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Features of Changes in Endothelial System Parameters in Patients with Diffuse Toxic Goiter

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Abstract

Background. The pathogenesis of diffuse toxic goiter is still not fully understood. In the literature, more and more attention is paid to issues related to the processes occurring in the thyroid gland itself: proliferation, apoptosis, and angiogenesis. These changes are known to be based on the development of endothelial dysfunction or endotheliitis because of a long course of hormonal disorders.

Purpose. To reveal the features of changes in the endothelial system parameters in patients with diffuse toxic goiter.

Methods. The study involved 293 patients with diffuse toxic goiter. All patients were subdivided by us into 3 subgroups: I subgroup of patients received thyreostatic conservative therapy for up to 1 year; II subgroup - for 1 to 3 years; III subgroup - more than 3 years. The state of the endothelial system was studied in terms of nitrates, nitrites, as well as the enzymatic activity of NO-synthases and Willebrand factor in the blood.

Results. A relatively stable picture of the ratio of NO in the dynamics of the examination of patients, has significant changes in parameters within the structural components of the constituent parts. The early periods of the survey were characterized by the prevalence of the nitrate component, and the later ones - by the nitrite component. At the same time, the average data on the activity of enzymes of the endothelial system were represented by bipolar values.

Conclusion. Compensatory changes aimed at utilization of the products of the nitroxidergic regulatory system, as shown by our observations, were of a differentiated nature. Lengthening the terms of conservative therapy of diffuse toxic goiter contributes to the suppression of changes in this functional activity.

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INTRODUCTION

The main method of treatment of diffuse toxic goiter remains surgical. [7,13,18,19] However, the high level of postoperative complications, the frequency of recurrence of the disease, determines the main direction of modern research in the field of diagnosis and treatment of diffuse toxic goiter.

The most pressing issue is the search for factors predisposing to the development of postoperative recurrence of thyrotoxicosis or hypothyroidism.

[4,14] Another argument is the expansion of the scope of surgical intervention, the main purpose of which is to reduce the frequency of recurrence of the disease and damage to the recurrent laryngeal nerve. [19]

The pathogenesis of diffuse toxic goiter is still not fully understood. [4,6,7,11,13] In the literature, more and more attention is paid to issues related to the processes occurring in the thyroid gland itself: proliferation, apoptosis and angiogenesis. [4] These changes are known to be based on the develop-

ment of endothelial dysfunction or endotheliitis because of a long course of hormonal disorders. [10,16]

Interest in indicators of endothelial dysfunction, namely nitric oxide (NO), is determined by the fact that it is the most stable of free radicals, is continuously formed in the vascular endothelium in many organs, provides adequate tissue perfusion, blood pressure level [15,17], protects the myocardium from arrhythmias [8,14]; lungs from hypoxia and toxic effects of thromboxane A₂ [2,3,5]; maintains cortical blood flow and normal renin secretion in the kidneys [12]; in the liver provides normal synthesis of coagulation proteins [1,9]. In addition, NO provides an anti-inflammatory effect on the walls of blood vessels and regulates the release of histamine by mast cells. [5,8] NO plays a role in damage to intestinal epithelial cells [9] by directly interacting with them. Reacting with oxidants, NO forms a highly toxic compound, peroxynitrite (ONOO⁻). [3,5]

In connection with the foregoing, the purpose of our study was to identify the features of changes in the parameters of the endothelial system in patients with diffuse toxic goiter.

MATERIAL AND METHODS

The study involved 293 patients with diffuse toxic goiter who were treated and examined at the Regional Multidisciplinary Clinic of the city of Bukhara from 2018 to 2022. The initial diagnosis was necessarily carried out by an endocrinologist. Given the different duration of the preoperative period of conservative therapy based on the use of thyreostatic drugs, we divided all patients into 3 subgroups: I subgroup - patients received thyrostatic conservative therapy for up to 1 year; II subgroup - for 1 to 3 years; III subgroup - more than 3 years. The distribution of subgroups of patients showed that most of all were patients with long-term preoperative thyrostatic conservative therapy from 1 year to 3 years - 129 (44.0%). The mean age of the patients was 50.5±18.7 years. There were 78.1% women, 21.9% men.

To achieve compensation for thyrotoxicosis, all patients underwent preoperative preparation, which consisted in prescribing thyreostatics and β-blockers before surgery at the outpatient stage. The criteria for compensation of the disease were the normalization of the level of free T₄ in the blood, the achievement of normosystole, target values of blood pressure.

The state of the endothelial system was studied in terms of nitrates, nitrites, as well as the enzymatic activity of NO-synthases (eNOS, iNOS) in the blood, which were determined by the Griess method modified by A.P. Solodko. The concentration of nitrites was calculated according to the equation of the calibration curve, considering the dilution during deproteinization. Optical density was measured on an SF-46 spectrophotometer at a wavelength of 520 nm. The Willebrand factor (VWF) was studied on a HumacLOT DUO closed-type automatic analyzer (Germany) using a set of reagents from Human (Germany).

Statistical analysis of the results obtained was carried out using modern statistical analysis packages: statgraphics Plusfor Windows version 4.0, Statis-

ticafor Windows version 8.0. Statistical methods of descriptive statistics, correlation analysis, establishing the reliability of the difference based on the calculation of the student's criterion were used for the work. Results with a significance level of <0.05 (95% confidence interval) were taken as significant. The procedure for calculating the correlation coefficient was built because of the method of squares, the use of rank methods and the strength of the relationship of the studied indicators.

RESULTS

The mean NO level in all patients was 16.04±1.54 μmol/l (table). Its maximum value was recorded in patients at the time of admission to the clinic (the concentration exceeded the total average value of this indicator by 1.51±0.03 μmol/l; p<0.05), and the minimum value was on the 7th day of the postoperative period (the decrease in concentration from the total average value of this indicator was 1.08±0.01 μmol/l; p<0.05). In general, the dynamics was characterized by a decrease in this indicator in blood samples both in the pre- and postoperative periods, and such dynamics was characterized by a 1.2-fold decrease in NO concentration (p<0.05).

Table
The nature of the change in the average value of the indicators of the endothelial system in the blood in the dynamics of the examination and treatment of patients with diffuse toxic goiter

INDICATORS	DYNAMICS OF THE SURVEY				
	Before operation		After operation		
	B/O	B ₀	1-day	3-day	7-day
NO (μmol/l)	17,55 ±1,15	16,62 ±1,4	15,65 ±0,92*	15,44 ±0,88*	14,96 ±0,72*
NO ₂ (%)	44,32 ±8,45	49,33 ±9,12*	49,85 ±8,75*	51,63 ±7,48*	54,42 ±8,11*
NO ₃ (%)	55,68 ±11,25	50,67 ±7,62*	50,15 ±6,12*	48,37 ±5,48*	45,58 ±3,45*
eNOS (μmol/min/l)	6,24 ±0,52	7,82 ±0,84	8,56 ±1,02*	10,71 ±2,11*	12,59 ±1,94*
iNOS (μmol/min/l)	4,55 ±0,41	4,25 ±0,61	2,52 ±0,32*	1,12 ±0,21*	0,75 ±0,01*
ONOO- (μmol/l)	0,36 ±0,42	0,31 ±0,1	0,24 ±0,08*	0,19 ±0,06*	0,19 ±0,01*
VWF (μmol/l)	29,53 ±3,85	38,44 ±4,12*	53,98 ±4,31*	64,84 ±6,7*	81,20 ±5,12*

B/O – when a patient comes to the clinic

B₀ – On the eve of the operation

*p0.05 - significant value in relation to the day of treatment of patients in the clinic.

In the structural changes of NO components, on average, nitrates (NO₃) prevailed, although the difference in their identity compared to nitrites (NO₂) was not significant. Thus, when contacting the clinic, the blood levels of patients with diffuse toxic goiter were dominated by nitrate NO components over nitrite ones (by 11.36±2.1%; p<0.05). Directly on the day of surgery and on the 1st day of the postoperative period, the ratio of the level of nitrate and nitrite components changes significantly in the direction of balancing. This leads to a decrease in their concentration difference by 1.34±0.1% (p<0.05) and by

0.3±0.07% ($p<0.05$), respectively. It is noteworthy that in the average value of concentrations, namely on the 3-7th day of the postoperative period, we recorded a characteristic trend towards normalization of the level of these studied components in the structure of NO, with a decrease in nitrate and an increase in its nitrite components by $10.1 \pm 1.5\%$ ($p<0.05$) compared with the first study period.

Changes in NO structural components were characterized by an increase in eNOS activity and a decrease in iNOS activity. Here it should be noted that the curve of change of this dynamic was absolutely opposite. At the same time, the dynamics of the study revealed a number of interesting patterns in the changes in the activity of these enzymes in the blood, namely: when patients came to the clinic, the percentage of changes in the activity of enzymes of the endothelial system was $49.6 \pm 11.4\%$ for eNOS ($p<0.05$) and $83.5 \pm 23.1\%$ for iNOS ($p<0.05$), respectively, on the day of surgery, the percentage change in the activity of these enzymes was $62.1 \pm 15.2\%$ for eNOS ($p<0.05$) and $82.4 \pm 14.7\%$ for iNOS ($p<0.05$), respectively, and on the 1st and 3rd days of the postoperative period - $75.5 \pm 12.8\%$ for eNOS ($p<0.05$) and $52.6 \pm 11.7\%$ for iNOS ($p<0.05$), respectively.

The high activity of iNOS, noted in the early stages of the examination of patients with diffuse toxic goiter in the preoperative period, was accompanied by a high production of ONOO⁻, which, as a product, was maximum in the preoperative period and significantly decreased only in the postoperative period. In other words, the high activity of iNOS, leading to the production of the toxic component of ONOO⁻ metabolism in the endothelial system, was directly related to the dynamics of the treatment period. In the postoperative period, a decrease in iNOS activity with its replacement by an increase in eNOS activity is characterized by both normalization of the structural ratio of NO components and a decrease in ONOO⁻ (1.9 times), indicating its pathological aggression on vascular endothelial cells.

This judgment can be confirmed by the dynamics of changes in the VWF level. The average value of this indicator in the dynamics of the survey increases significantly (from $29.53 \pm 3.85 \mu\text{mol/l}$ to $81.20 \pm 5.12 \mu\text{mol/l}$; $p<0.05$), reaching normal values in the blood. However, in the first stages of the examination, the level of this indicator indicated the presence of favorable conditions for possible bleeding.

A comparative analysis between subgroups of patients in terms of endothelial system indicators revealed that the dynamics of changes in its average value depends on the duration of diffuse toxic goiter. Thus, the maximum mean value of NO, exceeding the total mean value in patients by 1.1 times, was recorded among patients of the 3rd subgroup. In patients of the 1st and 2nd subgroups, the mean NO value was relatively lower.

In the dynamics of the survey, the peak values in the production of NO were unevenly distributed. In percentage terms, during the period when patients came to the clinic, patients of the III subgroup prevailed, the level of NO in which was about 39.5% of the total proportion of all patients. The difference in the level of NO between patients of subgroup I and

subgroup III were significant and amounted to 11.2%. On the eve of the operation in patients with diffuse toxic goiter, the level of NO changes in decreasing order in patients of subgroup III and in ascending order in patients of subgroup I. At the same time, the level of difference between the shares of each subgroup is reduced, decreasing by 7.3% compared with the previous study period. It should be noted that these changes throughout the entire preoperative period were significantly significant ($p<0.01$). We deliberately focus on this fact, since already on the 1st day after the operation, the difference in the level of NO formation in the blood between the studied subgroups of patients tends to average values. So, for example, in patients of subgroup III, there is a significant decrease in NO production on the 1st, 3rd, and 7th day of the postoperative period, while among patients in subgroup I, there is a stable increase in the production of one of the main indicators of the endothelial system of the lungs.

Such pronounced changes in the synthesis of NO and its components were due to certain changes in the activity of enzymes of the endothelial system. As mentioned above, the dynamics of the study showed a gradual increase in eNOS activity with a decrease in iNOS activity. Based on the average value of the entire group of patients, it should be noted that in the context of subgroups, these enzymes did not change unambiguously. In patients of subgroup I, the average value of the activity of the eNOS enzyme exceeded the overall significance by $2.73 \pm 0.2 \mu\text{mol/min/l}$ ($p<0.05$), while in patients of subgroup II, and especially in patients of III subgroups, the mean value of activity was lower than the overall significance by $0.36 \pm 0.02 \mu\text{mol/min/l}$ ($p<0.05$) and by $2.36 \pm 0.02 \mu\text{mol/min/l}$ ($p<0.05$) respectively.

Relative to the average value of iNOS enzyme activity, less than the total value was noted both in patients of subgroup I ($0.49 \pm 0.02 \mu\text{mol/min/l}$; $p<0.05$) and subgroup II ($2.54 \pm 0.21 \mu\text{mol/min/l}$; $p<0.05$). However, in patients of subgroup III, the activity of this enzyme was 1.85 times higher than the general average values ($p<0.05$), and it determined the general trend of the identified changes.

Analysis of changes in the activity of enzymes of the endothelial system within the subgroups themselves showed that in patients of subgroup I, these changes were diametrically opposed throughout the study period. If the relative difference in the eNOS/iNOS ratio on the day of the patients' visit was 12.34 times, then on the eve of the operation it increased significantly to 18.9 times ($p<0.05$). In the postoperative period in patients of subgroup I, the difference in changes in the activity of enzymes of the endothelial system averaged from 30.1 times to 45.2 times ($p<0.05$).

In patients in subgroup II, on the day of admission to the clinic, the level of activity of enzymes of the endothelial system was almost the same. eNOS activity was $5.22 \pm 0.92 \mu\text{mol/min/l}$, and iNOS activity was $5.23 \pm 0.82 \mu\text{mol/min/l}$ ($p<0.05$), and compared to patients of subgroup I, it was more active 6.5 times ($p<0.05$). On the eve of surgery and in subsequent periods of observation, the level of eNOS activity becomes higher than iNOS and averaged from

1.4±0.12 times ($p<0.05$) to 28.75±1.74 times on the 7th day of the postoperative period, respectively. ($p<0.05$). The level of activity of the iNOS enzyme in patients of subgroup II for a given period was equal to the level of activity of this enzyme on the 1st day after surgery in patients of subgroup I. We deliberately focus on this fact, since, apparently, such changes are associated with the performance of surgical intervention on the thyroid gland.

Regarding patients of subgroup III, changes in the activity of eNOS and iNOS enzymes were very difficult. During the entire period before the operation and in the early stages after the operation (1 day), the pathological enzyme iNOS prevailed in the ratio, which indicates possible destructive changes in the endotheliocytes of blood vessels. It should be emphasized that this trend in no way coincided with the nature of the change in the picture of the general dynamics of change in the entire group of patients. Excess iNOS in patients of subgroup III on the day of admission to the clinic and on the eve of surgery was recorded 2.1 times and 1.5 times, respectively ($p<0.05$). Already on day 1 after surgery, this difference decreased to 1.1 times ($p<0.05$), and on days 3-7 after surgery, the eNOS/iNOS ratio acquires a positive value and exceeded 4.1 and 7.7 times ($p<0.05$).

All this indicates the effectiveness of the surgical method for the treatment of diffuse toxic goiter, which also affected the functional state of the endothelial system. And confirmation of this conclusion can be presented by the results of changes in the level of formation of peroxynitrite, which is a strong oxidizing agent and, due to its properties, which can cause damage to a wide range of molecules in the cell, including DNA and proteins.

The level of peroxynitrite in the blood in patients of subgroup II reached the level of subgroup I only in the postoperative period. Exceeding the level of production of peroxynitrite in the II subgroup of patients was recorded in 2.3±0.2 times ($p<0.05$). Only starting from the early postoperative period, the decrease in the concentration of peroxynitrite in patients of subgroup II was at the level of patients of subgroup I in the preoperative period. However, it was not possible to fully acquire the significance of the I subgroup of patients in the II subgroup.

The same trend was noted by us among patients of the III subgroup. The level of excess peroxynitrite production in patients in this subgroup exceeded the values of patients in subgroup I already by 4.2±1.7 times ($p<0.05$). This exceeded the overall average value for the level of peroxynitrite by 2 times. After the surgical treatment of diffuse toxic goiter in patients of subgroup III, the level of peroxynitrite production decreased from 0.59±0.05 $\mu\text{mol/l}$ to 0.26±0.02 $\mu\text{mol/l}$ ($p<0.05$), but it was still higher than the values of I and II subgroups of patients in the corresponding period of the study.

Based on the above changes, the VWF level changed in the opposite direction in relation to the production of peroxynitrite. The minimum value of VWF (up to 15.25±2.4 $\mu\text{mol/l}$; $p<0.05$) was recorded by us in the III subgroup of patients on the day of their visit to the clinic. The maximum value of this indicator was noted by us on the 7th day after the operation period in patients of subgroup I

(98.66±14.6 $\mu\text{mol/l}$; $p<0.05$). At the same time, the level of VWF formation was almost identical, as in the previous case, in the II subgroup of patients (92.48±13.6 $\mu\text{mol/l}$; $p<0.05$).

It should be noted that the turning points in the change in the level of VWF in patients were: on the eve of surgery (53.84±13.5 $\mu\text{mol/l}$; $p<0.05$) in subgroup I of patients; on day 1 after surgery (53.72±18.5 $\mu\text{mol/l}$; $p<0.05$) in subgroup II of patients and on day 7 after surgery in subgroup III of patients (52.45±11.1 $\mu\text{mol/l}$; $p<0.05$).

DISCUSSION

It is known that the formation of peroxynitrite occurs because of the interaction of superoxide ion and nitric oxide under the condition of activation of the iNOS enzyme. [1,2,9,14] The increase in the activity of the latter, noted by us in patients with subgroups II and III, led precisely to such changes.

VWF is also known to be a large plasma multimeric glycoprotein that is continuously produced as ultra-large multimers by endothelial cells, megakaryocytes, and subendothelial connective tissue. [15,17] At the same time, VWF is also a blood plasma glycoprotein that plays an important role in hemostasis, namely, it ensures the attachment of platelets to the area of the damaged vessel. [10,16] All this, apparently, determines the dynamics of specific changes in VWF in patients of various subgroups.

Studies of the content of the isoenzyme of the nitroxidergic regulatory system (iNOS) showed a greater specificity of changes compared to eNOS. As you know, this enzyme, which is the product of activation of non-pathological cells. [3,5,15]

CONCLUSION

A relatively stable picture of the ratio of NO in the dynamics of the examination of patients, has significant changes in parameters within the structural components of the constituent parts. The early periods of the survey were characterized by the prevalence of the nitrate component, and the later ones - by the nitrite component. And all this characterized the absence of a reliable value of the difference between these indicators in terms of the total value for the entire period of the survey. At the same time, the average data on the activity of enzymes of the endothelial system were represented by bipolar values, which, in the dynamics of the postoperative period, changed their character of significance approaching normal values only on the 7th day after the operation.

The nature of the change in the content of various substrates of the metabolism of nitroxidergic homeostasis showed heterogeneity of changes. Compensatory changes aimed at utilization of the products of the nitroxidergic regulatory system, as shown by our observations, were of a differentiated nature. In subgroup I of patients, the system adjusted changes in the concentrations of certain studied substrates. Lengthening the terms of conservative therapy of diffuse toxic goiter contributes to the suppression of changes in this functional activity. The deviation in the physiological parameters in the endothelial system, which we observed in the dynamics after the operation, in our opinion, is natural.

Ethics approval and consent to participate - All patients gave written informed consent to participate in the study.

Consent for publication - The study is valid, and recognition by the organization is not required. The author agrees to open publication

Availability of data and material - Available

Competing interests - No

Financing - No

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DIFFUZ TOKSIK BO'QOQ BO'LGAN BEMORLARDA ENDOTELIY TIZIMI KO'RSATCHILARINI O'ZGARISH XUSUSIYATLARI

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Abu Ali ibn Sino nomidagi Buxoro davlat tibbiyot instituti

Abstrakt.

Dolzarbliqi. Diffuz toksik bo'qoqning patogenezi hali ham to'liq tushunilmagan. Adabiyotda qalqonsimon bezning o'zida sodir bo'ladigan jarayonlar: proliferatsiya, apoptoz va angiogenez bilan bog'liq masalalarga tobora ko'proq e'tibor qaratilmoqda. Bu o'zgarishlar gormonal buzilishlarning uzoq davom etishi natijasida endotelial disfunktsiya yoki endoteliitning rivojlanishiga asoslanganligi ma'lum.

Maqsad. Diffuz toksik bo'qoq bilan og'rigan bemorlarda endotelial tizim parametrlarining o'zgarishi xususiyatlarini aniqlash.

Usullari. Tadqiqotda diffuz toksik bo'qoq bilan kasallangan 293 bemor ishtirok etdi. Barcha bemorlar biz tomonimizdan 3 ta kichik guruhga bo'lindi: bemorlarning I kichik guruhi 1 yilgacha tireostatik konservativ terapiya oldi; II kichik guruh - 1 yildan 3 yilgacha; III kichik guruh - 3 yildan ortiq. Endotelial tizimning holati nitratlar, nitritlar, shuningdek, qondagi NO-sintazalar va Villebrand omilining fermentativ faolligi nuqtai nazaridan o'rganildi.

Natijalar. Bemorlarni tekshirish dinamikasida NO nisbatining nisbatan barqaror rasmi tarkibiy qismlarning tarkibiy qismlari ichidagi parametrlarda sezilarli o'zgarishlarga ega. Tadqiqotning dastlabki davrlari nitrat komponentining, keyingilari esa nitrit komponentining tarqalishi bilan tavsiflangan. Shu bilan birga, endotelial tizim fermentlarining faolligi bo'yicha o'rtacha ma'lumotlar bipolyar qiymatlar bilan ifodalangan.

Xulosa. Nitrooksidergik tartibga solish tizimining mahsulotlaridan foydalanishga qaratilgan kompensatsion o'zgarishlar differensial xarakterga ega ekan. Diffuz toksik bo'qoqning konservativ davolash muddatini uzaytirish ushbu funktsional faoliyatdagi o'zgarishlarni bostirishga yordam beradi.

Kalit so'zlar: diffuz toksik bo'qoq, tiroidektomiya, endoteliit, endotelial disfunktsiya, tiroidektomiyadan keyingi asoratlar, patogenez, molekulyar biokimyo

ОСОБЕННОСТИ ИЗМЕНЕНИЯ ПОКАЗАТЕЛЕЙ ЭНДОТЕЛИАЛЬНОЙ СИСТЕМЫ У БОЛЬНЫХ С ДИФFUЗНЫМ ТОКСИЧЕСКИМ ЗОБОМ

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Актуальность. Патогенез диффузного токсического зоба до сих пор до конца не изучен. В литературе все чаще основное внимание уделяется вопросам, связанным с процессами, происходящими в самой щитовидной железе: пролиферация, апоптоз и ангиогенез. В основе этих изменений, как известно, лежит развития эндотелиальной дисфункции или эндотелиита в результате длительного течения гормональных расстройств.

Цель. Выявить особенности изменения показателей эндотелиальной системы у больных с диффузным токсическим зобом.

Методы. В исследовании участвовали 293 пациента с диффузным токсическим зобом. Все больные были подразделены нами на 3 подгруппы: I подгруппа больных получали тиреостатическую консервативную терапию в течение до 1 года; II подгруппа - на протяжении от 1 года до 3 лет; III подгруппа - более 3 летнего периода. Постояние эндотелиальной системы исследовали по показателям нитратов, нитритов, а также ферментной активности NO-синтаз и фактора Виллебранда в крови.

Результаты. Относительно стабильная картина по отношению NO в динамике обследования больных, имеет существенные изменения параметров внутри структурных компонентов составляющих частей. Ранние сроки обследования характеризовались превалированием нитратового компонента, а поздние – нитритового. В то же время, средние данные активности ферментов эндотелиальной системы, были представлены разнополярными значениями.

Выводы. Компенсаторные изменения, направленные на утилизацию продуктов нитрооксидергической системы регуляции, как показали наши наблюдения, имели дифференцированный характер. Удлинение сроков консервативной терапии диффузного токсического зоба способствует угнетению изменению данной функциональной активности.

Ключевые слова: диффузный токсический зоб, тиреоидэктомия, эндотелиит, эндотелиальная дисфункция, осложнения после тиреоидэктомии, патогенез, молекулярная биохимия.