ISSN 2409-9988

Inter Collegas

Experientia docet

2021

№3(8)

INTER COLLEGAS

2021
Vol. 8 No.3

OFFICIAL JOURNAL OF KHARKIV NATIONAL MEDICAL UNIVERSITY
ISSN 2409-9988

Recommended for publishing by Scientific Council of Kharkiv National Medical University

30 – Sep.- 2021

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URL:
http://inter.knmu.edu.ua/pub

Periodicity:
4 times a year

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RESOURCES-BASED STRATEGIES FOR HEALTH PROMOTION OF STUDENTS WITH DIFFERENT GENERAL CONDITIONS AND DIFFERENT ORIGINS

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https://doi.org/10.35339/ic.8.3.132–143

Abstract

Background: The aim of this study is to investigate the study-/work-related behavior and experience patterns of students, taking into account their origins as well as the stressful general conditions. **Methods:** A total of 194 students (41.8% women, 58.2% men, 58.7% German and 41.3% international students) were evaluated to their strains during the study and study-/work-related Behavior and Experience Patterns (AVEM). Four potentially stressful conditions were taken into account. **Results:** For only 14% of international students, but 45% of German students risk patterns for work-related behavior and experience were found. Study-/work-related behaviour and expe-rience patterns depend on the origin of the students. Resources during study were significantly higher among students of German origin. **Conclusions:** A study-related strengthening of resources is necessary, which can be viewed as a competitive advantage when choosing a study location.

Keywords: *university students; origins; international students; study-/work-related Behavior and Experience Patterns; resources; prevention; health.*

Introduction

With the implementation of the Bologna Process, there were major changes in the demands and resource profiles of students throughout Europe. The European Higher Education Area (EHEA) and Bologna Process is an international collaboration on higher education of 48 countries, which adapted their higher education systems to making them more compatible and strengthening their quality assurance mechanisms. The aim is to increase staff and students' mobility and to facilitate employability. This is also in the context of increasing globalization and the growing international competition for expertise [1]. These changes also resulted in additional workloads for the students. Half of the students reported that they were regularly under stress, with multiple stressors frequently being present [2]. For 42% of the students, the strain is caused by a combination of various areas of life. 68% of them include their study. In addition, the financial situation (40%), parttime jobs (40%), leisure time (39%), partnerships (32%), as well as their own health (21%) and the household (19%) with children (13%) also have an impact on the students' reality of life [3, 4]. Mental strain factors as a potential health risk are confronted with numerous resources (organizational, social and personal) as compensation and protection components to avoid or reduce the negative consequences of stressors. Specific personal coping mechanisms across situations and, as a consequence, the management of the stress situation are the conditions for resources to develop their healthprotective effect [5].

The mental health of students

Mental disorders are prevalent among students. According to the WHO (World Health Organization), one fifth of students worldwide had a 12-month DSM-IV-based mental disorder (Diagnostic and Statistical Manual of Mental Disorders), which occurred in 83.1% of these cases before matriculation. However, only 16% of students with mental disorders received treatment [6]. Mental disorders have a negative influence on a possible

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degree and are a new focus of occupational medicine in recent years.

Resources for health promotion

The focus of the conservation of resources theory (COR) is on the resources, motivation, and stress management that apply beyond the individual to diverse people of the same background in similar cultures [7]. Defining the concept of culture enables to predict individual behavior in stressful demanding situations, since the influence of society forms the self-concepts [7]. In addition to COR, the demand-resource model based on Antonovsky's salutogenesis is usable [2]. The demands have an external effect on the individual from a professional, family or social point of view. At the same time the individual's own needs, values, norms, goals and expectations control behavior from within. These are supported by the environmental, material, occupational, social ressources. Only in combination they lead to a sustainable health of the person [8] .

In the course of coping with the demands, the social environment, an important source of support (e.g. partners, friends, parents, relatives, fellow students), is mainly used [9]. There is an increased requirement for emotional and informal support at the beginning of study[10], and in the progress of the study [11], positive communication leads to better learning outcomes. The third aspect of social support includes instrumental support, where students receive practical and financial support. The most important resources for the health of the students are their own decisions for the place of study, the potential for further qualification or development, the scope for action and the time available for their courses of study [12, 13]. In contrast the loss of these protective factors is equivalent to a loss of life. This is perceived as stress and is therefore more significant [7].

New findings show a change from intrinsic to extrinsic motives in the choice of study and point to the new weighting of subsequent fields of employment (71%) and the in-herent potential for development in the job [12]. In addition, living in proximity to the place of residence for keeping up social contacts including family, tutoring programs and the events for first-year students are of great importance. They are a support service in addition to the counselling centers for various problems (stress, university studies with children, legal advice) or the university sports programs for stress reduction (yoga, relaxation methods), they provide central points of contact for every student [14]. A special criteria that has a long-term effect on the health of the students is their study satisfaction. Following the person-job-fit theory [15], an increasing satisfaction is assumed if the discrepancy between the actual and the target value decreases, so that a balanced fit of all areas of life is achieved.

Whether a person can perform the necessary adaptation processes during studies also depends on the personality traits [16]. For example, emotion regulation is needed in examination situations so that fears of performance evaluations are not transformed into thinking blocks. A study showed, that 61% of the students reported that they can solve their problems by their own coping strategies [17]. Particularly positive values also arise in the self-assessment of health-related behavior and the emotional self-concept as aspects of internal resources [2]. The students show a significant optimism and are ready to face the demands of the course. Because a positive correlation between mood and cognitive performance exists, aspects of intrinsic motivation can have particularly promising effects [18]. These are particularly high when students experience themselves in flow while working on a topic. Complete fusion with a task is achieved when a feedback follows on the work done. In order to provide such constructive feedback, a communicative environment in teaching is necessary. If this can be generated, the study program provides a good learning environment for the individual development of stress management and working methods that will enable a future success in the labor market [3]. It is shown that about 40% (32% women; 52% men) are physically active at least three times a week and therefore meet WHO requirements [17]. The most important stress management strategy is compensation through sports activities or a particularly healthy lifestyle [2]. 75% of students would like to follow courses on health promotion. Especially, offers for relaxation and stress management are in high demand among women [19].

A strategy to avoid the long-term consequences of mental strain can only be developed by considering risks and resources together [5]. New models and concepts that explain the relationship between stress and health have resource-oriented approaches to health promotion. These include not only inappropriate strains (stressors) but also resources. The Work-Related Behavior and Experience Patterns (AVEM, German Arbeitsbezogenes Verhaltens- und Erlebensmuster) questionnaire is one survey instrument. It records engagement with work, resilience in dealing with the everyday stresses of work, and emotions

associated with work and with life in general [20]. In addition to the various dimensions, the questionnaire includes four different types of behavioral and experiential patterns that play a significant role in coping with occupational demands [20]. Two health-promoting and 2 health-hazardous patterns can be distinguished [20].

2. Purpose, subjects and methods:

2.1. The purpose of the present study is to describe the study-related behavior and experience patterns of students at higher education institutions across different situations and to analyze the available resources, taking into account the students' origins as well as the stressful general conditions. This serves as a baseline to plan a resource-oriented approach to health promotion. In addition, individual cross-situational patterns of action and behavior are presented, because these also represent an essential resource in the stress-mental health pathway. There is a gap in research examining resources among students of different origins.

The following questions were examined: Which resources as general conditions play a role as components in the extended stress-strain concept? Are the manifestations in the various dimensions of work-related behavior and experience patterns (AVEM) of national and international students different? What significance does this result then have for the distribution of AVEM patterns in the two groups of students? This results in the following hypotheses: 1) International students have more stressful conditions because they study in a non-native country. 2) AVEM dimensions and following re-sources differ between German and international students. 3) The international students show AVEM patterns that are hazardous to their health, especially of the B pattern.

2.2. Subjects & Methods

Subjects

A total of 194 students (41.8% women (n = 81) and 58.2% men (n = 113)) from the following faculties were included in the survey: Mechanical Engineering, Humanities, Social Science & Education, Engineering & Industrial Design, Medicine, Mathematics, and Social Work, Health & Media of two universities of a large city in Central Germany, and included network of international students from different matriculates and fields of study. The subsample of students with international origin comprises 80 participants (41.2%) aged between 20 and 30 years (24.7± 2.4 years). The subjects of the total sample were on average 23.0±3.4 years old (age range 18 – 34 years), of which 50% were younger than 22 years, 25% between 22 and 25 years and 25% older than 25 years. The average age of German students was 21.7±3.5 years. The home countries of students of international origin are widely represented in a total of 36 countries. The gender distribution within both groups of students was not significantly different (p = 0.442): 45 women (39.5%) and 69 men (60.5%) vs. 36 women (45.0%) and 44 men (55.0%).

All students answered the following questionnaires: 1) Questionnaire on strains during the study (and at the workplace) and 2) Study-/Work-related Behavior and Experience Patterns (AVEM) [20]

Procedure

The surveys of the cross-sectional study were performed in 2010–2013 and 2018. The invitation to participate in the study was made via flyers with information and contact details. In addition the questionnaires were available in paper form to all those present at the first-semester event in the auditorium. The questionnaires were handed out to the participants in paper form and completed independently without any time limit. In the case of language barriers faced by international students, they were supported by the research team. In case of language barriers of international students an interpreter helped to understand and answer the respective questions, because all questions were in German (bias). Due to the subjective questionnaire study, no specific exclusion criteria were defined to achieve a wide range of students.

Questionnaire on strains during the study (and at the workplace)

This questionnaire collects sociodemographic data of the subjects (including age, gender) and information on the study program, the time in hours per week required for the study program, individual protective factors and potentially stressful general conditions such as household, child, care of family members, financing of the study program, possible job opportunities and travel times of the students. This questionnaire asks about burdens in connection with the financing of studies, time burdens during studies and also family burdens.

The following 4 items of the study-related stress factors were used as potentially stressful general conditions, because these factors were identified as the main stressors of the total sample:

- part-time work/working alongside studying;
- children;

• nursing of relatives, and
• travel distance with a journey of more than 120 minutes.

(characteristics 9–11). The characteristics of the individual dimensions are shown in *Table 1*. Stanine values between 4 and 6 are classified as

Table 1

Expression of the AVEM dimensions within the 4 patterns (Schaarschmidt & Fischer, 2004), own presentation

AVEM	Pattern			
Variables	**G**	**S**	**A**	**B**
Subjective importance of work in personal life	↔↑	↓	↑	↓
Work-related ambition	↑	↓	↔↑	↓
Willingness to work until exhausted	↔	↓	↑	↔
Striving for perfection	↔↑	↓	↑	↔↓
Distancing ability (ability to recuperate mentally from work)	↔↑	↑	↓	↔↓
Tendency to resignation in the face of failure	↓	↔↓	↔↑	↑
Proactive problem-solving (active and optimistic attitude)	↑	↔↓	↔↑	↓
Inner calm and balance (experience of emotional stability).	↑	↔↑	↓	↓
Experience of success at work (satisfaction)	↑	↔↓	↔↑	↓
Satisfaction with life	↑	↔↑	↔↓	↓
Experience of social support	↔↑	↔	↔↓	↔↓
Stanine values: 1–3 under average ↓, 4–6 average ↔ (tendency to 4 additionally with ↓ and tendency rather to 6 additionally with ↑), 7–9 above average ↑. Health-promoting patterns G and S. Risk patterns A and B.				

Based on the results on potentially stressful conditions, the students were divided into subgroups with and without stressful conditions:

• no stressful conditions (nSC, n=108, 55.7%) and
• with ≥1 stressful conditions (SC, n = 86, 44.3%).

These are later included as covariates in the statistical analysis.

Study-/Work-related Behavior and Experience Patterns (AVEM)

The questionnaire measures work-related behavior, attitudes and habits [20]. Sixty-six items from the domains of "work commitment", "psychological resilience" and "job-related emotions" are summarized in 11 dimensions obtained by factor analysis as follows: 1) Subjective importance of work in personal life, 2) Work-related ambition, 3) Willingness to work until exhausted, 4) Striving for perfection, 5) Distancing ability (ability to recuperate mentally from work), 6) Tendency to resignation in the face of failure, 7) Proactive problem-solving (active and optimistic attitude), 8) Inner calm and balance (experience of emotional stability), 9) Experience of success at work (satisfaction), 10) Satisfaction with life, 11) Experience of social support. These 11 AVEM characteristics can be grouped into three major areas such as engagement with work (characteristics 1–5), resilience in dealing with everyday stress at work (characteristic 5 again, 6–8) and emotions associated with work and life in general "normal". Depending on their prominence in the particular category, they reflect the four typical work-related behavior and experience patterns (G, S, risk patterns A and B) [21]. We used only pure patterns with an expression of > 95% in one pattern, accentuated patterns with pattern expressions between > 80% and ≤ 95%, and tendential patterns (pattern expression ≥ 60 – ≤ 80%, with no other pattern with ≥ 30% expression). Pattern combinations were possible, but not considered in the present study. Cronbach's α for each AVEM characteristics range from 0.82 to 0.90.

Statistical methods

All analyses were performed in SPSS Statistics 26 for windows. It was tested for normal distribution using the Kolmogorov–Smirnov test. The Chi-square test was used to test the distribution of subgroups of different origin and subgroups with and without stressful conditions. The Fishers Exact Test was used to compare the distribution of the different frequency occurrence of different resources and the distribution of AVEM patterns in the subgroups of students of German and foreign origin. The Mann–Whitney U-test was used to assess the impact of low-value resources and the impact of the AVEM categories. In addition, the General Linear Model (GLM), test for intermediate subjects, corrected model) was applied, taking into account the general conditions. A Bonferroni test was performed. The significance level was based on a 5% significance level.

3. Results & Discussion

Results

For the presentation of the results, the following questions are examined: Which re-sources as general conditions play a role and what influence do they have? Are the manifestations in the various dimensions of AVEM of national and international students different?

General information about the students and conditions

More than half of the students have no stressful general condition, 38.7% have one, and 5.7% of the students have at least two or more general conditions (*Figure 1*). Of the 57 students of German origin with stressful conditions, 46 had only one, 10 had two and 1 had three or more stressful general conditions. Of 29 students from international countries with stressful conditions, all of them stated that they only had one potentially stressful condition. The allocation of the origin of the respondents with and without stressful conditions in the student groups did not differ significantly (p = 0.058). The age of respondents in these two subgroups with different conditions was also similar (22.5 ± 3.1 years for participants in group nSC, 23.5 ± 3.7 years for those in group SC).

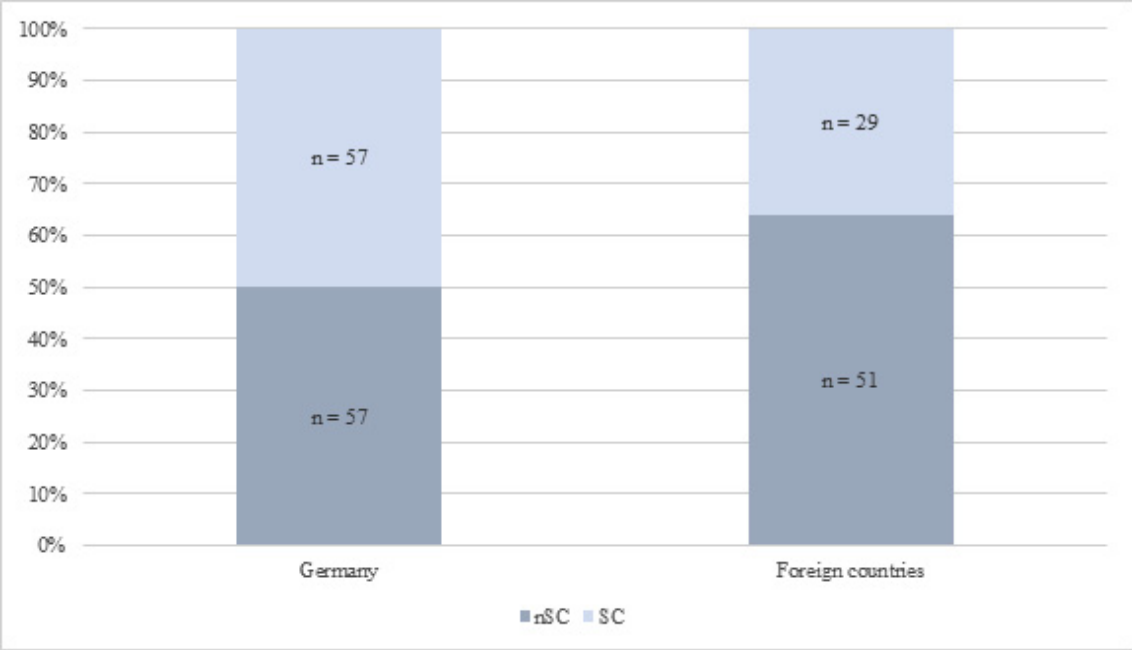

Figure 1. Allocation of subgroups with different stressful conditions among groups of students of different origins (p = 0.058)

The average distance to the university is between 8.2 ± 15.67 km (range 0.5 and 120 km) and the drive takes between 3 and 120 minutes. The time required for studying (lectures, seminars and practical training) was up to 45 hours per week (∅ 19.2 ± 9.4 hours per week). Taking into account the preparation and follow-up time, this was as much as 56 hours per week (∅ 15.6 ± 10.9 hours per week). The time invested in household activities during the semester and holidays is roughly comparable (6.1 ± 4.3 hours versus. 6.5 ± 5.0 hours). The students had an average employment of 5.6 ± 10.64 (range 0 – 80) hours per week during the semester and 12.8 ± 17.49 (range 0 – 120) hours per week during the semester break. 6 students of German origin (3.1% of the total sample) have children. All students from international countries are childless. The average percentage of financing for studies by parents was 57.9 ± 40.2% in the overall sample (German versus foreign origins 58.5%/41.5%). Other financing options were available to 13.8 ± 2.7% of the students through the BAfoG scholarship (state support for the training of pupils and students in Germany), 17.4 ± 28.5% through their own income, 5.6 ± 20.0% through other scholarships and 4.4 ± 16.2% through other income. In the case of 27 German students (23.9%) and 39 international students (48.8%), 100% of the financing for their studies was provided by their parents. Only 6 students from Germany financed 100% of their study with the BAfoG scholarship, for all others the BAfoG scholarship is only a part of the financing of their studies. Another 6 students (7.5 %) financed their studies with other scholarships. 1.8% of students of German origin (n = 2) and 7.5% (n = 6) of international

students financed their studies 100% from their own income.

Resources of the students

In the survey on resources during study, it was found that the enjoyment of studying and part-time work as well as the collegial and open atmosphere in the environment was subjectively significantly higher among students of German origin (*Table 2*). They also felt more support for professional interests from their immediate circle.

Table 2

Presence of different resources in the total sample and the subgroups of students

Resources	Total	Germany	International countries	$p_{Fishers\ exakt\ test}$
	incidence [%]			
Enjoyment of study and work				
never	1.6	0.9	2.5	< 0.001
rarely	10.9	4.5	20.0	
sometimes	41.1	35.7	48.8	
often	46.4	58.9	28.7	
Collegial and welcoming atmosphere in the environment				
never	2.1	0	5.0	0.001
rarely	9.4	6.3	13.8	
sometimes	37.0	31.3	45.0	
often	51.6	62.5	36.3	
Support of family/partner in their professional interests				
never	4.7	3.5	6.3	0.002
rarely	9.3	6.2	13.8	
sometimes	28.5	21.2	38.8	
often	57.5	69.0	41.2	

Table 3 shows the impact of scantly available or pronounced resources. In most cases, students do not feel stressed. International students felt more stressed by a less welcoming and collegial atmosphere or a lack of support, but no significant statistical differences between German and international students were found. Students from other countries feel more stressed if these three stress factors were more pronounced for them and the general conditions were taken into account.

Study-/Work-related Behavior and Experience Patterns (AVEM) of the students

Table 4 shows the stanine values of the total sample for the 11 categories of the AVEM. The Work-related ambition of the total sample reached the highest score of 6.1 ± 1.6 points; with an average value of 6.4 ± 1.6 points, the students of German origin were higher compared to norm values. The lowest values, which were also under the norm, were found in the categories of Proactive problem-solving (3.9 ± 1.7 points) and the Experience of success at work (satisfaction) (3.5 ± 2.00 points). Particularly low values were found in the group of foreign origin. In addition, the stanine values of the categories Satisfaction

Table 3

Expression of strain caused by low available resources in the total sample and in the subgroups of students

Resources	Total	Germany	International countries	$p_{Mann-Whitney-U}$	GLM with general conditions as covariate		
	AV±SD Median (min-max)				F	p	$p_{Bonferroni}$
Enjoyment of study and work	0.53 ± 0.876 0 (0 – 3)	0.41 ± 0.730 0 (0 – 3)	0.69 ± 1.001 0 (0 – 3)	0.080	2.352	0.098	0.031
Collegial and welcoming atmosphere in the environment	0.39 ± 0.770 0 (0 – 3)	0.29 ± 0.642 0 (0 – 3)	0.51 ± 0.900 0 (0 – 3)	0.081	1.908	0.151	0.055
Support of family/partner in their professional interests	0.38 ± 0.761 0 (0 – 3)	0.29 ± 0.592 0 (0 – 3)	0.53 ± 0.941 0 (0 – 3)	0.128	2.294	0.104	0.035
Note. AV= average value; SD = standard deviation; GLM = General Linear Model							

Table 4

Expression of the AVEM categories (stanine values) in the total sample and the subgroups of students

AVEM category	Total	Germany	International countries	$p_{Mann-Whitney-U}$	GLM with general conditions as covariate		
	AV±SD Median (min-max)				F	p	$p_{Bonferroni}$
Subjective importance of work in personal life	4.9 ± 1.82 5 (1 – 9)	4.4 ± 1.89 4 (1 – 9)	5.6 ± 1.49 5.5 (1 – 8)	< 0.001	11.558	< 0.001	< 0.001
Work-related ambition	6.1 ± 1.65 6 (1 – 9)	6.4 ± 1.65 6 (3 – 9)	5.8 ± 1.61 6 (1 - 9)	0.019	2.793	0.064	0.019
Willingness to work until exhausted	4.6 ± 1.81 5 (1 – 9)	4.3 ± 1.87 4 (1 – 9)	5.1 ± 1.66 5 (1 – 9)	0.004	4.385	0.014	0.005
Striving for perfection	4.6 ± 1.85 4 (1 – 9)	5.0 ± 1.93 5 (1 – 9)	4.1 ± 1.63 4 (2 – 9)	0.001	5.419	0.005	0.002
Distancing ability (ability to recuperate mentally from work)	5.6 ± 1.53 5 (2 – 9)	5.9 ± 1.61 6 (3 – 9)	5.3 ± 1.34 5 (2 – 9)	0.019	3.59	0.023	0.007
Tendency to resignation in the face of failure	5.4 ± 1.68 5 (1 – 9)	5.3 ± 1.90 5 (1 – 9)	5.5 ± 1.33 6 (2 – 9)	0.777	0.265	0.768	0.679
Proactive problem-solving (active and optimistic attitude)	3.9 ± 1.72 4 (1 – 9)	4.2 ± 1.72 4 (1 – 9)	3.4 ± 1.64 3 (1 – 9)	0.003	6.881	0.001	0.011
Inner calm and balance (experience of emotional stability)	4.9 ± 1.62 5 (1 – 9)	5.1 ± 1.85 5 (1 – 9)	4.6 ± 1.22 5 (2 – 9)	0.049	2.631	0.075	0.044
Experience of success at work (satisfaction)	3.5 ± 1.99 3 (1 – 9)	3.8 ± 2.17 3 (1 – 9)	3.0 ± 1.62 3 (1 – 8)	0.015	4.962	0.008	0.015
Satisfaction with life	4.2 ± 1.78 4 (1 – 9)	4.7 ± 1.88 5 (1 – 9)	3.4 ± 1.31 3 (1 – 7)	< 0.001	17.629	< 0.001	< 0.001
Experience of social support	4.8 ± 2.14 5 (1 – 9)	5.6 ± 1.93 5 (1 – 9)	3.6 ± 1.90 3 (1 – 9)	< 0.001	25.277	< 0.001	< 0.001
Note. AV= average value; SD = standard deviation; GLM = General Linear Model							

with life and Experience of social support among international students were below the normal range and differed significantly from the values of students of German origin ($p < 0.001$). Only in the AVEM category Tendency to resignation in the face of failure are the groups of different origin comparable. These differences in the AVEM categories among students of different origins are maintained if the general conditions are included as covariates in the statistical analysis and the Bonferroni correction. Also here, only in the category of resignation tendency, no significant differences between the groups can be demonstrated Tendency to resignation in the face of failure. Most categories of the work/study-related behavior and experience patterns depend on the origin of the person during their studies. Only the categories Subjective importance of work in personal life and Willingness to work until exhausted were less prominent among students of German origin than among their fellow students ($p < 0.001$ and $p = 0.005$). This questionnaire also shows significantly lower levels of subjectively evaluated Satisfaction with life and experience of social support among international students.

Students were classified into the four work-related behavior and experience patterns (AVEM patterns) based on the characteristics of the AVEM categories (*Figure 2*). Only students who were clearly assigned to an AVEM pattern were included; 34 of the respondents could not be classified into the 4 AVEM patterns. Among students of German origin, 45% (n = 36) exhibited risk patterns A (20%) or B (25%). The others in this subgroup were assigned to pattern G (n = 24; 30%) and pattern S (n = 20; 25%). This distribution was significantly different ($p < 0.001$) in the subgroups of students of German and foreign origin. Only 14% of students from international countries had risk patterns A (10.5%) or B (3.5%). A significantly larger proportion of students of foreign origin (86%) had the health-promoting patterns G (31.6%) or S (54.4%).

Further examination of these AVEM patterns shows no significant difference ($p = 0.811$) in the allocation of subgroups with and without

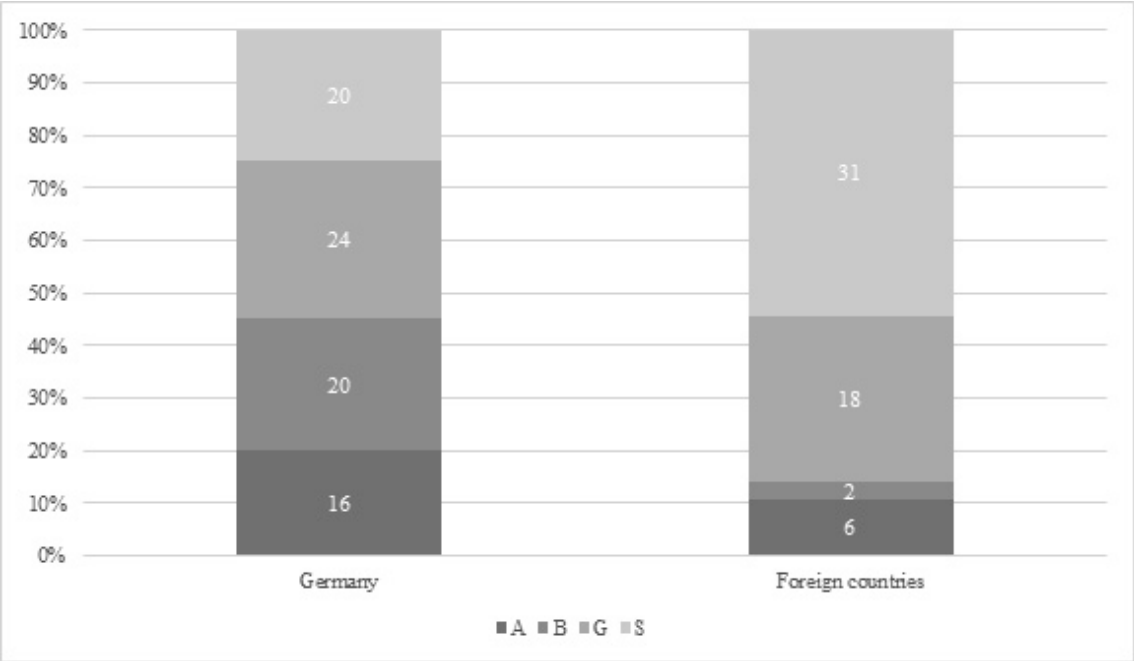

Figure 2. Allocation of subjects with different AVEM patterns in the groups of students of different origin ($p < 0.001$), only subjects with clearly classification to an AVEM pattern [20], n=137

potentially stressful conditions. In the group of students with pattern A and in the group with pattern G, half of the respondents stated that they had stressful conditions. The other half had no stressful conditions. In pattern B, this distribution is slightly different: 45.5% with vs. 54.5% without stressful conditions. In the case of the pattern S, 56.9 % of the test persons did not have any stressful conditions and 43.1 % indicated one or more stressful conditions.

Discussion

This study examines study-/work-related behavior and experience patterns and resources of students in comparison of German and foreign origin, taking into account potentially stressful conditions. There are significant differences between the groups. This work presents a theoretical background rather than a phenomenological description and shows that students also need help and support at the beginning of their professional careers. We assumed that studying in a foreign country produces less favorable conditions and strains. As a consequence, international students show more subjective stress and have lower resources.

There is limited data that has examined resources among students of diverse origins. Of the total sample of students, four factors were cited as the main stressors. These main stressors were working while studying, caring for children, nursing relatives and travel distance to place of work or study of more than 120 minutes and have mainly influence on the subjective importance of work in personal life, satisfaction with life, experience of social support and proactive problem-solving. The main stressors did not differ among students of different origins.

Regarding the AVEM, in contrast to what we expected, that only 14% of international students, but 45% of German students were found to have risk patterns for work-related behavior and experience. Nevertheless, there are differences in the study-/work-related behavior and experience patterns depending on the origin of the students. Satisfaction with life and Experience of social support was significantly lower and even under the norm among international students compared to their German colleagues. In contrast, the Willingness to work until exhausted was higher among international students than among German students, which seems unfavorable. A "no failure" in front of the family seems to be a reason here or the chance to get a job in Germany. All categories, with the exception of the Tendency to resignation in the face of failure, showed significant differences, with the international group scoring less favorably. A study of teaching students also indicates a problematic stress level among students. For more than 40% of the respondents, an AVEM risk pattern (A or B) with less favorable values in General Health Questionnaire 12 has been found [22]. The re-sults show the importance of health promotion and prevention programs for students, even in a university setting.

Unfortunately, only about 50% of all German universities offer health promotion and prevention [23]. Data from the German Student Union show that the need for consultation on study-related, performance-related, financial and personal problems has risen to 61% [24]. At 13% of the consultations are on the basis of a burnout-associated depressive disorder. Primary prevention in the context of psychotherapeutic student counselling (PSB) at the university location record an increase of 261 % in the number of clients and a simultaneous decrease by 12 % in the number of courses [25]. In 2018, 410 students used the services of the PSB, which at 15.9% is the highest level since data collection[26]. The students seeking counselling are most frequently affected by the impairment of their ability to study. In particular, 57.7% are affected by learning and work problems (including performance problems, difficulties in work organization or time management) and 54.8% by examination or failure fears[26]. A self-assessment showed that 14% of the students considered them-selves to be at risk of burnout; according to the consultants' assessment, the figure was as high as 21% [26]. It is alarming that 75.5% of the students seeking counselling suffered from one or more physical or psychosomatic complaints such as headaches or backaches, gastrointestinal problems or sleep disorders [26]. Nearly half of the students showed a small increase in their health status as a result of the PSB. The students developed an understanding of their problem situation, including the realization that further treatment is necessary. The PSB has often initiated conciliation, which confirms the usefulness of such consultations [25, 26].

In addition to counselling, the implementation of a study-related stress management course appears to be useful. A survey of work-related behavior and experience pat-terns among students found AVEM risk patterns in 88.9% of students before starting a stress management course, which was implemented over 8 weeks during the semester. It could be shown that health-promoting AVEM patterns increased in the course of the treatment and remained stable for 3 months even after independent application [27]. In a survey of German teachers and in contrast to this survey, the health-promoting patterns G and S were represented in the majority. Only one third of the teachers had AVEM risk patterns A and B [28]. Compared to other disciplines, student teachers generally show a predominance of health-promoting patterns.

Student resources also showed significant differences in occurrence between the two groups of students. However, the expression of resources showed rather higher scores among German students (not significant). This demonstrates how very differently one's own resources are interpreted. Resources can positively influence resilience [29]. Resilience describes the ability to preserve or quickly recover mental health during or after stressful life circumstances. [30]. Study results suggest better resilience among German students (higher prevalence of resources, more favorable expression resilience in dealing with everyday stress at work). One study consistently demonstrated more positive academic careers, lower intent to drop out, better grades, and life satisfaction among resilient students [31]. An empirical analysis found that international students have a more prominent risk awareness, also independent of family class. The analysis shows a stronger extrinsic motivation among international students when choosing a program of study; this includes high career prestige and good opportunities for advancement [32]. These data can be related to the increased subjective importance of work in personal life and willingness to work until exhausted of AVEM our data.

In summary, study/work-related behaviour and experience patterns are dependent on students' origin, and resources during study were significantly higher among German students. The results demonstrate the need for preventive and health promotion programs for students in the university setting – such as promoting health and social skills – regardless of their background. However, typical measures in the context of occupa-tional health management (e.g. massage, health-related education and training, dis-counts in health centers) are not available to students. Significant positive correlation was shown between social support and mental health [33]. A flexibilization and free scheduling of the attended modules increases the self-efficacy expectations of the students [13, 34], which can be examples of relationship prevention. Higher educational qualifications are an important predictor of individual and societal prosperity. It is a condition for mental health and well-being [35]. We support the view that universities have both - an obligation and a strong motivation to promote student health [36]. In the process, adequate resources should be created, thus ranging from resilience development and academic support resources, to crisis intervention and timely and effective care for students with emerging mental diseases.

The course of data collection shows that the number of students of foreign origin look-ing for counseling has increased from 13.8% in 2017 to 16.6% in 2018. This increase in our clientele developed equivalently to the proportion of international students at the universities (from 15.9% in 2015 to 21.7% in 2018) [26]. It seems quite important to pay attention to the origin of the students. One study showed that with similar levels of stress during studies, an increased suicidal tendency was observed among Chinese students compared to American students [37]. This could indicate, among other things, fear of failure in the family. In addition, social counselling, law advice, office hours of the health insurance companies in the Campus Service Center of the universities, the company relay races or health days and campaigns (Heart Health Project Week 2018, Bicycle Action Day 2017, Back Check 2012) are central offers for all those involved in the university institutions. Online courses can also enhance resources. Implementing an online course on sleep disorders can increase students' sleep quality [38], which could improve mental health and performance.

As a limitation, it should be noted that the period of the survey was not recorded reliably. It cannot be surely clarified whether strains on students during their studies or the general conditions are a greater strain factor. Surveys at the end of the semester can cause higher demands than at the beginning because the general conditions have already been passed for several weeks and especially at the end of the semester there are also exams. In the case of questionnaires on paper, answers in the sense of social wishful thinking are possible. If there are language barriers for international students, uncertainties in the answers are possible despite the presence of an interpreter. Due to the small sample size of international students from various countries this study has the character of a pilot study. More data should be collected.

Conclusions

In summary, it should be commented that a study-related strengthening of resources is necessary, which can definitely be viewed as a competitive advantage to be chosen as a study location. The identified framework conditions, the origin and resources of the students play a role in study- or work-related behavior and experience patterns. This should be taken into account in health promotion programs and, most importantly, not only minimize strains but also "work out" resource-oriented strategies. Improving organizational factors (e.g. information flow, exam scheduling, theoretical and practical teaching quality, time and performance pressure, social interactions and individual characteristics (e.g. self-expectation, fear of failure) has been shown to reduce stress [39]. These organizational factors could correspond to our recorded resources such as enjoyment of study and work or collegial and welcoming atmosphere in the environ-ment. A strengthening of resources could also be achieved through newer procedures such as "Telemental Health". This would reduce barriers in the search for psychosocial help and support students who are searching for advice [40].

Declarations

Ethics approval and consent to participate

The Otto von Guericke University in Magdeburg, Germany (register no. 65/08) gave positive ethical opinions. The study complied with the guidelines of Declaration of Helsinki. The consent of the study participants was given in writing. Informed consent was obtained from all subjects involved in the study.

Consent for publication

All authors give their consent to publication.

Funding Sources

This research received no external funding.

Competing Interests

The authors declare that there is no conflict of interest.

Availability of data and material (data transparency)

The data can be requested from the authors.

Authors' Contributions

Conceptualization, I.B., I.Z. and B.T.; methodology all authors.; software, I.B. and B.T.; validation, all authors; formal analysis, I.B. and B.T.; investigation, I.B.; resources, I.B. and S.D..; data curation, I.B. and S.D.; writing-original draft preparation, I.B. and B.T.; writ-ing-review and editing, all authors; visualization, I.B. and B.T.; supervision, I.B.; project administration, I.B.; funding acquisition, not applicable. All authors have read and agreed to the published version of the manuscript.

Acknowledgments

We would like to thank Jessica Linke, Shawki Bahmad, and Claudia Schupp, who were particularly involved in the initial phase of the study.

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Received: 07-Jul-2021
Accepted: 20-Sep-2021

ENDOTHELIAL FUNCTION IN PATIENTS WITH COPD AND CARDIOVASCULAR DISEASE (REVIEW)

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https://doi.org/10.35339/ic.8.3.144–151

Abstract

Cardiovascular pathology is one of the frequent comorbidities in patients with chronic obstructive pulmonary disease, due to both genetic predisposition and common risk factors (smoking, senile age, male gender, sedentary lifestyle, obesity). The article shows that development of endothelial dysfunction is one of the earliest phases of pathogenesis in this setting. Endothelial dysfunction mechanisms are defined and characterized, including imbalance of vasoconstricting and vasodilating agents with the emergence of "vicious circles" that violate hematovascular homeostasis. The role of nitric oxide, endothelin-1, intercellular adhesion molecule-1 (ICAM-1) in the development of endothelial dysfunction in COPD patients is discussed. The article defines the concept of oxidative stress, the most potent oxidants and mechanisms of their damaging effect are listed. A particular attention is paid to 8-isoprostane as a golden standard in assessment of oxidative stress in patients with COPD.

Keywords: *chronic obstructive pulmonary disease, hypertension, coronary artery disease, heart failure, nitric oxide, endothelin-1, intercellular adhesion molecule-1, 8-isoprostane.*

Background

Chronic obstructive pulmonary disease (COPD) is a medically, socially and economically relevant problem, both in Ukraine and worldwide, leading to limitation of exercise capacity and ranking third among causes of disability after coronary disease (CAD) and hypertension [1–3]. According to the World Health Organization (WHO), roughly every 10 seconds one person dies due to COPD. Currently, more than 210 million people suffer from this disease and by 2030, COPD trends to become the third leading cause of death in the world [2]. COPD is currently the 4th cause of death, which is primarily due to the high prevalence of smoking among both men and women. It is only surpassed by cardiovascular diseases, infectious diseases (including HIV infection/AIDS) and cancer [4].

According to the WHO estimates, about one third of the world's adult population are smokers. In our country, 58% of men and 14% of women consider themselves to be smokers. The prevalence of tobacco smoking among adolescents is impressive, reaching 50% by the age of 13–16 years. According to the British research company ERC, Ukraine ranks second in the world in terms of the number of cigarettes smoked per person per year. On average, a Ukrainian smokes 2,500 cigarettes a year, or seven a day [5]. More than 90% of COPD deaths occur in low- and middle-income countries.

The modern concept of COPD endorsed by the WHO experts emphasizes that severity and prognosis of COPD are often determined by extrapulmonary manifestations of concomitant diseases. This position was reflected in the Global Strategy for the Diagnosis, Treatment and Prevention of COPD (GOLD), 2011 [6].

Most patients with COPD have multiple concomitant diseases. A five-year follow-up of patients with COPD has shown that the risk of death increases not only in proportion to the severity of bronchial obstruction, but also with an increase in the number of concomitant diseases (from 1 to 3) [7].

COPD is accompanied by systemic manifestations, in particular, a significant increase in the incidence of cardiovascular diseases. In addition,

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it is cardiovascular complications that are the main cause of death in patients at the initial stages of COPD. The high frequency of the combination of COPD and cardiovascular pathology is due to genetic predisposition and common risk factors: smoking, senile age, male gender, sedentary lifestyle, obesity, obstructive sleep apnea/hypopnea, secondary hyperaldosteronism, as well as hypertensive effect of a number of drugs used for the treatment of patients with COPD (corticosteroids, beta-2 agonists, etc.) Hypertension, CAD (including myocardial infarction and angina pectoris), cardiac arrhythmias and heart failure (HF) are most common in patients with COPD [8].

The comorbidity of COPD and cardiovascular pathology is driven by a combination of complex multi-stage pathogenetic processes, among which it is difficult to single out the leading factor. Recent studies [9] emphasize the importance of the concept of comorbidity, which implies the formation of relationships and interactions between co-existing diseases, as well as presence of common pathogenetic mechanisms, such as chronic low grade inflammation, oxidative stress, and endothelial dysfunction.

The **purpose** of this review was to highlight the pathogenetic features of endothelial dysfunction in patients with comorbid course of chronic obstructive pulmonary disease and cardiovascular pathology.

Large epidemiological studies have demonstrated that the leading cause of mortality in patients with COPD and bronchial asthma (BA) is not respiratory failure, as it has been traditionally believed, but cardiovascular events. The severity of the course and prognosis in COPD and BA is determined by the involvement of heart and blood vessels in the pathological process [10], which can lead to development of concomitant cardiovascular pathology. At the annual ERS congress in 2009, J. Feary and N. Barnes from the UK presented the results of the Health Improvement Network, a computer database that unites more than 5 million case histories: – COPD patients are 5 times more likely to be diagnosed with cardiovascular diseases (CVD); – in the 35–45 years subgroup, patients with COPD have a 7.6 times higher risk of developing concomitant CVD; – in young patients with COPD, the risk of developing myocardial infarction increases 12-fold [11].

Endothelial dysfunction is a vascular complication of BA and COPD, which, in turn, aggravates the growing respiratory failure, hypoxemia and tissue hypoxia [12]. In this regard, the functional state of the endothelium at different periods of the disease is the subject of active study.

To date, more and more data are accumulating that not only local inflammation in the bronchi, but also persistent systemic inflammation, typical for patients with COPD, makes a significant contribution to the development and progression of endothelial dysfunction, atherosclerosis and CVD in patients with broncho-obstructive pathology, determining the interest to this problem.

8-isoprostane as the gold standard for assessing oxidative stress in patients with COPD

The main role in the mechanisms of development of endothelial dysfunction is played by oxidative stress developing against a background of hypoxia [13], which leads to an increase in the production of powerful vasoconstrictors, cytokines and tumor necrosis factor-α (TNF-α). For today, the term "oxidative stress" (OS) is understood as a state in which the amount of free radicals generated in the body significantly exceeds the capacity of endogenous antioxidant systems that ensure their elimination [14]. OS is a common pathway leading to damaging of the vascular endothelium. The disturbance of the equilibrium between synthesis and elimination of reactive oxygen species (ROS) such as (O2-) and (H2O2) affects the homeostasis of cellular oxidative stress, playing an important role in the development of cardiovascular disease [14]. Uncontrolled generation of ROS and their derivatives causes damage to proteins, nucleic acids, enzymes and biological membranes, which may lead to cellular death. OS might also lead to the appearance of cellular mutations and malignant transformation [15]. Toxic components of cigarette smoke can also induce OS, leading to disruption of the functional activity of the endothelium.

8-iso-PgF2α (8-isoprostane) is considered to be one of the most specific biological markers that allows estimation of the level of free radicals production with a sufficient degree of accuracy, reliability, and reproducibility. 8-isoprostane is a metabolic product in the reactions of peroxidation of arachidonic acid, isomeric prostaglandin F2, and its amount is directly proportional to the level of free radicals formed. Determination of the level of 8-isoprostane serves as the gold standard for in vivo oxidative stress evaluation [16].

8-isoprostane reflects the cellular effects of OS and, therefore, the inflammatory process in the airways. In recent years, there has been an increasing interest in the study of the lungs by means of non-invasive methods, including measurement of biomarkers in exhaled air and

exhaled breath condensate (EBC) [17]. These methods are safe, do not affect lung function and the level of exhaled mediators [18], which allows their use as epidemiological methods for studying pathological processes (OS and inflammation) in respiratory diseases.

The concentration of 8-isoprostane in the EBC was increased in patients with remission of COPD compared with healthy non-smokers [19, 20]. Also, the level of 8-isoprostane in EBC was increased in healthy smokers [20] and patients with exacerbation of COPD [19, 21, 22]. Montuschi P. et al. showed that the levels of 8-isoprostane in patients with COPD, both smokers and non-smokers, were 1.8 times higher than in healthy smokers. In healthy non-smokers, its concentration was 2.2 times lower than in healthy smokers. There were no correlations between the level of 8-isoprostane and forced expiratory volume in 1 second (FEV1), smoking experience, cellular composition of sputum or severity of dyspnea in patients with COPD [19, 20]. However, a 2-fold increase in 8-isoprostane level in EBC compared to healthy people was reported in patients with mild course of bronchial asthma, and in severe course, its level was 3 times higher than in patients with mild bronchial asthma, regardless of inhalation treatment received. After treatment, its concentration decreased [23, 24].

Pathogenetic features of endothelial dysfunction in patients with chronic obstructive pulmonary disease and cardiovascular pathology

Currently, the prominent role of endothelium and nitric oxide in the genesis of cardiovascular complications of COPD has been proven. The unique position of endothelial cells at the border between circulating blood and tissues, and in the case of the lungs, the air environment of the alveolar space and blood, makes them not only the most important, but also the most vulnerable to various pathogenic influences that can cause damage to endothelial cells, thereby contributing to the development of endothelial dysfunction (ED) [25]. ED is based on structural (apoptosis and desquamation of endothelial cells) and functional (imbalance between biologically active substances produced in the endothelium) changes. Endothelium forms a thin semi-permeable membrane lining the heart and blood vessels from the inside, continuously producing a huge amount of biologically active substances (BAS). Hence, the complex of endothelial cells may be considered a giant paracrine organ distributed throughout the human body [26]. Endothelial cells produce BAS that take part in the regulation of vascular tone, synthesis of growth factors and mediators of nonspecific inflammation. In healthy individuals, the effect of endothelial BAS is in dynamic equilibrium. The main role of the endothelium is associated with dilatation of the vascular bed, which provides the peripheral muscles and internal organs with adequate blood supply [27]. Under physiological conditions, secretion of vasodilating substances predominates. Nitric oxide (NO), which controls the basal tone of arterioles and, as a consequence, participates in blood pressure (BP) control, is the main endothelium-derived vasodilating factor. If the ability of endothelial cells to produce vasodilating substances decreases, and the formation of vasoconstrictors persists or increases, the so-called ED is formed – a disturbance of the equilibrium of oppositely acting BAS that violates hematovascular homeostasis. Endothelium is a dynamic system that maintains the normal properties of circulating blood by inhibiting hypercoagulation and preventing leukocyte adhesion [28].

In the pathogenesis of COPD, the main factor in the development of ED is a decrease in NO synthesis with preserved or increased secretion of vasoconstrictors (endothelin-1, thromboxane, angiotensin II), as well as cytokines and tumor necrosis factor-α (TNF-α) that further suppress nitric oxide production [28], which impairs endothelium-dependent vasorelaxation and leads to degradation and adverse changes in vascular cytoarchitectonics.

Many studies have assessed the diagnostic value of plasma ED biomarkers, since this is a simple and objective method that provides information both on normal physiological processes and in pathology. Taking into account the fact that the levels of circulating plasma BAS depend not only on the severity of ED but also on other factors (concomitant pathology, immune diseases, chronic infections), the results being significant in a separate study may not necessarily reflect the picture at the populational level. Therefore, an ED biomarker should optimally have a predictive role in relation to the cardiovascular risk. The results of earlier studies [29] showed that E- and P-selectins, endothelin-1, von Willebrand factor, cell adhesion molecules, and thrombomodulin have a significant prognostic value in this context.

A significant increase in the blood endothelin-1 (ET-1) level has been reported in patients with uncomplicated hypertension. In patients with stage 2 and 3 hypertension, the level of ET-1 and its precursor increases 10-fold [30]. ET-1 is a

large bicyclic polypeptide synthesized in the vascular endothelium, bronchial epithelium and in alveolar macrophages. Its main function is to activate vasoconstriction, particularly in small vessels. Another function of ET-1 is the ability to influence platelet adhesion, which contributes to formation of microthrombosis [31]. In hypoxia, the level of ET-1 in the blood increases. Especially high plasma levels are detected in COPD exacerbation. In patients with COPD with hypoxemia, the level of ET-1 in the arterial blood is higher compared to those without hypoxemia [32]. High levels of ET-1 contribute to the further progression of ED, thereby aggravating the course of the disease [33]. A significant association has been shown between the level of ET-1 and hemodynamic parameters of pulmonary circulation. Shao D. et al. have shown the correlation between ET-1 levels with pulmonary artery pressures and pulmonary vascular resistance [34]. Presence of high ET-1 levels in patients with COPD contributes to adverse cardiovascular and pulmonary remodeling with dilation of the cardiac chambers and formation of a chronic cor pulmonale [35–37]. ET-1 induces prolonged vasoconstriction, hypertrophy of the smooth myocytes and endothelial remodeling affecting arterial elasticity [38]. Thus, it can be assumed that impaired endothelial function triggers the process of structural and anatomical changes in the vascular wall and increases the arterial stiffness [39].

The interaction of leukocytes with the endothelium occurs through special adhesive molecules, which are present on both endothelial cells and leukocytes. Selectins (P, E, L) present a class of adhesion molecules. P- and E-selectins are expressed by the endothelium. An increase in the endothelial adhesiveness plays an important role in the pathogenesis of ED in inflammation, atherosclerosis, septic shock, and other pathological processes. P-selectin is accumulated in the endothelium and released from it during stimulation. Adhesion molecules may be getting into the bloodstream not only with stimulation of the endothelium, but also in its activation and damage, as evidenced by data provided by E. Oelsner et al. (2013), showing high levels of endothelial dysfunction biomarkers (endothelin-1 and adhesive molecules (P-selectin and ICAM-1)) in COPD patients with their level correlating to the severity of bronchial obstruction [40]. This data is also confirmed by the results of the Framingham study, in which patients with COPD had high levels of inflammation markers: CRP, ICAM-1 and P-selectin, the activity of which had an inverse relationship with the value of forced expiratory volume in 1 second (FEV 1) [41]. A study by J. Zhonghua et al. has also shown an increase of P-selectin levels in patients with COPD, which was more prominent during exacerbations [42]. As for the previously mentioned intercellular adhesion molecule-1 (ICAM-1), it belongs to the family of immunoglobulins and serves as a functional ligand for the leukocyte integrin LFA-1 (Lymphocyte Function-Associated Antigen-1). Adhesion of monocytes to activated endothelial cells due to overexpression of ICAM-1 on their surface is considered the earliest stage of endothelial damage. Inhibition of adhesion molecules expression, in particular ICAM-1, prevents the accumulation of inflammatory agents in the vascular wall, which reduces their ability to cause endothelial damage that is characteristic of COPD [43] and cardiovascular pathology [44].

The leading role in reduction of the endothelium-dependent vasodilation (EDVD) in patients with COPD is played by intracellular OS, and smoking is the most significant exogenous factor in its formation. Free radical oxidation significantly reduces NO production by endothelial cells [45], which is manifested by suppression of NO synthase expression by endothelial cells and stimulation of adhesion molecules expression, followed by increased adhesion of leukocytes to the luminal surface of the vascular wall [46]. It has been shown that cigarette smoking leads to impaired vascular reactivity, namely, weakening of endothelium-dependent vasodilation [47]. It was found that an increase in smoking intensity was characterized by a progressive decrease in EDVD, as well as development of not only endothelial damage, but an adverse remodeling of deeper layers of vascular wall in smoking COPD [48].

To date, the features of the formation and clinical significance of increased arterial stiffness in patients with CVD (atherosclerosis, hypertension, ischemic heart disease) are most fully studied [49]. Perhaps, it is the increased arterial stiffness and endothelial dysfunction that is the link between COPD and CVD.

Features of the course of hypertension, coronary artery disease, heart failure in COPD

Previous studies have shown that the patients with a comorbid course of COPD and CVD have distinct clinical features compared to isolated course of these diseases.

The patients with hypertension and COPD are characterized by a higher resting heart rate (HR) [50]; more frequent target organs damage, including renal failure, and a higher risk of

cardiovascular complications when compared with hypertensive patients without COPD at the same blood pressure (BP); hypertension in patients with COPD is characterized by earlier manifestation and higher BP values [51]. In patients with COPD, significant changes in the course of hypertension are related mainly to the night period: disturbance of the circadian rhythm of blood pressure with insufficient night dip; a more significant increase in DBP and an increase in the morning surge. All patients showed an increase in blood pressure variability [52]. It follows that such patients need to optimize BP control in the evening and night hours.

In a Spanish study evaluating airflow restriction using spirometry in patients with/without CVD in general population and among hospitalized CAD patients, airflow restriction was found in 19.2%, 17.5% and 33.6%, respectively [53]. The highest prevalence of COPD was observed among patients with CAD. Therefore, it would be beneficial for all CVD patients to undergo spirometry [54]. The patients with established CAD and COPD had more severe atherosclerosis vs those without COPD [55]. Another study showed that patients with COPD had more atherosclerotic lesions found in PCI compared with patients without COPD, and these patients had a higher mortality rate [56, 57].

The PREMIER study, which evaluated the course of myocardial infarction, showed that in patients with COPD, the risk of mortality and readmission was twice as high and the quality of life was lower [58,59]. A large retrospective observational study of Swedish COPD patients in primary care has shown that coexisting heart failure, stroke and myocardial infarction were the strongest predictors of death, highlighting the importance of early detection and treatment of comorbidities. A reduced risk of death was also found to be associated with the use of inhaled corticosteroids, beta-blockers and aspirin, and an increased risk associated with the use of long-acting muscarinic antagonists and N-acetyl-cysteine [60].

Conclusions

The development of cardiovascular diseases against a background of chronic obstructive pulmonary disease may be considered to some extent natural. The evidence shows that endothelial dysfunction is one of the main components in the pathogenesis of comorbid course of chronic obstructive pulmonary disease with hypertension, coronary heart disease. Assessment of the endothelial function may be of importance for expanding understanding of pathogenesis in many conditions and clinically for predicting the development of complications. This will make it possible to use drug therapy in the treatment of such patients, including the drugs that have a positive effect on the state of the endothelium.

Declarations

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Consent for publication

All authors give their consent to publication.

Disclosure Statement

The authors have no potential conflicts of interest to disclosure.

Funding Sources

There are no external sources of funding

Data Transparency

The data can be requested from the authors.

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Received: 05-May-2021
Accepted: 06-Sep-2021

THE ROLE OF ASSESSMENT AND CORRECTION OF NUTRITIONAL STATUS IN A COMPREHENSIVE APPROACH TO COVID-19 PATIENTS WITH METABOLIC DISORDERS (REVIEW)

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https://doi.org/10.35339/ic.8.3.152–156

Abstract

The article features the problem of coronavirus disease COVID-19 with emphasis on the nutritional status of the patients. An analytical review of the recent publications related to the aspects of nutritional support for people in outpatient and inpatient treatment for COVID-19 is presented. The article highlights the pathogenetic justification of the relationship between the immune response and metabolic balance of the body, the optimal content of trace elements, vitamins, components of lipid metabolism. The importance of nutrition as a strategy to support human immune function is considered. Methods for determining the adequate energy balance of patients with severe COVID-19 are presented. Groups of foods and key nutrients that may affect the consequences and clinical course of respiratory infections are described. The importance of assessing and optimizing nutritional status to improve the clinical course and consequences of COVID-19 in patients with comorbid pre-existing non-communicable diseases, such as diabetes, cardiovascular disease, obesity with systemic inflammation, is emphasized.

Keywords: *coronavirus disease COVID-19, nutritional status, microelements, vitamins, components of lipid metabolism, diagnosis of malnutrition.*

Coronavirus disease 2019 (COVID-19) is currently a pandemic that has far-reaching consequences for the health of both the individual and the population as a whole and causes serious damage to the society and economy of many countries. Given the great urgency of this problem, identifying the main risk factors for adverse disease and finding possible ways to correct it is one of the priorities of the modern medical community.

To date, a relationship between a number of risk factors, such as diabetes, cardiovascular, cerebrovascular, pulmonary disease, patient age and severe course of the disease, and mortality in patients with COVID-19 has been established. These pathological conditions are mostly characterized by systemic inflammation, which may be a common feature that affects the treatment outcome in patients with new coronavirus disease. An increase of scientific data also proves that the clinical course and consequences of COVID-19 are more unfavorable in those who are overweight or obese [1, 2].

The pathogenetic justification of this phenomenon can be explained by several mechanisms. On the one hand, the presence of obesity affects the immune system by altering the expression of proinflammatory cytokines, which leads to an increase in the cytotoxic response of immunocompetent cells that play a key antiviral role. Thus, according to O'Shea D., Corrigan M., Dunne MR (2013) dendritic cells, which play a crucial role in the relationship between innate and adaptive immunity, in obesity produced twice as much of the immunosuppressive cytokine interleukin-4 (IL-4) and four times more IL-10 than the control group [3]. On the other hand, angiotensin-converting enzyme 2 (ACE2) is known to be a probable receptor for penetration into target cells with extremely high affinity for SARS-CoV2. ACE2 expression in adipose tissue was found to be higher than in the lung, with

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ACE2 receptor expression being the same for adipose tissue in obese and non-obese patients. The difference lies in the mass of adipose tissue and, consequently, more ACE receptors [4].

It should also be noted that obesity is usually associated with the factors of the group of diseases constituting metabolic syndrome, and therefore have a negative impact on the clinical course of COVID-19 and increase the overall risk of mortality [5].

Given the above, the importance of correcting the nutritional status of patients in this cohort and assessing the impact of dietary characteristics on the clinical course of COVID-19 in the acute stage and in the rehabilitation period becomes relevant.

It is now known that almost all nutrients play a critical role in maintaining an "optimal" immune response. Insufficient or excessive consumption of certain substances can have negative effects on the immune status and increase susceptibility to various pathogens [6].

For example, the main functional role of microelements in the cells of the immune system is their participation as cofactors or catalysts for enzymes of free radical oxidation.

Zinc deficiency causes violation of hormonal regulation of growth and puberty in humans and animals, which leads to growth retardation and hypogonadism, reduces psychomotor development, increases susceptibility to infection. Depending on the degree of zinc deficiency, the characteristic features are thymic atrophy and loss of T and B lymphocyte precursors in the bone marrow by 50–70% due to induction of glucocorticoid-dependent apoptosis with subsequent lymphopenia and immunodeficiency [7]. Inhibition of the activity of natural killers, lymphokine-activated killers and mitogen-dependent lymphocyte proliferation is also observed. Such pathophysiological status contributes to the development of autoimmune pathology [8, 9].

Manganese is a component of many enzymes, including manganese-dependent superoxide dismutase, which is involved in lipid peroxidation in the cells of the immune system, as well as in other processes of free radical oxidation. Manganese-dependent superoxide dismutase acts as the main integral scavenger of reactive free radicals with a damaging effect, which are formed in the mitochondrial matrix [10]. Recent studies have shown that manganese-dependent superoxide dismutase, in addition to performing its antioxidant functions, also acts as a fundamental regulator of cell proliferation, a mediator of metabolism and apoptosis. This protein plays an anti-apoptotic role against oxidative stress, ionizing radiation, pro-inflammatory cytokines [11].

Dietary *phosphorus* helps to strengthen the cellular immune system and reduce the humoral immune response. As for magnesium, there are no studies that clearly prove its role in the dysfunction of the immune system, but its important contribution to the process of chronic subclinical inflammation. Individuals who consumed magnesium less than the recommended daily allowance showed a probable increase in the level of C-reactive protein [12].

Vitamins, similar to microelements, regulate the formation of superoxide anion by phagocytes in response to infectious agents, prevent oxidative-dependent tissue damage and increase the activity of natural killers. Thus, reducing the level of vitamin A helps to suppress the humoral immune response to T-dependent antigens, reduces the activity of cytotoxic lymphocytes and increases susceptibility to bacterial infection. At the same time, iodine excess has a suppressive effect on the immune system [13].

Vitamin E deficiency reduces mitogen-dependent lymphocyte proliferation and the activity of natural killers, and its regular intake provides an increase in overall resistance to infectious processes, especially in the elderly and senile [14]. However, there are still no convincing data on the role of vitamin E in prevention and treatment of new coronavirus infection.

Vitamin C mainly affects the non-specific part of the immune system, increasing the synthesis of macrophage proteins, proteins of the complement system and thus enhancing the non-specific resistance of the body and antiviral immunity. A large-scale multicenter clinical study of CITRIS-ALI previously confirmed a reduction in the risk of multiple organ failure and levels of markers of inflammation and vascular damage in patients with acute respiratory distress syndrome (ARDS) of various etiologies with high doses of vitamin C [15].

However, a preliminary study of 167 patients with ARDS due to COVID-19 conducted in the United States did not show a significant improvement with the introduction of 50 mg/kg of ascorbic acid in 5% glucose solution iv every 6 hours for 96 hours [16]. In China, a full-scale clinical study was launched using 24 g of vitamin C per day for 7 days to definitively address the feasibility of including high doses of vitamin C in treatment algorithms for patients with COVID-19 [17].

Vitamin D 3 is one of the most active factors in the regulation of the immune system, influen-

cing the processes of lymphocyte activation and synthesis of anti-inflammatory cytokines. This is mainly due to the inhibition of T-cell proliferation and, as a consequence, the transition from T-helper cells of type 1 (Th1) to T-helpers of type 2 (Th2). It can be argued that decreased Th1 proliferation leads to lower levels of pro-inflammatory cytokines and reduced acquired immune responses, which may be counter-productive to a successful immune response against viruses. Vitamin D also affects the maturation of T cells and can alter the development of inflammatory T-helper mass of cells type 17 (Th17) on the population of anti-inflammatory regulatory T cells (T-regulatory cells), which reduces the level of "provocative" cytokines such as IL-1, IL-6, IL-12, TNF alpha and IL-17 and increase the anti-inflammatory effect of IL-10. Thus, due to its opposite actions on cytokine regulation and T-cell differentiation, vitamin D plays a complex dual role in immunoregulation [18]. Today, in the current COVID-19 pandemic, vitamin D deficiency is considered as one of the potential risk factors and a possible factor in development of the process, which is called cytokine storm [19].

Components of *lipid metabolism* are of great importance in the regulation of immune system functions. Representatives of all classes of lipids have active immunomodulatory potential, especially for phospholipids, sphingolipids and fatty acids. Some researchers have shown that high levels of long-chain polyunsaturated fatty acids (PUFAs), especially omega-3 PUFAs, protect overweight or obese people from developing metabolic syndrome and inflammation from an early age [20]. The importance of lipids is determined by their physiological role: eicosapentaenoic acid (EPA) is required for the synthesis of eicosanoids, docose hexaenoic acid (DHA) is needed to support the vital functions of the immune system. Under inflammation, the DHA and EPA present are enzymatically converted into specialized mediators known as resolvins, protectins, and maresins. These molecules, among others, are responsible for reducing inflammation, including in the airways. Derivatives of omega-6 PUFA, in particular arachidonic acid and its metabolites (prostaglandins, leukotrienes, thromboxanes, prostacyclins), affect the expression of lymphocyte genes, and are direct effectors of many reactions in the cells of the immune system. It is known that deficiency of these essential fatty acids can lead to delayed or incomplete regression of inflammation. This may be important in the context of severe COVID-19 infection, which is manifested by uncontrolled inflammation and cytokine storm manifestations. In animal experiments, the protective effects of specialized mediators formed from EPA and DHA, which are manifested by the elimination of acute lung damage, were demonstrated [21–22]. Currently, a number of studies have also been conducted on the effect of pharmaconutrients, the so-called "immunological nutrition", on the clinical course of severe diseases and acute respiratory viral infections (ARVI). However, the recent Cochrane Review of 10 randomized controlled trials of varying quality involving 1,015 participants found no significant differences in the effects of omega-3 fatty acids and antioxidants on the clinical course of the disease in adults with ARVI according to the number of days of ventilation, duration of stay in the intensive care unit or the level of oxygenation of the blood [23].

Several studies linking the immune system and carbohydrate metabolism disorders are currently known, but insufficient data have yet been obtained on individual pathogenetic components of this process. Obesity and diabetes have been shown to have similar changes in T-cell immunity that may contribute to metabolic disorders. These integral indicators include an increase in the number of CD45 + T cells, a redistribution of leukocytes in the direction of the inflammatory phenotype, and a decrease in the number of suppressive regulatory T cells and protective NK cells. Metabolic changes in obese and diabetic patients may further affect the differentiation and functioning of components of innate and adaptive immunity [24].

Thus, all the main components of food, namely - proteins, fats, carbohydrates, microelements, vitamins, to some extent show immunomodulatory activity, affecting all parts of the immune response, including non-specific protective reactions and native immunity. Both the presence of obesity and the lack of nutrients are important for immune function. Starvation and malnutrition have been shown to suppress immune function and increase susceptibility to infections.

Appropriate assessment of human nutritional status and proper correction are effective tools to improve clinical outcomes, reduce complications, hospitalize and stay in the intensive care unit of patients with COVID-19 in various situations, including polymorbidity, obesity and old age.

Patients at risk of adverse effects should be evaluated for malnutrition using the MUST (Malnutrition Universal Screening Tool) or NRS-

2002 (Nutritional risk screening) criteria. GLIM (Global Leadership Initiative on Malnutrition) criteria can also be used to diagnose malnutrition. GLIM criteria provide a two-step approach to the diagnosis of malnutrition:

First level – risk assessment using proven screening tools such as MUST or NRS-2002.

Second Level – assessment of the malnutrition severity.

Human energy needs can be estimated by indirect calorimetry in the case of availability and guaranteed sterility of the measuring system, or, alternatively, by calculation. According to the ESPEN recommendations, it is recommended to consume 20–30 kcal/ kg/ day, for patients who are in a serious condition or have concomitant diseases – 27–30 kcal/ kg/ day. Clinical observations confirm the need for adequate energy balance in patients with severe COVID-19.

The daily requirement for protein is in the range from 1.2 to 2.0 g/kg. Muscle atrophy may develop in severe patients due to increased protein catabolism. In turn, increasing protein intake can reduce mortality. It is important to provide patients with foods with high energy value, high protein content and optimal bioavailability of nutrients.

Consumption of fats and carbohydrates should meet the energy needs, taking into account the per-centage of energy coming from fats and carbo-hydrates 30:70 (patients without respiratory failure) and 50:50 (patients who need respiratory support).

Optimal nutritional support for adequate immune function may require the consumption of some micronutrients above the recommended level, because infections and other stressors can worsen nutrient status.

In particular, during an infectious disease in humans, the level of vitamin C in the systemic circulation is reduced. To restore its normal level in the blood, it is necessary to prescribe a higher intake of this vitamin. According to some studies in viral pneumonia, the addition of vitamin C to patients ≥200 mg/ day restores depleted plasma and cellular levels of vitamin C and reduces respiratory symptoms and reduces the duration of hospitalization.

The addition of micronutrients and omega-3 PUFAs is a safe, effective and inexpensive way to eliminate nutritional deficiencies, ensure optimal immune function, and therefore reduce the risk and consequences of infections. Multivitamins and mineral supplements, which provide the basic needs for micronutrients, are recommended in addition to an optimally balanced diet.

To sum up, nutrition is an important determinant of a person's immune status. Disorders of cellular immunity, phagocyte function, complement system, cytokine production and immunoglobulin A secretion are directly related to protein-energy deficiency. Thus, assessment and correction of nutritional status should be considered as an integral part of a comprehensive approach to the management of patients with COVID-19 at all stages of the disease in order to personalize and enhance treatment.

Declarations

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Consent for publication

All authors give their consent to publication.

Disclosure Statement

The authors have no potential conflicts of interest to disclosure.

Funding Sources

There are no external sources of funding

Data Transparency

The data can be requested from the authors.

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Received: 05-Aug-2021
Accepted: 20-Sep-2021

THE ROLE OF RESISTIN IN THE PROGRESSION OF NON-ALCOHOLIC FATTY LIVER DISEASE

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https://doi.org/10.35339/ic.8.3.157–162

Abstract

The **aim** of the research was to study the relationship between plasma concentrations of resistin and indicators of enzyme and pigment metabolism in patients with non-alcoholic fatty liver disease (NAFLD) and its combination with type 2 diabetes mellitus (DM-2) depending on phenotype of patients. **Materials and methods.** On the base of Kharkiv Regional Hospital a total of 90 patients were examined, including patients with NAFLD (n = 20) and its combination with DM-2 with normal body weight (n = 20) and obesity (n = 50), as well as 20 healthy volunteers. A complex of clinical, laboratory and instrumental (including liver biopsy in 9 patients) examinations of patients was performed. **Results.** A direct relationship was established between the level of resistin and indicators of enzyme and pigment exchange in groups of patients with combined pathology. A significant increase of resistin plasma level, as well as disorders of the liver function were determined in all groups of patients in comparison with the controls. The most marked changes were revealed in patients with combination of NAFLD, DM-2 and obesity. **Conclusions.** The established relationship between the level of resistin and the indicators of the liver functional state suggests that an increase of resistin level may reflect the presence of impaired liver function in patients with NAFLD in combination with DM-2, predicting the progression of NAFLD. In order to detect the disorders of liver function in patients with DM-2, it is recommended to determine the level of resistin in patients with NAFLD, especially when concomitant obesity is present. The higher the body mass index in obese patients, the more pronounced the effect of resistin on liver function in patients with this comorbid pathology.

Keywords: *non-alcoholic fatty liver disease, type 2 diabetes, obesity, resistin.*

Introduction

Non-alcoholic fatty liver disease (NAFLD) is characterized by the presence of fatty liver infiltration, verified by visual tests or histology in the absence of alcohol abuse (<40 grams of pure ethanol per day for men and 20 grams for women), the use of steatogenic drugs, or hereditary diseases [1, 2]. NAFLD is associated with obesity and insulin resistance (IR) [3].

The issues of etiopathogenesis of this metabolic pathology still remain unresolved.

Adipose tissue is a key endocrine organ that communicates with brain, muscle, liver, and pancreas, thereby maintaining energy homeostasis. The communication between adipose tissue and other organs is mainly mediated by multiple endocrine substances secreted by adipose tissue, referred to as "adipocytokines" [4–8]. Adipose tissue hormones, for example, resistin, is considered in the literature as a pathogenic factor for the development of obesity and IR, it functions as a signal to reduce insulin-stimulated glucose uptake [9–14], and is also referred to as "intrahepatic cytokine" [15–17], which affects on function and creates a pro-inflammatory effect in the stellate cells of the liver, key modulators of fibrosis.

The search for common mechanisms between the development of NAFLD and metabolic disorders will reveal additional ways of preventing and diagnosing this comorbid pathology, therefore, requires additional study.

2. Purpose, subjects and methods:

2.1. The purpose of the research was to study the relationship between plasma concentrations of resistin and indicators of enzyme and pigment metabolism in patients with non-alcoholic fatty

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liver disease (NAFLD) and its combination with type 2 diabetes mellitus (DM-2) depending of phenotype of patients.

2.2. Subjects & Methods

On the base of Kharkiv Regional Hospital a total of 90 patients were examined. Of these, patients with NAFLD (group 1; n = 20) and its combination with DM-2 with normal body weight (group 2; n = 20) and obesity (group 3; n = 50), as well as 20 healthy volunteers (control group).

Verification of diagnoses was carried out according to the ICD-10 and WHO classifications. In all patients, the parameters of the functional state of the liver, body mass index (BMI) were determined.

The diagnosis of diabetes was verified by biochemical testing, which made it possible to assess the state of carbohydrate metabolism using standard generally accepted methods.

According to the Quetelet index, normal body weight was established with a BMI of 18.5 to 24.9 kg / m2, the diagnosis of "obesity" was made in patients with a BMI ? 30 kg/m2.

The diagnosis of NAFLD was verified by the results of a complex clinical and laboratory, biochemical (using reagent kits "DacSpectroMed" (Moldova)) and instrumental (ultrasound examination of the liver) examination in accordance with the standards of examination of patients with gastroenterological diseases. The resistin level was determined by the enzyme-linked immune-assay using the BioVendor reagent kit (Czech Republic).

To clarify the nature and degree of liver damage, selective puncture biopsy (PB) of the liver was performed, followed by morphological examination of biopsies in 9 patients. All examined patients had no previous viral hepatitis, alcoholism was excluded.

Statistical processing of research results was carried out using analysis of variance and correlation (BIOSTAT version 4.03 and Statistica version 6.1 software packages). Student's t-criteria was used in independent groups, taking into account the difference in the number of observations.

All patients gave informed consent to the interviews and all types of testing.

3. Results & Discussion

Results

In one of our studies, we have already provided some data on the study of resistin and its relationship with indicators of the functional state of the liver [18]. In this article, we additionally present data on the correlations between resistin and BMI in patients in order to demonstrate the dependence of this indicator on the phenotype of patients.

With regard to the investigation, the plasma levels of resistin in groups 1, 2 and 3 were significantly higher than those in control group ($p < 0.001$). Indicators of resistin in groups 2 and 3 were both significantly higher than those in group 1 ($p < 0.001$both), *Table*.

The fact that the studied parameters were increased in group 1 (patients with NAFLD without DM-2) indicates NAFLD as an independent factor for the endocrine dysfunction of adipose tissue.

We investigated indices of pigment and enzymatic metabolism as biochemical markers of liver function state.

Resistin balance (M ± m) in NAFLD patients with normal body weight and obesity

Group	Resistin level, ng/ml
control group n=20	4.87±0.11
group 1 NAFLD n=20	7.56±0.21*
group 2 NAFLD, DM-2 with normal body mass n=20	8.06±0.23*
group 3 NAFLD, DM-2 and obesity n=50	10.00+0.11**

Note:

* – $p < 0.001$ when compared with the control group;

** – $p < 0.001$ when compared with the indicators of group 1.

Analysis of the state of enzyme metabolism showed that serum ALT (mmol/l/g) was significantly increased in patients of groups 2 (0.81 ± 0.01) and 3 (0.86 ± 0.01) compared with control (0.46 ± 0.01; p <0.05), indicators of 1 (0.60 ± 0.01) group (p <0.05). Significantly higher values of serum ACT (mmol/l/g) in patients of groups 2 and 3 (0.67 ± 0.01; 0.73 ± 0.01; p <0.05, respectively) were found in comparison with the indicators of group 1 and the control group patients (0.79 ± 0.01; 0.41 ± 0.01; p <0.05, respectively). There was a significant decrease in the ratio of AST / ALT in the serum of patients in groups 2 and 3 (0.76 ± 0.01; 0.73 ± 0.01; p <0.05, respectively) compared with patients of group 1 and control group (0.79 ± 0.02; 0.98 ± 0.01; p <0.05, respectively). There was a significant increase in ALP (U/L) in the serum of patients of groups 2 and 3 (4.79 ± 0.11; 6.50 ± 0.079; p <0.05, respectively) compared with patients of group 1 and the control group (3.45 ± 0.11; 1.72 ± 0.06; p <0.05, respectively).

There was a significant increase in total bilirubin in the serum (?mol/l) in patients of groups 2 and 3 (14.19 ± 0.20; 16.12 ± 0.09; p <0.05, respectively) compared with indicators of patients of group 1 and control group (12.5 ± 0.18; 10.37 ± 0.15; p <0.05, respectively), as well as a significant increase in conjugated serum bilirubin (μmol/l) in patients of groups 2 and 3 (6.05 ± 0.17; 7.94 ± 0.1; p <0.05, respectively) compared with patients of group 1 and control group (5.75 ± 0.18; 2.47 ± 0.09; p <0.05, respectively).

It is important to note that all the above indicators of enzyme and pigment metabolism in patients of group 3 (comorbid pathology with obesity) significantly (p <0.05) increased when compared with patients in group 2 (comorbid pathology with normal body weight).

Evaluating the indicators of pigment and enzymatic metabolism, in addition to the detected significant (p <0.001) increase in all indicators reflecting these types of metabolism (except for AST/ALT, where a significant decrease was observed), a significant impairment of these indicators was revealed in group 3 in comparison with groups 1 and 2, the reliability was not revealed between the ALT and total bilirubin values in group 1 (NAFLD) in comparison with group 2 (NAFLD and DM-2 with normal body weight).

The correlations between resistin and some indicators of enzyme and pigment metabolism in patients, mainly in the group 3, were detected.

The correlations between resistin and AST/ALT were investigated (r = -0.32, p <0.05 in group 2; r = -0.39, p <0.05 in group 3), ACT (r = 0.57, p <0.05 in group 3), ALT (r = 0.49 p <0.05 in group 3), total bilirubin (r = 0.59, p <0.05 in group 3), conjugated bilirubin (r = 0.46, p <0.05 in group 2; r = 0.71, p <0.05 in group 3) and alkaline phosphatase (r = 0.82, p <0.05 in group 3).

Correlation links between these indicators were present and were significant mainly in group 3. In other groups, these relationships had the same direction, but were weak.

Also, resistin was directly related to BMI in all groups of patients. Resistin was associated with BMI (r = 0.83, p <0.05 in group 1; r = 0.36, p <0.05 in group 2; r = 0.84, p <0.05 in group 3).

The study implied a puncture biopsy of the liver with subsequent histological evaluation of biopsies for 9 examined patients [18], namely, two patients of group 1, three patients of group 2 and four patients of group 3.

The "gold standard" for the diagnosis of NAFLD is a liver biopsy. However this procedure is invasive and potentially associated with complications. In selected group of patients liver biopsy was performed. Assessment of the structure of fibrotic changes showed such signs as small and large droplet steatosis, mixed fibrosis with mono- and multilobular spread with moderately pronounced signs of parenchymal and stromal reactions.

Group 1 patients (patients with NAFLD without DM-2) were found to have large-droplet fatty degeneration of single hepatocytes, as well as diffuse large-small-droplet fatty degeneration of hepatocytes with some predominance of the process in its central parts, large-droplet fatty degeneration of single hepatocytes (*Fig. 1, 2*).

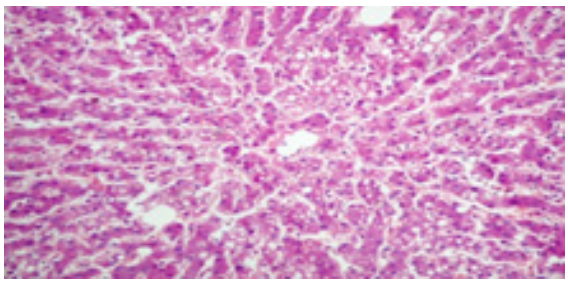

Fig. 1. Diffuse large-droplet fatty degeneration of the hepatic lobule with some predominance of the process in its central parts. Hematoxylin and eosin, × 200

Besides, ultrasound examination revealed hyperechoic liver tissue, due to diffuse fatty infiltration with a coarse-grained structure.

In group 2 patients with NAFLD in combination with DM-2 and normal body weight, attention was drawn to the presence of "hollow"

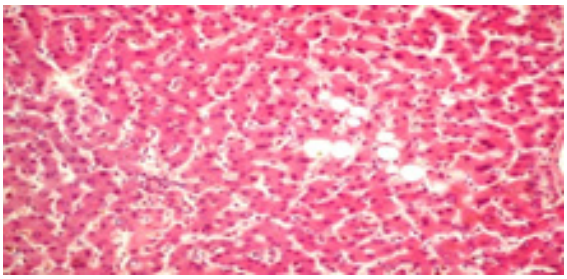

Fig. 2. Large-droplet fatty degeneration of separate hepatocytes. In separate hepatocytes, large "hollow" nuclei are detected. Hematoxylin and eosin, × 200

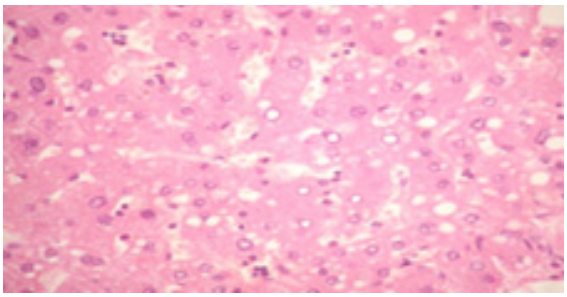

Figure 3. "Hollow" nucleus of hepatocytes against the background of hepatosis. Hematoxylin and eosin, × 400

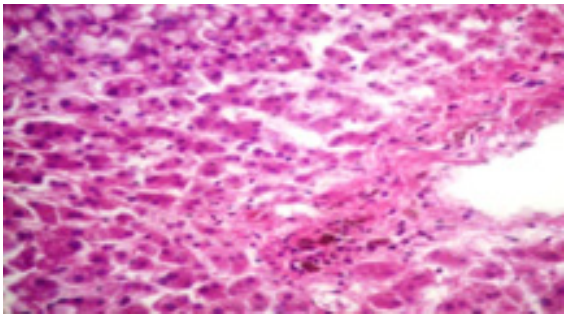

Figure 4. Small-large-droplet fatty degeneration of periportal hepatocytes. The bile ducts of portal tracts are full of bile. Hematoxylin and eosin, × 400

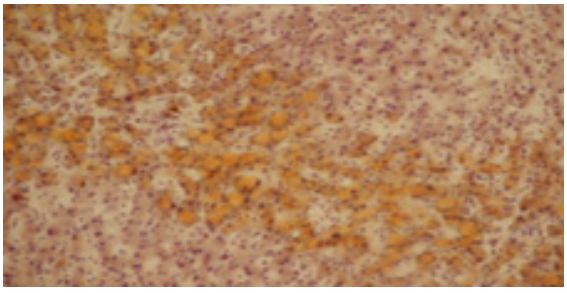

Figure 5. Sudanophil granules in the cytoplasm of hepatocytes. Sudan 3 on fat, × 200

nuclei of hepatocytes against the background of hepatosis (*Fig. 3*), as well as bile overcrowding of the bile capillaries (a sign of steatohepatitis),

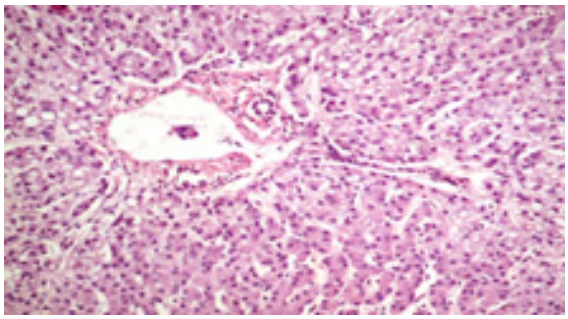

Figure 6. Focal large-droplet fatty degeneration of hepatocytes of the periporal zones. Hematoxylin and eosin, × 200

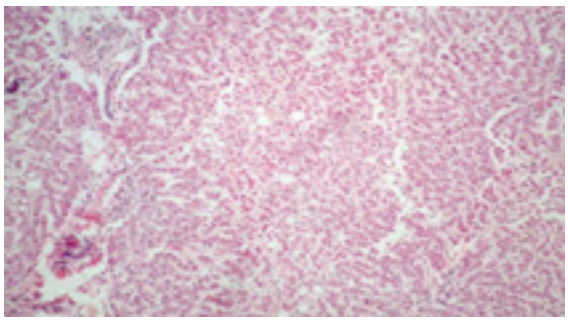

Figure 7. Focal large-small- droplet fatty degeneration of hepatocytes mainly of the central parts of the hepatic lobules. Portal tracts are significantly sclerosed with the presence of diffuse lymphohistiocytic infiltration. Hematoxylin and eosin, × 100

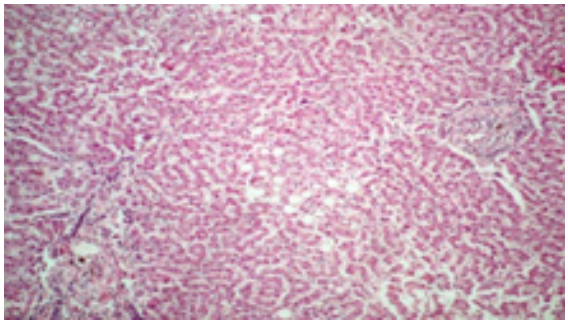

Figure 8. Sclerosis of the portal tracts with marked lymphohistiocyte infiltration against the background of focal steatosis. Hypertrophy of the walls of the hepatic arteries with some narrowing of their lumen. Hematoxylin and eosin, × 100

(*Fig. 4*) and sudanophilic granules in the cytoplasm of hepatocytes (*Fig. 5*).

In group 3 patients (NAFLD in combination with DM-2 and obesity), there was a picture of focal coarse fatty degeneration of hepatocytes in the periportal zones (*Fig. 6*). The study showed signs of focal large-small-droplet fatty degeneration of hepatocytes, predominantly of the central parts of the hepatic lobules, the portal

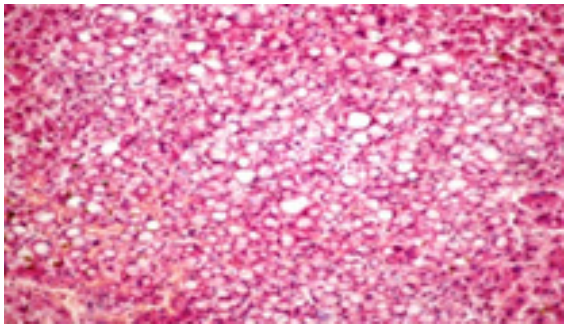

Figure 9. Large-droplet fatty degeneration of hepatocytes. Focal plethora of the hepatic parenchyma against the background of complete disorganization of its beam structure. Hematoxylin and eosin, × 200

tracts were significantly sclerosed with diffuse lymphohistiocytic infiltration, in particular against the background of focal steatosis – signs of liver fibrosis (*Fig. 7, 8*). Focal plethora of the hepatic parenchyma was observed against the background of complete disorganization of its beam structure – a sign of steatohepatitis (*Fig. 9*).

We appreciate that it is not possible to make a statistically significant conclusions concerning typical pathomorphological changes in liver tissue due to limited number of subjects involved in morphological study. However, analyzing the histological changes of biopsies of 9 examined patients, we noticed that severe inflammatory and fibrotic changes were as typical findings for patients with comorbid pathology (group 2 and group 3). The most progressive changes revealed liver biopsy results in patients of group 3, that demonstrates that obesity is an additional factor of NAFLD progression and it can become a promising vector for further research.

Discussion

Increased activity of AST and ALT in the blood serum and decreased AST/ALT ratio, indicates the development of cytolysis syndrome in the examined patients.

The tendency to an increase in bilirubin and excretory enzyme ALP confirms the development of cholestasis syndrome with impaired biliary function of the liver with impaired formation of bile micelles and damage to small bile ducts.

Increased biochemical markers of liver tissue damage against the background of IR indicates the presence of structural and functional changes in hepatocytes with the development of cytolysis and cholestasis syndromes, developing in patients with NAFLD and in comorbid pathology.

Monitoring the state of these types of metabolism has prognostic significance for diagnosing of the state of the liver in patients with NAFLD and with its combination of DM-2, especially in the presence of obesity.

Increased level of resistin mainly in groups of the patients with comorbid pathology demonstrates the relationship of metabolic, hormonal changes and functional disorders of the liver in patients with NAFLD and DM-2, which is significantly increased in obesity. Resistin indices were significantly increased in group 1 with NAFLD without DM-2, demonstrating that NAFLD is an independent factor for disorders of the endocrine function of adipose tissue, which are significantly compounded by disorders of carbohydrate metabolism and obesity.

It is important to note that the correlation between all indicators increased and was significant in all cases in group 3, which confirms the fact that obesity is a leading etiological factor in the pathogenesis of molecular cellular mechanisms of interaction of immune and metabolic processes in patients with NAFLD and DM-2.

In a previous scientific article, we have already suggested the relationship between resistance levels and markers of cytolysis and cholestasis [18].

We would like to focus on the pronounced relationship between the level of resistin and BMI in patients. Interestingly, the correlations between these parameters were significant in all groups, but the strongest one was found in the group with isolated NAFLD and in group 3 with comorbid pathology and obesity. In any case, we can conclude that the level of resistin increases in obese patients along with weight gain, which means that the higher the BMI in obese patients, the more pronounced the effects of resistin on liver function in this category of patients.

Conclusion

This study essentially shows the presence of significant correlations between resistin and some indicators of the functional state of the liver of the studied patients. The established relationship between the level of resistin and the indicators of the liver functional state suggests that an increase of resistin level may reflect the presence of impaired liver function in patients with NAFLD in combination with DM-2, predicting the progression of NAFLD. In order to detect the disorders of liver function in patients with DM-2, it is recommended to determine the level of resistin in patients with NAFLD, especially when concomitant obesity is present. The higher the BMI in obese patients, the more pronounced the effect of resistin on liver function in this category of patients.

Declarations

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Consent for publication

All authors give their consent to publication.

Disclosure Statement

The article reflects part of the research work of the department titled "Optimization of diagnosis and treatment of cardiovascular disorders in patients with type 2 diabetes mellitus in terms of combined pathology".

Authors have no potential conflicts of interest to disclosure.

Funding Sources

There are no external sources of funding

Data Transparency

The data can be requested from the authors.

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Received: 30-Mar-2021
Accepted: 06-Sep-2021

ALLERGIC RHINITIS SYMPTOMS PREVALENCE IN CHILDREN OF KHARKIV

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https://doi.org/10.35339/ic.8.3.163–167

Abstract

The purpose of the study was to identify the prevalence of allergic rhinitis (AR) symptoms in children of Kharkiv and to establish the dynamics of symptoms since 1998. The study conducted in 2015–2017 is phase IV of the international ISAAC program. 5735 children were interviewed, including 3238 children aged 6–7 years and 2197 children aged 13–14 years. The incidence of non-cold-related sneezing was found in 14.7 % and 16.1 %, respectively; during the past 12 months similar problems with nose breathing were noted in 9.1 % and 9.9 %; accompanied by conjunctivitis – in 3.4 % and 4.8 % of children of 6–7 and 13–14 years, respectively. Most patients had seasonal exacerbations and mild/moderate rhinitis. AR diagnosis was verified in 12.2 % and 11.3 % of children, respectively. Decreasing of AR symptoms prevalence was found in children of all ages. The dynamics of AR symptoms prevalence, "eye" symptoms over the past 20 years show a probable decrease in all indicators, which can be explained by the widespread introduction in medical practice of screening methods for the disease diagnosing, activation of primary and secondary prevention.

Keywords: *children, allergic rhinitis, prevalence, ISAAC.*

Introduction

The problem of allergic diseases is becoming more urgent every year due to epidemiological, social, scientific and economic aspects. Bronchial asthma (BA) prevalence in the pediatric population reaches up to 10 %, atopic dermatitis (AD) – up to 20 %. According to foreign epidemiological studies, up to 50% of children have AR [1–3]. Moreover, it is relatively rare up to 2 years old, and is most common pathological condition at the age of 6-17 years [4–6], when a child begins school, grows up and prepares to be a full successful member of the society. AR presence significantly reduces the life quality and children with AR have lower scores of life quality than those of patients with asthma [7–10]. It is a significant economic problem not only for the child, family, but also for society as a whole [11, 12].

It is possible to study the problem in a comprehensive way, which will make it possible to get as close as possible to scientifically based and personalized treatment measures only due to global international intervention. The International Study of Asthma and Allergies in Childhood (ISAAC) is the one of the most successful such global programs [13, 14].

The ISAAC study was condacted by professor Ognev V.A. (KhNMU) in Ukraine in 1997–2003 for first time. The true allergic diseases prevalence was established during the study: BA – 98.25 ‰, AR – 56.25 ‰, AD – 39.64 ‰. This result is significantly higher than the official statistics [15].

The ISAAC program provides for the repetition of Phase I in 10 years to establish the allergic diseases dynamics and trends in the world (Phase IV), which was performed in most countries except Ukraine. Therefore, the ISAAC program in Ukraine requires the next phase (phase IV), which will provide information on the current state of the allergic diseases problem, including AR.

2. Purpose, subjects and methods:

2.1. The purpose was to improve medical care for patients with AR in pediatric population by estimating the AR symptoms current prevalence in children of Kharkiv city and revealing the symptoms dynamics from 1998.

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2.2. Subjects & Methods

The work was performed as interdepartmental research of pediatric departments of Kharkiv National Medical University according to the topic: "Medical and biological adaptation of children with somatic pathology in modern conditions", "Improvement of diagnosis and prevention of allergic diseases in children according to the international program standards "International Study Asthma and Allergy in Children" (state registration number 0114U003393, 0118U000925). The results of the study in children with bronchial asthma were published previously [16].

The study has designed phase IV of epidemiological method ISAAC [16] which was conducted in 2015–2017. Authorization for the performance of the work was received from the official representative organization Global Asthma Network.

In conformance with the international ISAAC program standardized questionnaires were distributed among schoolchildren aged 6–7 years and 13–14 years. The questionnaires included demographic information, allergy related questions and the option of response in the "Yes/No" format.

The sampling amount for the study was calculated by the formula of sampling population with due account of the amount of pediatric population and allergic diseases prevalence ensuring representativeness of the obtained data (Lisitsin Y.P., 2010) and made 5434 children [17].

The results of phases I and III of the ISAAC study were compared to reveal the tendencies in AR prevalence (Ognev V.A., 1998, 2002) [15].

The obtained data were stored in the SQlite/MySql database, the calculation was conducted by variation statistics method.

The study was conducted with respect to human rights in accordance with the legislation in force in Ukraine, in compliance with international ethical requirements and did not violate ethical norms in science and standards for conducting biomedical research.

3. Results & Discussion

Results

5735 children were interviewed, among them 3238 children aged 6–7 years and 2197 children aged 13–14 years. During analyzing the data of the AR symptoms part on the prevalence of symptomatic manifestations of the disease, 1424 (12.3%) schoolchildren gave positive answers. 47.6% of children aged 6-7 years and 58.9% of all surveyed adolescents had nose breathing disorders. Boys predominated (n=868; 60.9 %; $P < 0.05$).

The answers to all 6 questions of the ISAAC questionnaire on the AR symptomatic manifestations are presented in *Table.*

As shown in *table*, adolescent children were more likely to experience symptoms of nose breathing disorders, as well as their combination with "eye" symptoms, although a significant difference in the values obtained was not identified in Kharkiv. In addition, these symptoms mostly did not bother the children, only a small number of respondents indicated their impact on daytime activities (0.4%). The seasonality most often pointed out by the respondents is autumn,

Results of children questioning according to the ISAAC program regarding symptomatic manifestations of AR in Kharkiv (n; %)

Questions about nose breathing problems is not associated with cold		6-7 y.o. n =3238	13-14 y.o. n =2197	Average value n =5735
1. Has your child ever had a problem with sneezing, or a runny, or blocked nose when he/she did not have a cold or the flu?		475 (14.7%)	354 (16.1%)	414.5 (15.4%)
2. In the past 12 months, has your child had a problem with sneezing, or a runny, or blocked nose when he/she did not have a cold or the flu?		296 (9.1%)	218 (9.9%)	257.0 (9.5%)
3. In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?		111 (3.4%)	105 (4.8%)	108.0 (4.1%)
4. In which of the past 12 months was this nose problem occurred? (Please tick any which apply)	Winter	54 (1.7%)	36 (1.6%)	45,0 (1,7%)
	Spring	114 (3.5%)	99 (4.5%)	106,5 (4,0%)
	Summer	90 (2.8%)	89 (4.0%)	90,0 (3,4%)
	Autumn	119 (3.7%)	81 (3.7%)	100,0 (3,7%)
5. In the past 12 months, how much did this nose problem interfere with your child's daily activities?	Not at all amount	58 (1.8%)	37 (1.7%)	47,5 (1,8%)
	A little	56 (1.7%)	57 (3.0%)	56,5 (2,3%)
	A moderate amount	55 (1.7%)	46 (2.0%)	50,5 (1,9%)
	A lot	9 (0.3%)	11 (0.5%)	10,0 (0,4%)
6. Has your child ever had hay fever?		396 (12.2%)	249 (11.3%)	322.5 (11.8%)

spring and summer. About 12% of children surveyed had already been diagnosed with allergic rhinitis.

The dynamics of allergic rhinitis symptoms prevalence for 1998–2017 period in children of the Kharkiv is presented in *pictures 1–3*.

There is a decrease of the complicated nose breathing symptoms prevalence in children of 6–7 years, while in adolescents, on the contrary, the tendency to increase, although the probability of this figure does not reach evidence level ($P > 0.05$).

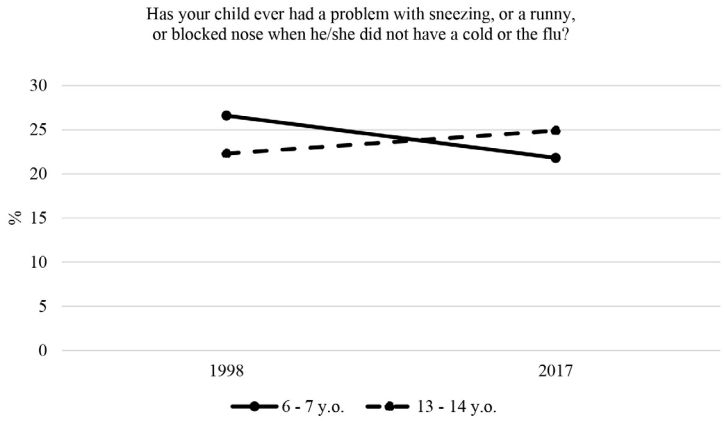

Fig. 1. Dynamics of the prevalence of complicated nose breathing in children of Kharkiv

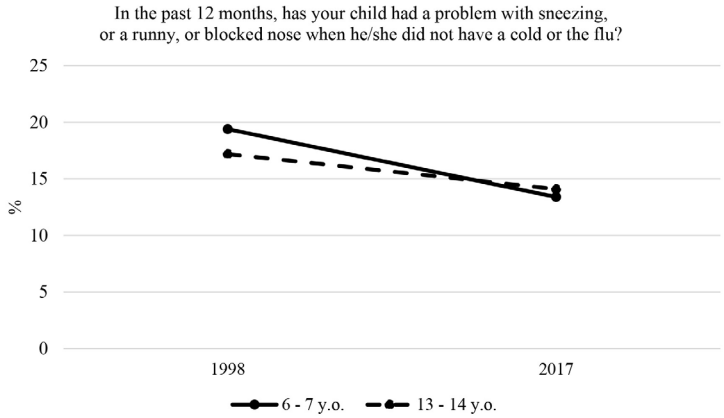

Fig. 2. Dynamics of the prevalence of complicated nose breathing in children of Kharkiv in past 12 months

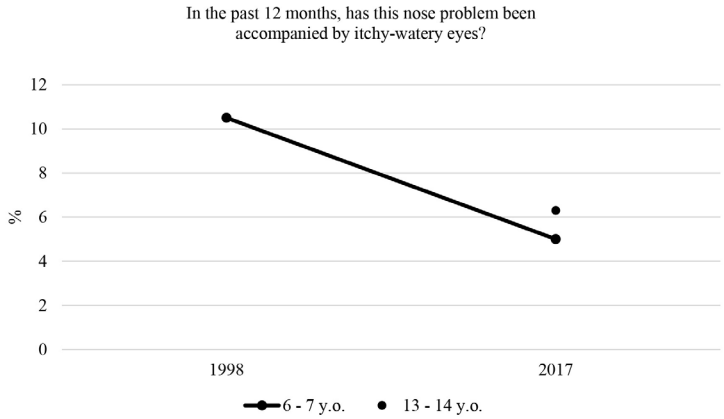

Fig. 3. Dynamics of the prevalence of complicated nose breathing by "eye" symptoms in children of Kharkiv in past 12 months

As can be seen from the picture, there is a probable reduction in the symptoms of nose breathing disorders in all age groups ($P > 0.05$), which indicates disease control and effective preventive measures.

"Eye" symptoms in all age groups of the city's residents have almost halved in the past 10 years ($P < 0.05$).

Thus, there is a decrease of AR symptoms prevalence in children of all ages. The dynamics of the prevalence of AR symptoms, "eye" symptoms, as well as the presence of attacks of difficult nose breathing over the past 12 months show a probable decrease in all indicators. These results can be explained by the widespread introduction into medical practice of screening methods for the disease diagnosing, the primary and secondary prevention methods intensification with the introduction of regulatory documents standards.

We can compare our results with epidemiological data from other countries. The study aimed to determine the prevalence of AR in school-age children was carried out in Budapest, Hungary. 3836 of the questionnaires (1857 M/1979F) were examined. The prevalence of current AR was 29.3%, physician-diagnosed AR was 9.7%, cumulative AR was 36.2% and current allergic rhinoconjunctivitis was 16.2% [18]. Prevalence of AR in Kharkiv is more than 2 times lower.

In Poland (Katowice) the prevalence of physician-diagnosed AR in 6–9-year-old children was 22.1%, that was lower in two times in comparison with Ukrainian children population (11.8%) [19].

But physician-diagnosed AR in Ukraine was higher significant than that in Eastern Croatia in 10–11-year-old children - 6.3% [20].

These differences in AR prevalence can be explained by differences in genetic factors, environmental factors, lifestyle and confirmed the topicality of national trials.

Conclusions

1. AR symptoms prevalence in the pediatric population of Kharkiv was 12.3 %.

2. AR symptoms in all age groups of city residents have tendency to decrease in the past 10 years.

3. The screening methods introduction of disease diagnosis into medical practice, the primary and secondary prevention methods have a positive effect and need further improvement.

Declarations

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Consent for publication

All authors give their consent to publication.

Disclosure Statement

Authors have nothing to disclosure.

Funding Sources

There are no external sources of funding

Data Transparency

The data can be requested from the authors.

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Received: 06-Apr-2021
Accepted: 06-Sep-2021

TREATMENT OF BRONCHIAL FISTULA ASSOCIATED WITH NON-SPECIFIC CHRONIC PLEURAL EMPYEMA (REVIEW)

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https://doi.org/10.35339/ic.8.3.168–176

Abstract
The purpose of the study was to identify the prevalence of allergic rhinitis (AR) symptoms in children of Kharkiv and to establish the dynamics of symptoms since 1998. The study conducted in 2015–2017 is phase IV of the international ISAAC program. 5735 children were interviewed, including 3238 children aged 6–7 years and 2197 children aged 13–14 years. The incidence of non-cold-related sneezing was found in 14.7 % and 16.1 %, respectively; during the past 12 months similar problems with nose breathing were noted in 9.1 % and 9.9 %; accompanied by conjunctivitis – in 3.4 % and 4.8 % of children of 6–7 and 13–14 years, respectively. Most patients had seasonal exacerbations and mild/moderate rhinitis. AR diagnosis was verified in 12.2 % and 11.3 % of children, respectively. Decreasing of AR symptoms prevalence was found in children of all ages. The dynamics of AR symptoms prevalence, "eye" symptoms over the past 20 years show a probable decrease in all indicators, which can be explained by the widespread introduction in medical practice of screening methods for the disease diagnosing, activation of primary and secondary prevention.
Keywords: *children, allergic rhinitis, prevalence, ISAAC.*

Unsatisfactory treatment of tuberculosis, purulent and destructive lung diseases and lung cancer contribute to the development of bronchial fistulae and pleural empyema. Treatment of chronic pleural empyema with unsealed tracheo-bronchial tree is a complicated task for thoracic surgeons. After lung surgeries, the incidence of bronchopleural complications is 40% and the mortality rate is 5.6% [1]. Pleural empyema usually develops after operative interventions for purulent lung diseases [2, 3]. After resection on the lungs with underlying pleural empyema, bronchial fistula develops in 1.9–13.3% of patients with the mortality rate 20–50% [4–6].

Late diagnosis at the organisation stage, three weeks after the onset of chronic pleural empyema significantly worsens the treatment outcomes [7].

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Treatment outcomes of bronchia fistula associated with chronic pleural empyema are also worsened by continuous contamination of the residual pleural cavity with resistant microbial agents. Therefore, the main objective of surgical treatment is bronchial fistula sealing and obliteration of the residual pleural cavity. Absence of well-defined surgical tactics aimed at solving these two issues accounts for unsatisfactory treatment outcomes [8–10].

Since the incidence of lung cancer is rapidly increasing and this condition is already the second most prevalent oncological disease with a five-year survival rate of 17.8%, the number of complications following surgeries for this condition is also rapidly growing [11–13].

Even the first surgical intervention for lung cancer in the form of pneumonectomy can be complicated by development of pleural empyema. Recently, the number of pneumonectomies has significantly decreased to 7.3% [14].

Leakage of the main bronchus stump is the main source of development of a bronchial fistula and, subsequently, pleural empyema, including a

chronic variety. The data of the European Society of Thoracic Surgeons report that bronchial fistula develops in 1.8% of cases after resections on the lungs [15, 16].

Development of bronchial fistulae in the early post-operative period usually results from intra-operative mistakes and inadequate artificial lung ventilation. Later development of fistulae usually has a secondary nature and results from infection processes in the tracheobronchial tree and pleural cavity; bronchial fistulae often develop as a result of a local relapse of the oncological process in the bronchial stump and in the presence of a residual tumour along the suture lines [17].

Single and multiple bronchial fistulae can be distinguished. Late bronchial fistulae usually appear after 8 to 10 weeks. In terms of size, bronchial fistulae are divided into three grades: with a diameter of up to 4 mm (Grade 1), from 5 to 10 mm (Grade 2), more than 10 mm (Grade 3) and complete branching of bronchial stump walls [18].

The main factors contributing to the development of bronchial fistulae and pleural empyema in the post-operative period remain residual pleural cavity, lack of aerostasis, long-lasting drainage of the pleural cavity, leakage of bronchial stump sutures due to ischemia, excessive skeletonization of mediastinum organs, bronchial stump diameter over 25 mm, long bronchial stump, prior chemo- and radiotherapy, massive intraoperative hemotransfusions, severe comorbidity, and immunodeficiency disorders [17, 19–23].

Furthermore, the bronchial stump closure technique and the extent of lung resection significantly affect the risk of bronchial fistula development [24].

According to other authors, development of the main bronchus stump leakage after lung resection or pneumonectomy occurs in 2.5–13.3% of cases and depends on numerous factors: etiological factor of the primary disease, severity of the general condition due to comorbidities, and method of bronchial stump formation [25–27].

The bronchial fistula development is caused not only by the above factors but also by the fact that extended lymph node dissection has become a standard in lung cancer surgeries [6, 28, 29].

Lack of bronchial stump isolation results in cavity formation near it, which creates favourable conditions for a bronchial fistula formation, mainly due to devascularization of the tracheal bifurcation area and the operational trauma [30].

There are three main objectives in the treatment of patients with bronchial fistulae – sanitation of the pleural cavity, removal of the bronchial fistula and removal of the chest wall defect. Some authors consider that the best technique for the treatment of bronchial fistulae after resection interventions on lungs are open surgeries [31].

Pleural cavity drainage, minimally invasive thoracoscopic techniques, and antibacterial therapy taking into account sensitivity to the microbial spectrum of causative agents do not achieve lung expansion, especially in the presence of a bronchial fistula [32, 33].

Bronchoscopic occlusion of the tracheobronchial tree defect is another widely discussed issue [34, 35].

There is data about spontaneous closure of the bronchial fistula with underlying chronic pleural empyema [36, 37].

The rigid lung and bronchial fistula prevent lung expansion by evacuating air from the pleural cavity, primarily due to the fibrine layers and several small fistulae or one fistula with a large diameter. The only way to achieve lung expansion is to seal the bronchial fistula. However, in the presence of pleural empyema it is reasonable to keep to a phased treatment tactics aimed at sealing the bronchial fistula only after pleural cavity sanitation. Throughout the history of thoracic surgery, many other techniques and devices have been developed to seal the bronchial fistula: different methods of endobronchial occlusion of the main bronchus – silver nitrate, ethanol, cyanoacrylate compounds, lead plugs, cylinder, fibrine and tissue glues, serum albumin, gel foam, autologous thrombi, antibiotics; transcervical occlusion of the bronchus stump, Angeo-Seal, Watanabe spigot, Amplatzer vascular plug, valves used for lung emphysema, devices for closing interatrial septum defects, valves, obturators used in cardiovascular surgery; variations of the transsternal transpericardial occlusion of the main bronchus stump first proposed by L.K. Bogush in 1972. Bronchi with fistulae are detected by bronchoscopy and bronchography. The above methods have many advantages as well as disadvantages [9, 38– 53].

The choice of the method and materials to achieve aerostasis also depends on the size of the bronchial fistula. In case of small fistulae (up to 3–4 mm), videothoracoscopic interventions can be performed using endoscopic methods, such as fistula site coagulation, glue sealing (fibrine glue), cuff link-type bone cyanoacrylate filling, 2–3 mm gelatine spherical obturators (with antibiotics), and closure. A positive aspect is the use of organic materials that dissolve and exclude the possibility

of a foreign body remaining in the pleural cavity. These techniques help avoid repeated operations for the resection of bronchial obturators or bronchial link closure. It is not possible to close large defects using the above techniques due to the physical and technical properties of the materials used [54].

One of the wide-spread sealing materials is fibrine glue. Due to its biological structure, it can be injected in the submucosal layer of the bronchial stump without the rejection reaction, especially in case of small fistulae (up to 3 mm). In case of fistulae over 3 mm, it is recommended to use collagen plaster with a fibrine surface [9, 43, 44].

The most common synthetic sealing material is cyanoacrylate glue. It is polymerized on contact with biological fluids and body tissues. The development of an inflammatory response to the foreign agent in the site of its injection in the bronchial stump leads to development of fibrosis and proliferation of the mucous membrane of the bronchus, thus sealing the bronchial fistula [55].

There are disputes about large defects (more than 5 mm) because they must be sealed but also healed. Foam rubber bronchial obturators, spheric or conic, can be applied bronchoscopically in such cases. A foam rubber bronchial obturator can migrate to larger bronchi, which may cause atelectasis in healthy lung segments [56].

Occluders that were initially developed for the closure of interatrial and interventricular septa are also used for the treatment of bronchial fistulae. This technique is believed to have almost no side effects and is indicated to patients who require artificial lung ventilation and extracorporeal membrane oxygenation (ECMO) [39, 40, 42, 57].

Occlusion of the bronchus with a fistula using a foam rubber obturator is effective in 65.7–80% of cases [58, 59].

The effectiveness of bronchoscopic setting of the endobronchial valve is 91.7%. This method does not guarantee complete sealing of the bronchial fistula. The main complication of the blocking the bronchus with a valve is the valve migration to the adjacent bronchi with development of lung atelectasis [60, 61].

The closure of large defects is a more complex problem than the closure of small ones. Traumatic approaches to the stump of the leaking bronchus, thoracotomy and sternotomy involve a number of risks in the post-operative period. The positive outcome of bronchial fistula closure in open surgeries is observed in 80–5% of cases. These surgeries are usually complemented with reinforcing the bronchial stump with different tissue flaps. When repeated closure of the bronchial stump is not possible, the tissue flap is attached directly to the fistula area. The flaps are usually taken from the broadest muscle of the back, greater pectoral muscle, intercostal muscles, greater omentum on the feeding vascular pedicle, or free tissue flaps. According to different authors, the sealing of the bronchial stump was achieved in 75% and complete obliteration of the residual pleural cavity was achieved in 95% of patients [62–73].

It is not recommended to use pericardial flaps because the exposure of the mediastinum becomes a portal of entry on contact with infected pleural cavity [74].

High risks of mediastinum organ infection during surgeries involving purulent inflammation in the residual pleural cavity dictate the need to perform transpericardial sealing of the bronchial stump [73].

Most methods aim to prevent the occurrence of the main bronchus stump leakage and subsequent formation of bronchial fistulae. The main aim of preventive measures is to strengthen the stump with different biological materials, such as larger omentum, muscles, pleura, pericardium; fibrine-collagen plates are also used as the final stage of bronchial stump treatment [5, 29, 75].

There is an ongoing discussion about the method of bronchial stump closure. Should it be manual or hardware-assisted? The most common method is the bronchial stump treatment with its suturing through all layers using Suit's method. Another rather wide-spread method is wedged bronchus and bifurcation resection with transversal trachea closure using Sprengler's technique. All these open methods are widely spread, but, taking into account the bronchial stump leakage due to the uneven compression of bronchial tissues, the penetration of foreign agents in the bronchial lumen ruins the conditions for initial healing of the bronchial stump suture line. A combination of manual stump treatment with the use of an appliance for suturing the root of the lung rendered this stage of the operative treatment safer, which is confirmed by data from different studies indicating decreased formation of bronchial fistulae as compared to isolated uses of individual methods of tracheobronchial tree sealing [76, 77].

Another disputable question concerns the reasonability of supporting the bronchial stump suture line with muscle or tissue flaps on the vascular pedicle [20, 78, 79].

Some authors report an increased risk of bronchial fistula development after resections on

lungs using additional methods for bronchial stump suture line sealing, thus indicating the ways to prevent the bronchial stump leakage: prevention of bronchus mucous membrane traumatization, tension-free closure of the bronchial stump, prevention of excessive skeletonization, precise approximation of stump edges "mucous to mucous" [24, 80].

Removal of the bronchial fistula does not guarantee recovery from chronic pleural empyema, and the tactics for the treatment of the residual cavity is controversial in such cases [81].

Resection of purulent and necrotic masses is the only way to treat pleural suppuration. Transcutaneous drainages with evacuation of the purulent content and sanitation of the pleural cavity help restore the evacuation function of the draining bronchus [82].

In 1961, J. Ambruzini proposed transsternal occlusion of the main bronchus stump, and in 1964 L.K. Bogush and Yu.L. Semenenkov modified the proposed method by exposing the pericardium widely along the anterior, superior and posterior side, repeatedly treating and dissecting the pulmonary artery stump, which made it possible to manipulate in the aortocaval space – Ambruzini space [47].

However, the above surgery is quite traumatic and complex, which makes it impossible to perform outside of a thoracic surgery department.

Lymph node dissection in extended pneumonectomy is difficult during the mobilization of the trachea and main bronchi due to the adhesive process, which becomes one of the main features in case of chronic pleural empyema. An indication to transsternal occlusion remains the length of the bronchial stump of at least 20 mm. However, L.K. Bogush believes that a 15 mm long bronchial stump is enough to perform this operation. Another disputable issue concerning the phases of transsternal main bronchus stump occlusion is the need to dissect the distal stump of the resected bronchus. Rejecting to resect the distal part of the bronchial stump, electrocoagulation of the mucous membrane is often opted for with closure from the mediastinal side. The authors separated the proximal and distal bronchial stumps with a pericardial flap and a muscle flap following Ginsberg in order to prevent bronchial stump recanalization. The advantages of transsternal occlusion include reduced relapse rates and duration of the in-patient stay [47, 83].

Since open transsternal surgeries are rather traumatic, thoracic surgeons are constantly searching for techniques allowing the closure of a bronchial fistula with a diameter of 2 to 10 mm and sealing of the pleural cavity. A two-component mushroom-shaped adhesive filling is used to fill the defect thoracoscopically from the side of the pleural cavity with the "cap" and the bronchoscopically from the side of the tracheobronchial tree with the "stem". The components of the filling are made of oxidized 100% cellulose impregnated with chlorhexidine solution and fibrine glue. Considering that tissues have homogeneous structure and composition, the bronchial fistula junctions on both sides stick together well and form a single complex that seals the fistula. The material of the filling prevents topical inflammation and development of the infection process due to the use of antiseptic solutions. It is good that no foreign bodies remain in the bronchial and pleural cavity after healing, tissue regeneration improves, and the fistula heals faster [84].

However, the removal of the bronchopleural fistula does not guarantee recovery from chronic pleural empyema. Another important issue in the treatment of pleural empyema remains the obliteration of the residual pleural cavity.

The history of residual pleural cavity obliteration dates back to the early 20th century. Different authors described the transposition of skeletal muscles to the pleural cavity, the use of a muscle flap on the feeding vascular pedicle, and a strand of the larger omentum and other tissue flaps to obliterate the residual pleural cavity [85–91].

There is a discussion about the use of different agents for obliteration, such as glycerine, fibrine with antibiotics taking into account the microbial sensitivity of the pathogenic flora, foam polymer compounds, and foam gel based on acrylic acids. Most of them were used historically [92].

Biological materials mostly used for the obliteration of the residual pleural cavity include the broadest muscle of the back, greater pectoral muscle, serratus anterior. Serratus anterior and rhomboid muscle are used less frequently [93–95].

Clinical trials indicate effective obliteration of the residual pleural cavity with muscles on the vascular pedicle with no pleural empyema relapses and a 5% mortality rate [96].

Thoracoplasty is another technique for the obliteration of the residual pleural cavity. There are many modifications of thoracoplasty, for example extrapleural subperiosteal thora-coplasty, intrapleural thoracoplasty using Schede's method, and thoracoplasty using Andrews' method [95, 97].

Foreign authors point to the effectiveness of thoracoplasty for obliteration of the residual pleural cavity in 77% of patients [95].

Other authors report a 11.7% mortality rate after thoracoplasty with the rhomboid muscle and serratus anterior [98].

There are no clear indications to thoracoplasty. Total thoracoplasties involve a large number of post-operative complications, pleural empyema relapses, a high mortality rate, and a high percentage of functional failures as compared with traditional and minimally invasive methods for the sanitation and obliteration of the residual pleural cavity [99].

Conclusions

The search for the optimal method of bronchial fistula sealing associated with non-specific chronic pleural empyema motivates thoracic surgeons to conduct further research aimed to improve the outcomes of traditional and minimally invasive surgical treatment. The literature contains many controversial opinions on using particular treatment methods, their phases and optimal terms. Upon analysing the above data it can be concluded that nowadays there is no single tactics for the surgical treatment of non-specific chronic pleural empyema, which motivates its creation.

Declarations

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Consent for publication

All authors give their consent to publication.

Disclosure Statement

Authors have nothing to disclosure.

Funding Sources

There are no external sources of funding

Data Transparency

The data can be requested from the authors.

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Received: 18-Jun-2021
Accepted: 06-Sep-2021

FORENSIC MEDICAL ASSESSMENT OF MORPHOLOGICAL CHANGES AT DIFFERENT POSTMORTEM INTERVAL

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https://doi.org/10.35339/ic.8.3.177–181

Abstract

Purpose: The postmortem interval (PMI) evaluation is one of priorities while performing a forensic medical examination of corpse. To date, there is lack of information on morphological postmortem changes of some internal organs. Considering the persistent need to develop the method for a precise assessment of PMI, postmortem changes in these potentially informative organs were evaluated. The aim of study was to analyze morphological postmortem changes in prostate and uterus. **Materials and Methods:** histological samples of 40 prostate and 40 uterine tissues (n=80) from corpses of deceased aged 18–75 years. Only cases with known time of death were included to study, the time of death was taken from police reports. Exclusion criteria were cases of violent death, death with massive blood loss, tumors of studied internal organs and cases when diagnosis was not made by a forensic medical examiner. The PMI of studied cases ranged from 1 to 6 days. Histological slides were made with a staining by hematoxylin and eosin, x200 magnification, using Olympus BX41 and Olympus BX46 microscopes, Olympus SC50 camera. Postmortem morphological changes were evaluated by a calculation of blank spaces percentage in microscopical structures using a JS-based software. Relationship between PMI and morphological changes was calculated by the Spearman's rank correlation. **Results:** the average percentage of blank spaces in uterine tissues was smaller than in prostate tissues (1.99 and 9.65, respectively). The slower growing of blank spaces was in uterus. In prostate samples, a notable increase of blank spaces was observed between 48 and 72 hours after death. After this period, the increase slowed down and then an increase was observed again between 120 and 144 hours after death. In uterine samples, a slight acceleration was observed between 72 and 120 hours after death and then slowing down between 120 and 144 hours after death. Blank spaces in evaluated histological slides were increasing directly proportional to the PMI, a statistically significant interconnection was defined ($p < 0.05$). **Conclusions:** The morphological postmortem changes in prostate and uterus were developing at certain time frames. Blank spaces percentage, in studied histological slides, were increasing directly proportional to the PMI increase, a statistically significant interconnection was defined. Therefore, the results of study show the possibility of the evaluation of a postmortem time interval by assessing such morphological changes in these organs, which could be used in forensic medical cases.

Keywords: *forensic medicine, forensic medical examination, postmortem interval, thanatology.*

1. Introduction

Postmortem interval evaluation is still one of topical issues. Variety of approaches are being applied to define PMI, methods from different fields, such as forensic botany, genetics, entomology, biochemistry, microbiology [1–11]. But most of these methods are useful only in relatively short term after death [12]. Uterus and prostate are considered to be the last internal organs to decay during human decomposition [13], so a study of these organs might be useful in cases when there was a longer time between time of death and forensic medical examination of the corpse.

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2. Purposes, Subjects and Methods

2.1. Purpose. The aim of the study was to assess morphological changes in prostate and uterus in the postmortem period. Hypothesis was that: 1) there is a correlation between PMI and morphological changes in studied organs (uterus

and prostate); 2) postmortem changes in the uterus and prostate take different time to develop in postmortem period.

2.2. Subjects & Methods

Design

This study was based on 40 tissue samples of prostate and 40 samples of uterus (n=80) from corpses of men and women aged 18–75 years. Only cases with known time of death were included to study, the time of death was taken from police reports. Exclusion criteria were cases of violent death, cases of death with massive blood loss, tumors of studied internal organs and cases when diagnosis was not made by a forensic medical examiner. The PMI of studied cases ranged from 1 to 6 days.

The study is permitted by Ethics Committee of Kharkiv National Medical University in October 2018. The practical part of study ended by June 2021. The following attributes of the corpses were studied: age, sex, body length, fat level, scene features, presence of clothing and its peculiarities. Evaluation of postmortem changes was made using calculation of average blank spaces percentage in histological slides, in PMI starting from 1 day up to 6 days. Time of death, in studied cases, was taken from police reports on the place of death, that were presented to the examiner.

Histological slides were made with a staining by hematoxylin and eosin, x200 magnification, using Olympus BX41 and Olympus BX46 microscopes, Olympus SC50 camera.

Program and Statistical Analysis

In the histological slides studied, on the area of 250x250 pixels, the percentage of blank spaces was defined. The JS-based software was used to calculate blank spaces percentage in histological slides. The average percentages of blank spaces were calculated for each organ and for different age groups. Based on the data received, mean values and standard deviations were defined. The distribution normality was checked by Shapiro-Wilk test. Considering the non-normality of distributions, the Spearman's rank correlation coefficients were calculated in order to detect the connections between PMI and morphological changes in studied organs. The significance level of $p < 0.05$ was set for all the tests. The calculations and graphs were made using StatSoft STATISTICA Version 8 (Tulsa, OK) and Microsoft Office Pro Plus 2019.

3. Results

The morphological changes in tissues of studied organs developed differently (*Figure 1*), the average percentage of blank spaces in uterus tissues was smaller than in prostate tissues (1.99 and 9.65, respectively).

The comparison of average values of the blank spaces percentage in different postmortem interval also showed the slower growing of blank spaces in uterus than in prostate – 0.08 and 0.94, respectively at PMI of 24–48 hours; 0.93 and 3.27 at PMI of 42–72 hours; 1.31 and 11.84 at PMI of 72–96 hours; 2.83 and 14.32 at PMI of 96–120 hours; 4.79 and 17.90 at PMI of 120–144 hours (*Table*).

The results have been rounded to two decimal places.

In prostate samples, a notable increase of blank spaces was observed between 48 and 72 hours after death. After this period, the increase slowed down and then an increase was observed again between 120 and 144 hours after death.

In uterine samples, compared to prostate, the increase of blank spaces was less intensive, with a slight acceleration observed between 72 and 120 hours after the death and then slowing down between 120 and 144 hours after death. Blank spaces in evaluated histological slides were increasing directly proportional to the PMI, a significant interconnection ($p < 0.05$) was defined. No significant differences of blank spaces percentage between age groups were observed ($p < 0.05$) (*Figure 2*).

4. Discussion

The histological study of uterus showed an increase of postmortem changes over postmortem period. In cases where the duration of the postmortem period was more than 145 hours, microscopically, there were eosinophilic fibrous, dusty masses, impossible to identify. The processes of autolysis occurred more intensely and faster in the mucous membrane of the uterus, in comparison with the muscular and serous membranes, and in inner membrane of vessels, in comparison with the middle and outer membranes. The autolytic changes in the muscular membrane and vascular walls occurred more intensely in muscle fibers compared to connective tissue fibers [14].

Uddin MS et al. have shown that the morphological structure of uterus is changing over time and there is a statistically significant positive correlation between age breadth and thickness of uterus. There were changes in the morphology of uterus in relation to age [15].

According to N Abdel Rahman Mahmoud et al., light microscopic examination of prostate samples cannot detect any structure abnormality

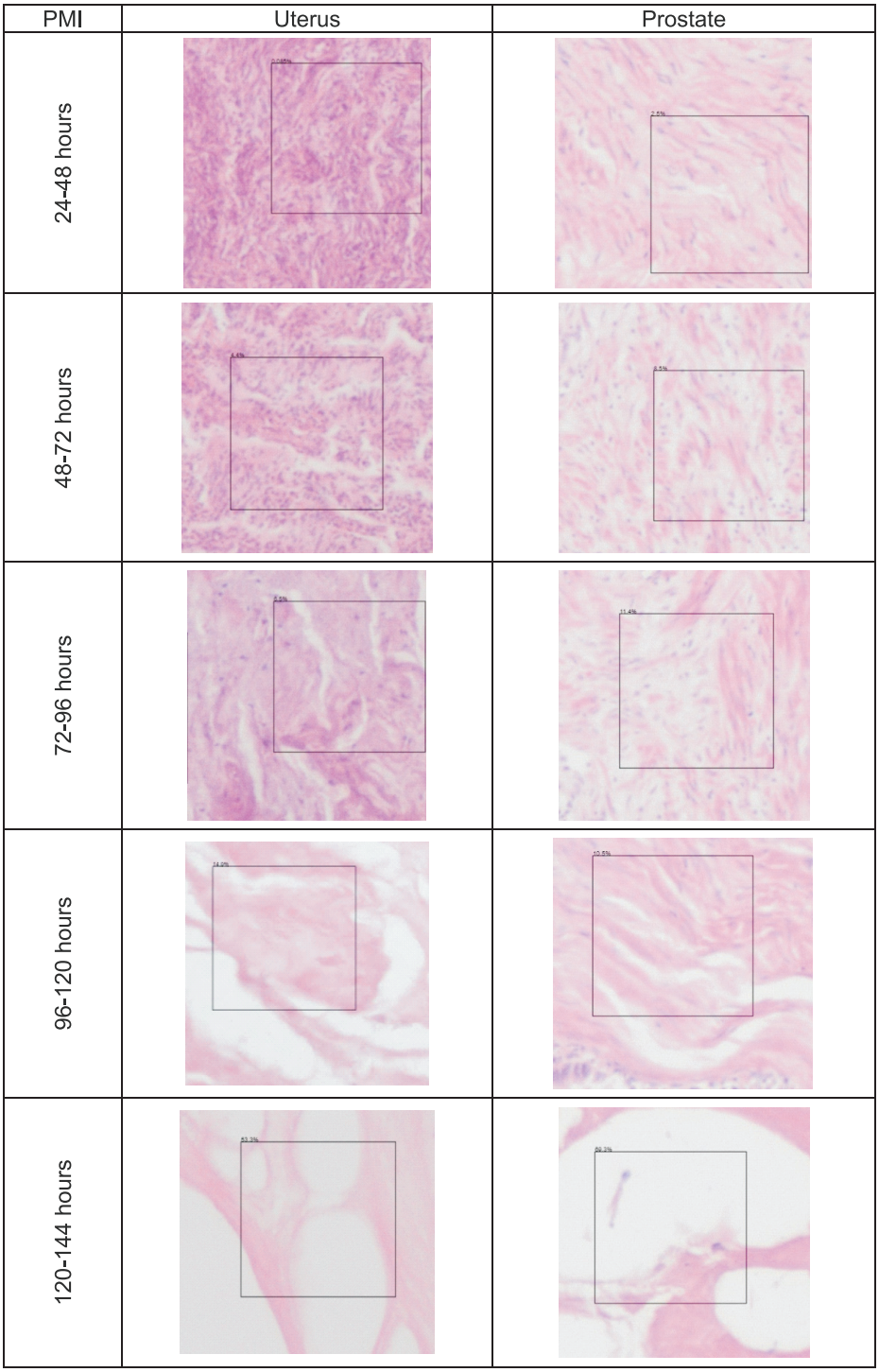

Figure 1. Histological slides of uterus and prostate tissues at different postmortem time interval

Average blank spaces percentage in uterus and prostate tissues at different postmortem time interval

Postmortem interval, hours	Average blank spaces percentage in uterus, %	Average blank spaces percentage in prostate, %
24-48	0.08	0.94
42-72	0.93	3.27
72-96	1.31	11.84
96-120	2.83	14.32
120-144	4.79	17.90
Average	**1.99**	**9.65**

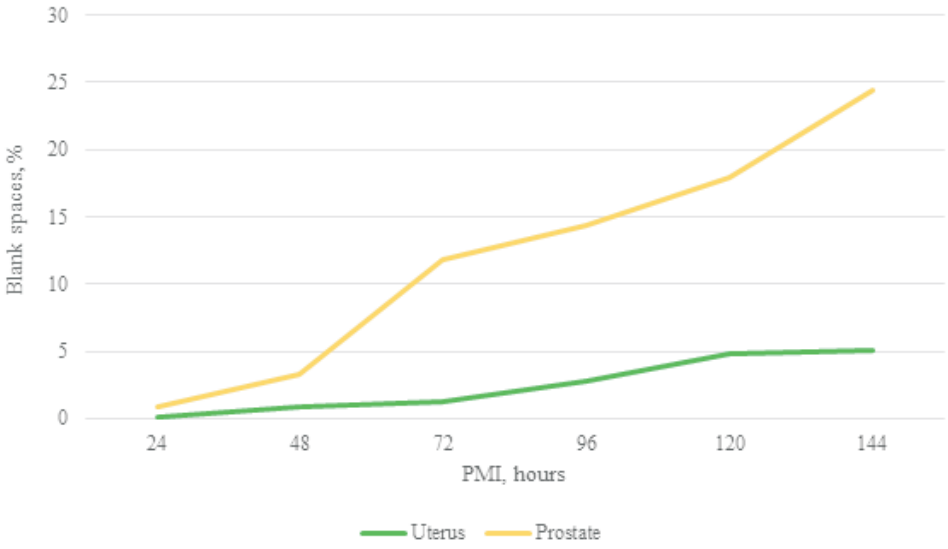

Figure 2. Blank spaces in uterus and prostate at different postmortem time interval

during the first twelve hours post mortem. In 24 hours after the death, a significant epithelial disruption, inflammatory cells and fatty degeneration began to appear in the prostatic acini. Two days PM, the prostatic acini showed significant atrophy and necrosis. By six days PM, stromal calcification started to appear. One week to four weeks PM, the prostatic acinar epithelial disruption, atrophic acini, necrosis and stromal calcification became extensive till no more normal glandular or fibromuscular architecture could be detected [16].

Elgawish, R et al note, that in prostate there was a normal histology at 0 and 6 hours postmortem. While, at 12 hours postmortem, most sections of the gland revealed no abnormalities except for mild focal widening between the acini. Starting from 24 hours postmortem, epithelial desquamation was seen in most acini. Seventy-two hours, obvious necrosis of prostatic acini appeared in most of samples. Degradation of collagen started and the spaces between acini became wide at 12 and 24 hours postmortem. Complete loss of stain reactivity was observed at both 60 and 72 hours postmortem. Moreover, a significant decrease in the amount of collagen stained areas in the prostate started from 12 hours postmortem. Positive immunohistochemical reaction of collagen III was detected at 0, 6 and 12 hours postmortem. However, it was completely lost at 60 and 72 hours postmortem. Interestingly, the immuno-reactive area of collagen III was significantly increased at 6 hours postmortem, then a remarkable decline in immuno-reactive area was observed at 12 hours postmortem [17].

Conclusion

The morphological changes in studied organs have certain postmortem timeframes, therefore they could be used for a determination of postmortem interval. The basic hematoxylin and eosin staining could be enough to observe specific time-dependent morphological changes in histological slides. No significant differences between age groups were observed, but, assuming the quantity of cases studied, there is a need for a further study of age differences in a bigger quantity of studied cases.

Declarations

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Consent for publication

All authors give their consent to publication.

Disclosure Statement

Manuscript is a part of PhD thesis by Edgar Grygorian

The authors report no conflicts of interest.

Funding Sources

There are no external sources of funding

Data Transparency

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Received: 03-Jul-2021
Accepted: 06-Sep-2021

MODERN DIAGNOSIS OF PLACENTAL DYSFUNCTION AND ITS COMPLICATIONS

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https://doi.org/10.35339/ic.8.3.182–187

Abstract

The aim of the study was to improve the modern diagnosis of placental dysfunction and its complications. **Materials and methods.** The study involved a prospective survey of 70 pregnant women divided into the main group (pregnant women with placental dysfunction) (n = 50) and the control group (n = 20). The main group was divided into subgroups of pregnant women with placental dysfunction and fetal growth retardation (n = 30) and pregnant women with placental dysfunction without fetal growth retardation (n = 20). The control group comprised 20 pregnant women with physiological gestation. Apart from history taking, the study comprised obstetric and general clinical examination, evaluation of endothelium-dependent vasodilation, serum concentrations of soluble forms of vascular and platelet-endothelial molecules of cell adhesion 1, indicators of athrombogenicity of the vascular growth wall, uterine-placental-fetal blood circulation, pathomorphological and histometric examination of the placenta. **Results.** Based on the obtained clinical-morphological and endotheliotropic criteria, a personalized clinical algorithm for managing pregnant women with placental dysfunction was developed and implemented. **Conclusions.** Assessment of pregnancy results in a prospective clinical study showed that the proposed algorithm for personalization of the risk of perinatal abnormalities not only helped to avoid antenatal mortality, but also to prevent intranatal and early neonatal losses in patients with placental dysfunction and fetal growth retardation.

Keywords: *gestational endotheliopathy, fetal growth retardation, placental dysfunction, personalized diagnostic algorithm.*

Introduction

Placental dysfunction (PD) remains one of the pressing problems of obstetrics.

According to the literature, the incidence of placental dysfunction (PD) in habitual miscarriage ranges from 50 to 77%, in preeclampsia this figure reaches more than 65%, in pregnancy complicated by extragenital abnormality it occurs in 24–45%, in pregnant women with viral or bacterial infections in more than 60% of cases [1–5]. Placental dysfunction is the cause of fetal distress, fetal growth retardation (FGR), abnormal conditions and diseases of the newborn. According to the WHO, the number of newborns with growth retardation ranges from 6.5% in the developed European countries to 31.1% in Central Asia. In the US, FGR occurs in every 10–15% of births; meanwhile, severe intranatal hypoxia is observed in 30%. Perinatal mortality in pregnant women with placental dysfunction is 8–15‰ among full-term infants and 40–50 ‰ among premature infants. Placental dysfunction results in the formation of fetal growth retardation syndrome in 60–70% of cases [1, 6–10].

Impaired placental function is due to cardiovascular diseases in pregnant (heart disease, circulatory failure, hypertension and hypotension), chronic infection, disorders of the lungs, liver, kidneys, blood, diseases of the endocrine system (diabetes, hypo- and hyperthyroidism), obstetric and gynecological diseases, harmful habits, social and household factors [1, 11].

Primary PD begins to develop in early pregnancy (up to 14–18 weeks) in the early stages of placental development and embryogenesis, under the influence of genetic, endocrine, infectious and

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environmental factors. Enzymatic insufficiency of decidual tissue (in luteal phase insufficiency), defects of structure and localization of the placenta, as well as impairment of vascularization and disturbance of chorion morphology play an important role in the development of primary PD. Patients with primary PD are more often found to have fetal malformations, chromosomal abnormalities and intrauterine infection [12–14].

Secondary placental dysfunction can develop secondarily to the already formed placenta after 18 weeks of pregnancy under the influence of exogenous factors. The morphological substrate of secondary PD is a violation of uteroplacental and fetoplacental blood flow, as well as related dystrophic changes of the chorionic villi, combined with cellular and tissue compensatory reactions of the placenta [15].

According to its clinical course, PD is divided into acute and chronic. Acute PD develops with a sudden violation of decidual perfusion and adequate hemodynamic support of pregnancy. Morphological examination reveals hemorrhages in the placenta. Acute PD can occur at any stage of pregnancy in the form of premature detachment of the normally located placenta, during childbirth and is the cause of acute distress and fetal death.

Chronic PD is observed in every third pregnant woman with a high risk of perinatal impairment, its course is longer due to impaired adaptive mechanisms in combination with circulatory disorders, involutive changes that may be associated with extragenital disorders in women during pregnancy [16, 17].

Methods of assessment of the fetoplacental complex are used in due time to diagnose placental disfunction and FGR. Prenatal diagnosis of these conditions includes Doppler ultrasound (US), cardiotocography (CTG), placental hormones (estriol, cortisol, placental lactogen, progesteron) [1, 18–21]. The content of vascular-endothelial growth factor, placental growth factor, interleukin-1, interleukin-1, endothelin-1, pulsation index of spiral arteries, umbilical arteries and uterine arteries are also considered to be early markers of PD prediction [4, 13, 19].

Despite the introduction of new methods of diagnosis and prevention of placental dysfunction into obstetric practice, there is no clear tendency to decrease its incidence. Therefore, it is important to use the latest research methods as prognostic criteria for placental dysfunction and its manifest form like FGR, which will improve the prognosis of gestation, develop an optimal strategy for the term and mode of delivery and, as a consequence, prevent the development of obstetric and perinatal pathology [1, 4].

2. Purposes, Subjects and Methods

2.1. Purpose of the study was to optimize the modern diagnosis of placental dysfunction and its complications.

2.2. Subjects & Methods

The study was conducted by Department of Obstetrics and Gynecology No.2 of Kharkiv National Medical University at Kharkiv Regional Perinatal Centre (2016–2020). The first stage of the study was a retrospective assessment of 100 individual pregnancy records of women with PD to determine the risk factors for the development of placental dysfunction. The second stage included prospective survey of 70 pregnant women, who were divided into the main group (50 pregnant women with PD) and the control group (20 pregnant women with physiological pregnancy). The main group was divided into groups of 20 pregnant women with PD and 30 pregnant women with PD and FGR.

The examination of women included history taking, general clinical examination, ultrasonography of the fetus and placenta, in particular, Doppler imaging of the uteroplacental complex, as well as homeostasis indicators such as vascular endothelial growth factor (VEGF), platelet-endothelial molecules of cell adhesion 1 (sVCAM and sPECAM), indicators of atrombogenicity of the vascular wall (thrombomodulin, thrombospondin, tissue plasminogen activator and plasminogen activator inhibitor-1), antioxidant (MDA, DC, catalase and SOD) and lipid peroxidation system. Morphological examination of the placenta was carried out [1]. Statistical processing of the study results was performed using the statistical analysis software Microsoft Excel and Statistica-6.0 (Statsoft), applying parametric and non-parametric methods for evaluating the results.

3. Results & Discussion

A study of social and household conditions showed that PD more often developed in patients who had low socio-economic status ($p = 0.0002$), smoked for 5–8 years ($p = 0.0001$), spent more than 5 hours a day working on the computer ($p = 0.04$), led a sedentary lifestyle ($p = 0.04$). 17.5% of women with placental dysfunction continued to smoke during their current pregnancy. Besides, 53.8% of women in the main group indicated that they had drunk soft alcoholic drinks before pregnancy [1].

The structure of extragenital morbidity in pregnant women with PD was associated with

the varicose veins (p = 0.02), cardiovascular (p = 0.05), gastrointestinal diseases, namely, dyskinesia of the biliary tract (p = 0.03), infectious diseases (p = 0.04). An important place in the development of PD was also occupied by hereditary family history, namely cases of arterial hypertension (p = 0.02), endocrine disorders (p = 0.02), thrombotic complications (p = 0.02) [1].

Assessment of the obstetric history of women with PD showed that previous pregnancies in women with placental pathology were complicated by spontaneous abortions (p = 0.03), induced abortions (p = 0.002), disorders of the ovarian-menstrual cycle (p = 0.04) and disorders of vaginal microbiocenosis (p = 0.03). Obstetric disorders included preterm birth (p = 0.04) and threatening miscarriage (p = 0.008). In general, the threat of miscarriages may be evaluated as an integral indicator of the clinical manifestation of inferiority of cytotrophoblast invasion, which may subsequently lead to PD [1].

Evaluation of endotheliotropic vasotonic properties in the examined pregnant involved employment of a test with reactive hyperemia of the brachial and posterior tibial arteries, applying high resolution ultrasound – an indicator of endothelium-dependent vasodilation. Pregnant women with manifested course of placental dysfunction, namely, fetal growth retardation, were found to have critical disorders of vasoregulatory function of the endothelium in both examined vessels, with a clear reliable vasoconstrictor component at the 28–40 weeks of pregnancy, even in comparison with women who had preclinical PD (p<0.05).

Pregnant women with PD and FGR in gestational endotheliopathy had an increase in serum indicators of VEGF (5.89±0.31 pg/ml). Serum thrombospondin concentration in patients with FGR increased by 2.2 times (3.37±0.40 pg / ml), compared with those in pregnant women of the control group and compared with the results of women with preclinical significant form of PD (p <0.05).

In addition to assessing the content of major vasoconstrictors and vasodilators, the functional state of the vascular endothelium allowed assessment of the level of soluble molecules of intercellular adhesion. I.B. Borzenko observed an increase in the level of soluble forms of vascular cell adhesion molecules 1 (sVCAM-1) to 1721.72±161.63 ng/ml in serum during placental dysfunction, which was complicated by fetal growth retardation compared to similar indicators during physiological pregnancy – 796.49 ± 75.90 ng/mg and donological placental dysfunction – 1065.78± 128.24 ng/ml (p <0.05). Assessment of the results of sPECAM -1 presence in the serum of pregnant women with placental dysfunction showed a decrease in the concentration of soluble form of the above-mentioned MKA compared with the samples obtained from almost healthy pregnant respondents (96.4±7.9 ng/ml). However, we did not observe a statistically significant difference (p>0.05) between serum levels of sPECAM-1 in women who had complicated placental dysfunction (68.4±7.3 ng/ml) and those diagnosed with non-manifest placental dysfunction (78.4±5.1 ng/ml). An increase in the concentration of sVCAM-1 with simultaneous significant reducing sPECAM-1 during placental dysfunction may evidence endothelial dysfunction, which may be useful for stratifying the risk of manifestation of perinatal disorder of placental origin, namely fetal growth retardation [1].

The study of serum thrombomodulin (the thrombin receptor expressed on endothelial cell membranes) showed that there was a significant increase in the indicated marker of vascular thrombogenicity in women with placental dysfunction, compared to the results of practically healthy pregnant women (4.28±0.47 ng/ml). However, a statistically significant difference (p<0.05) was observed in patients diagnosed with fetal growth retardation (7.92±0.84 ng/ml), not only in women with physiological pregnancy, but also in practically healthy pregnant women, who did not have any clinical manifestation of placental dysfunction (5.25±0.53 ng/ml) [1].

The study of tissue plasminogen activator in patients had a significant difference (p<0.05) between the results of tissue plasminogen activator in pregnant women with physiological gestational course and patients with fetal growth retardation. At the same time, there was no statistically significant difference between serum tissue plasminogen activator scores in women with normal pregnancy and patients with non-manifest placental dysfunction (p>0.05). The concentration of plasminogen-1 activator inhibitor in patients with fetal growth retardation exceeded that of women with normal gestation by 1.24 times and reached 76.43±5.77 ng/ml. Indicators of endotheliotropic marker of vascular thrombogenicity were predominantly predictive, as an additional risk factor for perinatal pathology [1].

During the study, I.B. Borzenko noted activation of the lipid peroxidation system and suppression of the antioxidant protection system in pregnant women with PD. A significant (p<0.05) increase in malondialdehyde level (7.21±0.76 μmol/l)

was found in patients with placental dysfunction complicated with fetal growth retardation, compared with malondialdehyde level in pregnant women with physiological gestational course (3.85± 0.51 μmol/l). The obtained data on the catalase activity indicated a significant ($p<0.05$) decrease in its indicators in patients with PD and FGR to 0.13±0.03 c.u./l, compared with the same indicators in practically healthy pregnant women (0.26±0.0 c.u./l) [1].

The results of Doppler metamorphosis of the placental fetal blood flow showed that women with placental dysfunction secondary to gestational endotheliopathy had violation of hemodynamic support of the fetus. On week 28 of pregnancy, the patients with FGR had a significant decrease in the pulsation index to 1.62±0.16 compared with a similar indicator in pregnant women from the control group (2.13±0.14) ($p<0.05$). These changes in Doppler parameters may be evidence of fetal-placental insufficiency and impaired blood supply to the fetal brain. At the end of the third trimester, a significant decrease ($p<0.05$) of the pulsation index (to 1.35±0.17) was found in Doppler ultrasound examination of blood flow of pregnant patients with fetal growth retardation compared with women who had a physiological course of the gestational process (1.82±0.11). A statistically significant result between women with manifested PD and pregnant women from the control group was also found in terms of GVA (2.14±0.5 and 3.32±0.31, respectively).

The labor in pregnant women with PD was associated with an increase in the number of premature births ($p = 0.05$), cesarean sections ($p = 0.02$), cases of acute fetal distress ($p = 0.01$), and development of birth abnormalities ($p = 0,04$). The clinically manifested form of PD was the reason for bearing newborns with significantly smaller weight ($p <0.05$), lower ($p <0.05$) Apgar score at the 1st and 5th minutes, and an increase in the incidence of adverse perinatal outcomes ($p = 0.05$) compared with women who had physiological pregnancies and deliveries. The infants whose mothers were diagnosed with FGR secondary to endothelial dysfunction also prevailed in frequency.

The evaluation of the morphological features of the placenta in pregnant women with PD of the endothelium showed a decrease in the height of endothelial cells by 4.81±0.04x10^{-6} mm, a decrease in cell diameter by 3.21±0.04x10^{-6} mm, an increase in the relative volume of damaged endothelial cells from 6.41 ± 0.24% to 48.02± 3.63%. The development of FGR in the presence of PD developed secondary to increased damage to the endothelium of the spiral arteries, characterized by the height of endothelial cells 4.04 ± 0.08x10^{-6} m, their diameters 2,92±0,04x10^{-6} m, the predominance of damaged endothelial cells by 80.57±0,23% followed by the development of ischemic lesions and sclerotic changes. Placental vessels in the course of early placental dysfunction were characterized by a 55% decrease in the area of the lumen accompanied by a decrease in the perimeter and area of these vessels. The endothelial proliferation, hypertrophy of the muscle layer, pronounced growth of perivascular connective tissue with the formation of the so-called "fibrous cuffs" in the myometrial segments of the spiral arteries were also evident. These changes resulted in an additional narrowing of the transparent vessels [1].

In the literature review, Salavati N. et al. [14] intended to give an overview on the clinical relevance of placenta morphometry in the detection of FGR. Future research can focus on the relationship between placental morphometry, FGR and its complications, to improve screening for FGR, and to determine the biological pathways that can be linked to placental dysfunction, in a group of optimally phenotyped cases of FGR.

In the study by Labarrere C.A. et al. [13] analyzing the results of a cross-sectional study of 123 placentas (19–42 weeks' gestation) obtained from normal pregnancies, preterm prelabor rupture of membranes, preterm labor, preeclampsia, intrauterine fetal death, and small for gestational age were noted. They found that 87% (94/108) of placentas having spiral arteries with failure of physiologic transformation in the basal plate, and 0% (0/15) of placentas having only spiral arteries with complete physiologic transformation, had arterial endothelial and/or interstitial extravillous trophoblasts reactive with the intercellular adhesion molecule-1 activation marker ($P < .001$). A significant correlation ($R2 = 0.84$) was found between expression of spiral artery endothelial and interstitial extravillous trophoblast intercellular adhesion molecule-1 ($P < .001$) in activated placentas.

Korzeniewski SJ. et al. [12] examined of 4006 women with singleton gestations. Maternal plasma angiogenic index-1 ratios were determined using enzyme-linked immunosorbent assays. Maternal plasma angiogenic index-1 (PlGF/sVEGFR-1) is the first biomarker for the burden of placental lesions consistent with maternal vascular underperfusion. They propose that an accumulation of these lesions in placentas

delivered before 34 weeks is a histologic counterpart of an antiangiogenic profile.

Thus, our clinical prospective study based on a comprehensive assessment of the endothelial component in the development of early PD has shown that gestational endotheliopathy is an independent prognostic factor associated with adverse pregnancy outcomes.

The obtained clinical-morphological and endotheliotropic criteria allowed us to develop and implement a personalized clinical algorithm for managing pregnant women with placental dysfunction. Having analyzed the results of pregnancy in the prospective clinical study, we proved that thanks to the proposed algorithm for personification of the risk of perinatal pathology, it was possible not only to avoid cases of antenatal mortality, but also to prevent intranatal and early neonatal losses in patients with placental dysfunction and fetal growth retardation.

Significant disorders of vasoregulatory, athrombogenic functions, intercellular integration of changes in parameters of uteroplacental-fetal hemodynamics, histomorphometric disorders were identified in pregnant women with PD, which allows better understanding of the pathogenesis of various forms of PD, identifying the ways to predict complications in the early stages of this group of patients. Adequate perinatal support and timely delivery have significantly improved pregnancy outcomes, significantly reduces the number of cases of obstetric impairments.

Declarations

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Consent for publication

All authors give their consent to publication.

Disclosure Statement

Authors have nothing to disclosure.

The manuscript is a part of the thesis of Borzenko I.B.

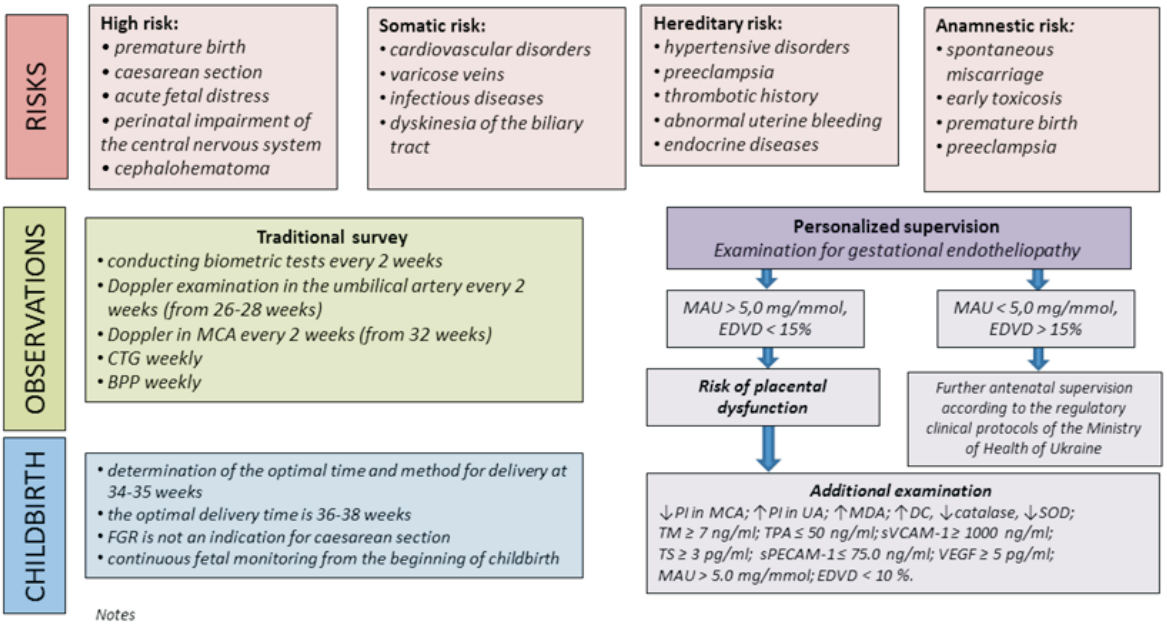
Funding Sources

There are no external sources of funding

Data Transparency

The data can be requested from the authors.

ALGORITHM FOR CLINICAL MANAGEMENT OF PREGNANT WOMEN WITH EARLY PLACENTAL DYSFUNCTION



Notes

MCA - middle cerebral artery; CTG - cardiotocography; BPP - biophysical profile; FGR - fetal growth retardation; MAU - microalbuminuria; EDVD - endothelium-dependent vasodilation; PI - pulsation index; UA - umbilical arteries; MDA - malonic dialdehyde; DC - diene conjugates; SOD - superoxide dismutase; TM - thrombomodulin; TPA - tissue plasminogen activator; sVCAM-1 - soluble vascular cell adhesion molecule-1; TS - thrombospondin; sPECAM-1 - soluble platelet-endothelial cell adhesion molecule-1; VEGF - vascular-endothelial growth factor.

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Received: 30-Mar-2021
Accepted: 06-Sep-2021

COMPUTER TECHNOLOGIES FOR DETERMINING INDEX ASSESSMENT OF HARD DENTAL TISSUES DESTRUCTION

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https://doi.org/10.35339/ic.8.3.188–193

Abstract

The aim of the study was to compare the obtained data of hard dental tissues destruction indices with the corresponding indications for the choice of the method of treatment by means of mathematical analysis. **Materials & methods.** 120 patients aged 20 to 55 were examined and 358 teeth hard tissue defects were identified in them. The data of indices was obtained and compared with the indications for orthopedic treatment according two indices in the same clinical situation. **Results.** The study showed that the indices had different meanings and different indications for treatment in the same situations. Such discrepancies in indications for treatment indicate the subjective data of one of the indices, which does not take into account the depth of destruction and the volume of the remaining natural tissue of the teeth. Comparison of these indices showed different figures in the same clinical situation, identifying corresponding incorrect indications for the choice of the design of the first investigated index, as well as more accurate data of the proposed index. **Conclusion.** The index assessment of hard dental tissues destruction serves as the main guideline for the dentist when choosing a method for tooth restoration, and can be calculated using photographs, scans and computer software.

Keywords: *inlays, crown defect, index assessment, microprostheses, orthopedic treatment, indications for tooth restoration method, tooth destruction.*

Introduction

One of the main tasks of prosthetic dentistry is to correct the choice of denture design. Dentists must choose a method of restoration of tooth destruction from the following: filling, inlay, veneer, crown, pin construction. Often dentists unreasonably expand the indications for the use of composite restorations, which in the future leads to the destruction of natural tooth tissues, and violation of the warranty period [1, 2].

The main criteria for choosing a method of tooth restoration are the degree of hard tissues destruction, height, area and thickness of the tooth walls, presence of pulp, direction of masticatory pressure, material of the future structure, and the method of artificial material for fixation [3–5].

It is very important to determine the extent of the defect using different methods of tooth restoration (direct or indirect restoration) and the material of restoration, for predicting the service life of microprosthesis. Also, the composite structure, which is formed when restoring the integrity of the tooth, creates an inseparable synthesis of "natural tooth and filling material", "tooth-inlay", "tooth-crown", etc. [6, 7].

All-ceramic inserts made in the laboratory by injection molding or milling have been widely used recently. The volume ratio of natural and artificial tooth tissues determines the reliability for each design and also determines the indication for a particular method of tooth restoration [8, 9].

The development of adhesive systems in dentistry has achieved some success, in connection with which the need to completely dissect all tooth surfaces under the full crown has disappeared. The principle of biological expediency and minimal invasion during tooth preparation has gained new popularity in modern dentistry. Partial orthopedic restorations, such as half-crowns, overlays, equatorial and three-quarter crowns, are increasingly used to preserve natural tooth tissues [10–12].

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To assess the degree of hard tissues destruction of the lateral teeth, Milikevich proposed an index of occlusal surface destruction of the tooth (IOSD) in 1984 [13]. It is possible to use different methods of IOSD assessment by Milikevich, namely visual detection, by means of a graduated dental mirror, on models of jaws, by means of a transparent plate and a millimeter paper, and use of photos of a tooth. Milikevich identified the following indications for treatment:

IOSD – up to 0.4 – the defect is replaced by direct restoration;

IOSD – from 0,4 to 0,6 – the defect is restored by an inlay, onlay, and overlay;

IOSD – from 0.6 to 0.8 – restoration by artificial crowns;

IOSD – from 0.8 to 1.0 – restoration by various modifications of pin constructions.

However, the IOSD index has not been widely used, due to inaccuracies, as in the process of determining the degree of destruction and due to not taking into account the volumetric destruction [14].

The index of volumetric destruction of tooth tissues (PORTZ) proposed by Yanishen and Golik in 1997. It is calculated by the ratio of the volume of destroyed tooth tissue to the volume of crown tissue [15]. Identification of the destruction degree by the index of volumetric destruction of tooth tissues (PORTZ) is not only a diagnostic test, but also a determining factor in choosing a method of treatment (filling, tab, pin tooth and artificial crown) to prevent further destruction of the crown, tooth extraction [16].

To solve the problem of index assessment of tooth destruction, it is advisable to use an optical impression with subsequent mathematical analysis of the three-dimensional image. It is also possible to use a combination of digital and analog approaches, get prints, cast models, followed by scanning. Such technologies for making dental inlays have been used for a long time. The most well-known computer technology for making tabs is the "CEREC" method, which was developed in 1980 by Morman and Brandestini. In addition to the "CEREC" system, there are others, such as "The Duret system" (developed in 1985 in Grenoble, France). "The Minnesota system" (developed by Kekon in 1986 at the University of Minnesota, USA), "CAD/CAM" system Sopha Bioconcept" developed in 1991 [17–20].

Given all the above, the definition of indications for treatment, as well as the correct index assessment of tooth destruction is still a topical issue in dentistry.

2. Purposes, Subjects and Methods

2.1. Purpose of the study was to compare the obtained data of dental hard tissues destruction indices and the corresponding indications for the choice of the treatment method by means of mathematical analysis.

2.2. Subjects & Methods

The study was conducted on the base of the University Dental Center of Kharkiv National Medical University. Among the examined 120 patients, 358 teeth with hard tissue defects were identified.

The obtained indicators of the index of occlusal surface destruction (IOSD) of the tooth were compared, with the proposed index, as well as the obtained indications for orthopedic treatment according to the two indices in the same clinical situation. Milikevich's IOSD index was determined by obtaining a clinical photograph or a screenshot of a digital impression from Exocad (Version 3.0 Galway), followed by image processing in "Adobe Photoshop" graphics editor. The display of the grid in the image included View – Show – Grid. The image was unfolded and aligned along the edges of the grid (Ctrl-A, Ctrl-T). The areas of the cavity were marked with the letter "П" in those squares where the area of the destroyed tooth surface was much larger than the preserved one. Calculation of the total area of the occlusal surface, squares were taken into account, where the tooth tissue occupied more than a half of it. Then the number of these squares with destruction was divided by the total number of squares to receive the index. In our example shown in *Figure 1*, the total area of the occlusal surface of the tooth was 28 squares, and the area of the cavity comprised 13 squares. Thus, this tooth had IOSD = 13: 28 = 0.46.

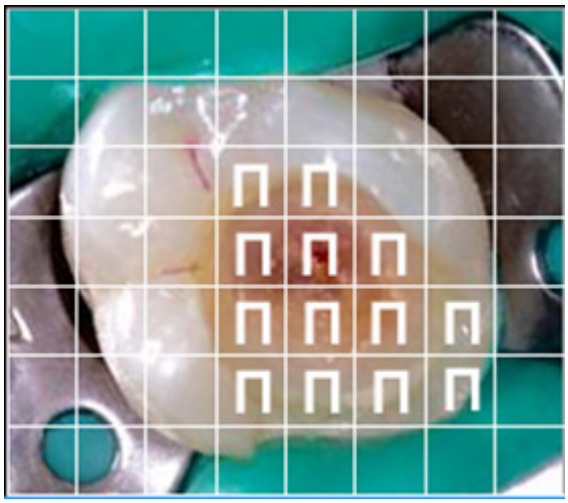

Fig. 1. An example of IOSD calculation

To increase the accuracy of the study it is necessary to clarify some parameters used in the calculation. The shape of the tooth is far from the correct geometric. In this regard, calculations should involve determination of the maximum and minimum dimensions, followed by determination of the average value. The occlusal surface and the shape of the defect should be considered as a geometric figure - an ellipse, and the tooth as an elliptical cylinder. Given that the height of the tooth crown and the depth of the cavity in most cases do not match, we have proposed an index of volumetric destruction of the clinical crown of the tooth (IVDCC) (*Fig. 2*) which is calculated by the formula:

$$IVDCC = \frac{rmax * rmin * (hmax + hmin)}{Rmax * Rmin * (Hmax + Hmin)}$$

where r_{max} – the maximum radius of the defect;
r_{min} – the minimum radius of the defect;
R_{max} – maximum radius of the occlusal surface;
R_{min} – minimum radius of the occlusal surface;
h_{max} – maximum depth of the defect cavity;
h_{min} – the minimum depth of the defect cavity;
H_{max} – the maximum height of the clinical crown of the tooth;
H_{min} – the minimum height of the clinical crown of the tooth.

IVDCC degree 2 from 0.2 to 0.55 – the defect is replaced by a direct filling or indirect tab (inlay, onlay, overlay);

IVDCC degree 3 from 0.55 to 0.75 – the defect is replaced by artificial crowns or overlay;

IVDCC degree 4 from 0.75 to 1.0 – the defect is replaced by various modifications of pin designs.

3. Results & Discussion

Among the examined 120 patients, 358 teeth with hard tissue defects were identified. The two indices were calculated for each tooth according to the described methods. As a result, a significant difference was found in the values and indications for treatment among the compared indexes (*Table*).

There were 58 teeth with value <0.4 according to the indications of IOSD, the method of treatment of which should be a direct composite restoration, while the index IVDCC with value <0.2 revealed 141 cases, which should be restored by dental fillings.

Among the indications for treatment with tabs IOSD 0.4–0.59 there were 105 teeth, and 124 cases for IVDCC 0.2–0.55. Crowns according to IOSD with data of 0.6–0.8 should be applied 133 times. As for IVDCC with value of 0.55–0.74, there were only 65 cases. Pin structures were indicated 62 times for IOSD 0.8–1.0, while for IVDCC 0.75–1.0 only 28 times.

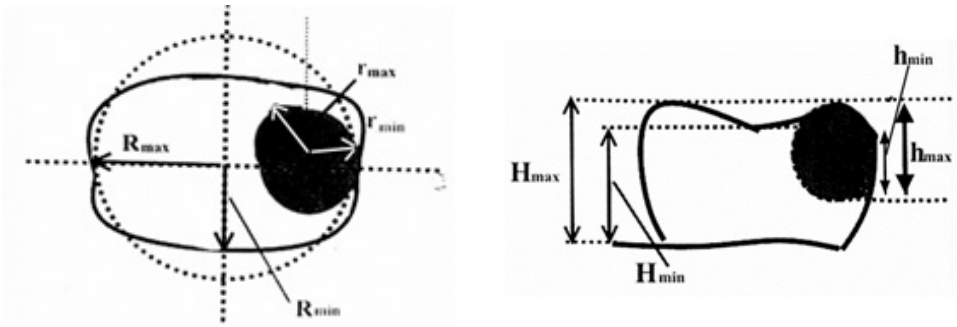

Fig. 2. A scheme of a tooth with designations for IVDCC

A differentiated choice of a method of hard dental tissues defect restoration involved determination of the following indications by IVDCC:

IVDCC degree 1 to 0.2 – the defect is replaced by direct filling;

The percentage of data obtained by the two indices are presented in *Figure 3*.

The study showed different values and different indications for treatment according to IOSD and IVDCC in the same situations. Such

Data of the examined teeth according to the index assessment

Indications for treatment by the method	The value of the IOSD	Number of teeth	Percentage	The value of the IVDCC	Number of teeth	Percentage
Filling	<0.4	58	16.2%	<0.2	141	39.4%
Inlay, onlay (tabs)	0.4-0.59	105	29.3%	0.2–0.55	124	34.6%
Crowns, overlays	0.6–0.79	133	37.2%	0.55–0.74	65	18.1%
Pin designs	0.8–1.0	62	17.3%	0.75–1.0	28	7.8%
Total		358	100		358	100

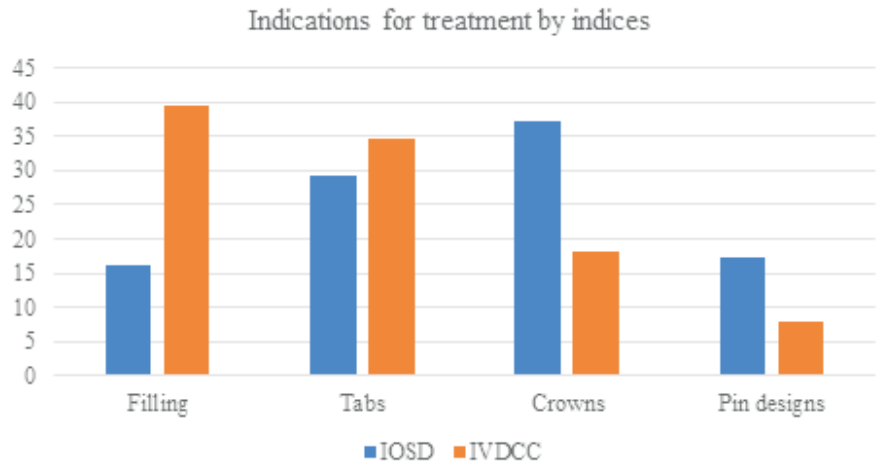

Fig. 3. Percentage of indications for treatment by indices

discrepancies of the indications indicate the subjective data of IOSD, which does not take into account the depth of destruction and the volume of the remaining natural tooth tissues.

Let us consider a clinical situation that demonstrates the inaccuracy of indications for structures according to only one occlusal surface.

Calculation of IOSD of the clinical situation of tooth 2.6, shown in *Figure 4*, is as follows:

IOSD = 25: 30 = 0.83 which means indications for a pin design.

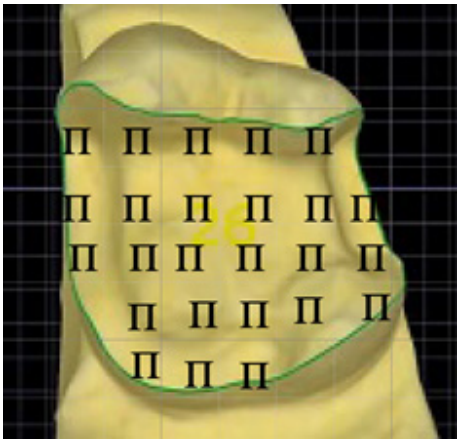

Fig. 4. Calculation of IOSD for 2.6 tooth

Let us consider the same clinical situation using the IVDCC, calculating the minimum and maximum height, diameter of the defect and the tooth (*Fig. 5*).

$$IVDCC = \frac{200 * 150 * (300 + 150)}{240 * 140 * (460 + 360)} \approx 0.49$$

As a result, two indices in the same situation have different values and indications, respectively. The IOSD recommend the pin design, and the IVDCC indicate the production of the tab. Taking into account presentation, tooth vitality, and IVDCC data, the second option was chosen and an overlay tab was created (*Figure 6*).

As discussed by Jason Smithson [21], there will never be a completely black and white guide to dental treatment, and grey areas will always exist. As long as treatment is performed with care, to a high standard and with a nod to the underlying science, it will more than likely be successful.

According to the Riccardo Ammannato [22], it is necessary to take into account the principles of bioeconomics (maximum conservation of healthy tissue) and reinforcement of residual dental structure. Depending on the strength of enamel and dentin wear, the amount of caries, and the size of existing restorations, different treatment options can be applied to each tooth: direct and indirect partial restorations, or full crowns. The author believes that the index technique is a fast and conservative approach for the planning and management of a full-mouth adhesive treatment in all cases of worn dentition.

As discussed by Mykyevych [23], high-quality treatment of defects in the masticatory group of teeth can be carried out by using a clinically tested choice of restorative material and method of restoration. According to him, the results of the study of wear resistance and microhardness of different dental materials are contradictory and debatable due to different methodological approaches to determining these indicators.

Conclusion

Index scores showed differences in indications for treatment. Among the 358 examined destroyed teeth, filling was required in 16.2% for IOSD and in 39.4% for IVDCC. Tabs for IOSD were indicated in 29.3% of cases, while for

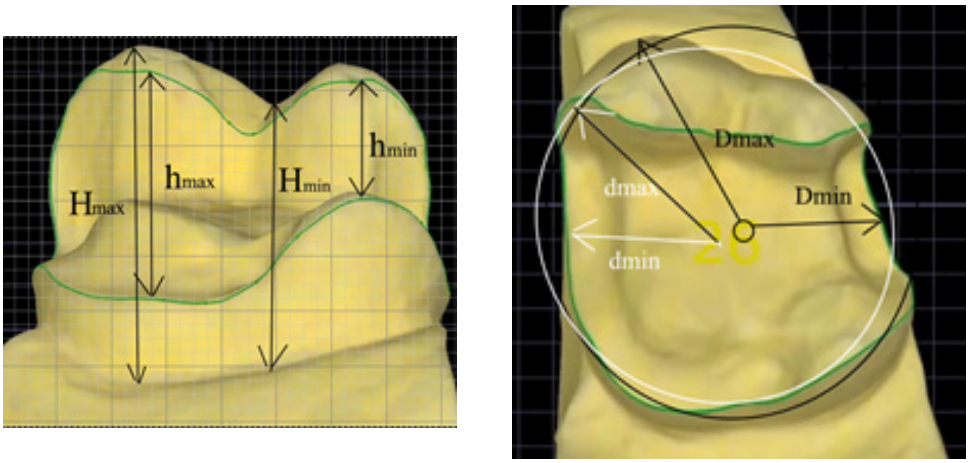

Figure 5. Calculation of IVDCC for 2.6 tooth

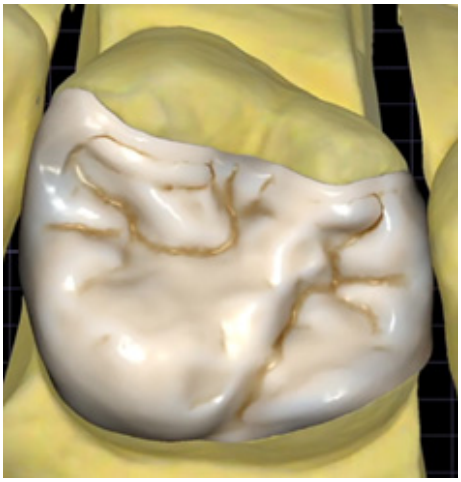

Fig. 6. Simulated overlay tab according to IVDCC indications

IVDCC in 34.6%. Crowns for IOSD were needed in 37.2% of cases, and for IVDCC only in 18.1%. Pin structures according to IOSD were justified in 17.3% of cases, and according to IVDCC only in 7.8%. The discrepancies in the data are explained by the fact that according to Milikevich, IOSD has a significant disadvantage of taking into account only the occlusal plane. IVDCC is a more accurate index method for choosing a method of tooth restoration, as it takes into account the destruction of the tooth in all planes. The comparison of these indices showed different figures under the same clinical conditions, indicating the corresponding incorrect indications for the choice of the design by IOSD according to Milikevich, as well as more accurate data of IVDCC. The index assessment of hard dental tissues destruction serves as the main guideline for the dentist when choosing a method for tooth restoration, and can be calculated using photographs, scans and computer software.

Declarations

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Consent for publication

All authors give their consent to publication.

Disclosure Statement

Authors have nothing to disclosure.

Funding Sources

There are no external sources of funding

Data Transparency

The data can be requested from the authors.

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Received: 30-Mar-2021
Accepted: 13-Sep-2021