of an immunoassay method, the principle of which is described above. The measurements have been carried out using an immunoassay analysis apparatus, STAT Fax 303 Plus, US.

The principle behind the method for determining the amount of CRP in a blood serum is based on the creation of an immune complex against it using the antibodies in a specific serum (latex reagent). This is accompanied by a visible agglutination of a latex reagent (Human, Germany).

The NUP concentration was determined with the help of a standard reagent kit produced by Human (Germany). This was carried out by using two-site, noncompetitive immunoassays method (also known as «sandwich» type immunoassay) (N-terminal pro-B-type natriuretic peptide, NT Pro-BNP).

The principle of the method is based on the interaction, in a patient's blood serum, between monoclonal mouse antibodies that cover the walls of the test tube of free NT pro-BNP and biotinized polyclonal rabbit antibodies prepared against the human NUP and the combination of alkaline phosphatase and conjugated streptavidin.

The results were evaluated by measuring the intensity of the color produced by conjugation with a specific chromogen (chromogenic substrate).

To compare and determine the significance of differences of quantitative values in paired groups, non-parametric Wilcoxon test was used (Mann-Whitney), and between multiple groups, Kruskal-Wallis test. The correlations between the studied parameters were defined using Spearman criterion. The calculations were performed using SPSS-20 software package.

Results and discussion. A total of 51 patients with CDLT met the inclusion and exclusion criteria. Demographic, respiratory function, biologic and hemodynamic data of the study population are presented in *table 1*.

There was no difference between CDLT+COPD patients with (*n*=26) and those without PAH (*n*=25) regarding age and sex ratio. In the comparison groups

Table 1

Patient characteristics

Characters	CDLT with COPD, without PAH (*n*=25)	CDLT+COPD with PAH (*n*=26)	Control (*n*=12)	*p* value
Sex, *m/f*	20 / 5	18 / 8	9 / 3	0,677
Age, *year*	45,2±2,5 (29-69)	44,7±2,2 (29-69)	43,2±3,2 (25-59)	0,905
Diaskintest	Positive	Positive	Negative	
Dyspnea, mMRCs	0,92±0,14 (0-2)	3,31±0,23 (1-5) ***^^^	0,50±0,15 (0-1)	< 0,001
Respiratory function				
FEV1,%	69,7±1,3 (58,1 – 78,4)***	68,4±1,1 (56,6 – 77,9)***^^^	93,3±1,0 (89-99)	< 0,001
FVC,%	59,4±1,5 (45 – 67)***	47,3±1,4 (36 – 59)***^^^	99,2±1,6 (90-106)	< 0,001
FEV1/FVC	98,1±2,2 (79,3-123,9)	65,8±1,1 (55 – 74,7)	94,3±1,6 (84,8-100,0)	0,430
RV1,%	68,46±2,67 (58 – 79)**	82,9±1,0 (72-90) ***^^	94,9±0,8 (90-99)	< 0,001

Characters	CDLT with COPD, without PAH (*n*=25)	CDLT+COPD with PAH (*n*=26)	Control (*n*=12)	*p* value
TLC,%	80,6±1,3 (68-93) ***	70,7±1,6 (60-86) ***^^^	89,3±1,3 (84-96)	< 0,001
DLco,%	65,4±1,4 (54-76) ***	48,8±1,6 (33-61) ***^^^	88,8±1,3 (82-96)	< 0,001
Arterial blood gases (room air)				
PaO_2, *mm Hg*	76,3±1,5 (65-92) ***	56,2±2,2 (36-75) ***^^^	94,3±1,0 (86-98)	< 0,001
$PaCO_2$, *mm Hg*	42,6±0,6 (37-46) **	43,0±1,3 (32-55)	39,6±0,8 (36-45)	0,071
Biological tests				
CRP, *mg/ml*	13,2±0,6 (6-19) ***	19,5±1,4 (8-32) ***^^^	2,9±0,3 (1,2-4,2)	< 0,001
Il-6, *pg/ml*	27,3±1,9 (15,6-45,6) ***	38,2±1,9 (20,1-59,2) ***^^^	14,2±2,8 (2,9-30,6)	< 0,001
TNFa, *pg/ml*	69,3±1,7 (59-85) ***	86,1±3,4 (60-137) ***^^^	35,3±5,4 (11-67)	< 0,001
NTproBNP, *ng/ml*	652,8±44,2 (390-1000) *	874,8±77,2 (380-1800) **^	490,3±48,0 (340-785)	0,001
LVEF (echo), %	54,3±0,7 (49-62)	63,8±1,6 (49-77) ***^^^	52,9±0,8 (49-58)	< 0,001
RHC				
PAPs, *mm/Hg*	36,2±2,2 (25-48) **	45,6±1,0 (39-50) ***^^	25,0±0,9 (23-29)	< 0,001
PAPm, *mm/Hg*	27,4±1,3 (21-34) ***	32,0±1,4 (24-38) ***^	13,7±0,7 (12-16)	< 0,001
PAPd, *mm/Hg*	15,7±1,4 (9-23) **	20,3±1,7 (12-28) ***	9,8±0,7 (7-12)	0,001
PVR, *w.u.*	3,11±0,16 (2,3-3,7) **	4,24±0,28 (2,9-5,2) ***^^	2,35±0,14 (2-2,9)	0,001
PCWP, *mm/Hg*	6,03±0,22 (4,8-7,2) **	6,65±0,21 (5,8-7,6) ***	4,70±0,18 (4-5,2)	0,001
CI, *L/min/m²*	2,89±0,06 (2,6-3,2) *	2,92±0,07 (2,6-3,3) *	3,13±0,09 (2,8-3,4)	0,085
AP/AO	0,842±0,021 (0,75-0,96) *	0,986±0,021 (0,86-1,06) ***^^^	0,757±0,017 (0,7-0,8)	< 0,001

Note: 1) a statistically significant difference (U-Wilkoxon (Mann – Whitney):
– with the control group: *p<0,05; **p<0,01; ***p<0,001;
– with indicators of Group without PAH: ^p_1<0,05; ^^p_1<0,01; ^^^p_1<0,001;
2) a statistically significant difference between groups (Kruskal – Wallace) – p value.

Definition of abbreviations: CDLT-chronic destructive lung tuberculosis; LVEF-left ventricular ejection fraction; mMRCs – modified Medical Research Council scale; PAPd = diastolic pulmonary arterial pressure; PAPm = mean pulmonary arterial pressure; PAPs = systolic pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; RHC = right heart catheterization; RV = residual volume; TLC = total lung capacity; DLco = transfer lung capacity of carbon monoxide. AP/AO = diameter ratio between the pulmonary arterial truncus and the ascending aorta.

(CDLT with COPD without PAH and CDLT+COPD with PAH) no one had discovered negative anergy. In both groups of comparison, different intensity, positive reactions to Diaskintest were revealed. Negative Diaskintest was detected in all persons belonging to the control group. The FEV1 was also not significantly different. DLco measurement was significantly less in patients with PAH (p<0,001) which suggested about more markedly affecting area of lung (two and more pulmonary lobes) with nonreversible morphological changes. Hypoxemia was more severe in patients CDLT+COPD with PAH.

At the vascular level, the diameter ratio between the pulmonary arterial truncus and the ascending aorta (AP/AO) was higher in patients with CDLT+COPD with PAH (p<0,001). The occurrence of bronchiectasis also was higher in patients with CDLT+COPD with PAH (p<0,001). It suggested that in such patient's chronic destructive lung tuberculosis nonreversible morphological changes are not single mechanism for development of PAH.

When we assessed each CDLT+COPD population with and without PAH separately, as well as the whole study population, we found that positive correlation coefficients between PAPm and the extent of nonreversible morphological changes in the lung parenchyma *(table 2)*.

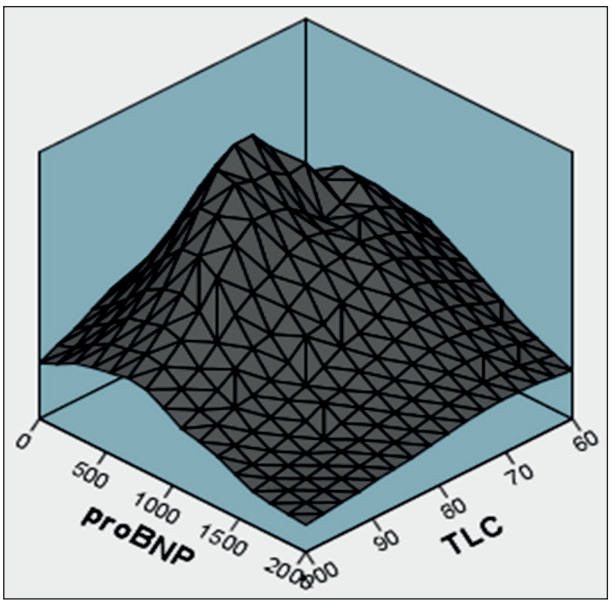
The analysis of proinflammatory cytokines and peptides shown positive correlation between these and the level of mPAP *(Figure)*. More significantly elevation of mPAP was noted in patients with NT-pro BNP level more than 500 ng/ml.

Table 2

Correlation Matrix between PAPm, Respiratory Function, and CT parameters in 51 patients with CDLT+COPD

Characters		TLC	PO_2	CRP	Il-6	proBNP	PAPm	AP/AO
TLC	r		0,411**	-0,200	-0,471**	-0,322*	0,131	-0,085
	p		0,003	0,160	0,000	0,021	0,582	0,722
PaO_2	r			-0,225	-0,508**	-0,203	-0,094	-0,649**
	p			0,112	0,000	0,152	0,693	0,002
CRP	r				0,363**	0,114	0,282	0,597**
	p				0,009	0,424	0,229	0,005
Il-6	r					0,159	0,137	0,364
	p					0,265	0,565	0,115
NTproBNP	r						-0,059	-0,088
	p						0,803	0,712
PAPm	r							0,331
	p							0,154

Note: Correlation is significant (2-sided) at the level: *p<0,05; **p<0,01.



Correlations between mean pulmonary arterial pressure (PAPm) and NTproBNP in patients with CDLT+COPD with and without PAH

Our results may indicate that, using relevant information related to vessels (AP/AO), extent of nonreversible morphological changes in lung, hypoxia (PaO_2), and more important to NTpro-BNP level, a multivariate model can improve this alternative strategy to estimate PAPm noninvasively.

Finally, our results give evidence that in CDLT+COPD, lung parenchyma, bronchi vessels is involved in complex processes coupling the bronchopulmonary and cardiovascular systems. This may provide further understanding of the burden of lung parenchyma and airway remodeling to explain CDLT+COPD severity and mortality. Specifically, our study suggests a critical contribution of lung parenchyma, bronchi and vessels remodeling to explain PAH in CDLT+COPD at the fringe of nonreversible morphological changes in the lung, gas exchange, and chronic lung inflammation with elevation of the level proinflammatory cytokines and peptides.

Transparency of the study. *The study did not have sponsorship. The authors are solely responsible for the provision of the final version of the manuscript for publication.*

Declaration of financial or other relationships. *All authors participated in the conception and design of the study and in the writing of the manuscript. The final version of the manuscript was approved by all the authors. The authors did not receive a fee for the study.*

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ДИНАМИКА КОЛИЧЕСТВА И ОБЪЕМА ХИРУРГИЧЕСКИХ ОПЕРАЦИЙ УЗЛОВЫХ ФОРМ ЗОБА В УСЛОВИЯХ ЙОДООБЕСПЕЧЕННОСТИ (1984–1990) И ЙОДОДЕФИЦИТА (1999–2005) В УЗБЕКИСТАНЕ

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Реферат. ***Цель исследования*** – изучить динамику количества и объема хирургических операций узловых форм зоба в условиях йодообеспеченности (1984–1990) и йододефицита (1999–2005) в Узбекистане по архивным данным отделения эндокринной хирургии Научно-исследовательского института эндокринологии Министерства здравоохранения Республики Узбекистан (НИИ эндокринологии МЗ РУз). ***Материал и методы.*** Представлены данные из историй болезни 4256 больных, оперированных по поводу узлового зоба с 1984 по 2005 г. в НИИ эндокринологии МЗ РУз. Количество и характер (объем) хирургического вмешательства при узловом зобе были проанализированы по архивным данным. ***Результаты и их обсуждение.*** С 1984 по 2005 г. в НИИ эндокринологии МЗ РУз были прооперированы 4256 больных по поводу узлового зоба. В годы йодообеспеченности (1984–1990) количество таких операций было меньше, а в годы йододефицита (1999–2005) наблюдается их резкое увеличение. Количество более радикальных и агрессивных операций на щитовидной железе при узловом зобе за годы йододефицита резко возросло по сравнению с годами йодообеспеченности: гемитиреоидэктомия от 13 до 163 случаев, тотальная тиреоидэктомия от 7 до 90 случаев. Количество экономных резекций щитовидной железы изменилось сравнительно немного (от 27 до 35 операций) за счет увеличения количества многоузловых зобов, требующих более радикальных операций. В годы йододефицита стали преобладать субтотальные и тотальные тиреоидэктомии, в том числе за счет увеличения числа карцином щитовидной железы: количество папиллярного рака увеличилось с 44 до 135, медуллярного – с 9 до 65, регистрированы случаи анапластического рака от 0 до 39. ***Выводы.*** В условиях йододефицита (1999–2005) возрастает количество узловых и многоузло-