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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

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გამოიცემა თბილისის სახელმწიფო სამედიცინო უნივერსიტეტთან
თანამშრომლობით და მისი პატრონაჟით

This special issue of the journal is dedicated to II International Conferense "From Maturity to Aging"
Guest Editors – Prof. Tamar Sanikidze, Prof. Irina Kvachadze

Данный номер журнала посвящается II Международной конференции
"От зрелости к старению"
Приглашенные редакторы – проф. Тамар Саникидзе, проф. Ирина Квачадзе

ჟურნალის ეს ნომერი ეძღვნება II საერთაშორისო კონფერენციას
"სიმწიფიდან სიბერემდე"
მოწვეული რედაქტორები – პროფ. თამარ სანიკიძე, პროფ. ირინა კვაჭაძე

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

ТБИЛИСИ - НЬЮ-ЙОРК

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board and The International Academy of Sciences, Education, Industry and Arts (U.S.A.) since 1994. **GMN** carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.
GMN is indexed in MEDLINE, SCOPUS, VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

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Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო რეცენზირებადი სამედიცინო ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ, ინგლისურ და გერმანულ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები, რეცენზიები.
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1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx,** размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

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В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Библиографическое описание литературы составляется на языке текста документа. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующему номеру данной работы в списке литературы.

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Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

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2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 6 pages and not exceed the limit of 15 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

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6. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

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8. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

9. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

10. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: introduction, material and methods, results and conclusions) and a list of key words.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

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Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

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რედაქციაში სტატიის წარმოდგენისას საჭიროა დაცული იქნას შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx,** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის ავტორთა რაოდენობა არ უნდა აღემატებოდეს 5-ს; სტატიის მოცულობა არ უნდა შეადგენდეს 6 გვერდზე ნაკლებსა და 15 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

5. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

6. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

7. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით.

8. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

9. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა.

10. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: შესავალი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

Содержание:

НАУКА

CANCER SCREENING PROGRAM IN GEORGIA (RESULTS OF 2011)

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Early detection of cancer greatly increases the chances for successful treatment. There are two major components of early detection of cancer: education to promote early diagnosis and screening**.** Detecting cancer early remains the best strategy for reducing cancer deaths [1]. The health policy makers should develop specific programs to increase cancer awareness and to detect cancer early [2].

Recognizing possible warning signs of cancer and taking prompt action leads to early diagnosis. Increased awareness of possible warning signs of cancer, among physicians, nurses and other health care providers as well as among the general public, can have a great impact on the disease. Some early signs of cancer include lumps, sores that fail to heal, abnormal bleeding, persistent indigestion, and chronic hoarseness. Early diagnosis is particularly relevant for cancers of the breast, cervix, mouth, larynx, colon and rectum, and skin [2].

Screening refers to the use of simple tests across a healthy population in order to identify individuals who have disease, but do not yet have symptoms. Examples include breast cancer screening using mammography and cervical cancer screening using cytology screening methods, including Pap smears [2].

Considering WHO recommendations and other developing countries experience Georgian health policy makers with collaboration international organizations have gradually started to establish cancer screening programs namely: the partnership between the Health and Social Affairs Department (HSAD) under the Municipality of Tbilisi and UNFPA Georgia for Reproductive Tract (RT) cancers prevention and early detection has been launched in 2006 in Tbilisi; Based on the analyses of the data and accumulated experience, at the beginning of 2008, the project has been redesigned to focus on breast and cervical cancer screening for the targeted population in Tbilisi and the National Screening Centre (NSC) has been selected to implement this project. This project is an important intervention to make the quality RH services more accessible for the population and runs under patronage of the First Lady of Georgia.

This innovative project is one of the first of its kind among the countries of Eastern Europe and Central Asia that aims to increase the detection of reproductive system cancers at early stages, in order to reduce the early mortality of women caused by these diseases; the project aims to achieve this through ensuring equitable access for the women of the target ages to the breast and cervical cancers screening services and at the same time to maintain high standards of the programme management, service delivery, monitoring & evaluation and accountability.

The remarkable achievements of the project, contributing to the reduction of women's morbidity and mortality, made the federal government decide to replicate the project at the national level in 2009 – in 2010 the breast cancer screening programme has been launched in four regions of Georgia; starting from June 2011 the cancer screening programme in full scope (breast, cervical, colorectal cancer screening and prostate cancer risk management) is available for all population of Georgia through the national programme under the National Centre for Diseases Control and Public Health NCDC&PH (MoLHSA) which is also implemented by NCS.

National capacity building for Breast and Cervical Cancer Screening Programme planning and implementation

National capacity building to strengthen strategic planning, clinical management, implementation and quality assurance of the breast and cervical cancer screening programme has been one of the priorities for UNFPA; in this regard several significant activities were undertaken during the reporting period:

1. Responding to the need identified by national partners on developing strategic recommendations on planning and implementation of the national screening programme in Georgia, UNFPA engaged leading European technical institutions and experts to develop national capacities in this direction.

In partnership with the European Cervical Cancer Association (ECCA), as a leading partner in this initiative a Strategic Planning Meeting for the Implementation of Cancer Screening in Georgia was organised on October 10 and 11 at NCDC, which was attended by the management and technical staff of NCDC, NSC and MoLHSA. Professor Marek Spaczyński, founder and the Director of Polish Breast and Cervical Screening programme was invited as a guest speaker to share the experience of Poland, as a country, which in many aspects resembles the situation in Georgia. The meeting provided the forum for assessing the current status of the health system, reviewing and refining the cancer screening and prevention control objectives. The key aspects of the Report and Recommendations for Cancer Screening in Georgia have been agreed and the first draft of the Report has been developed, which will be further discussed with NCDC/MoLHSA and finalized accordingly.

2. Two gynaecologists- colposcopists from the National Screening Centre participated in two weeks training in UK organized by the European Federation of Colposcopy and Cervical Pathology. The training contributed to improved theoretical knowledge and practical skills in colposcopy. UNFPA supported and funded travel expenses of trainees.

3. UNPFA followed up the last year activity on quality assurance measures of Pap test cytology diagnosis supported in partnership with the European Cervical Cancer Association and the Union for International Cancer Control (UICC); in particular, an independent external evaluation of cervical cytology was conducted in 2010 in two quality-controlled laboratories serving the population-based screening programmes in Reggio Emilia and Viareggio, Italy. This independent evaluation was undertaken to review the work of the Tbilisi cytopathology laboratories serving Tbilisi Screening Programme and to identify the specific skills that needed to be improved.

Based on this evaluation instructional programmes were designed for two cytopathologists heading the labs in Tbilisi and training sessions were organised for them in Reggio Emilia laboratory. This programme was designed to address the specific problems identified in the evaluation and to provide the local cytopathologists with a better knowledge of the operation of a Western European quality-controlled laboratory.

The training in Italy was followed by a Gynaecology Cytopathology Workshop in Tbilisi on 8-14 September, 2011 conducted by three experts from Italy (supported by UICC): Prof Cesare Gentilli, Chief Consultant of Pathology; Prof Luigi Di Bonito, Professor of Anatomic Pathology and Cytopathology and Ms Clara Bosco, Director of Education for Diagnostic Services and Technical Coordinator for Pathology Services; 15 cytopatologists from the laboratories of Tbilisi and regional centres of Georgia involved in the Georgian Cervical Screening Programme were trained at this workshop.

This workshop succeeded in achieving the following results:
a. Disseminate the knowledge from the Italian training to a wider audience of cytopathologists who would participate in the expansion of the cervical screening programme in Georgia;
b. Establish the reputation of the two Tbilisi cytopathologists as the cytopathology leads in the country so they would be better positioned to lead the ongoing training that will be required as the programme expands;
c. Refine and validate the format of the workshop and the training materials so they would better serve as the model for further workshops to be held in the country.

It is planned to repeat the independent review of cytology to verify and measure the progress that had been achieved.

4. The project partnered with the National professional association Georgian Society of Gynaecological Oncology (GSGO) and contributed to the Batumi International Cervical Pathology Conference held on June 24-26 in Batumi Georgia organized by this association. In particular, through UNFPA support 15 gynaecologists from Tbilisi and regions of Georgia involved in the cervical cancer screening programme have improved their knowledge and skills through attending the conference and the EFC Colposcopy Course conducted by EFC experts.

5. To improve quality of clinical services of breast cancer screening program and to develop quality assurance instrument the partnership has been established with Dutch National Experts and Training Centre for Breast Cancer Screening LRCB, Netherlands. The objective of this partnership is to assess the accuracy of mammographic screening and diagnoses in Georgia compared to established standards in use in Western Europe and establish quality assurance mechanisms of the national Breast Cancer Screening Program.

Under this collaboration three hundred and fifty mammograms taken during the six-month period from 1 November 2010 to 30 April 2011 were randomly and proportionally selected (stratified by abnormality) from the Georgian screening program archives held at the Georgian National Screening Center (GNSC), the Tatishvili Medical Center (TMC) and Tbilisi Cancer Center (TCC). Mammograms were stripped of patient identifiers and sent together with the relevant clinical information (sample number, age and clinical history, but blinded to the original results) to the Dutch National Experts and Training Centre for Breast Cancer Screening (LRCB), where the mammograms were double red. The consensus result will then be correlated with the original results from Georgia. The initial phase of this study will be completed by the end of January 2012 and results will be reviewed by Georgian colleagues.

Anticipated outcomes of this study are the following:
- This study will provide an independent assessment of the accuracy of mammography as conducted in Georgia. These data will be used to identify areas where improvements are required and they will form a current baseline from which to measure progress;
- It is recognised that the number of negative mammograms is insufficient to provide a statistically significant estimate for the false negative rate of Georgian mammography. However, this study will indicate whether a larger study to establish this parameter should be undertaken;
- Depending on the outcomes of this study, the results could be incorporated into an article and submitted for publication should all participants agree to do this.

6. In 2011 an additional European technical institution has been involved in the project on the initiative of the National Screening Centre – the European School of Oncology (ESO). ESO has outlined 3-5 years plan of activities in Georgia in coordination with UNFPA/Georgia to complement already planned and ongoing capacity development interventions.

ESO experts conducted the first workshop in Georgia on 13-14 December 2011 - two days theoretical and practical training for radiologists and radiographers on breast cancer screening was held at the Tbilisi State Medical University facilities. This training for 35 local professionals from Tbilisi and regions of Georgia was co-supported by European School of Oncology (ESO) and UNFPA/Georgia. It was conducted by ESO experts Dr. Rosselli and Dr. Ambrogetti. After theoretical sessions on different topics of special interest for screening radiologists, large amount of time was devoted to showing clinical cases of specific interest, in order to show the main criteria for differentiating benign from malignant breast lesions and to improve the criteria for recall. The on-the-job training for 20 radiographers was conducted at the M. Kachinski branch of the National Screening Centre. According to observations of ESO experts further training of radiologists and radiographers is needed in sterotaxic biopsy. In addition, the experts outlined necessity of involving the medical physicist in the mammography screening program on permanent basis, who will follow radiation safety according to international standards.

The National Screening Center and ESO agreed to continue the cooperation between ESO and the Georgian Screening Programme with the support of the Georgian Ministry of Health, Municipality of Tbilisi, UNFPA, Italian Embassy in Georgia, with the aim of contributing to quality assurance of national breast cancer screening programme.

For this purpose the parties agreed on following:
- To establish a multidisciplinary National Reference Centre (NRC) at the National Screening Center in Tbilisi consisting of professionals of each specialty - epidemiologist, radiologist, radiographer, medical physicist or engineer and pathologist;
- To develop a training educational programme, with the advice of ESO, for the NRC specialists who will be committed to spread the professional skills to the other units operating in the national breast cancer screening programme of Georgia.

ESO plans for 2012 include:
- Training of the Medical Physicist or engineer for 2-4 weeks in Europe (probably Nijmegen NL);
- Training of a pathologist for 2-4 weeks in an European Institution;

- Training of the radiologists in Tbilisi for initiating the stereotaxic examinations and the use of core-biopsies under ultrasound guide, by sending a visiting professor in Tbilisi for 1 week;
- Review of data collection modalities for epidemiological evaluation of the national programme, through sending a visiting professor in Tbilisi for 1 week;
-Organization of a pathology workshop and a second national radiology workshop in September/October 2012.

7. The project supported increased involvement of the Primary Health Care providers in the screening programme. For this purposes the traditional seminars for PHC providers were conducted In December 2011 in Gori. The objectives of workshop were the following:
- To Provide detailed information to doctors about the importance of primary care involvement in breast and cervical cancer screening program
- To involve primary care physicians in educating general population about breast and cervical cancer programs.

Both the basic clinical and the managerial aspects of breast and cervical cancer screening programmes were presented during the seminars. A special manual on breast and cervical cancer screening for PHC providers "Main aspects of breast and cervical cancer prevention and screening; Guidelines for primary care doctors" developed through UNFPA support, were distributed among participants of the workshops; In total 50 primary care providers benefited from the workshops.

8. UNFPA further supported strengthening of screening programme implementing partners' capacities to manage the programme – in this conjunction two workshops on Screening Programme Management Quality Assurance for the managers and lead professionals from all implementing partners involved in the project in Tbilisi and regions were supported (05.06.11 and 17.11.2011).

9. Understanding the importance of developing a modern and well organized **cancer registry** in the country for monitoring the morbidity and mortality caused by cancer diseases, UNFPA in partnership with ECCA supported NCDC in this effort through organizing a study visit of two leading NCDC professionals to Comprehensive Cancer Centre in the Netherlands on December 7-9, 2011. Georgian professionals had an opportunity to get familiar with the Data collection system by the Cancer Registry (CR); the data quality monitoring and evaluation and classification system for CR. As a result a set of recommendations was developed to be considered in developing the Georgian Cancer Registry model. These recommendations were presented and discussed at the strategic meeting organized by NCDC on 16 December 2011 with participation of all local and international stakeholders.

Population behavior change communication campaign
Through UNFPA support National Screening Centre has been rebranded through involvement of the creative designer: new logo, new templates of IEC materials were prepared; the design and structure of the NSC website (www.gnsc.ge) was changed according to the new "style" to make it more clinet-friendly. Rebranded NSC and the Screening Programme in whole are more visible and recognizable among the general population, which will indeed contribute to increased utilization of services.

The following activities were accomplished within the reporting period in this regard:
- A new PSA was created on cancer screening program and telecasted free of charge regularly on Public TV free of charge;
- UNFPA supported TV PSA telecasting on the most popular commercial TV channels covering whole territory of Georgia (for three months period – September-December 2011);
- Special banners with the information about the screening programme were placed on public buses, metro stations and in the metro train carriages from September 1, 2011 for 3 months period;
- Flash banners with information about screening programme were posted on popular public and medical websites;
- Twenty thousand copies of brochures on cancer early detection and about benefits of breast and cervical cancer screening programme were printed and distributed among the women who were screened and among Tbilisi population. In addition, twenty thousand copies of breast self-examination and twenty thousand special advertisement flyers were printed and distributed.

Breast, Cervical, Prostate and Colon cancer screening and early diagnostic services provided within the reporting period
The purpose of the screening programme is to maximise early detection of Breast, Cervical, Prostate and Colon

cancer among the target population and to decrease morbidity and mortality caused by these diseases.

During January-December 2011:
- total of **13,912** women aged 40-70, residing in Tbilisi and its surroundings were screened for **breast cancer,**
- total of **14,372** women aged 25-60, residing in Tbilisi and its surroundings were screened for **cervical cancer,**
- **3,784** men aged 45-70 were screened for **prostate cancer**, and
- **1,368** clients – both women and men aged 50-70 were screened for **colon cancer** (Table 1).

Table 1. Number of Breast, Cervical, Prostate and Colon cancer screening cases, 2011

Screening Program Component	Number	Percent
Breast Cancer (mammography)	**13,912**	**100%**
National Screening Center (NSC)	11,487	82.6%
Tatishvili Medical Center (TMC)	1,295	9.3%
Tbilisi Cancer Center (TCC)	1,025	7.4%
Gudushauri Medical Center (GMC)	51	0.4%
Tbilisi Balneology Resort	54	0.4%
Cervical Cancer (PAP Test)	**14,372**	**100%**
National Screening Center (NSC)	11,877	82.6%
Tatishvili Medical Center (TMC)	1,197	8.3%
Tbilisi Cancer Center (TCC)	1,239	8.6%
Tbilisi Balneology Resort	59	0.4%
Prostate Cancer (PSA)	**3,784**	**100%**
National Screening Center (NSC)	3,136	82.9%
Tatishvili Medical Center (TMC)	400	10.6%
Tbilisi Cancer Center (TCC)	125	3.3%
Express-Diagnostics	82	2.2%
Tbilisi Balneology Resort	41	1.1%
Colorectal Cancer (FOBT)	**1,368**	**100%**
National Screening Center (NSC)	1,219	89.1%
Tatishvili Medical Center (TMC)	64	4.7%
Tbilisi Cancer Center (TCC)	37	2.7%
Tbilisi Balneology Resort	8	0.6%

More than 82 % of the cases screened in each direction were conducted at the National Screening Centre, the rest were done by the sub-contracted medical institutions at their diagnostic facilities.

Recall rate for further deeper investigations that were performed during the reporting period is distributed as follows: 28% and 3.3% of women screened for breast cancer, had performed the ultrasound and cytology investigations respectively (Table 2); 15% and 1.75% of women screened for cervical cancer had performed colposcopy investigations and biopsies respectively (Table 3); and 4% of subjects screened for colon cancer had performed colonoscopy.

Table 2. Breast cancer screening: total number and percentage of performed investigations, 2011

	Mammography	Ultrasound	Cytology
National Screening Center (NSC)	11,487	3,671 (32%)	453 (3.9%)
Tatishvili Medical Center (TMC)	1,295	153 (12%)	11 (1.1%)
Tbilisi Cancer Center (TCC)	1,025	116 (11%)	2 (0.2%)
Gudushauri Medical Center (GMC)	51	0	0
Tbilisi Balneology Resort	54	6 (11%)	0
Total	13,912	3,946 (28%)	466 (3.3%)

Table 3. Cervical cancer screening: total number and percentage of performed investigations, 2011

	PAP Smear	Colposcopy	Biopsy
National Screening Center (NSC)	11,877	2,024 (17%)	252 (2.1%)
Tatishvili Medical Center (TMC)	1,197	50 (4%)	0
Tbilisi Cancer Center (TCC)	1,239	86 (7%)	0
Tbilisi Balneology Resort	59	0	0
Total	14,372	2,160 (15%)	252 (1.75%)

Table 4. Colon cancer screening: total number and percentage of performed investigations, 2011

	FOBT test	Colonoscopy
National Screening Center (NSC)	1,219	49 (4%)
Tatishvili Medical Center (TMC)	64	0
Tbilisi Cancer Center (TCC)	37	5 (13.5%)
Tbilisi Balneology Resort	8	0
Total	**1,368**	**54 (4%)**

The second round for the Breast Cancer screening has already started in 2010. This year 2,153 women out of the totally screened 13,912 ones were admitted for breast cancer screening Round-2, which is ~25% of the source female population screened during the year of 2009 and 51% of female population screened within 2009 that were reached by NSC and invited by phone.

In May 2011 the second round for the Cervical Cancer screening has started. Since then 718 women were admitted for cervical screening Round-2, which comprises ~17% of the source female population that were screened through May to December 2008 and ~34% of female population screened within same period that were reached by NSC and invited by phone.

Out of 466 women with breast cytological investigation results, 88 (19%) were detected to have a malignant breast cancer, 28 (6%) were suspicious for malignancy, 47 (10%) atypical /undifferentiated, 253 (54%) benign cases and 50 (10%) were considered as non adequate specimen for the test (Table 5).

Table 5. Cytological results of the Breast Cancer Screening, 2011

Cytology Result	N	%
Non-adequate	50	10.7%
Benign	253	54.3%
Atypical/Undifferentiated	47	10.1%
Suspicious for Malignancy	28	6.0%
Malignant	88	18.9%
Total	466	100,00%

630 women from Breast Screening program in Tbilisi suspected for cancer were referred by the assessment team including radiologist, pat/cytologist and breast surgeon to the specialized medical facilities for further examinations and treatment (Table 6).

Table 6. Referral from the National Screening Program for Specialized Breast cancer care, 2011

Facility	Number of patients referred	% out of total (N=13,912)
National Screening Center (NSC)	463	4%
Tatishvili Medical Center (TMC)	31	2.4%
Tbilisi Cancer Center (TCC)	136	13.3%
Total	**630**	**4.5%**

The follow-up information for every patient regarding the outcomes of their treatment is being collected and will be available by end of the March 2012. According to preliminary results during first 6 months of 2011 78% of breast cancer cases were detected at the stages I-II within the frames of the screening program (Fig.).

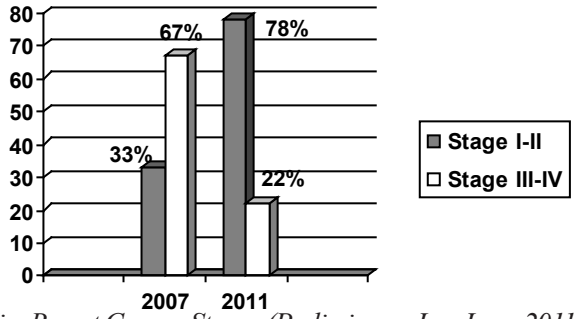

Fig. Breast Cancer Stages (Preliminary, Jan-June, 2011)

Out of the 14,372 PAP tests conducted in 2011, 90.5% of tests were evaluated to be normal ones; the rest 1,369 tests (9.5%) were evaluated as abnormal, with the results distributed as follows: 808 (59%) were Atypical Cells of Undetermined Significance (ASCUS), 116 (8.47%) were Atypical Squamous Cell – cannot exclude HSIL (ASC-H), 272 (19.9%) were Low-grade Squamous Intraepithelial Lesion (LSIL), 159 (11.6%) were High-grade Squamous Intraepithelial Lesion (HSIL), 7 (0.51%) were Atypical Glandular cells of Uncertain Significance or Atypical Glandular Cells (AGUS/AGC) and 7 (0.51%) results were classified as Carcinoma (Table 7). Women with abnormal PAP-test result were given a recommendation to repeat PAP testing in 6-12 months.

Table 7. Cytological Results of PAP smears, 2011

Atypical PAP Test	Number	Distribution (%) of abnormal PAP Results (N=1,369)	(%) abnormal PAP results among totally screened (N=14,372)
ASCUS	808	59.02%	5.62%
ASC-H	116	8.47%	0.81%
LSIL	272	19.87%	1.89%
HSIL	159	11.61%	1.11%
AGUS/AGC	7	0.51%	0.05%
Carcinoma	7	0.51%	0.05%
Total	1369	100.00%	9.53%

The National Screening Program performs colposcopy investigations for two indications: abnormal PAP test result and recommendation by gynaecologist. In 2011, 1197 females with abnormal PAP test had colposcopy investigation done and among those, 33.2% were found to have normal histology, 20.6% showed un-satisfactory colposcopy, 35.5% CIN1, 8.9% were CIN2,3 and 1.5% had Invasive Cancer based on the colposcopy investigation. Detailed analysis of the colposcopy investigation results by the atypical PAP test is shown in Table 8.1.

Table 8.1. Colposcopy investigation Results among women with abnormal PAP test, 2011

Histology/ Colposcopy Diagnosis	Norm		Not Satisfactory Colposcopy		CIN1		CIN2,3		Invasive Cancer	
	n	%	n	%	n	%	n	%	n	%
ASCUS (n=725)	310	42.8	146	20.1	254	35.0	15	2.1	0	0.0
ASC-H (n=97)	16	16.5	38	39.2	29	29.9	9	9.3	5	5.2
LSIL (n=239)	69	28.9	37	15.5	128	53.6	5	2.1	0	0.0
AGUS/AGS (n=5)	1	20.0	3	60.0	1	20.0	0	0.0	0	0.0
HSIL (n=130)	2	1.5	22	16.9	17	13.1	77	59.2	12	9.2
Carcinoma (n=1)	0	0.0	0	0.0	0	0.0	0	0.0	1	100.0
Total (n=1197)	398	33.2	246	20.6	429	35.8	106	8.9	18	1.5

Colposcopy investigation results of women with normal PAP test showed that, 34% were normal by colposcopy as well, 18% had a polyp, 12.4% had unsatisfactory colposcopy, 33.8% had CIN1, 1.3% were CIN2,3 and 0.1% had Invasive Cancer based on their colposcopy findings (Table 8.2).

Table 8.2. Colposcopy investigation Results among women with Normal PAP test, 2011

Histology/ Colposcopy Diagnosis	Norm		Polyp		Not Satisfactory Colposcopy		CIN1		CIN2,3		Invasive Cancer	
	n	%	n	%	n	%	n	%	n	%	n	%
Normal Pap test (n=992)	338	34.1	182	18.3	123	12.4	335	33.8	13	1.3	1	0.1

Patients with CIN 2, 3 or suspicion for invasive cancer are given a recommendation to refer to the specialized facilities for an adequate treatment. In 2011, 41 women with a suspicion on cervical cancer were given such recommendation. Within National Screening Canter 96 excision and 5 ablation treatment have been conducted.

The histological-pathologic biopsy results revealed 33 cases of CIN1, 34 cases of CIN2, 21 cases of CIN3, 6 cases of CIN3-CIS, 1 case of Invasive Cancer and 1 case of vaginal neoplasia – VAIN1.

Out of 3,784 PSA conducted males, 292 (7.7%) tested positive and all of them were given a recommendation to refer to the specialized clinic.

Out of 1,368 FOBT conducted subjects 54 (4%) tested positive, all of them were conducted colonoscopy and referred to the specialized clinic.

Ambulatory surgery

168 patients underwent surgical operations and manipulations for precancerous conditions during the reporting period at the national screening center (Table 9).

Table 9. Ambulatory care (surgery), 2011

Manipulation with local anaesthesia cyst aspiration	23
Sectoral resection with local anaesthesia	107
Bilateral Sect oral resection with local anaesthesia	21
Resection of cancerous skin lesion with local anaesthesia	38
Ablation	1
LEEP	73
Total	263

Implementation of cancer screening programs is of great medical and social importance. Cancer screening, using simple tests that can cover the general population, and also promotes the early diagnosis of cancer and its treatment in a timely manner, increasing life expectancy and reduce mortality.

REFERENCES

1. http://www.who.int/cancer/detection/en/index.html
2. Standard Progress Report 2011; Support to Breast and Cervical Cancer Prevention; UNFPA; National Screening Centre
3. Standard Progress Report 2011; Support to Breast and Cervical Cancer Prevention; UNFPA; National Screening Centre

SUMMARY

CANCER SCREENING PROGRAM IN GEORGIA (RESULTS OF 2011)

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This paper reviews and summarizes the results and epidemiological data of 2011 Cancer Screening Program in Georgia. The first paragraph of paper underlines main results of capacity building of the program and its implementation. The second paragraph is focused on activities conducted within the program on population behaviour change and communication campaign and the final paragraph analyses the data of epidemiological results collected during year 2011 of breast, cervical, prostate and colorectal cancer screening, reviews and summarizes. Implementation of cancer screening programs is of great medical and social importance. Cancer screening, using simple tests that can cover the general population, and also

promotes the early diagnosis of cancer and its treatment in a timely manner, increasing life expectancy and reduce mortality.

Keywords: cancer, epidemiology, Georgia (Caucasus).

РЕЗЮМЕ

ПРОГРАММА СКРИНИНГА РАКА В ГРУЗИИ (ИТОГИ 2011 г.)

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В статье анализируются и обобщаются эпидемиологические данные программы скрининга рака в Грузии в 2011 году. Подчеркнуты основные результаты создания программы и ее реализации. Описаны мероприятия, проводимые в рамках программы по изменению поведения населения и коммуникационной кампании, проанализированы данные эпидемиологических результатов, полученных при скрининге рака шейки матки, молочной железы, предстательной железы и толстого кишечника.

По заключению авторов, реализация программы скрининга рака имеет большое медико-социальное значение, поскольку при этом используются легкодоступные простые тесты, позволяющие охватить широкие слои населения, способствующие ранней диагностике рака и, соответственно, своевременному лечению, увеличению продолжительности жизни и снижению уровня смертности.

რეზიუმე

კიბოს სკრინინგის პროგრამა საქართველოში (2011 წლის შედეგები)

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სტატიაში გაანალიზებულია და შეჯამებულია 2011 წლის კიბოს სკრინინგის პროგრამის შედეგები და ეპიდემიოლოგიური მონაცემები. აღწერილია სკრინინგის პროგრამის შესაძლებლობების გაზრდისა და მისი განხორციელების საშუალებები, ყურადღება ფოკუსირებულია იმ აქტივობებზე,რომლებიც პროგრამის ფარგლებში ტარდება მოსახლეობის ქცევის ცვლილების და კომუნიკაციის კამპანიის მიმართებით. გაანალიზებულია საშვილოსნოს, ძუძუს, პროსტატის, მსხვილი ნაწლავის კიბოს ეპიდემიოლოგიური სკრინინგის შედეგები.

ავტორთა დასკვნით, კიბოს სკრინინგის რეალიზაციას დიდი სამედიცინო-სოციალური მნიშვნელობა აქვს, ვინაიდან ამ მიზნით გამოიყენება მარტივი ხელმისაწვდომი ტესტები, რაც ხელს უწყობს კიბოს ნაადრევ დიაგნოსტიკას და,შესაბამისად,დროულ მკურნალობას, სიცოცხლის გახანგრძლივებასა და სიკვდილიანობის დონის შემცირებას.

ОСОБЕННОСТИ МЕТАБОЛИЧЕСКОГО СИНДРОМА И НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНИ ПЕЧЕНИ У ЖЕНЩИН В ПЕРИОД МЕНОПАУЗЫ

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Менопаузальный метаболический синдром (ММС) - это совокупность метаболических нарушений, возникающих с наступлением менопаузы и включающих быструю прибавку массы тела с формированием абдоминального ожирения, инсулинорезистентности и дислипидемии [3]. ММС представляет собой предстадию сахарного диабета (СД) 2 типа и отличается от последнего отсутствием стабильной гипергликемии, поскольку инсулинорезистентность в этой стадии еще может преодолеваться за счет гиперинсулинемии. Компонентами метаболического синдрома являются инсулинорезистентность (ИР), дислипопротеинемия, гиперактивность симпатической нервной системы, все они взаимообусловлены и каждый из них неизбежно связан с избытком абдоминального и висцерального жира [1,20,24]. Именно на этом основании абдоминальное ожирение считается ключевым признаком метаболического синдрома [31,33,34]. Метаболический синдром является одним из ведущих факторов риска развития сердечно-сосудистых заболеваний, нарушений углеводного и липидного обмена, а также патологии гепато-билиарной системы, в частности, неалкогольной жировой дистрофии печени [6,16,18,22,23]. В развитии ММС немаловажную роль играют как внешние, так и внутренние факторы, в первую очередь, дефицит половых гормонов – эстрогенов и прогестерона. В нарушении баланса половых гормонов немаловажная роль, как известно, принадлежит печени. Половые гормоны определяют характер распределения жировой ткани: эстрогены и прогестерон влияют на локализацию жира в ягодично-бедренной области (гиноидный тип), андрогены отвечают за андроидный тип ожирения с абдоминальной локализацией жира. [6,21,33,35]. При ММС дефицит половых гормонов ведет к снижению уровня глобулина, связывающего половые стероиды, что способствует увеличению содержания свободных андрогенов в кровотоке, которые сами по себе могут снижать холестерин липопротеидов высокой плотности (ЛПВП) и вызывать инсулинорезистентность, гиперинсулинемию и андроидное распределение жира. В период менопаузы в первую очередь снижается концентрация эстрадиола [17], имеет место снижение и прогестерона. Дефицит эстрадиола обуславливает прогрессирование ИР, снижение уровня соматотропина и активности адренорецепторов адипоцитов, что уменьшает мобилизацию жира из депо. Дефицит эстрогенов сопровождается снижением уровня лептина, угнетающего глюконеогенез в печени, транспорт глюкозы в адипоциты, которые регулируют синтез инсулиновых рецепторов в мышечной ткани, активность симпатической нервной системы и пищевые поведенческие реакции. Дефицит прогестерона способствует нарушению конкурентных отношений с глюкокортикостероидами в адипоцитах, а также подавляет эндогенную продукцию глюкозы печенью [26]. С наступлением менопаузы одним из критериев МС является значительная прибавка массы тела (5-10 кг) за короткий период времени (6-12 месяцев). Обнаружено, что после 48 лет скорость метаболизма замедляется на 4-5% каждые последующие 10 лет, что объясняется как «фактором хронологического возраста», так и секс-гормональными нарушениями. Установлено, что быстрая прибавка массы тела после менопаузы происходит примерно у 60% женщин. По данным Hhealthy Women‘s Study, в первые три года после менопаузы масса тела, в среднем, увеличивается на 2,3 кг, а через 8 лет – на 5,5 кг, причём прибавка в весе, в основном, происходит за счет увеличения жира и его перераспределения в область брюшной стенки и уменьшения мышечной ткани [33]. Согласно классификации ВОЗ, при индексе массы тела (ИМТ) (отношение массы тела в килограммах к росту в метрах в квадрате), превышающем 25 кг/м^2, фиксируют избыточный вес, а при 30 кг/м^2 и более – ожирение [12]. ИМТ не дает точной информации о количестве и характере распределения жировой ткани. В клинической практике используют наиболее простой и распространенный способ - вычисление отношения окружности талии (ОТ) к окружности бедер (ОБ)

- ОТ/ОБ. По данному показателю при ОТ/ОБ >0,8 классифицируют абдоминальное ожирение, при ОТ/ОБ < 0,7 - гиноидное, оно характеризуется избытком жира на бедрах. В зависимости от показателей ИМТ выделяют умеренную полноту - ИМТ от 25 до 29,9, ожирение - ИМТ ≥30 и тяжелое ожирение - ИМТ ≥40. В апреле 2005 г. Международная диабетическая федерация представила новые диагностические критерии метаболического синдрома [32]. Согласно современному определению метаболического синдрома центральное ожирение характеризуется ОТ ≥94 см у мужчин и ≥80 см у женщин в сочетании как минимум с двумя из следующих нарушений:
- повышенные уровни триглицеридов: >1,7 ммоль/л (150 мг/дл);
- пониженные уровни холестерина ЛПВП: <1,04 ммоль/л (40 мг/дл) - у мужчин; <1,29 ммоль/л (50 мг/дл) - у женщин;
- гипергликемия натощак: ≥5,6 ммоль/л (100 мг/дл);
- повышенное АД: > 130/85 мм рт. ст.

Дефицит гормонов, абдоминальное и, особенно, висцеральное ожирение являются факторами риска возникновения не только МС, СД2, но развития патологии сердечно-сосудистой и гепатобилиарной систем в менопаузальный период у женщин. Дефицит гормонов сопровождается устранением положительного воздействия эстрогенов на сосудистую стенку, а именно - антипролиферативного влияния на гладкомышечные клетки сосудов и подавления ими секреции коллагена, а также эндотелий-зависимого и эндотелийнезависимого сосудорасширяющего эффекта [19]. Прогестерон, как известно, участвует в регуляции тонуса артериол, действуя подобно антагонистам кальция (АК). Наряду с этим он снижает реабсорбцию натрия вследствие антиальдостеронового действия на уровне почечных канальцев.

Проблема ММС привлекает внимание в связи с увеличением риска развития у больных не только сердечно-сосудистых, но и других коморбидных заболеваний (остеоартроза, стеатоза печени, желчнокаменной и мочекаменной болезней, легочно-сердечной недостаточности, рака почки, поперечно-ободочной и прямой кишки, желчного пузыря, поджелудочной железы и печени) [26,32]. Практически все исследования прошлых лет, касающиеся патогенеза и лечения МС, сконцентрированы на сердечно-сосудистых заболеваниях, эндокринных нарушениях и функции почек. В последние годы в литературе сообщается о наличии у многих больных МС неалкогольной жировой дистрофии (ЖД) печени [22,26]. С повышением степени ожирения и тяжести ИР возрастает риск развития неалкогольной жировой дистрофии печени. Жировая дистрофия печени, или стеатоз, рассматривалась как одна из форм течения алкогольной болезни печени (АБП). Однако в 1980 году Ludwig описал явления стеатоза у лиц, не злоупотребляющих алкоголь [цит. по 31]. Жировая дистрофия печени развивается у пациентов, не употребляющих алкоголь в гепатотоксичных дозах (не более 40 г этанола в сутки для мужчин и не более 20 г - для женщин). Ввиду отсутствия связи выявленных изменений с приемом алкоголя, они были названы неалкогольным стеатозом/стеатогепатитом. Далее обнаружено, что признаки жировой дистрофии печени обнаруживают у лиц с самыми разнообразными заболеваниями и патологическими состояниями [29]. В настоящее время состояние, проявляющееся стеатозом/стеатогепатитом и ассоциируемое с ИР и МС, причисляют к отдельной самостоятельной нозологии - неалкогольной жировой болезни печени (НАЖБП) [22,26]. В настоящее время исследователи считают, что каждый из компонентов МС сопровождается вторичным метаболическим поражением печени, когда более 5% массы органа составляет жир, накапливаемый в гепатоцитах преимущественно в виде триглицеридов (ТГ) [24,26,30]. НАЖБП встречается во всех возрастных группах, распространенность в Европе и США колеблется в пределах от 5 до 20%, а стеатогепатита - в пределах 2-3% [35-37]. Частота у больных СД 2 типа и ожирения по данным различных исследований, варьирует в пределах от 70 до 100%. При этом СД 2 типа или нарушение толерантности к глюкозе (НТГ) отмечаются у 10-75%, ожирение - у 30-100%, гипертриглицеридемия - у 20-92% пациентов с НАЖБП [2,4,12,13,18,31,36]. Большинство пациентов (65-80%) - женщины, средний возраст в момент диагностики – 50 лет. Во время менопаузы риск развития повышается в 2 раза по сравнению с фертильным возрастом. Заместительная гормональная терапия (ЗГТ) снижает риск развития данной патологии. Женщины с НАЖБП отличаются более выраженным абдоминальным ожирением. При НАЖБП выделяют следующие варианты течения: стеатоз (тип 1) - преобладание жировой

дистрофии гепатоцитов над всеми другими морфологическими изменениями, стеатогепатит (тип 2) преобладание выраженных воспалительных инфильтратов, как в строме, так и в паренхиме с наличием очаговых некрозов, стеатофиброз (тип 3) - преобладание фиброза портальной стромы, без нарушения дольковой структуры, стеатофиброз (тип 4) - нарушение дольковой структуры печени с наличием узлов-регенератов [29,31].

В целом неалкогольная ЖД печени характеризуется относительно доброкачественным клиническим течением, самой благоприятной форме болезни свойственно стабильное, не прогрессирующее течение. Однако, НАЖБП примерно в 20-25% переходит в стеатогепатит печени (НАСГ). НАСГ у 20-37% больных прогрессирует с развитием выраженного фиброза печени, у 20% из них в течение 20 лет формируется цирроз печени (ЦП), печеночно-клеточная недостаточность и в 10% вызывает смерть. У половины больных НАСГ стадии ЦП не происходит. Среди лиц с НАЖБП повышена частота гепатоцеллюлярной карциномы [31]. В индустриально развитых странах клинически манифестированная НАЖБП нередко является показанием к трансплантации печени [1,7,9,10,13,23,31]. Необходимо отметить возможность обратного развития ЖД и НАСГ на фоне плавного снижения массы тела (1,2-2,0 кг/мес). Быстрая потеря массы тела, напротив, способствует ухудшению течения болезни. Постановка диагноза достаточно сложна ввиду необходимости исключения всех других причин, в частности токсических лекарственных поражений печени, сопровождаемых цитолизом, макровезикулярным стеатозом и воспалительно-деструктивнымии изменениями и др.[1,18,27,36,37]. Абсолютно надежных клинических или биохимических критериев прогрессирования НАЖБП на сегодняшний день нет. По обобщенным данным специализированных клиник у 50-90% больных НАСГ выявляются лабораторные признаки цитолиза. Активность сывороточных трансаминаз стабильная и составляет не более 4 норм. Чаще активность АЛТ превышает таковой показатель у АСТ. Выраженность цитолиза не имеет достоверной связи с проявлениями стеатоза и фиброза печени. У 30-60% больных НАСГ повышена активность щелечной фосфотазы (ЩФ) и гаммаглутамилтранспептидазы (ГГТП), но не более чем в 2 раза. Гипербилирубинемия в пределах 25-35 мм/л наблюдается в 12-17% случаев. Следует отметить, однако, что отсутствие изменений лабораторных показателей, характеризующих функциональное состояние печени (АЛТ, АСТ, ЩФ, ГГТП), не исключает наличия воспалительно-деструктивного процесса и фиброза. Для оценки клинико-функционального состояния печени рекомендовано обязательное проведение ультразвукового исследования и компьютерной томографии. Наиболее точным диагностическим методом является биопсия печени [4,12,13,27]. Признаки НАЖБП иногда обнаруживаются у 10-15% людей без клинических проявлений МС, что может быть обусловлено другими патогенетическими механизмами формирования НАЖБП, например, синдромом избыточной пролиферации бактерий в кишечнике или дисбиозом, приводящих к нарушению синтеза аполипопротеидов классов А и С, являющихся транспортной формой для триглицеридов (ТГ) в процессе образования липопротеидов очень низкой плотности (ЛПОНП), а также к развитию кишечного эндотоксикоза, усиливающего окислительный стресс [24,25,26]. Традиционно считается, что отмеченное – удел пациентов с повышенной массой тела и индексом массы тела (ИМТ) более 25 кг/м^2. Действительно НАЖБП встречается у 60-95% больных с повышенной массой тела [22,31]. Однако, неалкогольный стеатоз встречается и у пациентов с нормальным ИМТ, редко и у худых, не страдающих СД, не имеющих ни одного критерия МС. Ведущую роль имеет ИР [3,7,8,24,34]. Так, у больных с НАЖБП, не страдающих сахарным диабетом, с нормальной массой тела, выявлялась ИР. Стеатоз, по мнению исследователей, формируется при самом процессе увеличения веса, независимо от того, превышает ли ИМТ нормальные значения. Даже незначительное увеличение массы тела может привести к перераспределению содержания липидов в тканях и нарушению их нормального метаболизма, а это, в свою очередь, приводит к повышенному риску сердечно-сосудистых заболеваний [6,10,28]. Патогенез НАЖБП неразрывно связан с МС, а сам факт развития указанной патологии усугубляет неблагоприятный прогноз для этих пациентов, как в виде прогрессирования печеночной недостаточности, так и в виде значительного увеличения частоты осложнений ССЗ. Абдоминальное, и особенно висцеральное, ожирение повышает риск развития ССЗ и риск летального исхода от данной патологии. Больные НАЖБП имеют большую

выраженность атеросклероза. Корреляция между НАЖБП и ССЗ сильнее у женщин: риск ССЗ у женщин при наличии НАЖБП возрастает в 7 раз, а у мужчин - в 3 раза.

Причины и механизмы возникновения НАЖБП до конца не изучены. ИР, оксидативный стресс и воспалительный процесс по-прежнему считаются ключевыми патогенетическими механизмами НАЖБП [1,3,7,8,9,12,13,24,34,36,37]. Возможно, комбинированное воздействие оксидативного стресса, повреждения клеток и воспаления приводят к данному состоянию. Для описания патогенеза предложена теория «множественных ударов» (multi-hit). Весь процесс биохимических изменений берет начало с ИР. Утрата чувствительности к инсулину гормонзависимых тканей приводит к дисбалансу липидного обмена, накоплению жира гепатоцитами в результате влияния адипокинов (цитокинов, вырабатываемых жировой тканью) [7,23,36,37]. В печени накапливаются ТГ и формируется жировой гепатоз (ЖГ) - первый удар или «толчок» заболевания. Активируются ферменты, расщепляющие триглицериды в жировой ткани, высвобождающиеся жирные кислоты накапливаются в печени. В гепатоцитах блокируется бета-окисление жирных кислот (ЖК), таким образом, ферментная система печени не в состоянии метаболизировать их избыток. Формируются липидные вакуоли - стеатоз печени. Высвобождение из жировой ткани и синтез de novo в гепатоцитах свободных жирных кислот (СЖК), способствует возникновению окислительного стресса. Повышение уровня гепатоцеллюлярных липидов, и усиленное отложение СЖК в печени сопровождается дисбалансом адипоцитокинов - снижением уровня адипонектина и/или повышением уровня провоспалительных цитокинов. СЖК и адипоцитокины вызывают активацию воспаления через протеинкиназу С, транскрипционный ядерный фактор kB. На фоне стеатоза и образования активных форм кислорода за счет сложных взаимодействий между клетками иммунной системы (макрофаги, гепатоциты), развиваются воспалительно-деструктивные изменения печени, что является вторым ударом и приводит к прогрессии стеатоза до стеатогепатита и НАЖБП [31]. Прогрессирование стеатоза в стеатогепатит реализуется тремя путями. Оксидативный стресс увеличивает выработку свободных радикалов и цитокинов (ФНО-альфа, интерлейкин-8, FAS-лиганды). Перекисное окисление липидов индуцирует воспаление, снижает антиоксидантную активность глутатиона, активирует звездчатые клетки, усиливая образование коллагена. Избыток, лептина, эндотоксинов и перегрузка железом завершают формирование неалкогольного стеатогепатита. Выявлена роль адипоцитокинов в патогенезе и развитии фиброза. В частности, лептин играет профибротическую роль, индуцирует выработку коллагена звездчатыми клетками [9].

В прогрессировании НАЖБП важная роль отводится генетическим факторам. В развитии НАЖБП важным считается наличие полиморфизма генов, регулирующих иммунные процессы [5,8,9,11,14-16]. В частности, при неалкогольном поражении печени существенную роль играют CD8+ Т-лимфоциты и генетический полиморфизм генов, участвующих в регуляции метаболизма липидов и углеводов. Т-лимфоциты посредством цитокинов обеспечивают проникновение макрофагов в жировую ткань, их активацию, что поддерживает воспалительный процесс на определенном уровне. Исследователи считают, что активные факторы, секретируемые макрофагами, вызывают прогрессирование стеатоза и стеатогепатита, усугубляют ИР. Заслуживает внимания, что активность супрессорных и регуляторных Т-лимфоцитов заметно снижена. Делается вывод, что переход от стеатоза к стеатогепатиту может быть обусловлен нарушением иммунной системы и дисбалансом в работе отдельных ее звеньев.

Кроме вышеперечисленных генов, в патогенезе НАЖБП немаловажную роль играет полиморфизм гена PNPLA3. Данный ген кодирует синтез белка адипонутрина. Уровень мРНК PNPLA3 увеличивается в адипоцитах и гепатоцитах у больных ожирением; предполагается, что адипонутрин приводит к увеличению концентрации триглицеридов за счет снижения диглицеридов и других видов липидов, при этом снижается его триацилглицеролгидролазная активность [5,8].

Как указывалось выше, определенную роль в патогенезе НАЖБП отводят оксидативному стрессу [13], поэтому недостаточность синтеза ферментов антиоксидантной защиты также может приводить к стеатозу. У пациентов описан полиморфизм гена GCLC - 129 C/T, кодирующий

каталитическую субъединицу глутаматцистеин липазы, участвующей в синтезе глутатиона. Неполноценность этого белка приводит к нарушению транспорта липидов из клетки печени и гепатостеатозу [11]. Развитие ИР, которая считается первичным нарушением метаболизма, приводящим к НАЖБП, имеется у 98% больных, связывают с геном TRB 3, который ингибирует путь передачи сигнала инсулина [8,9,23], а также с геном фетуина-А, полиморфизм которого связан не только с СД типа 2, но и со снижением чувствительности адипоцитов к инсулину и возможностью развития НАЖБП [16]. Отмечается также генетический вариант гена APOC3, кодирующего аполипопротеин С3, который блокирует активность липопротеинлипазы, что вызывает замедленный катаболизм хиломикронов. Ремнантные хиломикроновые частицы захватываются печенью, способствуя повышению диацилглицеридов, активирующих протеинкиназу С, которая блокирует передачу сигнала инсулина, способствуя развитию ИР в печени [13]. У пациентов с полиморфизмом указанных генов отмечается повышенный риск фиброза, ожирения, сахарного диабета, метаболического синдрома и более тяжелого течения заболевания [5]. Известно также, что в патогенезе стеатоза важную роль играют микроРНК-10b (miRNA-10b). Показано, что микроРНК регулирует дифференцировку адипоцитов, метаболизм липидов, глюкозоопосредованную секрецию инсулина, способствует накоплению липидов и уровень триглицеридов, подавляя синтез альфа-рецепторов, активирующих пролиферацию пероксисом (PPAR-альфа) [23], активирующих гены ферментов окисления ЖК и их транспорта в гепатоциты. Даже при наличии доказанных патогенетических факторов, таких как ожирение, ИР, гипертриглицеридемия и известных факторов риска МС, таких как избыточное количество жира в рационе, дефицит антиоксидантов, низкий уровень физической активности, избыточный бактериальный рост в тонкой кишке, эпизоды гипоксии при синдроме ночного апноэ, только у 20% развивается явный неалкогольный стеатогепатит. Вышеотмеченное, по всей вероятности, указывает на то, что в прогрессировании патологии печени, немаловажную роль играет также полиморфизм тех генов, которые не связаны с ожирением и СД 2 типа, а это диктует необходимость проведения дальнейших исследований.

Таким образом, НАЖБП нередко приводит к ухудшению качества жизни, инвалидизации и смерти, характеризуется высоким риском прогресирования заболевания с развитием неалкогольного стеатогепатита, фиброза, цироза, печеночной недостаточности, гепатоцеллюлярной карциномы и представляет одну из важных медико-социальных проблем. Ключевыми патогенетическими механизмами при НАЖБП являются инсулинорезистентность, оксидативный стресс и воспаление. Инсулинорезистентность - основной этиологический фактор развития неалкогольного стеатоза и сахарного диабета 2. Абдоминальное и особенно висцеральное ожирение являются факторами риска ММС, НАЖБП и сердечно-сосудистых заболеваний. При НАЖБП жировая ткань находится в условиях персистирующего воспаления, которое сопровождается повышенным синтезом макрофагами провоспалительных цитокинов, в частности фактора некроза опухоли-альфа (ФНО-альфа), который снижает секрецию адипонектина, адипокина, обладающих также и противоатерогенными свойствами. В развитии инсулинорезистентности существенную роль играют генетические и иммуноопосредованные звенья, в частности полиморфизм генов, регулирующих процессы иммунитета, окисления ЖК и окислительное равновесие. Причины и патогенез данного заболевания требуют дальнейшего уточнения. Внешними факторами риска рассматриваются: гиперкалорийная диета, низкая физическая активность, патологические состояния, сопровождающиеся избыточным бактериальным ростом в кишечнике. НАЖБП имеет особенно большую распространенность у женщин в менопаузальный период, риск развития у них в 2 раза выше, по сравнению с фертильным возрастом и у них отмечается более выраженное абдоминальное ожирение и высокий уровень ИР. Эта особенность, в основном связана, с дефицитом эстрогенов в менопаузе, поскольку риск развития НАЖБП частично снижает гормональная заместительная терапия. Ожирение, имеющее место у пациентов с НАЖБП, особенно в период менопаузы, является одним из факторов риска сердечно-сосудистых заболеваний и смертности, а также рассматривается как дополнительный, независимый фактор риска сердечно-сосудистых заболеваний.

ЛИТЕРАТУРА

1. Adams L.A., Angelo P., Lindor K.D. Nonalcoholic fatty liver disease L.A. Adams CMAJ 2005; 172; 7: 899-905.
2. Almeida A. M., Cotrim H. P., Barbosa D. B. et al. Fatty liver disease in severe obese patients: Diagnostic value of abdominal ultrasound. World J Gastroenterol. 2008; 14(9):1415-1418.
3. Bugianesi E., Gastaldelli A., Vanni E. et al. Insulin resistance in non-diabetic patients with non-alcoholic fatty liver disease: sites and mechanisms. Diabetologia 2005; 48: 634-642.
4. Chang Y., Ryu S., Sung E. et al. Weight gain within the normal weight range predicts ultrasonographically detected fatty liver in healthy Korean men. Gut. 2009; 58: 1419-1425.
5. Dongiovanni P., Valenti L., Rametta R. et al. Genetic variants regulating insulin receptor signalling are associated with the severity of liver damage in patients with non-alcoholic fatty liver disease. Gut. 2010; 59: 267-273.
6. Isomaa B., Almgren P., Tuomi T. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diab. Car. 2001; 24: 683-68.
7. Lewis J. R. Mohanty S. R. Non-alcoholic Fatty Liver Disease: A Review and Update. Digestive Diseases and Sciences. 2010; 55: 560-578.
8. Loos R.J.F., Savage D.B. Inherited susceptibility to non-alcoholic fatty liver disease. Diabetologia. 2009, 52: 1000-1002.
9. Marra F. Molecular mechanisms of inflammation/ fibrosis in NASH. 13th United European Gastroenterology Week. Copenhagen: 2005.
10. Misra Vijay Laxmi, Khashab Mouen, Chalasani Naga. Nonalcoholic fatty liver disease and cardiovascular risk. Current Gastroenterology Reports 2009; 11: 50-55.
11. Oliveira Claudia Pinto Marques Souza, Stefano Jose Tadeu, Ana Mercedes Cavaleiro Ana Mercedes et al. Association of polymorphisms of glutamate-cystein ligase and microsomal triglyceride transfer protein genes in non-alcoholic fatty liver disease. Journal of Gastroenterology and Hepatology 2010; 25: 357-361.
12. Park J.W. Predictors reflecting the pathological severity of non-alcoholic fatty liver disease: comprehensive study of clinical and immunohistochemical findings in younger Asian patients. J. Gastroenterol. Hepatol. 2007; 22: 4: 491-497.
13. Petta S., Muratore C., Craxi A. Non-alcoholic fatty liver disease pathogenesis: The present and the future. Dig Liver Dis. 2009; 41 (9): 615625.
14. Petersen K.F., Dufour S., Hariri A. et al. Apolipoprotein C3 gene variants in nonalcoholic fatty liver disease. N Engl J Med. 2010; 362: 1082–1089.
15. Popov Y., Schuppan D. CD8+ T cells drive adipose tissue inflammation - A novel clue for NASH pathogenesis? Journal of Hepatology 2010; 52: 130-132.
16. Reinehr T., Roth Christian L. Fetuin-A and its relation to metabolic syndrome and fatty liver disease in obese children before and after weight loss. J Clin Endocrinol Metab. 2008; 93: 4479-4485.
17. Баранова Е.И., Большакова О.О. Метаболический сердечно-сосудистый синдром в постменопаузе. Обзоры клин. Кардиологии 2005; 1: 2-11.
18. Богомолов П.О., Цодиков Г.В. Неалкогольная жировая болезнь печени. Consilium medicum 2006; 4(1): 56-60.
19. Быстрова М.М. ЗГТ у женщин с артериальной гипертонией в пери и постменопаузе: гемодинамические эффекты и др. Терапевт. архив 2001; 73: 10: 33-38.
20. Гинзбург М.М., Крюков Н.Н. Ожирение. Влияние на развитие метаболического синдрома. М.: Медпрактика; 2002: 128.
21. Григорян О.Р.Современные принципы коррекции метаболического синдрома у женщин в период постменопаузы Consilium medicum 2005; 9: 734-736.
22. Драпкина О.М., Гацолаева Д.С., Ивашкин В.Т. Неалкогольная жировая болезнь печени у больных с метаболическим синдромом. Клиницист 2007; 6: 46-50.
23. Драпкина О.М., Смирин В.И., Ивашкин В.Т. Неалкогольная жировая болезнь печени - современный взгляд на проблему. Лечащий врач 2010; 5(5): 57-61.
24. Звенигородская Л.А., Егорова Е.Г. Поражение печени при инсулинорезистентности. Экспер. и клин. Гастроэнтерол. 2007; 1: 20-24.
25. Корочина И.Э. Гастроэнтерологические аспекты метаболического синдрома. Российский журнал гастроэнтерологии, гепатологии, колопроктологии 2008;18:1:26-37.
26. Лазебник Л.Б., Звенигородская Л.А. Метаболический синдром и органы пищеварения. М.: Анахарсис, ПиАр-Медиа Групп: 2009; 184.
27. Мехтиев С.Н., Гриневич В.Б., Кравчук Ю.А., Бращенкова А.В. Неалкогольная жировая болезнь печени: клиника, диагностика и лечение Лечащий врач. 2008; 2: 29-37.
28. Подзолков В.И., Хомицкая Ю.В., Можарова Л.Г. Менопаузальный метаболический синдром как один из аспектов сердечно-сосудистых за-

болеваний. Сердце: журнал для практикующих врачей 2004; 3(6): 290-294.
29. Подымова С.Д. Жировой гепатоз. Неалкогольный стеатогепатит (эволюция представлений о клинико-морфологических особенностях, прогнозе, лечении). Тер. Арх. 2006; 78(4): 32-38.
30. Ройтберг Г.Е., Шархун О.О., Кондратова Н.В., Ушакова Т.И. Роль метаболического синдрома и его компонентов в патогенезе и прогрессировании неалкогольного стеатогепатита. Гепатология 2005; 5: 30-36.
31. Сметанин М.Ю., Пименов Л.Т., Пименова Л.И. Клинико-функциональное состояние печени при менопаузальном метаболическом синдроме «Практическая медицина» 2010; 4(43): 146-150.
32. Сметник В.П. Менопаузальный метаболический синдром. Лечащий врач 2006; 3:39-41.
33. Сметник В.П., Шестакова И.Г. Современные представления о менопаузальном метаболическом синдроме «Consilium medicum" 2003; 5(9): 543-546.
34. Чазова И.Е., Мычка В.Б. Метаболический синдром. М.: Медиа Медика; 2004: 168.
35. Чорбинская С.А., Борисенко Е.Г., Кравцова Н.Н. Метаболический синдром и неалкогольная жировая болезнь печени. Врач 2009; 3: 26-29.
36. Шульпекова Ю.О. Неалкогольная жировая болезнь печени: патогенез, диагностика, лечение. Фарматека 2007; 6(141): 48–53.
37. Щекина М.И. Неалкогольная жировая болезнь печени. Consilium medicum 2009; 8(11): 37-39.

SUMMARY

PECULIARITIES OF METABOLIC SYNDROME AND NONALCOGOLIC FATTY LIVER DISEASE IN MENOPAUSAL WOMEN

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Correlation between menopause metabolic syndrome and nonalcogolic fatty liver disease (NAFLD) is reviewed. NAFLD refers to a wide spectrum of liver disease ranging from simple fatty liver (steatosis), to nonalcoholic steatohepatitis, to cirrhosis. The causes and pathogenetic factors of the disease are still under investigation. The risk of development of NAFLD during menopause is twice higher in comparison with fertile age and abdominal obesity and insulin resistances is more apparent. This feature is associated with deficit of estrogens during menopause, as risk of development of NAFLD is diminished with substitutive hormonotherapy. The obesity, particularly in the period of menopause, is discussed as additive, independent risk factor of metabolic syndrome and of diseases of hepatobiliare and cardiovascular systems.

Keywords: menopause metabolic syndrome, obesity, risk of nonalcogolic fatty liver disease.

РЕЗЮМЕ

ОСОБЕННОСТИ МЕТАБОЛИЧЕСКОГО СИНДРОМА И НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНИ ПЕЧЕНИ У ЖЕНЩИН В ПЕРИОД МЕНОПАУЗЫ

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В обзоре анализируются современные данные о взаимосвязи менопаузального метаболического синдрома и неалкогольной жировой болезни печени. В настоящее время нарушения гепатобилиарной системы, проявляющиеся стеатозом, стеатогепатитом и ассоциированные с инсулинорезистентностью (ИР) и метаболическим синдромом (МС), выделены в самостоятельную нозологию - неалкогольная жировая болезнь печени (НАЖБП). НАЖБП характиризуется высоким рис-ком прогрессирования заболевания с развитием фиброза, цирроза, печеночной недостаточности, гепатоцеллюлярной карциномы и приводит к ухудшению качества жизни, инвалидизации и смерти. Ключевыми патогенетическими механизмами при НАЖБП является ИР, оксидативный стресс и воспаление. При НАЖБП жировая ткань находится в условиях персистирующего воспаления, которое сопровождается повышенным синтезом макрофагами провоспалительных цитокинов, в частности фактора некроза опухоли-альфа. Существенную роль в развитии НАЖБП играют генетические и иммуноопосредованные звенья, обсуждается наблюдаемый при НАЖБП полиморфизм генов.

В результате анализа и синтеза имеющейся по вопросу научной литературы делается заключение, что риск развития НАЖБП у женщин в период менопаузы в 2 раза выше, по сравнению с фертильным возрастом, у них отмечаются более выраженное абдоминальное ожирение и высокий уровень ИР. Эта особенность, в основном, связана с дефицитом эстрогенов в менопаузе, поскольку гормональная заместительная терапия частично снижает риск развития ИР, ожирения и НАЖБП. Ожирение у пациентов, особенно в период менопаузы, рассматривается как дополнительный, независимый фактор риска МС, заболеваний сердечно-сосудистой и гепатобилиарной систем. Причины и патогенез НАЖБП требуют дальнейшего уточнения.

რეზიუმე

მეტაბოლური სინდრომისა და ღვიძლის არაალკოჰოლური ცხიმოვანი დაავადების თავისებურებები ქალებში მენოპაუზის დროს

ნ. ანთელავა, ა. ანთელავა, მ. ღონღაძე,
მ. ოკუჯავა, ქ. პაჭკორია, მ. გოგოლაური

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, ფარმაკოთერაპიისა და ფარმაკოლოგიის დეპარტამენტი, სამედიცინო ფარმაკოლოგიის დეპარტამენტი, საქართველო

მიმოხილვაში გაანალიზებულია თანამედროვე მონაცემები, რომლებიც ეხება მეტაბოლურ სინდრომსა (მს) და ღვიძლის არაალკოჰოლურ ცხიმოვან დაავადებებს (ღაცდ) შორის ურთიერთკავშირს ქალებში მენოპაუზის დროს. ამჟამად ჰეპატობილიარული სისტემის დარღვევები, რომლებიც ვლინდება სტეატოზით, სტეატოჰეპატიტით და ასოცირებულია ინსულინრეზისტენტობასთან (ირ) და მს-თან, გამოყოფილია როგორც დამოუკიდებელი ნოზოლოგია – ღაცდ. ღაცდ-ს ახასიათებს დაავადების პროგრესირების მაღალი რისკი - ფიბროზის,ციროზის, ჰეპატოცილიარული კარცინომის, ღვიძლის უკმარისობის განვითარებით და თან სდევს პაციენტების სიცოცხლის ხარისხის გაუარესება, ინვალიდიზაცია და სიკვდილი. ღაცდ-ს საკვანძო პათოგენეზური მექანიზმებია ირ, ოქსიდაციური სტრესი და ანთება. ამ დაავადების დროს ცხიმოვანი ქსოვილი იმყოფება პერსისტირებული ანთების პირობებში, რომელსაც თან სდევს მაკროფაგების მიერ სინთეზირებული ანთების ციტოკინების მომატებული სინთეზი, კერძოდ, სიმსივნის ნეკროზის ფაქტორი-ალფა. ღაცდ-ს განვითარებაში მნიშვნელოვან როლს ასრულებს გენეტიკური და იმუნური ფაქტორები. სტატიაში გაანალიზებულია ღაცდ-ს დროს გენების პოლიმორფიზმი.

გაკეთებულია დასკვნა, რომ ღაცდ-ის განვითარების რისკი ქალებში მენოპაუზის დროს ორჯერ მეტია, ვიდრე ფერტილურ ასაკში, მეტადაა გამოხატული აბდომინური სიმსუქნე და ირ-ის მაღალი დონე, რაც, ძირითადად, დაკავშირებულია მენოპაუზის დროს ესტროგენების სიმცირესთან, ვინაიდან ჩანაცვლებითი ჰორმონული თერაპია ნაწილობრივ ამცირებს ირ-ს, სიმსუქნეს და ღაცდ-ს. პაციენტებში წონის მატება, განსაკუთრებით მენოპაუზის დროს, განიხილება, როგორც დამატებითი,დამოუკიდებელი რისკ-ფაქტორი მეტაბოლური სინდრომის, გულ-სისხლძარღვთა და ჰეპატობილიარული სისტემის დაავადებების განვითარებაში. დაავადების მიზეზებისა და პათოგენეზის დასადგენად აუცილებელია მათი ღრმა შესწავლა.

ЛЕЧЕНИЕ НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНИ ПЕЧЕНИ

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Неалкогольная жировая болезнь печени (НАЖБП) широко распространенное заболевание, в Европе и США встречается от 5 до 20% и может проявлятся в виде стеатоза, стеатогепатита, стеатофиброза, стеатоцирроза, печеночно-клеточной недостаточности, а в ряде случаев прогрессирует с развитием гепатоцеллюлярной карциномы [30,34]. НАЖБП является значимой медико-социальной проблемой, так как нередко приводит к ухудшению качества жизни, инвалидизации и смерти. В связи с высокой возможностью неблагоприятного течения НАЖБП все больные независимо от тяжести заболевания нуждаются в динамическом наблюдении и лечении. Общепринятых рекомендаций по лечению НАЖБП не существует, однако, на основании знаний о патогенезе заболевания, выделяются основные направления в терапии таких пациентов [16,20,21,28,34-36]. Направлениями патогенетической терапии больных НАЖБП являются фармакологическая терапия инсулинорезистенстости, которая включает повышение чувствительности клеточных рецепторов к инсулину (метформин, тиазолидиндионы); снижение массы тела (диета и физические нагрузки, фармакологическая терапия ожирения); фармакологическая коррекция дислипопротеинемии (фибраты, статины); фармакологическая коррекция окислительного стресса - антиоксиданты; гепатопротекторы - силибинин, бетаин, N-ацетилцистеин, урсодеоксихолевая кислота (УДК), а-липоевая кислота (АЛК) и др.; снижение концентрации TNFa (пентоксифиллин); восстановление микробиоза кишечника (эубиотики, пробиотики, пребиотики). В случае сочетания ММС-заместительная гормональная терапия, а с гипертензией - антигипертензивная терапия (антагонисты рецепторов ангиотензина II). Существуют медикаментозные и немедикаментозные методы коррекции избыточной массы абдоминально-висцеральной жировой ткани [19]. Немедикаментозное лечение включает: обучение больных, рациональное гипо- и эукалорийное питание, повышение физической активности, изменение образа жизни. С учетом современных представлений об этиологии, патогенезе и факторах прогрессирования НАЖБП больным рекомендуются диетические режимы [8,20,21,26]: для пациентов с избыточной массой тела и ожирением - снижение общей энергетической ценности пищевого рациона. Суточная калорийность подбирается индивидуально в зависимости от массы тела, возраста, пола, уровня физической активности с использованием специальных формул. Доказано, что снижение массы тела на 5-10% сопровождается уменьшением печени, активности АЛТ, АСТ и коррелирует с регрессированием стеатоза печени [26]. Следует учесть, что быстрая потеря веса может привести к развитию «острого» неалкогольного стеатогепатита (НАСГ) с формированием портального фиброза, центральных некрозов на фоне значительного повышения воспалительной активности, вызванной увеличением поступления СЖК в печень. Для больных ожирением и НАЖБП безопасным и эффективным является снижение массы тела на 500 г в неделю для детей и на 1-2 кг в неделю для взрослых [8]. Кроме того, всем пациентам с НАЖБП рекомендуется: ограничение жиров до 25-30% от общей энергетической ценности пищи; соотношение полиненасыщенных и насыщенных жирных кислот (ЖК) в пище более единицы (исключение сливочного масла, животного жира, твердых сортов маргарина и пр., употребление продуктов, богатых полиненасыщенными ЖК, - растительное масло, морепродукты, рыба, птица, маслины, орехи с учетом энергетической потребности); уменьшение потребления продуктов с высоким содержанием холестерина (не более 300 мг в сутки) - исключение субпродуктов (печени, почек), икры, яичного желтка, сырокопченых колбас, жирных сортов мясных и молочных продуктов; продуктов, приготовленных в результате такой обработки пищи, как жарка, фритюр и т.д.; обогащение пищи витаминами и естественными пребиотиками. Наряду с рациональным гипо- и эукалорийным питанием обязательным условием лечения больных НАЖБП является физическая нагрузка. Она оказывает положительный эффект на снижение массы тела и чувствительность к инсулину, при этом увеличивается поступление СЖК

в мышечную ткань, где происходит их окисление, тем самым уменьшается ИР [3,19,20,21]. Степень снижения ИР, как правило, коррелирует с интенсивностью физических упражнений, которые рекомендуется проводить не менее 3-4 раза в неделю, продолжительностью 30-40 минут. При неэффективности этих методов могут быть использованы фармакологические препараты, снижающие массу тела. При менопаузальном метаболическом синдроме для профилактики развития и лечения висцерального ожирения, как одного из факторов риска возникновения НАЖБП применяется заместительная гормональная терапия (ЗГТ), а также анорексигенные препараты разных подгрупп [31]: селективный ингибитор обратного захвата серотонина и норадреналина - сибутрамин [17]; препарат периферического действия - орлистат. В ряде случаев для коррекции пищевого поведения применяют антидепрессанты. Лекарственные средства, используемые в лечении НАЖБП должны быть максимально безопасны с точки зрения гепатотоксичности и оказывать положительное воздействие на клинико-лабораторные и морфологические показатели печени. В некоторых случаях при наличии показаний возможно применение хирургических методов лечения ожирения. Выбор того или иного препарата ЗГТ при ММС определяется характером менопаузы (естественная или хирургическая), длительностью периода постменопаузы (циклические режимы при постменопаузе до 2 лет, непрерывные комбинированные режимы при постменопаузе более 2 лет), а также степенью выраженности метаболических нарушений [23,26,31,32]. При выборе режима ЗГТ у пациенток с ММС крайне важно тщательно анализировать наличие и степень метаболических нарушений, а также присутствие различной сопутствующей патологии (жировой гепатоз, обструктивное апноэ, остеоартроз и др.). Женщинам при сохраненной матке назначается низкодозированная, комбинированная (эстроген-гестагенная) терапия анжелик (Шеринг), фемостон1/5 (Солвей Фарма). Лечение проводится в непрерывном режиме в течение 3-5 лет и более. Женщинам без матки назначается монотерапия эстрогенами без прогестагенов.

При наличии у пациентки дополнительных факторов риска сердечно-сосудистых заболеваний (семейный анамнез, курение), а также при выявлении патологии печени, гиперкоагуляции, выраженной гипертриглицеридемии показана парентеральная ЗГТ [19] например, эстрогены в виде пластыря (климара) или геля (эстрожель, дивигель), а при необходимости добавление гестагенного компонента - аналоги натурального прогестерона (дюфастон) или утрожестан в непрерывном режиме. В последние годы активно разрабатываются и изучаются режимы ЗГТ с минимально эффективными дозами эстрогенного и прогестагенного компонентов. По данным множества авторов, применение ЗГТ независимо от типа препарата и способа введения способствует снижению массы тела и уменьшению количества абдоминально-висцерального жира у женщин с ММС [14,15,25]. Данная терапия не решает полностью проблему возрастной инсулинорезистентности и не влияет на многие звенья как самого ММС, так и физиологического старения в целом. Важным направлением в лечении НАЖБП является улучшение чувствительности тканей к инсулину[16,19,22, 24,26,28]. К базисным медикаментозным средствам лечения синдрома ИР у больных НАЖБП могут быть отнесены - бигуаниды (метформин) и тиазолидиндионы (пиоглитазон, росиглитазон) - препараты, повышающие чувствительность клеточных рецепторов к инсулину. Метформин вызывает: повышение чувствительности тканей к инсулину; подавление продукции глюкозы печенью; снижение гиперинсулинемии; стабилизацию, либо снижение массы тела; уменьшение дислипидемии; улучшение реологических свойств крови; гипотензивный эффект; снижение активности адипокинов, макрофагов. Отмечено наиболее широкое применение метморфина; у которого наблюдается наименьшее число побочных эффектов. На сегодняшний день метморфин является одним из антидиабетических препаратов, обладающим доказанным влиянием на снижение частоты осложнений СД2 [4,6,9,18].

При применении этого препарата отмечалось улучшение клинико-морфологических проявлений НАЖБП в виде уменьшения активности показателей цитолитического синдрома, степени стеатоза и воспаления и фиброза печени. Однако, вопрос применения этих препаратов у больных НАЖБП требует проведения дальнейших исследований, что обусловлено отсутствием адекватных методов контроля эффективности лечения (гепатобиопсия). Учитывая патогенез заболевания, у пациентов с НАЖБП эффективным может оказаться также применение гиполипидемических

средств из группы фибратов и статинов [11,26]. Однако, результаты исследования с назначением клофибрата больным НАЖБП показали его неэффективность, указывается и на возможность развития фибрат-индуцированных гепатитов. Статины могут применяться у пациентов с дислипидемией и гиперхолестеринемией. Показано, что данная группа препаратов уменьшает выраженность стеатоза. Плейотропные эффекты статинов на эндотелий сосудов, воспаление, стабилизирующее действие на атеросклеротические бляшки вносит дополнительный вклад в снижение сердечно-сосудистого риска. Однако, в отношении статинов также существует ряд противопоказаний, связанных с их гепатотоксическим действием. В целом, данные выполненных работ противоречивы и указывают на необходимость дальнейшего изучения возможности использования этих препаратов у пациентов с НАЖБП.

В настоящее время в патогенезе НАЖБП и НАСГ кроме инсулинорезистентности признана роль оксидативного стресса, который является следствием разобщения процессов окисления и фосфорилирования под влиянием СЖК. Учитывая патогенез НАЖБП, в схемы терапии данной патологии необходимо включать антиоксидантные препараты и гепатопротекторы [13]. В настоящее время активно изучается возможность использования витамина Е, эффективность которого была продемонстрирована в ряде исследований [5], а также препаратов тиоктовой (а-липоевой) кислоты (АЛК) [22,26]. В отношении АЛК установлено, что она обладает плейотропным действием на весь организм, оказывая положительное влияние на энергетический, липидный (тормозит синтез холестерина, подавляя высвобождение СЖК из жировой ткани, что предупреждает развитие стеатоза гепатоцитов) и углеводный (снижает ИР, усиливает захват и утилизацию глюкозы клеткой, повышает чувствительность клеточных рецепторов к инсулину) виды обменов. Кроме этого, АЛК, имея низкий оксислительно-восстановительный потенциал, обладает мощным антиоксидантным эффектом и способствует повышению детоксицирующих субстанций в гепатоцитах (восстанавливает глутатион) и улучшению морфологических изменений. Доказана эффективность препарата тиоктовой (а-липоевой) кислоты - берлитиона 300, как высокоэффективного антиоксиданта.

Берлитион 300 уменьшает дистрофию гепатоцитов - выраженность некровоспалительных изменений печени, способствует регрессу фиброзных изменений; уменьшает проявления болевого абдоминального,астеновегетативного, холестатического и цитолитического синдромов; оказывает положительное влияние на состояние липидного и углеводного обмена; улучшает белково-синтетическую функцию печени; оказывая антитоксическое действие в отношении препаратов ртути,мышьяка, селена,цианидов,сурьмы.

Способ применения и дозы: I этап: 2 недели берлитион 300 в/в капельно 600 мг в сутки (2 амп.), разведенный в 250 мл физ. р-ра; II этап: до 6 месяцев прием таблетированного препарата берлитион 300 в дозе 600 мг в сутки; (по 1 таб. 2 раза в сутки).

При анализе работ, посвященных лечению НАЖБП, указывается на более широкое применение, среди гепатопротекторов, урсодезоксихолевой кислоты (УДХК) и эссенциальных фосфолипидов. УДХК - гепатопротектор, минимизирующий токсичность желчных кислот и обладающий антиоксидантными, мембраностабилизирующими, иммуномодулирующими свойствами, [1,2,7,10,11] включен в схему лечения пациентов с НАЖБП. УДХК, нормализуя гепатоэнтеральную циркуляцию желчных кислот и целого ряда биологически активных веществ, вытесняя токсичные желчные кислоты, способствует ликвидации избытка холестерина в гепатоцитах, путем уменьшения его синтеза и всасывания из кишечника. УДХК также обладает цитопротективным и антиапоптотическим действием, препятствуя развитию окислительного стресса. Урсодезоксихолевая кислота (урсосан, урсофальк) - дозы 10-15 мг/кг в сутки. Курсы лечения индивидуальны.

Эссенциальные фосфолипиды (эссенциале, фосфоглив, эсливер форте). Эссенциале форте Н применяется в клинической практике более 50 лет, доказана эффективность этого препарата при НАЖБП [20,21,22,27,35], он рекомендован при данном заболевании. Мембраностабилизирующее и гепатопротективное действие обеспечивается путем восстановления барьерной функции липидного слоя мембран печеночных клеток. Ненасыщенные жирные кислоты фосфолипидов способствуют повышению активности и текучести мембран, нормализации проницаемости, а

также пособствуют активации расположенных в мембране фосфолипидзависимых ферментов, что, в свою очередь, поддерживает обменные процессы в клетках печени, способствует повышению ее детоксикационного и экскреторного потенциала [27,29]. Кроме того, данный препарат при НАЖБП оказывает гиполипидемическое и гипогликемическое действие (повышает чувствительность инсулиновых рецепторов), замедляет синтез коллагена и повышает активность коллагеназы (торможение фиброгенеза) [36]. Дозы эссенциальных фосфолипидов - 2капсулы 3 раза в день, не менее 3-х месяцев.

В настоящее время обсуждается возможность применения блокаторов ангиотензиновых рецепторов [12,26] и ингибиторов ангиотензинпревращающего фермента в качестве средств, уменьшающих и предотвращающих развитие фиброза, что обусловлено ролью ангиотензина в прогрессировании НАСГ. Установлено, что ангиотензин, способствуя пролиферации миофибробластов, клеточной миграции, синтезу коллагена и провоспалительных цитокинов, активирует процессы фиброгенеза в печени. При лечении лозартаном было выявлено значительное уменьшение воспаления, фиброза, стеатоза, активности печеночных трансаминаз. Так, прием лозартана у пациентов с НАСГ и артериальной гипертензией в суточной дозе 50 мг в течение 38 недель приводил к достоверному снижению АЛТ и ГГТП, что сочеталось с уменьшением степени стеатоза и воспалительной активности [12,20,21].

Для снижения прогрессирования НАЖБП имеет значение уменьшение концентрации тумор-некротизирующего фактора-а (TNFa). Обладая высокой биологической активностью, TNFa усиливает ИР и приводит к развитию окислительного стресса. Уменьшение уровня TNFa в крови связано с регрессом клинических и морфологических проявлений НАЖБП. Пентоксифиллин уменьшает эффекты TNFa. Назначение этого препарата у пациентов с НАСГ в суточной дозе 1200 мг на протяжении 12 месяцев было связано со снижением показателей цитолитического синдрома и достоверным улучшением гистологических показателей у 67% больных [26].

При лечении НАЖБП уделяется внимание и восстановлению микробиоценоза кишечника. Вопрос проведения санации кишечника антибактериальными препаратами остается открытым. Антибиотики рекомендуются только при наличии верифицированной чувствительной условно-патогенной флоры в кишечнике. Преимущество выбора при этом принадлежит препаратам, обладающим способностью хорошо накапливаться в желчи с эффектом вторичного прохождения через желудочно-кишечный тракт, к которым относятся фторхинолоны первого поколения (ципрофлоксацин). Также могут использоваться кишечные антисептики, типа метронидазола или нифуроксазид, и невсасывающиеся в кишечнике препараты. Когда нет показаний для применения антибиотиков, кишечная санация у больных НАЖБП проводится пребиотиками, а препаратом выбора в данном случае является эубикор. Его преимуществом является сбалансированный состав, куда входят пищевые волокна и винные дрожжи (S. vini). Кроме мощного пребиотического эффекта, эубикор обладает хорошими сорбционными свойствами, что позволяет не только восстанавливать нормальную микрофлору, но и проводить дезинтоксикацию. По результатам исследований, прием эубикора у данной категории пациентов способствует дополнительному уменьшению дислипопротеидемии и повышению чувствительности к инсулину. Предлагается следующая схема лечения НАЖБП [26], которая не является стандартизированной, однако патогенетически обоснованной:
- на этапе гепатоза - АЛК (берлитион) и пребиотик (эубикор);
- на этапе НАСГ — дополнительно метформин (сиофор) и УД (урсосан).

На практике рациональный выбор того или иного препарата может определяться сочетанием НЖБП с одним из компонентов МС (ожирением, СД2, артериальной гипертензией при одновременном сочетании нескольких проявлений МС - НАЖБП, ожирения, СД 2 типа, артериальной гипертензии). Предлагается следующая схема оптимальной терапии при одновременном сочетании нескольких проявлений МС (НЖБП, ожирения, СД 2 типа, артериальной гипертензии):
- гипокалорийная гиполипидемическая диета;
- физические нагрузки — не менее 4-5 раз в неделю по 30-40 минут;
- эубикор по 2 пакетика 3 раза в день;
- метформин (сиофор) в индивидуально подобранной дозе;
- АЛК (берлитион) 600 ЕД в сутки;
- УД (Урсосан) 15 мг/кг/сутки;
- антагонист рецепторов ангиотензина II (например, лозартан);

Пациентам с тяжелым декомпенсированным циррозом показана трансплантация печени.

НАЖБП, по сей день, привлекает внимание исследователей и практических врачей. Изучаются причины и патогенез развития этого заболевания и его взаимосвязь с метаболическим синдромом, в особенности, с менопаузальном метаболическим синдромом; накапливаются новые данные по диагностике НАЖБП, установлению факторов риска неблагоприятного течения заболевания и его лечения. Разрабатываются, апробируются основные направления патогенетической фармакотерапии и рекомендации по лечению и профилактике заболевания. Вместе с тем требуются дальнейшие исследования для доказательной базы, о возможности применения рекомендуемых комбинаций лекарственных препаратов с целью улучшения качества и продолжительности жизни больных, замедления прогрессирования заболевания и предупреждения смертности. У всех пациентов с МС, особенно в период менопаузы, пациентам, у которых имеется высокая вероятность развития НАЖБП должна быть проведена оценка морфофункционального состояния печени. Несмотря на то, что разработка стандартов диагностики и лечения НАЖБП окончательно не разрешена медицинские специалисты могут использовать в своей практике, имеющиеся в литературе рекомендации по лечению, накапливать данные относительно предложенных алгоритмов, усовершенствуя их.

ЛИТЕРАТУРА

1. Bellentani S. Immunomodulating and antiapoptotic action of ursodeoxycholic acid: where are we and where should we go? Eur J Gastroenterol Hepatol. 2005; 17: 137–140.
2. Beuers U. Drug insight: mechanisms and sites of action of ursodeoxycholic acid in cholestasis. Nat Clin Pract Gastroenterol Hepatol. 2006, 3: 318-328.
3. Bugianesi E., Gastaldelli A., Vanni E. et al. Insulin resistance in non-diabetic patients with non-alcoholic fatty liver disease: sites and mechanisms. Diabetologia 2005; 48: 634–642.
4. Chan N. Improved endothelial function with metformin in type 2 diabetes mellitus. JAM Coll Cardiol 2001; 38: 2131–2.
5. Chang C.Y., Argo C.K., Al-Osaimi A. M., Caldwell S. H. Therapy of NAFLD: antioxidants and cytoprotective agents. J Clin Gastroenterol. 2006; 40 (Suppl 1): 51–60.
6. Despres J. Potential contribution of metformin to the management of cardiovascular disease risk in patients with abdominal obesity, the metabolic syndrome and type 2 diabetes. Diabet Metabol. 2003; 29: 53–61.
7. Dufour J.F., Oneta C.M., Gonvers J.J. et al. Randomized placebo-controlled trial of ursodeoxycholic acid with vitamin E in nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol. 2006; 4: 1537–1543.
8. Farrell G. C., Chitturi S., K. K. Lau G. et al. Guidelines for the assessment and management of non-alcoholic fatty liver disease in the Asia–Pacific region: Executive summary // Journal of Gastroenterology and Hepatology 2007; 22: 775–777.
9. Giannarelli R, Aragona M, Coppelli A, Del Prato S. Reducing insulin resistance with metformin: the evidence today. Diabet Metabol 2003; 29: 6S28–6S35.
10. Heuman D. M., Bajai R. Ursodeoxicholate conjugates protect against disruption of cholesterol-rich membranes by bile salts. Gastroenterology 1994; 106: 1333–1341.
11. Laurin J., Lindor K. D., Crippin J. S. et al. Ursodeoxycholic acid or clofibrate in the treatment of nonalcohol-induced steatohepatitis: a pilot study. Hepatology 1996; 23: 1464–1467.
12. Yokohama S., Yoneda M., Haneda M. Okamoto S., Okada M., Aso K., Hasegawa T., Tokusashi Y., Miyokawa N., Nakamura K. Therapeutic efficacy of an angiotensin II receptor antagonist in patients with nonalcoholic steatohepatitis. Hepatology 2004; 40: 1222–1225.
13. Бакулин И.Г.,Сандлер Ю.Г Возможности применения гепатопротекторов в практике врача-терапевта Consilium Medicum. 2010; 12(8): 72-76.
14. Баранова Е.И., Большакова О.О. Метаболический сердечно-сосудистый синдром в постменопаузе. Обзоры клин. Кардиологии 2005; 1: 2-11.
15. Баранова Е.И., Маслова Н.П. Гипертоническая болезнь у женщин [монография]. СПб.: Изд-во СПбГМУ: 2000; 274.
16. Богомолов П.О., Цодиков Г.В. Неалкогольная жировая болезнь печени. Consilium medicum 2006; 4(1): 56-60.
17. Бутрова С.А. Сибутрамин (Меридиа) в лечении ожирения: опыт применения в России. Клин. фармакол. и тер. 2001; 10(2): 55–8.
18. Бутрова С.А. Эффективность глюкофажа в профилактике сахарного диабета типа 2 (по результатам исследования DPP). Пробл. эндокринол. 2004; 4: 51–6.
19. Григорян О.Р. Современные принципы кор-

рекции метаболического синдрома у женщин в период постменопаузы Consilium medicum 2005; 9: 734-736.
20. Драпкина О.М., Гацолаева Д.С., Ивашкин В.Т. Неалкогольная жировая болезнь печени у больных с метаболическим синдромом. Клиницист 2007; 6: 46-50.
21. Драпкина О.М., Смирин В.И., Ивашкин В.Т. Неалкогольная жировая болезнь печени – современный взгляд на проблему. Лечащий врач 2010; 5(5): 57-61.
22. Ивашкина В.Т. Рациональная фармакотерапия заболеваний органов пищеварения: Рук. для практикующих врачей. М.: Литтерра; 2003: 1046.
23. Кулаков В.И., Сметник В.П. Руководство по климаксу: Руководство для врачей. М.: Мед. инф. Агентство: 2001; 404-494.
24. Лазебник Л.Б., Звенигородская Л.А. Метаболический синдром и органы пищеварения. М.: Анахарсис, ПиАр-Медиа Групп; 2009: 184.
25. Мамедов М.Н. Руководство по диагностике и лечению метаболического синдрома. М.: Полиграф Холдинг; 2004: 78.
26. Мехтиев С.Н., Гриневич В.Б., Кравчук Ю.А. Бращенкова А.В. Неалкогольная жировая болезнь печени: клиника, диагностика и лечение Лечащий врач 2008; 2: 29-37.
27. Минушкин О.Н. Опыт терапии заболеваний печени эссенциальными фосфолипидами. Consilium medicum. 2001; 9-11.
28. Подымова С.Д. Жировой гепатоз. Неалкогольный стеатогепатит (эволюция представлений о клинико-морфологических особенностях, прогнозе, лечении). Тер. Арх. 2006; 78: 4: 32-38.
29. Сергеева С. А., Озерова И. Н. Сравнительный анализ фосфолипидного состава препаратов эссенциале форте и эсслив форте. Фармация 2001; 3: 32–34.
30. Сметанин М.Ю., Пименов Л.Т., Пименова Л.И. Клинико-функциональное состояние печени при менопаузальном метаболическом синдроме. Практическая медицина 2010; 4 (43): 146-150.
31. Сметник В.П. Менопаузальный метаболический синдром. Лечащий врач 2006; 3: 39-41.
32. Сметник В.П, Шестакова И.Г.Современные представления о менопаузальном метаболическом синдроме. Consilium medicum 2003; 5(9): 543-546.
33. Чазова И.Е., Мычка В.Б. Метаболический синдром. М.: Медиа Медика; 2004: 168.
34. Чорбинская С.А., Борисенко Е.Г., Кравцова Н.Н. Метаболический синдром и неалкогольная жировая болезнь печени. Врач 2009; 3: 26-29.
35. Шульпекова Ю.О. Неалкогольная жировая болезнь печени: патогенез, диагностика, лечение. Фарматека 2007; 6 (141): 48–53.
36. Щекина М.И. Неалкогольная жировая болезнь печени. Consilium medicum 2009; 8(11): 37–39.

SUMMARY

TREATMENT OF NONALCOGOLIC FATTY DISEASE OF LIVER

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The experimental and clinical data concerning of treatment of nonalcogolic fatty liver disease (NAFLD) are summarized and analyzed in the review. Some aspects of pathogenetic pharmacotherapy of NAFLD have been discussed (correction of insulin resistance, obesity, dislipidemia, oxidative stress, hepatoprotectors, restoration of intestine microbiosis, replacement hormonal, syndrome and antihypertensive drugs). Medical and non - medical methods of treatment is compared. It is concluded that further study to improve methods of prevention and treatment of NAFLD are required.

Keywords: nonalcogolic fatty liver disease, treatment.

РЕЗЮМЕ

ЛЕЧЕНИЕ НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНИ ПЕЧЕНИ

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В обзоре обсуждаются разрабатываемые и апробируемые основные направления патогенетической фармакотерапии и рекомендации по лечению и профилактике неалкогольной жировой болезни

печени (НАЖБП). Направлениями патогенетической терапии больных НАЖБП являются: фармакологическая терапия инсулинорезистенстости, ожирения, дислипопротеинемии, окислительного стресса, применение гепатопротекторов, восстановление кишечного микробиоза; при наличии менопаузального метаболического синдрома применение заместительной гормональной терапии, а в случае сочетания с гипертензией - гипотензивной терапии. Рассматриваются также методы немедикаментозной терапии. Анализируются механизмы эффективности фармакопрепаратов, применяемых при НАЖБП. Вместе с тем, отмечается, что требуются дальнейшие исследования возможности применения рекомендуемых комбинаций лекарственных препаратов, разработка методов профилактики и лечения НАЖБП, основанных на принципах доказательной медицины.

რეზიუმე

ღვიძლის არაალკოჰოლური ცხიმოვანი დაავადების მკურნალობა

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თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, ფარმაკოთერაპიისა და ფარმაკოლოგიის დეპარტამენტი, სამედიცინო ფარმაკოლოგიის დეპარტამენტი, საქართველო

მიმოხილვაში განხილულია ღვიძლის არაალკოჰოლური ცხიმოვანი დაავადების (ღაცდ) ფარმაკოთერაპიის ძირითადი პრინციპები და ამ დაავადების მკურნალობისა და პროფილაქტიკის რეკომენდაციები. ღაცდ-ის პათოგენეზური მკურნალობის ძირითადი მიმართულებებია: ინსულინრეზისტენტობის, სიმსუქნის, დისლიპოპროტეინემიის, ოქსიდაციური სტრესის ფარმაკოთერაპია, ასევე, ჰეპატოპროტექტორების გამოყენება, ნაწლავის მიკრობიოზის აღდგენა; თანმდევი მენოპაუზალური მეტაბოლური სინდრომის დროს ჩანაცვლებითი ჰორმონული თერაპიის, ხოლო თანმდევი ჰიპერტენზიის დროს – ანტიჰიპერტენზიული საშუალებების გამოყენება. განიხილება, აგრეთვე, ღაცდ-ის არამედიკამენტოზური მკურნალობა. გაანალიზებულია ღაცდ-ის დროს გამოყენებული ფარმაკოპრეპარატების ეფექტურობის მექანიზმები. ამავე დროს, აღინიშნება, რომ ღაცდ-ის პროფილაქტიკისა და მკურნალობისათვის აუცილებელია კვლევის ისეთი მეთოდების შემუშავება, რომლებიც დაფუძნებულია მტკიცებითი მედიცინის პრინციპებზე.

PECULIARITIES OF CARDIOVASCULAR DISEASES IN WOMEN

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Diseases of the heart and circulatory system remain the biggest cause of deaths worldwide. In 2007, Cardiovascular Diseases (CVD) caused 1 death per minute among women in the United States. These represent 421.918 deaths in women – more than from cancer, chronic lower respiratory disease, Alzheimer disease, and accidents combined [2]. Cardiovascular Diseases is the main cause of death in Europe: accounting for over 4.30 million deaths each year (54% of deaths in women and 43% of deaths in men). CVD

is the main cause of death in women in all countries of Europe and is the main cause of death in men in all countries except France, the Netherlands and Spain [9]. CVD is also the main cause of death in the European Union (EU) accounting for over 2.0 million deaths each year (45% deaths in women and 38% deaths in men). The main forms of CVD are coronary heart disease (CHD) and stroke [9]. Over a third of deaths from CVD is from CHD and just over a quarter is from stroke. Over one in five women (22%) and over one in five men (21%) die from CHD; one in ten men (9%) and one in eight women (12%) die from stroke. Generally CVD was the main cause of death for women in all 48 countries of Europe: accounting for 1.24 million deaths in Europe each year. Over one in six women (17%) and one in ten men (11%) die from the disease [9,40]. CVD causes more than 50% of deaths in men in eight countries: Armenia, Azerbaijan, Bulgaria, Georgia, FYR Macedonia, Serbia and Montenegro, Romania, and Ukraine in 2010. CVD is the main cause of death before the age of 65 for men in 26 of the 48 countries of Europe and for women in 17 countries. In women, the countries where CVD is the main cause of death before the age of 65 are all Central and Eastern European countries [1,7,9]. CVD causes between 50% (Georgia) and 15% (France) of deaths before the age of 65 in men, and between 46% (Georgia) and 11% (France) of deaths before the age of 65 in women [7]. The frequency of CVD in Georgia was raised during last 10 years. The morbidity of CVD (the cases diagnosis for the first time) were: 56, 8 thousands on 2002; 64 1 on 2003; 70,7 on 2004; 83,2; on 2005. The statistical data for last years is as following: 74,4 on 2008; 96,6 on 2009; 98,2 on 2010 and 103,5 on 2011 [11]. In 2002 age-standardized DALY s (Disability Adjusted Life Year) – lost per 100,000 rates for CHD, stroke and other CVD in Georgia were: 2,103 from CHD; 1,552 from Stroke and 504 from other CVD. Risk of CVD is directly related to both systolic and diastolic blood pressure levels. The World Health Report 2002 estimates that that over 50% of CHD and almost 75% of stroke in developed countries is due to systolic blood pressure levels in excess of the theoretical minimum (115 mmHg). More recently the WHO has provided estimates of systolic blood pressure for the European region for 2002 and projected estimates for 2005 and 2010. Among men aged 15 or over WHO data suggest that mean systolic blood pressure ranges between 118 mmHg (Turkey) and 140 mmHg (Georgia). Among women aged 15 or over WHO data suggest that the mean systolic blood pressure ranges between 115 mmHg (Switzerland) and 135 mmHg (Georgia). Concerning 2010 statistical data the rate of arterial Hypertension in Georgia -51,7% ,in 2008 raised by 8%, rate of CVD- 26,3% raised by 7%. There is no tendency of rise of acute myocardial infarction rate 34,7% [1,7]. The Women's Ischemia Syndrome Evaluation (WISE) Study, supported by the National Heart, Lung, and Blood Institute, evaluated gender differences in the presentation and treatment of ischemic heart disease. Several anatomical and physiological differences exist in the cardiovascular system of women compared to men. Because women's bodies are generally smaller in stature, the female heart and thoracic cavity are smaller and lighter. A woman's heart weighs approximately 229 grams; a man's heart weighs about 56 grams more. The female heart also has smaller coronary arteries than a man's heart. The right coronary artery appears to be more dominant in women [3,12,34]. On the electrocardiogram (EKG), resting heart rate is higher, PR and QRS intervals tend to be shorter, the amplitude of the R, S, and T waves are smaller in women. Stroke volume and resting ejection fractions (EF) tend to be higher in women than in men. Up to 30% of women with normal coronary arteries do not have an increase in EF with exercise, a finding that has important implications for exercise testing [16]. All intravascular ultrasound studies have found that women had less atheroma volume than men, including both luminal plaque and atheroma within the media, despite older age and more risk - factors, and even after accounting for body surface area and vessel size. After adjusting for body size, women also have smaller coronary vessels [34]. Hematologic differences also exist between men and women. Women's hematocrit and blood volumes tend to be lower, along with their oxygen-carrying capacity. Cholesterol levels tend to rise in women around 55 years of age; however, the natural estrogens of peri menopause are believed to provide protection against heart disease by conferring beneficial effects to the lipid -profile. It has also been suggested that estrogen receptors located within the walls of blood vessels may affect the proliferation of smooth muscle cells, reduce platelet aggregation, and alter the degradation of collagen and elastin [12,30]. The most important role for women protection from CVD belongs to estrogens. In general, premenopausal women are protected from coronary heart disease (CHD) compared with aged-matched men but this female protection' appears to be lost after menopause, suggesting ben-

eficial effects of female sex hormones on the cardiovascular system. Two double-blind randomized clinical trials are underway in postmenopausal women. One in women with coronary disease is known as HERS (Heart Estrogen-progestin Replacement Study) and another in predominantly healthy women is the WHI (Women's Health Initiative). Several mechanisms of estrogen mediated protection from cardiovascular disease have been identified including Increased HDL, lower LDL, lower VLDL-cholesterol/triglyceride ratio, increased clearance of intermediate density lipoprotein (IDL) and LDL via an unregulated LDL receptor, diminished penetration and degradation of LDL in the arterial wall, an inhibition of LDL oxidation by various estrogens and a reversal of inappropriate acetylcholine (EDRF)-mediated vasoconstriction in arteriosclerotic vessels. Two classical estrogen receptor subtypes, ERα and ERβ, have been identified in the heart and vasculature. The long-term effects of estrogen may be mediated by both ERα and ERβ through alteration of gene expression and protein synthesis (genomic action) The rapid no genomic effect of estrogen may involve calcium-mediated activation of endothelial nitric oxide synthesis [35]. GMP and intracellular signal transduction pathways [12,38]. Recently, a third membrane-bound and G-protein-coupled estrogen receptor (GPER), GPR30, has been identified. In the heart, activation of GPR30 with the specific agonist G1 reduced ischemia/reperfusion injury and preserved cardiac function acting through PI3K-dependent Act pathways [35]. There are other recently discovered mechanisms by which estrogens could provide cardio protection. Estrogen has been shown to increase expression of superoxide dismutase and inhibit NADPH oxidase activity, thereby reducing oxidative stress [12,30]. Inflammation is considered a key element in the pathogenesis of hypertension, atherosclerosis and development of coronary heart - disease (CHD), and estrogen has been reported to reduce inflammatory markers [12]. Estrogen also attenuates after load- or agonist-induced cardiac hypertrophy via inhibition of calcineurin, hypertrophic transcription factor NF-AT, and MAPK signaling pathways [8]. In addition, estrogen has a profound anti apoptotic and pro-survival effect on cardiomyocytes [6]. Moreover, estrogen has been shown to promote endothelial progenitor cell mobilization and enhance mesenchymal stem cell-mediated vascular endothelial growth factor (VEGF) release [5,6], improving endothelial and myocardial functional after ischemia.

Risk factors of CVD in women. The traditional cardiovascular risk factors, of CVD are the same for males and females. Besides the traditional risk factors women have gender specific risk factors. The traditional risk factors are no alterable and alterable factors. No alterable risk factors are: Age; family story Ethnic Background. Alterable risk factors include smoking, hypertension, hyperlipidemia, diabetes, - obesity, metabolic syndrome, sedentary lifestyle, and Type A behavior pattern. Type A behavior is - characterized by hurriedness, impatience, sense of time urgency, restlessness, hyper alertness, a passive pattern of competitive striving, and frequently aroused angry and hostile feelings and behaviors. In contrast to their Type A counterparts, Type B people are less harried [8]. Recognition of the Type A behavior pattern as a risk for heart disease was primarily based on the Western Collaborative Group Study, a prospective study of 3,524 employed men. This more than eight-year investigation found that men initially assessed as Type A individuals had twice the rate of heart diseases. Framingham Women gender-specific risk factors include: Employment conflict, oral contraceptives, and menopause [34,41]. One study of 35,038 women, which was conducted within the NHS, found no relationship between job demands, job control, or social support and heart disease. The Study examined four types of work experience based on the level of job demands (i.e., low or high) and the level of job control (i.e., low or high). Examples of job demands examined included excessive work, conflicting demands, insufficient time to work, fast work pace, and working hard. Examples of job control examined included skill discretion (e.g., learning new things, task variety) and decision authority (e.g., freedom to make decisions, having a voice in the workplace). The level of support received from coworkers and managers was also included in the assessment. The Framingham Offspring Study found that women with active job strain (i.e., high job demand, high job control) had a 2.8-fold increased risk of coronary heart disease when compared to women with high job strain (i.e., high job demand, low job control). Other studies have indicated that women in male-dominated jobs, women who perform care giving outside work, and women experiencing marital stress may be at increased risk for heart disease [19,21,23,32].

Oral Contraceptives. Women who use combination hormonal contraceptives have risk of MI, particularly

in conjunction with other cardiovascular risk factors, such as smoking. If a woman takes hormonal contraceptives and smokes, she increases her risk level 20 times over that of a woman who neither smokes nor uses oral contraceptives. However, the risk of heart disease diminishes after the contraceptives are stopped. Research has indicated that the newer, third-generation contraceptives are the first to have been associated with no excess risk of MI [15]. However, other studies have found that women taking third-generation oral contraceptives have an estimated twofold increased risk of venous thrombosis compared with those taking second generation oral contraceptives [15,18]. Additionally, The debate over which contraceptives have the least possibility of harmful side effects continues; more research is needed for a definitive answer.

Menopause. At the time of the risk appears to depend upon the class of estrogen, the dose, and the duration of use. Menopause, serum estrogen levels decrease. The absence of estrogen increases a postmenopausal woman's vulnerability to heart disease due to the effects on lipoprotein metabolism. These changes include a decrease in HDL levels and an increase in LDL levels. In addition, blood vessels become less flexible after menopause due to the reduction in circulating estrogen. Research has demonstrated that elevated iron levels greatly increase a man's risk of heart disease. However, additional studies are needed to determine if the iron retention that occurs in no menstruating women is a significant cardiovascular risk factor [38,44]. Symptoms of CVD in women: women are typically 10 years older than men, when presenting with heart disease. When women do present, other conditions (e.g., osteoporosis, diabetes, and hypertension) and the clinician's interpretation of the woman's chest pain may obscure the indications of disease. There is a greater prevalence of no coronary causes of chest pain in the female population, and chest pain is frequently accompanied by abdominal pain, dyspnea, nausea, fatigue, and greater functional disability [22,26,36]. Additionally, a variety of structures may cause symptoms, such as mitral valve prolapse, pericarditis, or gallbladder disease that localize to the chest. The clinical history and physical exam have limited value in women, except for women older than 65 years of age with definite angina. The history and physical exam do provide information on the occurrence of prior events and risk factors, such as diabetes and hypertension, and also uncover symptoms of more advanced disease, such as heart failure [22,40]. The presence of new physical findings, such as arrhythmias, mitral regurgitation, a fourth heart sound (atrial gallop), increases the chances of a positive diagnosis of heart disease [3]. The diagnosis is also favored by the presence of other cardiovascular risk factors or by EKG changes at rest or during angina episodes. Women most often than men have Coronary micro vascular disease (MVD) - X Syndrome, which affects the tiny coronary arteries. In coronary MVD, the walls of the heart's tiny arteries are damaged or diseased. In CHD, plaque builds up in the large coronary arteries narrows them and reduces the flow of oxygen-rich blood to heart muscle [22]. In coronary MVD plaque doesn't create blockages in these vessels as it does in the heart's large arteries. The cause and path physiologic mechanism of MVD is unknown. However it's known that Syndrome X is more common in women. About 70% of patients are women who are approaching or have already gone through menopause. In WISE study of 936 women. Undergoing cardiac catheterization for chest pain, 60% did not have a major blockages in the arteries of their heart. These women are commonly diagnosed with "Syndrome X," defined as chest pain, an ischemic stress test response and angiographic normal coronary arteries [3]. "Syndrome X" likely results from coronary micro vascular dysfunction, which is a disordered function of the smaller coronary resistance vessels.The WISE study is indirectly exploring the hypothesis that this syndrome is associated micro vascular endothelial dysfunction by measuring coronary flow responses to intracoronary adenosine and acetylcholine, risk factors for endothelial dysfunction, and subclinical atherosclerosis [36].

Diagnosis of heart diseases in women. Several non-invasive tests are used to diagnose coronary heart disease. These include the resting EKG, exercise EKG, nuclear medicine stress test, radionuclide and exercise echocardiogram. The resting EKG is the first-line screening test in men as in women due to the increased proportion of unrecognized or "silent" infarctions seen in the female population. The presence or Absence of abnormal Q waves on the resting EKG may be affected by the use of HRT in women older than 50 years of age. Study results have shown that there is a lower occurrence of abnormal Q waves on the EKG in postmenopausal women who received HRT compared to women who have not [34].

Exercise EKG. Although the exercise EKG may not be as accurate in the diagnosis of heart disease in women as in men, the American College of Cardiology (ACC) and the American Heart Association (AHA) have recommended the routine use of the exercise EKG for evaluating suspected coronary artery disease in women who have a normal resting EKG and good exercise tolerance [27]. Women are more prone to false positive results than men with this test; however, a test result that is clearly negative has been found to be equally reliable in both women and men [22]. In women with normal coronary arteries, this test is associated with a higher false-positive rate (30% to 40%) as ST-segment depression is fairly nonspecific in women. A true positive test is indicated in women if there is profound ST-segment depression (3-4 mm rather than 1-2 mm) representing MI or ST-segment abnormalities that are widespread and persist into the recovery phase [22]. A second difficulty associated with the exercise EKG is that for the test to work, a woman must be able to raise her heart rate up to 85% of maximum capacity by exercising for about 15 minutes. . When test results are either clearly positive or not clearly positive or negative, additional diagnostic tests (i.e., echocardiography or nuclear stress test) are usually performed [22]. The ACC/AHA have recommended cardiac imaging for symptomatic women with established coronary artery disease, women who have an indeterminate or intermediate-risk exercise EKG test, and women with an intermediate-risk Duke treadmill score [27]. With multivessel disease, greater than 90% accuracy has been reported, while only about 50% accuracy has been seen in patients with single vessel or no disease [21].

Nuclear Medicine Stress Test The nuclear medicine stress test is another noninvasive diagnostic test that may be used in women. At peak exercise, a small amount of radioactive tracer is injected and a series of images of myocardial blood flow are then evaluated. Normal myocardial blood flow is indicated by a homogeneous distribution of thallium throughout the myocardium, while myocardial ischemia and/or infarction is suggested by either a transient or persistent defect in tracer uptake. Compared to the exercise EKG, the nuclear medicine stress test has better accuracy in women [40]. It has also been associated with fewer false-positive tests in women, especially in those patients with multivessel disease. The major limitation of the nuclear medicine stress test in women is the attenuation of radioactivity in the overlying breast tissue, leading to a false-positive diagnosis. Other disadvantages are the cost of the test and exposure of the patient to radiation. Although, the radiation dose is minimal, women who are pregnant or breastfeeding should not undergo any type of radiation procedure [40].

Exercise Echocardiogram. The exercise echocardiogram is a two-dimensional exam used to assess synergy of myocardial contraction. The exercise echocardiogram is more specific and reliable than the exercise EKG, with a 90% accuracy rate in women It is a useful diagnostic test in women because of its sensitivity to single-vessel disease, involving greater than 50% narrowing, which occurs more frequently in women compared to men (18% versus 9%). Due to the difficulty of diagnosing changes with exercise, drugs such as dipyridamole or adenosine may also be used [36]. Dipyridamole is a potent coronary artery vasodilator; side effects from its use include dizziness, gastrointestinal upset, nausea and vomiting, headache, and rash. Adenosine has a more rapid onset but wears off more quickly. When properly performed the exercise echocardiogram has been found to have high sensitivity and specificity (86%) for the detection of coronary artery disease in women [26].

Electron Beam Computerized Tomography (EBCT). Electron beam computerized tomography (EBCT), also called an ultrafast CT scan, is a rapid form of x-ray imaging technology that results in a clear image of the heart and the surface of the coronary arteries. EBCT measures calcium deposits in the coronary arteries, which would correlate to the amount of atherosclerosis. Experts have indicated, however, that the amount of coronary calcification does not necessarily indicate that an individual will suffer an MI, and the absence of calcification does not rule out coronary artery disease. Another limitation of the test is that it cannot reliably determine which blockages are likely to lead to an infarction. 60 years of As a result of limitations, EBCT has not been recommended for routine screening for coronary artery disease [45].

Invasive diagnostic tests. Cardiac Catheterization Cardiac catheterization is the definitive diagnostic test to detect heart disease [19]. While the number of catheterizations performed on women has increased, men are more likely to be referred for a catheterization than women. However, women may be at greater risk of adverse events, including death, following

catheterization. One study found that men were 40% more likely to undergo angiography than women, despite data that indicates women have more functional impairment and unstable symptoms, as measured by angiography, than men [26]. Compared to men, when cardiac catheterization is performed in women the test usually reveals less extensive disease Single-vessel disease occurs in 50% of women, with the left anterior descending artery the most common site of lesions (i.e., in 43% to 54% of cases). In the remaining 50% of women, 25% have two-vessel disease and 25% have three-vessel disease. In addition, left main disease is less common in female cardiac patients compared to men [24,41].

REFERENCES

1. Allender S. et al. European CVD statistics 2008. Edition P. Scarboroush. 2009.
2. American Heart Association. Women and Cardiovascular Diseases - Statistics 2010.
Available at http://www.americanheart.org/presenter.jhtml?identifier=3000941. Last accessed September 14, 2010.
3. Beery T. Gender bias in the diagnosis and treatment of coronary artery disease. Heart Lung. 1995;24(6):427-435.
4. Bairey Merz CN, Shaw LJ, Reis SE, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) study: part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. J Am Coll Cardiol. 2006;47(3 suppl S):21-29.
5. Baruscotti I, Barchiesi F, Jackson EK, et al. Estradiol stimulates capillary formation by human endothelial progenitor cells: role of estrogen receptor-alpha/beta, heme oxygenase 1, and tyrosine kinase. Hypertension 2010;56:397–404.
6. Bolego C, Rossoni G, Fadini GP, et al. Selective estrogen receptor-alpha agonist provides widespread heart and vascular protection with enhanced endothelial progenitor cell mobilization in the absence of uterotrophic action. FASEB J 2010;24:2262–2272.
7. Coronary Heart Diseases. Statistics British Heart Foundation. www. heartstats.org 2010.
8. Donaldson C, Eder S, Baker C, et al. Estrogen attenuates left ventricular and cardiomyocyte hypertrophy by an estrogen receptor-dependent pathway that increases calcineurin degradation. Circ Res. 2009;104:265–275.
9. European cardiovascular disease statistics 2008. http://www.changingdiabetesbarometeritaly.com/pdf/statistics-2008-web-161229A.pdf
10. Eaker ED, Sullivan LM, Kelly-Hayes M, D'Agostino RB Sr., Benjamin EJ. Does job strain increase the risk for coronary heart disease or death in men and women? The Framingham Offspring Study. Am J Epidemiol**.** 2004;159(10):950-958.
11. Geostats.com
12. Hay M, Huxley VH. Sexual dimorphism in hypertension. In: Dipette D, Schiffrin E, Re R, Sowers JR (eds). Molecular Mechanisms of Hypertension**.** Philadelphia, PA: Taylor and Francis; 2006.
13. Jacobs AK. Women, ischemic heart disease, revascularization, and the gender gap. What are we missing? J Am Coll Cardiol. 2006;47(suppl S):S63-S65.
14. Jensen L, King KM. Women and heart disease: the issues. Crit Care Nurse**.** 1997;17(2):45-53.
15. Jick SS, Kaye JA, Russmann S, Jick H. Risk of nonfatal venous thromboembolism with oral contraceptives containing norgestimate or desogestrel compared with oral contraceptives containing levonorgestrel. Contraception 2006;73(6):566-570.
16. Judelson DR. Examining the gender bias in evaluating coronary disease in women. Med Gen Med. 1999;1(2).
17. Kaczmarek RG, Liu CH, Gross TP. Medical device surveillance: gender differences in pulmonary artery rupture after pulmonary artery catheterization. J Womens Health (Larchmt). 2003;12(9):931-935.
18. Kemmeren JM, Algra A, Grobbee DE. Third generation oral contraceptives and risk of venous thrombosis: meta-analysis. BMJ. 2001;323(7305):131-134.
19. King KM, Ghali WA, Faris PD, et al. Sex differences in outcomes after cardiac catheterization: effect modification by treatment strategy and time. JAMA 2004;291(10):1220-1225.
20. Kimble LP, McGuire DB, Dunbar SB, et al. Gender differences in pain characteristics of chronic stable angina and perceived physical limitation in patients with coronary artery disease. Pain 2003;101(1-2):45-53.
21. Kivimaki M, Virtanen M, Elovainio M, Kouvonen A, Vaananen A, Vahtera J. Work stress in the etiology of coronary heart disease-a meta-analysis. Scand J Work Environ Health**.** 2006;32(6):431-442.
22. Kyker KA, Limacher MC. Gender differences in the presentation and symptoms of coronary artery disease**.** Curr Womens Health Rep**.** 2002;2(2):115-119.
23. Lee S, Colditz G, Berkman L, Kawachi I. A prospective study of job strain and coronary heart disease in US women. Intl J Epidemiol**.** 2002;31:1147-1153.

24. Lori Mosca et al. Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women - 2011 Update A Guideline From the American Heart Association. Circulation 2011; 123: 1243-1262.
25. Mieres JH, Shaw LJ, Arai A, et al. Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention.
26. Merck Manuals Online Medical Library. Radionuclide Imaging. Available at http://www.merck.com/mmpe/sec07/ch070/ch070i.html. Last accessed September 14, 2010.
27. Mieres JH, Shaw LJ, Arai A, et al. Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention. Circulation 2005;111(5):682-696.
28. Murdaugh C. Coronary artery disease in women. J Cardiovasc Nurs. 1990;4(4):35-50.
29. Orth-Gomer K, Wamala SP, Horsten M, Schenck-Gustafsson K, Schneiderman N, Mittleman MA. Marital stress worsens prognosis in women with coronary heart disease: the Stockholm Female Coronary Risk Study. JAMA 2000; 284(23):3008-3014.
30. Pepine CJ, Kerensky RA, Lambert CR, et al. Some thoughts on the vasculopathy of women with ischemic heart disease. J Am Coll Cardiol**.** 2006;47(3 suppl S):S30-S35.
31. Penckofer S, Holm K. What you should know about women and heart disease. Nursing. 1993 ;23(6):42-46.
32. Peter R, Hammarstrom A, Hallqvist J, Siegrist J, Theorell T, The SHEEP Study Group. Does occupational gender segregation influence the association of effort-reward imbalance with myocardial infarction in the SHEEP study? Int J Behav Med**.** 2006;13(1):34-43.
33. Roger V, Farkouh ME, Weston SA, et al. Sex differences in evaluation and outcome of unstable angina. JAMA 2000;283(5): 659-661.
34. Romeo KC. The female heart: physiological aspects of cardiovascular disease in women. Dimens Crit Care Nurs**.** 1995;14(4)170-177.
35. Rexrode KM, Manson JE, Lee I, et al. Sex hormone levels and risk of cardiovascular events in postmenopausal women. Circulation**.** 2003;108:1688-1693.
36. Redberg RF. Coronary artery disease in women: understanding the diagnostic and management pitfalls. Medscape Womens Health**.** 1998;3(5):1.
37. Shapiro S, Dinger J. Risk of venous thromboembolism among users of oral contraceptives: a review of two recently published studies. J Fam Plan Reprod Health Care**.** 2010;36(1):33-38.
38. Sun Q, Ma J, Rifai N, Franco OH, Rexrode KM, Hu FB. Excessive body iron stores are not associated with risk of coronary heart disease in women. J Nutr**.** 2008;138(12):2436-2441.
39. Wang F, He Q, Sun Y, et al. Female adult mouse cardiomyocytes are protected against oxidative stress. Hypertension 2010;55:1172–1178.
40. WHO Regional office for Europe. Report Heart disease leading cause of death in women 27-04-2010.
41. Wingate S. Women and coronary heart disease: implications for the critical care setting. Focus Crit Care**.** 1991;18(3):212-214, 216-218.
42. Xiao-Ping Yang, Reckelhoff J.F. Estrogen, hormonal replacement therapy and cardiovascular disease. Curr Opin Nephrol Hypertens. 2011; 20(2): 133.
43. Xing D, Nozell S, Chen YF, et al. Estrogen and mechanisms of vascular protection. Arterioscler Thromb Vasc Biol. 2009;29:289–295.
44. Zegrean M. Association of body iron stores with development of cardiovascular disease in the adult population: a systematic review of the literature. Can J Cardiovasc Nurs**.** 2009;19(1):26-32.
45. Women and heart diseases.www. netce.com

SUMMARY

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In a review article peculiarities of cardiovascular disease among women are considered. The analysis of published data showed that cardiovascular disease (CVD) is common in women. Gender-specific risk factors include oral contraceptives and menopause. Clinical manifestations, major causes of various forms of cardiovascular disease in women are revealed. It was found that women most often than men have coronary micro vascular disease - X Syndrome, which affects the tiny coronary arteries. Coronary microvascular dysfunction

is prevalent in women with chest pain. There is a greater prevalence of no coronary causes of chest pain in the female population, and chest pain is frequently accompanied by abdominal pain, dyspnea, nausea, fatigue, and greater functional disability. Women tend to suffer from more single vessel and two-vessel disease as opposed to the three-vessel disease seen more often in men. It is concluded that specific research is required to identify risk factors of cardiovascular disease in women in Georgia.
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Keywords: cardiovascular diseases, women, mortality, risk factors.

РЕЗЮМЕ

ОСОБЕННОСТИ СЕРДЕЧНО-СОСУДИСТЫХ ЗАБОЛЕВАНИЙ У ЖЕНЩИН

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В обзорной статье на основе анализа литературных данных рассматриваются особенности сердечно-сосудистых заболеваний среди женщин. Гендер-специфическими риск факторами являются оральная контрацепция и менопауза. Выявлены особенности проявления, течения и диагностики различных форм сердечно-сосудистых заболеваний у женщин. Данные литературного анализа указывают, что для женщин характерна малая симптоматика и высокая частота болей некоронарного генеза в грудной клетке, что затрудняет диагностику данного заболевания среди женщин. Кроме того, у женщин чаще наблюдаются поражения одного или двух сосудов, тогда как для мужчин характерны трехсосудистые поражения коронарных артерий. Результаты анализа литературы диктуют необходимость проведения специальных исследований по выявлению сердечно-сосудистых заболеваний среди женщин Грузии.

რეზიუმე

გულ-სისხლძარღვთა სისტემის დაავადებების თავისებურებანი ქალებში

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სტატიაში ლიტერატურის მონაცემების ანალიზის საფუძველზე წარმოდგენილია ქალებში გულ-სისხლძარღვთა სისტემის დაავადებების კლინიკური გამოვლინებისა და დიაგნოსტიკის თავისებურებები.

ხაზგასმულია, რომ ქალთა პოპულაციაში გენდერსპეციფიკურ რისკ-ფაქტორებს მიეკუთვნება ორალური კონტრაცეფცია და მენოპაუზა.

გამოტანილია დასკვნა, რომლის მიხედვით ქალებისათვის დამახასიათებელია გულ-სისხლძარღვთა პათოლოგიის მცირე სიმპტომატიკა და გულმკერდის არეში არაკორონარული გენეზის ტკივილის მაღალი სიხშირე, რაც ხელს უშლის ქალებში ამ ჯგუფის დაავადებების დიაგნოსტიკას. ამ კონტინგენტში ხშირია ერთი ან ორი კორონარული არტერიის დაზიანება, მაშინ როდესაც მამაკაცებისათვის დამახასიათებელია სამი კორონარული არტერიის დაზიანება.

საქართველოში ქალთა მოსახლეობის გულ-სისხლძარღვთა სისტემის დაავადებების გამოვლინებისა და თავიდან აცილების მიზნით აუცილებელია სპეციალური კვლევების განხორციელება.

MAINSTREAMING GENDER IN DISASTER (REVIEW)

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We live in a world of risk and are surrounded by potential hazards, whether these are natural or environmental, technological, or deliberately induced (explosions, attacks), when these transcend the ability of people and system to cope without external assistance it's a disaster [16]. A disaster can be defined as an emergency of such severity and magnitude that the resultant combination of deaths, injuries, illness, and property damage cannot be effectively managed with routine procedures or resources [1,14]. The importance of this subject has in recent years helped bring a more academic approach to emergency and disaster management in the world [10]. All disasters are unique in that they affect areas with different levels of vulnerability and with distinct social, health, and economic conditions [13]. There is some evidence showing that women and men may suffer different negative health consequences following a disaster. It is not clear whether this is because of biological differences between the sexes, because of socially determined differences in women's and men's roles and status or because of an interaction of social and biological factors [4,16]. There is a general lack of research on sex and gender differences in vulnerability to and impact of disasters. The limited information available from small scale studies suggests that there is a pattern of gender differentiation at all levels of the disaster process: exposure to risk, risk perception, preparedness, response, physical impact, psychological impact, recovery and reconstruction [4]. Emergency planners, government relief agencies and community-based organizations would benefit from applying a gender-based analysis to their work. By understanding the particular ways that women are likely to be affected by a disaster or an emergency and the contributions that women typically make to coping with and recovering from such events, we can ensure that our communities are better prepared to manage should the worst happen [16].

In this review we're focused on the gender aspects of disaster. Describing the general effects of disasters on gender, it does not pretend to cover every contingency.

In this article we address one important, yet hitherto relatively neglected aspect of disasters, namely the gendered nature of disaster vulnerability as revealed by gender-specific disaster mortality [9]. Women's health is an important, yet inadequately addressed aspect of disaster planning [7]. Anderson (2000) in a World Bank publication on managing disaster risk, is adamant that ''much more research is needed to fully understand the extent to which gender plays a role in differential casualty rates'' [9]. With the support of leading UN authorities, disaster research and planning in many parts of the world are moving to think more about gender. There is growing recognition that gender is a cross-cutting principle in the disaster cycle [16].

Women and men, girls and boys may go through the same disaster, but they are likely to experience it differently [16]. We explain the differential impact of natural disasters on female relative to male life expectancy not merely by recourse to different physical exposures and biological or physiological gender differences, but also by the different socially constructed vulnerabilities that derive from the social roles men and women assume, voluntarily or involuntarily, as well as existing patterns of gender discrimination [9].

Some authors address the specific vulnerability of girls and women with respect to mortality from natural disasters and their aftermath. Biological and physiological differences between the sexes are unlikely to explain large-scale gender differences in mortality rates [5,9]. Studies show that women, boys and girls are 14 times more likely than men to die during a disaster [3,11].

The health of women and men is affected differently during disasters due to factors which intensify individual, social and economic vulnerabilities [8]. The higher women's socioeconomic status, the weaker is this effect on the gender gap in life expectancy. Taken together their results show that it is the socially constructed gender-specific vulnerability of females

built into everyday socioeconomic patterns that lead to the relatively higher female disaster mortality rates compared to men [9].

Not only are women differently affected than men by disasters, but also different groups of women will have different needs and will respond differently in the midst of emergencies [16]. For example: Poor or low-income women, Senior women/frail elders, Women living with chronic health conditions, Women living with disabilities, Women heading households, Single mothers, Widows, Refugee women, Homeless women, Aboriginal women, Minority women, Immigrant women, Women with language barriers, Isolated women, Rural women, Women with large families, Battered women/women at risk of violence, Orphaned girls, Girls with heavy caregiving responsibilities [6].

Psychological responses to disasters include short-term effects such as shock, anxiety, sleep disturbances and guilt. There are differences between women and men and girls and boys in the nature of psychological impact [4]. For instance women and men may face different health risks: men are statistically more likely than women to suffer heart disease and their risks of heart attack may be increased by the stress of an emergency [16]. Several studies have found that a greater proportion of women and girls report suffering from emotional disorders and distress as compared to men and boys [4]. Although the appearance of postdisaster psychological symptoms in adults varies, the incidence of psychopathology in women and children is high after disasters [2]. Postdisaster stress symptoms are often but not universally reported more frequently by women than men [4,5].

Although a "one-size fits all" emergency plan is difficult to apply to all disasters, there are common distresses experienced by all pregnant women regardless of the nature of the disaster. Pregnant women, infants, and children are adversely affected by disasters resulting in an increased number of infants with intrauterine growth restriction, low birth weight, and a small head circumference. There is an increased incidence of preterm delivery. During a disaster, women who are not breastfeeding may have difficulty in providing food for their newborns. Some new mothers may plan to bottle-feed their newborns [7,8,12].

Although hard evidence on the influence of disasters on domestic and sexual violence is limited, several field reports suggest that the safety of women experiencing violence in the home may be compromised in the aftermath of disaster and they may not have access to disaster relief and recovery resources [4]. Because women involved in disasters are also at increased rates of sexual and domestic violence, there should be provided a safe and secure environment in evacuation shelters [5,8,12,15]. Moreover, gender roles dictate that women become the primary caretakers for those affected by disasters – including children, the injured and sick, and the elderly – substantially increasing their emotional and material work load. Women's vulnerability is further increased by the loss of men and/or livelihoods, especially when a male head of household has died and the women must provide for their families [4,5,15].

Women are portrayed as the victims of disaster, and their central role in response to disaster is often overlooked [5]. Women should be included in all stages of disaster planning to help to ensure a gender-balanced response, and organizations should continue to strive to implement tools such as those in the Sphere Handbook in their relief efforts. Addressing these issues can assist relief organizations with improving the quality and efficacy of the care that they deliver to the female patient population [7].

To target scarce resources effectively, disaster practitioners should be aware of gender patterns in disaster, and respond appropriately. Seeing disaster through a gender lens can help identify key issues for policymakers, planners and practitioners, expose critical system gaps, and bring a gender focus into the analysis of disaster mitigation and response [5].

The results of literature review show that the socially constructed gender-specific vulnerability of females lead to the relatively higher female disaster mortality rates compared to men; the disaster impact differ across economic class, ethnicity, gender and other factors; natural disasters exacerbate previously existing patterns of discrimination that render females more vulnerable to the fatal impact of disasters. The adverse impact of disasters on females relative to men vanishes with rising socio-economic status of women. However, more inter-disciplinary research is needed to fully understand the interplay between mortality and gender in the presence of natural disasters. More research is needed to fully understand why and how disaster strength interacts with female mortality.

REFERENCES

1. Alexander D.A., Klein S., First Responders after Disasters: A Review of Stress Reactions, At-Risk, Vulnerability, and Resilience Factors Prehospital and Disaster Medicine 2009; 3-4: 87-94.
2. Corrarino J.E. Disaster-related mental health needs of women and children. MCN Am J Matern Child Nurs. 2008; 33(4):242-8.
3. Disaster and gender statistics; 17.VI. 2009; http://cmsdata.iucn.org/downloads/disaster_and_gender_statistics.pdf
4. Gender and Health in Disasters; World Health Organization, 2002.
5. Gender, Women and Heath; http://www.searo.who.int/en/Section13/Section390_8282.htm
6. How Gender Factors Put Women at Increased Risk; Improving Women's Health – Before, During and After Disasters 2012; www.whealth.com.au
7. Miller A.C., Arquilla B. Disasters, Women's Health, and Conservative Society: Working in Pakistan with the Turkish Red Crescent following the South Asian Earthquake. Prehospital and Disaster Medicine 2007; 271-273.
8. Natural Disasters, Gender and Health: Maximizing the Role of Women in Disaster Response and Recovery. Wood, Lindsay Martin (2011) http://d-scholarship.pitt.edu/9900/
9. Neumayer E., Plümper Th. The Gendered Nature of Natural Disasters: The Impact of Catastrophic Events on the Gender Gap in Life Expectancy, 1981–2002. Annals of the Association of American Geographers 2007; 97(3): 551–566.
10. Peleq K. Disasters and emergency situations: what have we learned from the past to prepare for the future? Harefuah 2010; 149(7):410-2.
11. Phillips B.D. Gender and disasters: women and men experience disasters in different ways, challenging employers to design disaster preparedness strategies that meet the needs of both genders. 2005.
12. Preparing for Disasters: Perspectives on Women; Committee opinion. number 457.1 -4; june2010.
13. Sheridan K. Post-disaster health woes plague New Orleans. http://www.physorg.com April 3, 2011
14. Types of Disasters and Their Consequences; American Public Health Association © 2005 http://www.medscape.com/viewarticle/513258
15. United States National Action Plan on Women, Peace, and Security; 2011; http://www.whitehouse.gov
16. Women in emergencies and disasters; Women and Health Care Reform 2009; www.womenandhealthcarereform.ca

SUMMARY

MAINSTREAMING GENDER IN DISASTER (REVIEW)

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The results of literature review show that the socially constructed gender-specific vulnerability of females lead to the relatively higher female disaster mortality rates compared to men; the disaster impact differ across economic class, ethnicity, gender and other factors; natural disasters exacerbate previously existing patterns of discrimination that render females more vulnerable to the fatal impact of disasters. The adverse impact of disasters on females relative to men vanishes with rising socio-economic status of women. However, more inter-disciplinary research is needed to fully understand the interplay between mortality and gender in the presence of natural disasters. More research is needed to fully understand why and how disaster strength interacts with female mortality.

Keywords: disaster; gender; health.

РЕЗЮМЕ

ГЕНДЕРНЫЕ АСПЕКТЫ КАТАСТРОФ (ОБЗОР)

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Результаты анализа литературных данных показали, что последствия стихийного бедствия зависят от экономического благосостояния. Неблагоприятные воздействия стихийных бед-

ствий на женщин по сравнению с мужчинами зависят от социально экономического статуса женщин. Социально детерминированная уязвимость женщин при катастрофах приводит к более высокой их смертности, чем среди мужчин. Однако для того, чтобы понять взаимосвязь между смертностью и полом при стихийных бедствиях, необходимо провести междисциплинарные исследования в области медицины и социальных наук.

რეზიუმე

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თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი,საგანგებო სიტუაციებზე სამედიცინო რეაგირებისა და მართვის სასწავლო ცენტრი; ციტოლოგიის, ჰისტოლოგიისა და ემბრიოლოგიის დეპარტამენტი; საქართველოს შრომის, ჯანმრთელობისა და სოციალური დაცვის სამინისტრო,საგანგებო სიტუაციების კოორდინაციისა და რეჟიმის დეპარტამენტი

თანამედროვე პირობებში ადამიანი მუშაობს და ცხოვრობს პოტენციური საფრთხის შემცველ გარემოში. რთული საგანგებო სიტუაციები, სტიქიური და ანთროპოგენული კატასტროფები მნიშვნელოვან გავლენას ახდენენ საზოგადოებრივ ჯანმრთელობასა და უსაფრთხოებაზე. გაეროს განმარტებით, კატასტროფა არის საზოგადოების ფუნქციონირების მნიშვნელოვანი ნგრევა, რომელიც იწვევს ადამიანების, ფინანსებისა და გარემოს ფართომაშტაბიან დაზიანებას,რაც სცილდება ადამიანების შესაძლებლობას გაუმკლავდნენ არსებულ სიტუაციას საკუთარი რესურსების გამოყენე-ბით. საგანგებო სიტუაციების გენდერული ასპექტები ბოლომდე არ არის გაანალიზებული. არსებული ლიტერატურული მონაცემების საფუძველზე, სტატიაში აღნიშნულია, რომ არსებობს გარკვეული მტკიცებულებანი, რომლებიც ქალსა და მამაკაცზე საგანგებო სიტუაციების განსხვავებულ ზეგავლენაზე მიუთითებს,რაც სოციალურ, ასაკობრივ თუ ჯანმრთელობის მხრივ განსხვავებულ ქალთა ჯგუფებზეც ვრცელდება. სტატიაში წარმოდგენილი არსებული ლიტერატურის მიმო-ხილვის მიზანია – საგანგებო სიტუაციების გენდერული ასპექტების ზოგადი განხილვა. გამოტანილია დასკვნა, რომ აღნიშნული თემის გარშემო არსებული ლიტერატურის მიმოხილვა მიუთითებს საგანგებო სიტუაციების გენდერული ასპექტების მნიშვნელობაზე, რაც აუცილებელ წინაპირობას წარმოადგენს საგანგებო სიტუაციების სწორი სამედიცინო მართვის სტრატეგიის შემუშავებისათვის.

РОЛЬ НЕЙРОЭНДОКРИННЫХ МЕДИАТОРОВ В РЕГУЛЯЦИИ АКТИВНОСТИ Т-КЛЕТОК

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Антитела, высвобождаемые Т-клетками, являются значимым компонентом адаптационного иммунитета, участвующим в механизмах антимикробной, антивирусной защиты организма, патогенезе аутоиммунных заболеваний, как-то: рассеянный склероз, ревматоидный артрит, красная волчанка

и др. [3]. Активность Т-клеток является критической при развитии различных физиологических (беременность) и патологических процессов [13]. Функционирование иммунной системы в значительной мере зависит от баланса лимфоцитов, их функциональной активности, пролиферации и гибели. С целью регуляции функциональной активности лимфоцитов, протекторного и повреждающего действия Т-клеточных антител в иммунной системе выработан ряд ауторегуляторных механизмов, основанный на взаимодействии иммунных клеток с медиаторами нервной и эндокринной систем [6,7], которые обеспечивают поддержание гомеостаза и регуляцию иммунного ответа при различных заболеваниях. Эта регуляция осуществляется посредством модуляции активности различных рецепторов, экспрессируемых на поверхности клеток, в частности, β-адренергических рецепторов, сопряженных с аденилатциклазной системой, генерирующей cAMP [12] и рецепторов, чувствительных к прогестерону (прогестероновые и σ-рецепторы) [2].

Целью исследования явилось определение роли некоторых медиаторов нейроэндокринной системы (агонисты и антагонисты β-адренорецепторов, прогестерон) в регуляции активности Т-клеток.

Материал и методы. *Клеточная культура:* Исследования проведены на культуре лейкемия-трансформированных Т-клетках, т.н. Jurkat клетках (DSMZ-Deutshe Sammulung von Mikroorganismen und Zellkulturen, Германия). Клетки размножали в биоактивной влажной среде, содержащей RPMI 1640 (GIBSO), инактивированную эмбриональную телячью сыворотку (Sigma), L-глутамин (4mM), пенициллин (100ед/мл) и стрептомицин (100ед/мл) при температуре 37^0C и 5% CO_2. Эксперименты проводили при концентрации клеток Jurkat 0,3-0,6 x 10^6 в 1 мл среды.

Клетки Jurkat ($4x10^5$ клеток/мл) стимулировали посредством 50 μг/мл фитогемаглутинина A (PHA) при 37^0C в течение 5 минут. Затем PHA удаляли центрифугированием, клетки отмывали 3 раза, добавлением RPMI-1640, ресуспендировали, переносили в ячейки (25000 клеток/ячейка) и культивировали в течение 24 часов отдельно, или совместно с агонистом β-адренергических рецепторов, изопротеренолом (в концентрации 10^{-5} M, 10^{-6} M), либо антагонистом β-адренергических рецепторов, пропанололом (в концентрации 10^{-5} M, 10^{-6} M) или прогестероном (в концентрации 0,07 μл, 0,7 μл), добавляемых в среду инкубации Jurkat клеток; жизнеспособность клеток Jurkat определяли посредством MTT теста.

В основе MTT теста лежит расщепление 3-(4,5-диметилтиазол-2-ил)-2,5-дифенилтетразол бромида (MTT) в имеющий голубую окраску формазан, посредством митохондриальных дегидрогеназ. После 24-часовой инкубации клетки 2 раза промывали инкубационной средой с HEPES-буффером (HBM; 140 mM NaCl, 5 mM KCl, 5 mM $NaHCO_3$, 1.1 mM $MgCl_2$, 1.2 $CaCl_2$, 5.5 mM глюкоза, и 20 mM HEPES, pH 7.4) и инкубировали в течение 45 минут при температуре 37^0 C в HBM содержащем MTT (0.5 мг/мл). Затем HBM отделяли и продукт голубого формазана растворяли в 300 μл 100% диметилсулфоксида (DMSO). Интенсивность поглощения (A) измерялась при длине волны 570 нм.

Коэффициент жизнеспособности клеток рассчитывался по формуле: $K=A_{эксп.}/A_{контроль}$,

MTT-тест предоставляет информацию об активности митохондриальных дегидрогеназ и, соответственно, жизнеспособности клеток.

Результаты исследования обрабатывали статистически с помощью программного пакета SPSS v11.0. Критерий Стьюдента использовался с целью анализа достоверности разницы между значениями параметров; разница значений в интервале $p<0,05$ считалась статистически достоверной.

Результаты и их обсуждение. β-адренорецепторы под воздействием эндогенных и экзогенных стимулов инициируют каскад биохимических реакций и межмолекулярных взаимодействий и модулируют активность клеток. Механизм их действия включает G-белок-опосредованную активацию аденилатциклазы, внутриклеточную аккумуляцию цАМФ, активацию протеинкиназы A (PKA), которая посредством фосфорилирования регулирует активность многочисленных мишеней (тирозин и серин-треониновые киназы), конституционно связанных с CRE-ом (cAMФ ответственный элемент), транскрипционных факторов, участвующих в регуляции транскрипции генов [8].

Результаты наших исследований показали, что агонист β-адренорецепторов, изопротеренол, не

влияет на активность митохондриальных дегидрогеназ в интактных клетках и способствует их незначительной активации (на 12%) в митоген-активированных клетках Jurkat (рис. 1).

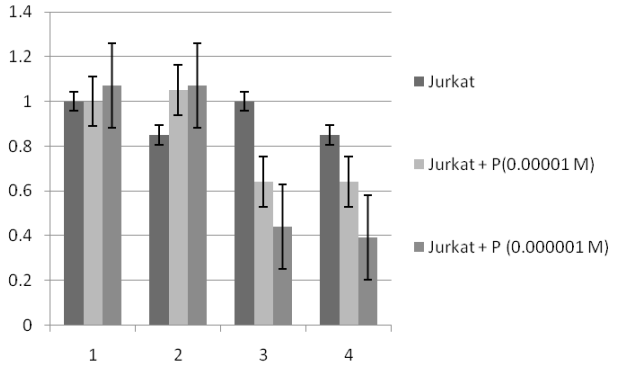

Рис. 1. Жизнеспособность клеток Jurkat под воздействием агониста и антагониста β-адренорецепторов (Р – препарат)
1 – интактные клетки+изопротеренол;
2 - Jurkat+PHA +изопротеренол;
3 – интактные клетки Jurkat+пропанолол;
4 - Jurkat+PHA+пропанолол

В более ранних исследованиях [1] показано, что изопротеренолиндуцированное (в концентрации 10^{-5} М-10^{-4}М) возрастание уровня cAMP в лимфоцитах обуславливает снижение их пролиферативной активности. Позднее выявлено, что экзогенное добавление cAMP способно подавить пролиферацию PHA-стимулированных лимфоцитов только в первые часы стимуляции. Низкие концентрации изопротеренола (10^{-6}–10^{-9} М) обладают противоположным эффектом - способствуют незначительному пролонгированному повышению уровня пролиферации. Вышеприведенные данные свидетельствуют о том, что активированные β-AR дозо- и времязависимо участвуют в регуляции пролиферативной активности Т-клеток. Наши данные не противоречат данным литературы [1], отклонения в дозах, очевидно, обусловлены различными условиями экспериментов.

Антагонист β-адренорецепторов, пропранолол способствует значительному снижению активности митохондриальных дегидрогеназ и, следовательно, жизнеспособности как интактных (40-60%), так и митогенстимулированных клеток Jurkat (20-40%). Цитотоксическая активность β-блокаторов выявлена и в других исследованиях на различных типах клеток [4,5]. Известно, что для активации митохондриальных дегидрогеназ необходимо увеличение содержания ионов Ca^{2+} [9]. Takemura H и соавторы показали, что β-адренорецепторзависимая мобилизация кальция в клетках Jurkat осуществляется посредством активации cAMP и IP_3 [11]. Таким образом, цитотоксическая активность β-адреноблокаторов может быть обусловлена блокированием cAMP-зависимой мобилизацией Ca^{2+} в митохондриях с последующим снижением активности их дегидрогеназ, а значит и жизнеспособности клеток Jurkat. Возможные нарушения активности иммунной системы необходимо учитывать при использовании β-адреноблокаторов для лечения различных заболеваний.

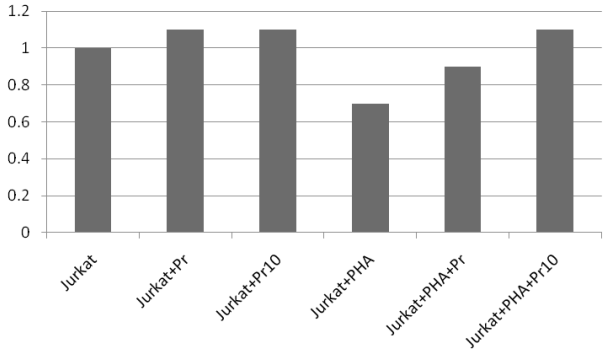

Рис. 2. Жизнеспособность клеток Jurkat под воздействием прогестерона

В результате наших исследований показано, что жизнеспособность интактных клеток Jurkat не изменялась на фоне воздействия прогестерона; добавление прогестерона к PHA-стимулированным клеткам Jurkat способствует дозозависимому увеличению жизнеспособности клеток (рис. 2).

Прогестерон – важнейший гормон, необходимый для поддержания беременности. Во время физиологической беременности большое количество прогестерона синтезируется в плаценте, что способствует увеличению уровня прогестерона в крови в 4-6 раз по сравнению с уровнем у небеременных женщин. Известно, что значимая роль прогестерона в развитии беременности обусловлена его участием в регуляции функциональной активности Т-клеток [2,10]. На основании результатов проведенных нами экспериментов, предполагаем, что недостаток прогестерона в крови у женщин с патологическим течением беременности может нарушить активность клеточного иммунитета, что, в свою очередь, создает угрозу неблагоприятного исхода.

Таким образом, следует заключить, что жизнеспособность Т-клеток, т.е. их функциональная активность, в значительной мере чувствительна к воздействию β-адреноблокаторов и прогестерона. Эти данные необходимо учитывать при клиническом применении соответствующих препаратов.

ЛИТЕРАТУРА

1. Carlson et al. Preventing amsacrine-induced cardiac arrhythmias. J Clin Oncol. 1989; 5(12):2041.
2. De León-Nava M.A., Nava K., Soldevila G., López-Griego L., Chávez-Ríos J.R., Vargas-Villavicencio J.A., Morales-Montor J. Immune sexual dimorphism: effect of gonadal steroids on the expression of cytokines, sex steroid receptors, and lymphocyte proliferation. J Steroid Biochem Mol Biol. 2009.
3. Goodnow C.C. Balancing immunity, autoimmunity, and self-tolerance. Ann N Y Acad Sci. 1997; 815:55-66.
4. Hajighasemi F. Abbas Mirshafiey Propranolol effect on proliferation and vascular endothelial growth factor secretion in human immunocompetent cells. Journal of Clinical Immunology and Immunopathology Research 2009; 2(2): 22-27.
5. Kastelova A., Dimova S., Nemery B. Propranolol cytotoxicity in rat and human lung in vitro. Methods Find Exp Clin Pharmacol. 2003;25(7):509-15.
6. Kin N.W., Sanders V.M. It takes nerve to tell T and B cells what to do. Leukoc. Biol. 2006;79: 1093-1104.
7. Kohm A., Sanders V., Norepinephrine and β2-Adrenergic Receptor Stimulation Regulate CD4+ T and B Lymphocyte Function in Vitro and in Vivo. Pharmacol Rev. 2001; 53(4): 487–525.
8. Montminy M. Transcriptional regulation by cyclic AMP. Annu Rev Biochem. 1997;66:807-22.
9. Nichols B.J., Denton R.M. Towards the molecular basis for the regulation of mitochondrial dehydrogenases by calcium ions. Mol Cell Biochem. 1995; 150: 203–212.
10. Raghupathy R. Manipulation of cytokine production profiles as a therapeutic approach for immunologic pregnancy loss. Indian J Biochem Biophys. 2008; 45(4):229-36.
11. Takemura H., Hatta Sh., Yamada K., Ohsika H. β-adrenergic receptor-mediated calcium mobilozationn in the human Jurkat T cell line. Life Science 1995; 56(18): 1443-1454.
12. Takemura H., Hatta Sh., Yamada K., Ohashika H. β-adrenergic receptor-mediated calcium mobilization in the human Jurkat cell line. Life Science 1998; 18: 1443-1454.
13. Xu B., Nakhla S., Makris A., Hennessy A. TNF-α inhibits trophoblast integration into endothelial cellular networks. Placenta 2011;32(3):241-6.

SUMMARY

THE ROLE OF NEUROENDOCRINE MEDIATORS IN REGULATORY ACTIVITY OF T-CELLS

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The aim of the study was to establish the role of some neuroendocrine mediators (agonists and antagonists of β-adrenergic receptors, progesterone) in regulating T-cells activity.

Studies conducted on the culture of leukemiatransformed T-cells (Jurkat cells) (DSMZ-Deutshe Sammulung von Mikroorganismen und Zellkulturen (Germany)). Jurkat Cells ($4x10^5$ cells/ml) stimulated with 50 μg/ml fitogemaglutinin A (PHA) at 37^0C for 5 minutes and then incubated for 24 hours alone, or together with β- adrenergic receptors agonist izopretonolom (at dose of 10^{-5} M, 10^{-6} M), an antagonist, propranolol (dose of 10^{-5} M, 10^{-6} M) and progesterone (dose 0,07 μl, 0,7 μl) added to the incubation medium. The viability of Jurkat cells was determined by MTT test. It was shown that β-adlenoretseptors agonist, izoprotenol didn't affect the activity of mitochondrial dehydrogenases in intact and contributed to their low activation (12%) in the mitogen-activated Jurkat cells. β-adrenergic receptors antagonist, propranolol, promotes a significant reduction in activity of mitochondrial dehydrogenases, and hence the viability of both intact (40-60%) and mitogenstimulated Jurkat cells (20-40%). Viability of intact Jurkat cells didn't change, and dose-dependently increased in PHA-stimulated Jurkat cells durng progesterone exposure.

It was concluded that viability of the T-cells and hence their functional activity is largely sensitive to the influence of the β-adrenoceptor antagonists and progesterone. These data should be considered in the clinical application of appropriate drugs.

Keywords: T cells activity, neuroendocrine mediators.

РЕЗЮМЕ

РОЛЬ НЕЙРОЭНДОКРИННЫХ МЕДИАТОРОВ В РЕГУЛЯЦИИ АКТИВНОСТИ Т-КЛЕТОК

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Регуляция функциональной активности Т-лимфоцитов в организме осуществляется посредством взаимодействия иммунных клеток с медиаторами нервной и эндокринной систем.

Целью исследования явилось определение роли некоторых медиаторов нейроэндокринной системы (агонисты и антагонисты β-адренорецепторов, прогестерон) в регуляции активности Т-клеток.

Исследования проведены на культуре лейкемия-трансформированных Т-клетках - Jurkat клетки (DSMZ-Deutshe Sammulung von Mikroorganismen und Zellkulturen, Германия). Клетки Jurkat ($4x10^5$ клеток/мл) стимулировали посредством 50 μг/мл фитогемаглутинин А (PHA) при 37^0 в течение 5 минут, а затем культивировали в течение 24 часов - отдельно или совместно с агонистом β-адренергических рецепторов, изопротеренолом (в концентрации 10^{-5} M, 10^{-6} M), их антагонистом, пропанололом (в концентрации 10^{-5} M, 10^{-6} M) и прогестероном (в концентрации 0,07 μл, 0,7 μл), добавляемых в среду инкубации клеток Jurkat. Жизнеспособность клеток Jurkat определялась с помощью MTT теста. Показано, что агонист β-адленорецепторов - изопротеренол, не влияет на активность митохондриальных дегидрогеназ в интактных клетках и способствует их незначительной активации (на 12%) в митогенактивированных клетках Jurkat. Антагонист β-адренорецепторов – пропранолол способствует значительному снижению активности митохондриальных дегидрогеназ и, следовательно, жизнеспособности как интактных (40-60%), так и митогенстимулированных клеток Jurkat (20-40%). Жизнеспособность интактных клеток Jurkat не изменялась и дозозависимо увеличивалась в PHA-стимулированных клетках Jurkat на фоне воздействия прогестерона.

На основании проведенного исследования следует заключить, что жизнеспособность Т-клеток, а значит их функциональная активность, в значительной мере чувствительна к воздействию β-адреноблокаторов и прогестерона, что необходимо учитывать при клиническом применении соответствующих препаратов и требует дальнейшего углубленного изучения.

რეზიუმე

ნეიროენდოკრინული მედიატორების როლი Т-უჯრედების აქტივობის რეგულაციაში

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Т-ლიმფოციტების ფუნქციური აქტივობის რეგულაცია ორგანიზმში ხორციელდება იმუნური უჯრედების ნერვული და ენდოკრინული სისტემების მედიატორებთან ურთიერთქმედების მეშვეობით.

კვლევის მიზანს წარმოადგენდა ზოგიერთი ნეიროენდოკრინული სისტემის მედიატორების (β-ადრენერგული რეცეპტორების აგონისტები და ანტაგონისტები, პროგესტერონი) როლის დადგენა Т-უჯრედების აქტივობის რეგულაციაში.

კვლევები ჩატარდა ლეიკემიატრანსფორმირებული Т-უჯრედების კულტურაზე - Jurkat უჯრედებზე (DSMZ-Deutshe Sammulung von Mikroorganismen und Zellkulturen, გერმანია). ვახდენდით Jurkat უჯრედების ($4x10^5$ უჯრედი/მლ) სტიმულირებას ფიტოგემაგლუტინინით (PHA) 50 μგ/მლ 37^0 ტემპერატურაზე 5 წუთის განმავლობაში და შემდგომ 24 საათიან ინკუბაციას ცალკე ან β-ადრენორეცეპტორების აგონისტთან – იზოპროტერენოლთან (კონცენტრაციაში 10^{-5} M, 10^{-6} M), ანტაგონისტთან – პროპანოლოლთან (კონცენტრაციაში 10^{-5} M, 10^{-6} M) da პროგესტერონთან (კონცენტრაციაში 0,07 μლ, 0,7 μლ), რომლებიც ემატებოდა Jurkat უჯრედების საინკუბაციო არეში. Jurkat უჯრედების სიცოცხლისუნარიანობას ვსაზღვრავდით MTT-ტესტის მეშვეობით. დადგინდა, რომ β-ადრენორეცეპტორების

აგონისტი – იზოპროტერენოლი არ მოქმედებს მიტოქონდრიული დეჰიდროგენაზების აქტივობაზე ინტაქტურ უჯრედებში და ხელს უწყობს მათ უმნიშვნელო აქტივაციას (12%) გააქტიურებულ Jurkat უჯრედებში; β-ადრენორეცეპტორების ანტაგონისტი პროპანოლოლი კი ხელს უწყობს მიტოქონდრიული დეჰიდროგენაზების აქტივობის მნიშვნელოვნად შემცირებას და,შესაბამისად, სიცოცხლისუნარიანობის დაქვეითებას ინტაქტურ (40-60%) და მიტოგენსტიმულირებულ Jurkat უჯრედებში (20-40%). ინტაქტური Jurkat უჯრედებში სიცოცხლისუნარიანობა უცვლელი რჩება, ხოლო PHA-სტიმულირებულ Jurkat უჯრედებში დოზადამოკიდებულად იზრდება პროგესტერონის ზემოქმედების ფონზე.

ჩატარებული კვლევის შედეგები უფლებას აძლევს ავტორებს დასკვნისა,რომ T-უჯრედების სიცოცხლისუნარიანობა და,შესაბამისად, მათი ფუნქციური აქტივობა მნიშვნელოვნად მგრძნობიარეა β-ადრენორეცეპტორების ანტაგონისტებისა და პროგესტერონის მიმართ. ეს მონაცემები ყურადსაღებია ამ პრეპარატების კლინიკური გამოყენების დროს.

SOME ASPECTS OF PATHOGENESIS OF NONALCOHOLIC FATTY LIVER DISEASE IN POSTMENOPAUSAL WOMEN

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Nonalcoholic fatty liver disease (NAFLD) - the most common chronic liver disease in developed countries is found in 12-48% of the population [15], includes a wide range of clinical and morphological disorders that are manifested in the liver starting with a simple reversible steatosis and in the non-specific inflammatory processes typical for alcoholic steatohepatitis [15,28]. Balloon degradation and reversible fibrosis of hepatocytes during the steatohepatitis develop into the cirrhosis (15%), characterized by a high mortality risk (3%) due to development of terminal failure in liver [22].

In view of the the reversibility of steatosis and steatohepatitis, their early diagnosis is one of the most significant problems of modern medicine [5,9,10,24]. The early identification of clinical and biochemical factors associated with NAFLD, the establishment of mechanisms of its transformation into a severe form of the disease will provide the prevention of its progression [6]

It should be noted the age- and gender-specificity of NAFLD [23]. It is established that the the disease is much more common among men and incidence increases with age. Among women aged 45-50 years NAFLD [1,19] (with the exception of young women with polycystic ovariesis) is rare and becomes more frequent in the age of postmenopause.

The aim of the study was the establishment features of the pathogenesis of NAFLD in postmenopausal women.

Material and methods. The study was conducted on postmenopausal women (n=5), with metabolic syndrome (diagnosis of metobolic syndrome posed in the presence of at least 2 of the characteristic markers for him (hypertension, obesity, dyslipidemia) and rate of ALT in the blood at least 4 times greater than its normal maximal value. According to the protocol women with possible causes of liver disease in history (B, C hepatitis, a positive test for antynucleatic antibodies,

diseases related to the violation liver metabolism and accumulation of iron and copper in the liver, deficiency of α_1-antitrypsin, the use of hepatotoxic drugs, excessive alcohol consumption (daily more than 20g) and increased concentration of GTT in the blood, patients with diabetes. applying hormone (estrogen) replacement. glukokrtikoids, aspirin, Ca-channels blockers therapy were excluded from the study. of the study were also excluded. Verification of the diagnosis of steatosis was based on ultrosonografic examination and histological analysis of liver bioptats obtained by biopsy.

In addition to collecting history, study of blood lipid profile and ALT, AST, estrogen content in patients enrolled in the study free nitric oxide content in the blood and liver bioptats was determined by Electron Paramagnetic Resonance (EPR) method.

The study protocol approved by the Ethics Committee of the Tbilisi State Medical University. Patients by written form confirmed their agreement to participate in the study.

Electron Paramagnetic Resonance (EPR) Study
Nitric oxide (NO) was measured by EPR spin labeling (radiospectrophotometer RE-1307 (X- band), with a modulation frequency of 50 KHZ and a TM-110 cavity). Diethyldithiocarbamic acid (DETC) (Sigma) was used as an NO trap. Blood and liver samples were incubated with $Fe^{2+}(DETC)_2$ stock solutions. The 0.8 mM Fe^{2+} (DETC) colloid solution formed was yellow-brown in color and was used immediately after preparation. EPR specters of NO-Fe^{2+} $(DETC)_2$ complexes were defined at the temperature of liquid nitrogen on a microwave power of 20 mVt. The amount of detected NO was determined from the calibration curve for integral intensity of the EPR signal of $NOFe^{2+}$ $(DETC)_2$, prepared at various concentrations (1-20 μM) of the NO-donor MAHMANONOate [11].

The obtained data were analyzed using SPSS 11.0 computer software. Normally distributed continuous variables were compared with repeated measure ANOVA, and the Kruskall-Wallis test compared abnormally distributed variables. The χ^2-test was used to assess associations among categorical variables.

Results and their discussion. Biochemical analysis of blood of women with metabolic syndrome, high level of ALT and ultrusonographycally proofed NAFLD are showed in the table. Level of lipoproteins, such as total cholesterol, LDL-cholesterol and triglycerides are generally increased in the serum of patients with NAFLD.

Table. Patients Clinical Characteristics and NO content

Parameters	Postmenopausal aged women with NAFLD	Postmenopausal aged healthy women
BM (kg/m^2)	33,0±3,4	23,4±2,6
LDL (mg/dl)	117,6±10,0	60,5±18,3
HDL (mg/dl)	34,2±6,4	42,0±10,6
TG (mg/dl)	214,6±11,2	105,1±14,5
Total Chol (mg/dl)	240,0±60,2	140,2±36,0
ALAT (U/l)	135,1±15,4	33,5±10,5
ASAT (U/l)	43,1±8,5	32,0±10,9
Estradiole (pg/ml)	2,13±0,75	2,13±0,75
NO In blood (mm/mg)	2,3±0,5	1,6±0,2
NO In liver (mm/mg)	1,8±0,12	

In patients' blood and liver bioptats EPR signal of spin-trapped free nitric oxide (NO) had been measured, these data of are shown in the Table. Correlative analysis between liver NO content and alteration of explores biochemical parameters of the blood revealed correlation between level of NO EPR signal intensity in liver bioptant and triglycerides content in blood of patients with NAFLD (r=0,96; p=0,009) (Fig.).

Liver steatosis accompanies hyper alimentation, obesity, metabolic syndromes, and hyperlipidemia [15,16]. Its development might be initiated by different mechanisms, including imbalanced of fatty acid supply, hyperglycemia, upset hormonal balance between hormones responsible for anabolic and catabolic activities in the portal circulation, and endotoxemia in starvation [4,8]. Oxidative stress that

damages mitochondria and induces peroxidation of lipids occurs in pathogenesis of chronic liver injury by different mechanisms (metabolic disturbances, iron deposition, high fatty acid concentrations).

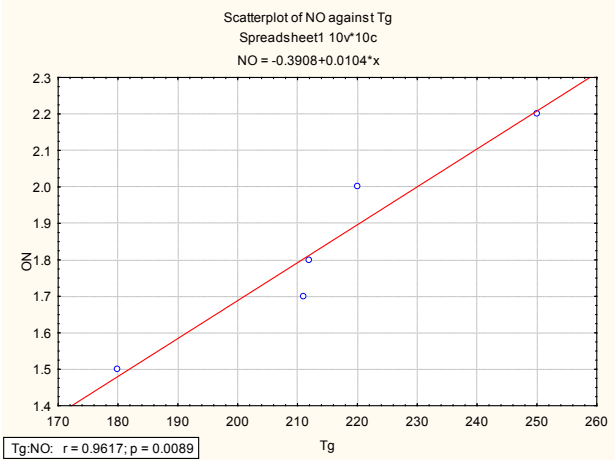

Fig. Correlation between liver NO content and alteration of explores biochemical parameters of the blood and alteration of triglicerides content in the blood

As reveals from the results of our study lipoproteins such as total cholesterol, LDL-cholesterol, and triglycerides are generally increased in the serum of patients with hepatosteatosis. Triglycerides, localized in the cytoplasm of hepatocytes, are the main component of lipids. Accumulation of lipids can result from insulin resistance, damaged disposal of triglycerides from the cells, β-oxidation damage in mitochondria, or very low density lipoproteins [18]. It has been suggested that free fatty acids can play a crucial role in steatosis intensification and development of necrotic-inflammatory processes. Lipids cytotoxicy is suggested to influence cell survival. Long term accumulation of free fatty acids may lead to hepatocyte necrosis or apoptosis [16]. Cellular free fatty acids show cytotoxic effects, such as elevation of cytochrome P450 activity [26], which belongs to the generators of reactive oxygen species and contributes to intensification of chronic oxidative stress, lipid peroxidation and progression of hepatostatosis [17]. Oxidative stress and oxidant-antioxidant imbalance may be part of the cytotoxic mechanisms leading to liver cell injury [2]. It was found that increase of the intracellular lipid peroxidation and oxidation of DNA correlates with the stage of necroinflammatory changes of steatosis in patients with NAFLD (17). In *in vitro* studies it was observed that free fatty acids administration results increase proapoptotic and antiproliferative effects in cells [27].

The pathophysiological role of NO is not specific for hepatosteatosis; involvement of NO has also been observed in chronic liver diseases [25]. Reports concerning the role of NO in liver damage during inflammatory conditions are contradictory. NO is a free radical with an unpaired electron allowing it to reduce other molecules and it may act as a potential antioxidant agent. It was found that NO protects against liver injury by scavenging lipid radicals and inhibiting the lipid peroxidation chain reaction [29]. Data according decrease of NO's level in non-alcoholic steatohepatitis might be due to intensification of oxidative stress [3].

On the other hand it was reported that iNOS-derived NO regulates proinflammatory *genes in vivo*, contributing to inflammatory liver injury [21]. Other investigators have reported that in the pathogenesis of NAFLD NO may potentiate cytotoxicity by reaction with superoxide anion to form peroxynitrite, a strong oxidant that promotes nitration of tyrosine to form nitrotyrosine [7,12].

In NAFLD patients serum levels of NO had been increased [14]; this may reflect the early stage of the disease in most of NAFLD patients where NO may have a protective role. At the beginning of hepatic injury, when only a small amount of NO is being produced, it may protect the liver through vasodilatatory, antioxidative, and antiapoptotic effects. However, in the presence of massive injury (egg, high level of ptooxidants and elevated oxidative stress), greatly increased NO production might induce progression of irreversible necrosis and cell death in the hepatocytes to [13].

According above mentioned discussion it is clear that reactive oxygen and nitrogen species play important role in the pathogenesis of NAFLD. On the first stages of hepatosteatoss in moderate oxidative stress conditions NO reveal its antioxidant effects and provides hepatocytes defense. But increase intensity of oxidative stress promotes expression of iNOS, which generates NO in high concentrations. In these conditions transformation of NO in cytotoxic peroxintrite takes plays with following cellular damage and NAFLD progression.

It should be noted inhibitory effect of estrogens on the iNOS activity and lipid metabolism [18]. They increase hepatic expression of the apoprotein genes

and the LDL receptors and decrease the transcription of the Lipoprotein Lipase (LPL) gene through plasma membrane estrogen receptors (ERα-s).

So it may be concluded that lack of estrogens in postmenopausal women associates with- impairment of LPL activity and accumulation of triglycerides and free fatty acids n the liver, which in conditions of oxidative stress reveal their cytotoxity. Increase expression of iNOS (induced by citotoxic stimulus) stipulates generation excess amounts of nitric oxide and manifestation of its toxic activity in oxidative stress conditions. Both of these estrogen dependent factors promote progression of NAFLD in postmenopausal women.

REFERENCES

1. Angulo P, Keach JC, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. Hepatology 1999; 30:1356–1362.
2. Atamer A, Bilici A, Yenice N, Selek S, Ilhan N, Atamer Y. The importance of paraoxonase 1 activity, nitric oxide and lipid peroxidation in hepatosteatosis. J Int Med Res. 2008; 36(4):771-6.
3. Baskol G, Baskol M., Kacer D. Oxidative stress and antioxidant defence in serum of patients with non-alcoholc steatohepatitis. Clin Biochem. 2007; 40: 776-780.
4. Browning JD, Horton JD. Molecular mediators of hepatic steatosis and liver injury. J Clin Invest 2004; 114: 147-152.
5. Bugianesi E, Gentilcore E, Manini R, Natale S, Vanni E, Villanova N, David E, Rizzetto M, Marchesini G. A randomized controlled trial of metformin versus vitamin E or prescriptive diet in nonalcoholic fatty liver disease. Am J Gastroenterol 2005; 100: 1082–1090.
6. Clark JM The epidemiology of nonalcoholic fatty liver disease in adults**,** J Clin Gastroenterol - 01-MAR-40 2006; Suppl 1: 5-10.
7. Clemens MG. Nitric oxide and liver injury. Hepatology 1999; 30:1-5.
8. Dam-Larsen S, Franzmann M, Andersen IB, Christoffersen P, Jensen LB, Sorensen TI, Becker U, Bendtsen F. Long term prognosis of fatty liver: risk of chronic liver disease and death. Gut 2004; 53: 750-755.
9. Dixon JB, Bhathal PS, Hughes NR, O'Brien PE. Nonalcoholic fatty liver disease: improvement in liver histological analysis with weight loss. Hepatology 2004; 39:1647–1654.
10. Drenick EJ, Simmons F, Murphy JF. Effect on hepatic morphology of treatment of obesity by fasting, reducing diets and small-bowel bypass. N Engl J Med 1970; 282:829–834.
11. Fink B, Dikalov S, Fink N.ESR techniques for the detection of nitric oxide in vivo as an index of endothelial function. Pharmacol Rep. 2006; 58 Suppl:8-15.
12. Garcia-Monzon C, Majano PL, Zubia I, Sanz P, Apolinario A, Moreno-Otero R. Intrahepatic accumulation of nitrotyrosine in chronic viral hepatitis associates with histological severity of liver disease. J Hepatol 2000;32: 331-338.
13. Hon WM, Lee KH, Khoo HE. Nitric oxide in liver diseases. Ann NY Acad Sci 2002;962:275-295
14. Koruk Mehmet, Seyithan Taysi, M. Cemil Savas, Omer Yilmaz, Fatih Akcay, and Metin Karakok, Oxidative Stress and Enzymatic Antioxidant Status in Patients with Nonalcoholic Steatohepatitis. Annals of Clinical & Laboratory Science 2004; 34.
15. Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ: Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology 1999; 116:1413–1419.
16. Miner JL, Cederberg CA, Nielsen MK, Chen X, Baile CA. Conjugated linoleic acid (CLA), body fat, and apoptosis. Obes Res 2001; 9: 129-134.
17. Perlemuter G, Davit-Spraul A, Cosson C, Conti M, Bigorgne A, Paradis V, Corre MP, Prat L, Kuoch V, Basdevant A, Pelletier G, Oppert JM, Buffet C. Increase in liver antioxidant enzyme activities in non-alcoholic fatty liver disease. Liver Int 2005; 25: 946-953.
18. Pfeilschifter J., Ditz R., Pfohl M., Schatz H. Changes in Proinflammatory Cytokine Activity after Menopause. Endocrine Reviews. 2002; 23(1):90.
19. Ratziu V, Giral P, Charlotte F, Bruckert E, Thibault T, Theodorou I, Khalil L, Turpin G, Opolon P, Poyard T. Liver fibrosis in overweight patients. Gastroenterology 2000; 118:1117–1123.
20. Sanyal AJ, Campbell-Sargent C, Mirshahi F, Rizzo WB, Contos MJ, Sterling RK, Luketic VA, Shiffman ML, Clore JN. Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities. Gastroenterology 2001; 120: 1183 -1192.
21. Sass GK, Koerber R, Bang R et al. Inducible nitric oxide synthase is critical for immune-mediated liver injury in mice. J Clin Invest 2001;107:439-447.
22. Sheth SG, Gordon FD, Chopra S: Nonalcoholic steatohepatitis. Ann Intern Med 1997; 126:137–145.

23. Tobari M, Hashimoto E, Kabutake A, et al. Gender-specific clinicopathological features in nonalcoholic steatohepatitis. Gastroenterology 2007; 132:815.
24. Ueno T, Sugawara H, Sujaku K, Hashimoto O, Tsuji R, Tamaki S, Torimura T, Inuzuka S, Sata M, Tanikawa K Therapeutic effects of restricted diet and exercise in obese patients with fatty liver. J Hepatol 1997; 27:103–107.
25. Videa LA, Rodrgo R, Araya I et al. Oxidatve stress and depletion of hepatic kong-chan polysaturated fatty acids may contribute to nonalcoholic fatty liver dsease. Free Radical Bol. Med., 2004; 37: 1499-1507.
26. Weltman MD, Farrell GC, Hall P, Ingelman-Sundberg M, Liddle C. Hepatic cytochrome P450 2E1 is increased in patients with nonalcoholic steatohepatitis. Hepatology 1998; 27: 128 -133.
27. Yasui Y, Hosokawa M, Sahara T, Suzuki R, Ohgiya S, Kohno H, Tanaka T, Miyashita K. Bitter gourd seed fatty acid rich in 9c,11t,13t-conjugated linolenic acid induces apoptosis and up-regulates the GADD45, p53 and PPARgamma in human colon cancer Caco-2 cells. Prostaglandins Leukot Essent Fatty Acids 2005; 73: 113-119.
28. Younossi ZM, Gramlich T, Liu YC, Matteoni C, Petrelli M, Goldblum J, Rybicki L, McCullough AJ: Nonalcoholic fatty liver disease: assessment of variability in pathologic interpretations. Mod Pathol. 1998; 11:560-565.
29. Zhu W, Fung PC. The roles played by crucial free radicals like lipid free radicals, nitric oxide, and enzymes NOS and NADPH in CCl4-induced acute liver injury of mice. Free Rad Biol Med. 2000; 29:870-880.

SUMMARY

SOME ASPECTS OF PATHOGENESIS OF NONALCOHOLIC FATTY LIVER DISEASE IN POSTMENOPAUSAL WOMEN

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In view of the reversibility of steatosis and steatohepatitis, their early diagnosis is one of the most significant problems of modern medicine. The aim of the study was the establishment futures of the pathogenesis of NAFLD in postmenopausal women.

The study was conducted on postmenopausal women (n=5), with metabolic syndrome and rate of ALT in the blood at least 4 times greater than its normal maximal value. Patients had to fulfill the following inclusion criteria: at least 12 month of amenorrhea. Verification of the diagnosis of NAFLD was based on abdominal ultrosonografic examination. In addition to collecting history, study of blood lipid profile and ALT, AST, estrogen content in patients enrolled in the study free nitric oxide content in the blood and liver bioptants was determined by Electron Paramagnetic Resonance (EPR) method. The study protocol approved by the Ethics Committee of the Tbilisi State Medical University. Patients by written form confirmed their agreement to participate in the study.

In patients with NAFLD levels of total cholesterol, LDL-cholesterol and triglycerides were generally increased in the blood serum, direct correlation revealed between level of NO EPR signal intensity in liver bioptat and triglycerides content in blood (r=0,96; p=0,009). It was concluded that estrogen-dependent factors, such as impaired lipid metabolism and increase expression of iNOS induce accumulation of triglycerides and free fatty acids in the liver, generation excess amounts of NO, which in oxidative stress reveal their cytotoxity and promote progression of NAFLD in postmenopausal women.

Keywords: nitric oxide, metabolic syndrome, nonalcoholic fatty liver disease, estrogens, postmenopausal women.

РЕЗЮМЕ

НЕКОТОРЫЕ АСПЕКТЫ ПАТОГЕНЕЗА БЕЗАЛКОГОЛЬНОГО СТЕАТОГЕПАТИТА У ЖЕНЩИН ПОТМЕНОПАУЗНОГО ВОЗРАСТА

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Ранняя диагностика стеатоза и стеатогепатита, ввиду их обратимости, является одной из важнейших проблем современной медицины.

Целью исследования явилось установление особенностей патогенеза безалкогольного стеатогепатита у женщин постменопаузного возраста.

В исследовании участвовали женщины постменопаузного возраста (n=5) с метаболическим синдромом и содержанием ALT в крови, почти в 4 раза превышающим максимальный показатель нормы. Помимо сбора анамнеза, определения липидного спектра, содержания АЛТ, АСТ, эстрогенов в крови и биоптатах печени исследовали также уровень свободного оксида азота (NO) методом электронного парамагнитного резонанса (ЭПР). Протокол исследования утвержден Этическим комитетом Тбилисского государственного медицинского университета. В письменной форме подтверждено информированное согласие пациентов на участие в исследовании.

В результате проведенного исследования у женщин с безалкогольным стеатогепатитом в сыворотке крови выявлено повышение уровня липопротеинов, общего холестерина, липопротеидов низкой плотности и триглицеридов; обнаружена прямая зависимость между интенсивностью сигнала ЭПР спин-меченного NO в биоптатах печени и уровнем триглицеридов в крови (r=0,96; p=0,009). Установлено, что эстрогензависимые факторы (нарушение липидного обмена и увеличение экспрессии iNOS) вызывают накопление триглицеридов, свободных жирных кислот и избыточного количества NO в печени, которые в условиях окислительного стресса проявляют цитотоксичность и способствуют прогрессированию безалкогольного стеатогепатита у женщин постменопаузного возраста.

რეზიუმე

ღვიძლის არაალკოჰოლური ცხიმოვანი დაავადების პათოგენეზის ზოგიერთი ასპექტი პოსტმენოპაუზური ასაკის ქალებში

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სტეატოზისა და სტეატოჰეპატიტის შექცევადობიდან გამომდინარე, მათი ადრეული დიაგნოსტიკა თანამედროვე მედიცინის ერთ-ერთ უმნიშვნელოვანეს პრობლემას წარმოადგენს.

კვლევის მიზანს წარმოადგენდა ღვიძლის არაალკოჰოლური ცხიმოვანი დაავადების პათოგენეზის თავისებურებების დადგენა პოსტმენოპაუზური ასაკის ქალებში.

კვლევა ჩატარდა მეტაბოლური სინდრომით დაავადებულ პოსტმენოპაუზის ასაკის ქალებზე (n=5), რომელთა ALT-ს მაჩვენებელი სისხლში 4-ჯერ აღემატებოდა ნორმას. ანამნეზის შეგროვებისა და სისხლის ლიპიდური პროფილის (ALT, AST, ესტროგენების შემცველობა) შესწავლის გარდა, პაციენტების ღვიძლის ბიოპტატებში და სისხლში ისაზღვრებოდა თავისუფალი აზოტის ჟანგის შემცველობას ელექტრონული პარამაგნიტური რეზონანსის (ეპრ) მეთოდით. კვლევის ოქმი დამტკიცებულია თბილისის სახელმწიფო სამედიცინო უნივერსიტეტის ეთიკის კომიტეტის მიერ; პაციენტებმა წერილობით დაადასტურეს ინფორმირებული თანხმობა კვლევაში მონაწილეობისთვის.

პაციენტების სისხლში საერთო ქოლესტერინის,LDL-ქოლესტერინის და ტრიგლიცერიდების დონე მომატებული აღმოჩნდა; გამოვლინდა პირდაპირი კორელაცია ღვიძლის ბიოპტატში აზოტის ჟანგის ეპრ-სიგნალის ინტენსივობასა და სისხლში ტრიგლიცერიდების შემცველობას შორის (r=0,96; p=0,009).

ავტორთა დასკვნით, პოსტმენოპაუზური ასაკის ქალებში ესტროგენდამოკიდებული მეტაბოლიზმის ცვლილებები (ლიპიდური მეტაბოლიზმის დარღვევა და iNOS ექსპრესიის გაძლიერება) ხელს უწყობს ღვიძლში ტრიგლიცირიდებისა და თავისუფალი ცხიმოვანი მჟავების დაგროვებას და აზოტის ჟანგის ჭარბ წარმოქმნას, რაც ოქსიდაციური სტრესის პირობებში ავლენს ციტოტოქსიკურობას და ხელს უწყობს ღვიძლის არაალკოჰოლური ცხიმოვანი დაავადების პროგრესირებას.

INFLAMMATORY MARKERS OF GALLSTONES DISEASE IN MENOPAUSAL WOMEN

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Gallstone disease is one of the most common pathologies of digestive tract. The prevalence of gallstone disease varies worldwide. High rates occur in the United States, and Europe, Pima Indian women have the highest rates of gallstone disease in the world (in 32% of population), Asian populations have a low incidence of gallstones (in Japan - 3,5%), among Australian aborigines found in a 1%, among the Masai people of East Africa have none at all. In Georgia this pathology occurs in 10-12% of the population [3].

It was shown that gallstone formation is complex traits, in which there are potentially many factors that impact on the disease process. It is believed that among the factors contributing to the gallstones formation, such as hypercholesterolemia, impaired bilirubin metabolism, bile stasis, various metabolic disorders, inflammation induced by liver, pancreatic disease, infectious and genetic factors, age, obesity and etc., factors associated with increased oxidative stress and alteration of cytokines release play an important role [2]. In the billiard fluid of patients with cholangitis increased concentrations of the inflammatory cytokines (TNF-α and IL-6) was detected [6]. A significant increase in the level of IL-8 (neutrophil chemotactic factor) in the group of patients with gallstone was also found [4]. In the experments on the mice with gallstones increased activity of mieloperoxidase and IL-1α were established. It was shown that IL-4 deficiency resulted in enhanced gallstone formation. In bile from dogs with pigment gallstones myeloperoxidase activity and IL-1α content were increased. This soluble factors involve in the development of the inflammation in the gallbladder wall. In numerous studies high concentration of cholesterol into the bile, induced by decreased bile acid synthesis, or mutaton of genes involved in cholesterol metabolism, was detected, resulting in enhanced gallstone formation [1]. It was sugested that several specific cytokines have been implicated in cholesterol and lipoprotein metabolism; inflammation may be considered as an early event associated with the appearance of gallstones crystals in bladder [5].

The goal of our research was determination of alterations of the redox balance and cytokines (IL-1α, IL-6, IL-8, T NF-α) concentration in the blood of postmenopausal women with and without gallstone disease.

Material and metods. 58 menopausal women with gallstone disease, who had been admitted to the LTD ”1-st Clinic” (Tbilisi, Georgia) during 2009-2011 were studied. Gallstone disease was proved by Ultrasonography method. The control group consisted of 25 menopase aged women without gallstone disease. The study protocol was approved by Local Ethics Committee, and informed consent was obtained from all participants.

Patients was conducted for blood redox status parameters (prooxidant (superoxide (O_2^-) and lipoperoxide ($LOO^\cdot$) radicals (by Electron Paramgnetic Resonance (EPR)) and cytokins (IL-1, IL-6, IL-8, TNF-α) content examinaton.

EPR spectra of blood were registered on the Radiospectrometer RE-1307 (X-band) (high-frequency (HF) - 9,1 GHz, magnetic field HF modulation 100 KHz, spectrometer sensitivity 2x10 spin/gauss). EPR spectra were carried out at supper HF field powerequal 5 mW, amplitude of field modulation 0,1 mTl at liquid nitrogen temperature (-196^0 C). For detection lipoperoxide ($LOO^\cdot$**)** and superoxide (O_2^-) free radicals the spin–traps (α-phenil-tertbutilnitron (PBN) and 5,5dimetil-I-pirolin-IV-oxide (DMPO) (SIGMA)) were used.

Cytokines content in blood was provided by standart ELISA method.

Descriptive statistical analysis for each variable were performed by statistical analysis software STATISTICS-8.

Results and their discussion. In the table 1 it is shown alteration of EPR signals intensity, reflecting blood redox-status of postmenopausal women with gallstones desease.

Table 1. Blood EPR signals intensity (I mm/mg) of menopausal women blood with and without gallstone desease

Parameters/Groups	n	O_2^- (mm/mg)	$LOO^\cdot$ (mm/mg)
Healthy women	40	-	-
Women with gallstone desease	25	1,4±0,1	2,8±0,1

Increase signals intensity of oxygen (O_2^-) and lipids ($LOO^\cdot$) free radical species of in blood EPR spectra of menopausal women with gallstones disease in comparision to healthy menopausal women was detected. This data indicates on the desorders of the blood redox balance in women with gallstones disease.

In the table 2 it is shown alteration of citokins (IL-1, IL-6, IL-8, TNF-α) content in postmenopausal women blood with gallstones desiase.

Table 2. Blood cytokins (IL-1, IL-6, IL-8, TNF-α) content in menopausal women with and without gallstone disease

Parameters/Groups	n	IL-1α (pg/ml)	IL-6 (pg/ml)	IL-8 (pg/ml)	TNF-α (pg/ml)
Healthy women	40	2,0±0,5	35,0±3,0	20,0±2,5	3,0±1,5
Women with gallstone desiase	25	4,0±0,9*	43,0±5,4*	26,0±5,4	5,8±2,4*

**- statistical significance differenc*

In menopausal women blood with gallstones disease increased content of IL-1α (100%) IL-6 (23%) and TNF-α (93%) was detected, IL-8 (30%) was not changed importantly in comparision to healthy menopausal women. It was detected statistically significant difference of IL-1 content in blood of above mentioned patients groups. This data indicates on the desorders of immune balance and development inflammation in women with gallstones disease.

Conclusion. As a result of our investigation it may be concluded, that the inflammation plays an important role gallstone disease in postmenopausal women. It is associated with increase production of oxygen and lipoperoxide free radical, macrophage inflammatory cytokines (IL-6, IL-1α, TNF-α) content in blood of menopausal women. As it seems macrophages play a dominant role in the inflammatory and oxidative response during gallbladder stones disease in postmenopausal women.

REFERENCES

1. King V.L., Szilvassy S. J., Daugherty A. Interleukin-4 deficiency promotes gallstone formation. Journal of Lipid Research 2002; 43: 768-771.
2. Koppisetti S, Jenigiri B, Terron MP, Tengattini S, Tamura H, Flores LJ, Tan DX, Reiter RJ. Reactive oxygen species and the hypomotility of the gall bladder as targets for the treatment of gallstones with melatonin: a review. Dig Dis Sci. 2008;53(10):2592-603.
3. Laura M. Stinton, MD, MSc, Robert P. Myers, MD, MSc, FRCPC, Eldon A. Shaffer, MD Epidemiology of Gallstones. Gastroenterology Clinics of North America 2010; 39(2): 157-169.
4. Novovic S, Andersen AM, Ersboll AK, et al. Proinflammatory cytokines in alcohol or gallstone induced acute pancreatitis. JOP 2009; 10(3) :256-62.
5. Rege R.V., Prystowsky J.B. Inflammation and a thickened mucus Layer in mice with cholesterol gallstones. Journal of Surgical Research 1998; 74(1): 81-85.
6. Savard C. E, Blinman T. A, Choi1 Ho-Soon, Lee Sung-Koo, Pandol S. J., Lee Sum P. Expression of cytokine and chemokine mRNA and secretion of tumor necrosis factor-α by gallbladder epithelial cells: Response to bacterial lipopolysaccharides. BMC Gastroenterology 2002; 2: 1-7.

SUMMARY

INFLAMMATORY MARKERS OF GALLSTONES DISEASE IN MENOPAUSAL WOMEN

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Among the factors contributing to the gallstones formation an important role belongs to the inflammation. The goal of our research - determination alterations of

the redox balance and cytokines (IL-1α, IL-6, IL-8, TNF-α) content in the blood postmenopausal women with gallstone disease.

58 menopausal women with gallstone disease, who had been admitted to the LTD ”1-st Clinic” (Tbilisi, Georgia) during 2009-2011 were studied. Gallstone disease was proved by Ultrasonography method. The control group consisted of 25 menopause aged women without gallstone disease. The Local Ethics Committee approved the protocol, and informed consent was obtained from all participants or their surrogates. Patients was conducted for blood redox status (EPR signals of superoxide (O_2^-) and lipoperoxide ($LOO^\cdot$) radicals) and citokins (IL-1α, IL-6, IL-8, TNF-α) content.

It was revealed increase production of oxygen and lipoperoxide free radicals, macrophage inflammatory cytokines (IL-6, IL-1α, TNF-α) in blood of menopausal women with gallstone disease. It was concluded that macrophages play a dominant role in the inflammatory and oxidative response during gallbladder stones disease in postmenopausal women.

Keywords: gallstone disease, blood redox status, cytokines, postmenopausal women.

РЕЗЮМЕ

МАРКЕРЫ ВОСПАЛЕНИЯ ПРИ ЖЕЛЧНОКАМЕННОЙ БОЛЕЗНИ У ЖЕНЩИН В МЕНОПАУЗЕ

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Среди факторов, способствующих образованию камней в желчном пузыре, значимую роль играет воспаление. Целью данного исследования явилось определение изменений окислительно-восстановительного баланса и цитокинов (IL-1α, IL-6, IL-8, T NF-α) в крови женщин с желчнокаменной болезнью в постменопаузальном возрасте.

Обследованы женщины (n=58) постменопаузального возраста с желчнокаменной болезнью, проходивших лечение в ООО “Первая клиника” (Тбилиси) в 2009-2011 г.г. Диагноз желчнокаменной болезни подтверждали с помощью метода ультрасонографии. Контрольная группа состояла из 25 практичес-ки здоровых женщин постменопаузального возраста. Протокол исследования одобрен Этическим комитетом. Исследовали редокс-баланс крови (ЭПР сигналы супероксид - O_2^- и липопероксид радикалов - $LOO^\cdot$) и содержание цитокинов (IL-1α, IL-6, IL-8, TNF-α).

При желчнокаменной болезни у женщин менопаузального возраста в крови установлено увеличение образования свободных радикалов кислорода и липидов, макрофагальных воспалительных цитокинов (IL-6, IL-1α, TNF-α). Полученные данные позволяют заключить, что цитокины играют доминирующую роль в развитии воспалительных реакций при желчнокаменной болезни у женщин постменопаузального возраста.

რეზიუმე

ანთების მარკერები ნაღვლკენჭოვანი დაავადების დროს მენოპაუზური ასაკის ქალებში

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მრავალ ფაქტორს შორის, რომლებიც მონაწილეობენ ნაღვლის ბუშტის კენჭების ფორმირებაში, ანთებას მნიშვნელოვანი როლი ენიჭება.

კვლევის მიზანს წარმოადგენდა მენოპაუზური ასაკის ქალების სისხლში რედოქს-ბალანსისა და ციტოკინების (IL-1ά, IL-6, IL-8, TNF- ά) შემცველობის დადგენა ნაღვლკენჭოვანი დაავადების დროს.

გამოკვლეულია მენოპაუზის ასაკის ქალები ნაღვლკენჭოვანი დაავადებით (n=58), რომლებიც მკურნალობდნენ შპს “პირველი კლინიკა”-ში (თბილისი) 2009-2011 წლებში. ნაღვლის კენჭების არსებობის დადასტურება ხდებოდა ულტრასონოგრაფიის მეთოდით. საკონტროლო ჯგუფი შედგებოდა მენოპაუზის ასაკის ქალებისაგან (n=25) ნაღვლის კენჭების გარეშე. კვლევის ოქმი დამტკიცებული იყო ადგილობრივი ეთიკის კომისიის მიერ. პაციენტებს ჩაუტარდა სისხ-

ლის რედოქს-სტატუსის (სუპეროქსიდ - O_2^- და ლიპო-პეროქსიდის - LOO^- რადიკალების ეპრ სიგნალები) და ციტოკინების (IL-1ά, IL-6, IL-8, TNF-ά) გამოკვლევა.

მენოპაუზის ასაკის ქალების სისხლში დადგენილია ჟანგბადისა და ლიპიდების თავისუფალი რადიკალების, მაკროფაგული ანთებითი ციტოკინების (IL-1ά, IL-6, IL-8, TNF-ά) პროდუქციის ზრდა. გამოტანილია დასკვნა მაკროფაგების დომინანტური როლის შესახებ მენოპაუზური ასაკის ქალებში ნაღვლკენჭოვანი დაავადების დროს ანთებითი პროცესის განვითარების შედეგად.

THE EPR STUDY OF NITRIC OXIDE IN PLACENTA DURING PREECLAMPSIA

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In 4-5% of all human pregnancies preeclampsia (PE) develops. This condition is characterized by an elevated blood pressure and proteinuria, developing after 20 weeks gestational age. The pathogenesis of PE is complex and still under intense investigation. Most if not all of the theories proposed for the pathogenesis of PE are somewhat pointed to impaired spiral artery remodeling and insufficient trophoblast invasion [5]. The placenta has a central role in PE as evidenced by rapid disappearance of the disease symptoms after delivery or elective removal of the placenta but not the fetus [2,6].

Nitric oxide (NO) is synthesized in placenta via the NOS family of enzymes including neuronal (NOS1), inducible (NOS2), and endothelial (NOS3) NO-isoforms. Due to its potent vasodilator effects, nitric oxide (NO) plays a crucial role in lowering vascular resistance of the uterus and placenta unit throughout pregnancy. NO also regulates trophoblast function [8], but the current understanding of NO biology in pregnancy remains unclear. NO is a gaseous molecule; its short half-life (<1 sec) makes its working distance relative short (<30 μm). Logically, endogenously synthesized NO can be trapped to act only within a few layers of cells. However, once formed, NO can be quickly converted to reactive nitrogen species (RNS) (N_2O_3, $ONOO^-$, NO_2^-, NO_3^-, and others). These RNS can induce protein nitration, donate an NO moiety (NO•) to cysteines in a protein or peptide to produce S-nitrosothiols, which possesses many NO-like biological functions but with a much longer biological half-life than NO, serving as a reservoir for bioavailable NO [9]. This ability is of major importance in NO biology and medicine because this mechanism extends the biological functions of NO to an endocrine fashion so that NO can act on cells and/or organs far from where it is produced. S-nitrosylation alters enzyme activity by either modifying cysteines of the enzyme or changing protein conformation. How NO regulates placental protein functions and how this relates to placental biology and pregnancy are unknown.

The aim of our study was to establish alteration of NO metabolism in placenta and its role in pathogenesis of physiological and complicated with preeclampsia pregnancy.

Material and methods. 50 women with preeclampsia and 30 control pregnant women were enrolled. Ten of preeclamptic women had severe and twenty had moderate preeclampsia. Subjects were selected at the Gudushauri National Hospital and Chachava Clinic (Tbilisi, Georgia). The control group was selected

from healthy pregnant women. The preeclamptic group consisted of women who were normotensive before pregnancy and during the first 20 weeks of gestation, and developed hypertension (blood pressure of 140 mm Hg or higher, or a diastolic blood pressure of 90 mmHg or higher on two or more occasions, 6hr apart) associated with new onset proteinuria of either greater than 100mg/dl by urine analysis (>1+ dipstick) or greater than 300mg/dl in a 24-h urine collection. No subject had co-morbid conditions such as diabetes, asthma, congenital heart disease, connective tissue disorders or an autoimmune disease. None of the pregnancies were complicated by preterm rupture of membranes. Subjects with any symptom of infection were excluded from the study. All subjects submitted written informed consents. The study was authorized by the Ethical Investigation Committee of Tbilisi State Medical University.

NO content in placenta tissue was studied by Electron Paramagnetic Resonance (EPR) method. EPR studies were perfomed on the Radiospectrometer РЭ1307 (Russia) with Super High Friquensy 9.77 GHz, Friquency of Modulation 50 kHz. Placenta from pregnant women was frosen in liquid nitrogen at the temperatire -196^{0}C. In order to determine free Nitric Oxide (NO) content spin-trap Diethil-ditiocarbomate (DETC, Sigma) was used (DETC 500 mg + Fe^{2+}-citrate (50 mg $FeSO_4$+7H_2O+37,5 mg Sodium Citrate). EPR signals of NO-Fe^{2+}-$(DETC)_2$ complexes in placenta were detected at liquid Nitrogen temperature and Microwave Power 20 mVt. For the detection of Lipoperoxil Radicals ($LOO^{\cdot}$) spin-trap α-phenil-*tert* butilnitron (PBNm Sigma), (PBN 150 мМ/l + Tris-bufer 25мМ (pH=7,4)) was used. EPR spectra of $LOO^{\cdot}$ were detectes at room temperature and Microwave Power 20 mVt.

All data were analysed using SPSS, version 13 for Windows software. The data were tested for normal distribution by Kolmogrov-Smirnov test. Student t-test or the Mann-Whitney U-test was used for comparisons between the two groups where appropriate. Differences at $p<0.05$ were considered as statistically significant.

Results and their discussion. In Table alterations of paramagnetic centers of placenta during physiological and complicated with PE pregnancy are shown. It was revealed that that during PE intensity of EPR signal of adrenodoxin FeS-centres reduced by 60%, while the EPR signal of cytochrome P-450 increased by 60% - compared to the same parametres during physiological pregnancy; intensive EPR signal of spin-trapped Lipoperoxide (LOO.) was also detected. During pregnancy complicated with PE in the EPR spectrum of placenta a significant reduction of NO content and complexes of NO with hemic (Fig.) and nonhemic iron were detected (Table).

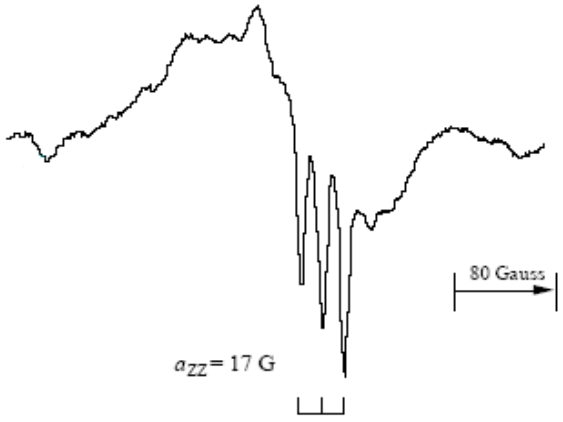

Fig. EPR spectra of nitric oxide (NO) complexes with hemic iron in placenta during pregnancy complicated with PE

Table. Paramagnetic centres intensity (mm/mg) of placenta during physiological and complicated with PE pregnancies

Groups	**NO $g_{\perp}$=2,01**	**$LOO^{\cdot}$**	**HbNO g_e=2,01**	**FeSNO g=2,03**	**FeS $g_{\parallel}$=1,94**	**cytochrom P-450 $g_{\perp}$=2,25**
Physiological pregnancy	14,0±0,9	2,0±0,8	-	-	15,0±1,2	2,7±0,9
Pregnancy complicated with PE	8,0±1,2 P_{12}<0,001	9.5±1,2 P_{12}<0,001	14,0±2,8	6,5±1,5	6,5±0,5 P_{12}<0,001	6,8±0,7 P_{12}<0,001

A human placenta contains at least two types of mitochondrial electron transport chain [4] - one is responsible for the mitochondrial respiration and synthesis of the ATP, and another - for steroidogenesis. Respectively, the electron transport chain participating in the energogenesis contains FeS-centres of NADH-dehydrogenese which transports electrons from NADH on ubichinons and father on the cytochrome C. The electron transport chain responsible for the steroidogenesis carry electrons from FeS-centres of adrenodoxine to cytochrom P-450, which involve in the transformation of cholesterol and hydroxylation of steroid hormones.

In patients with PE placental blood flow disorders induce unsuficiency of oxygen supply of placenta with following decrease activity of mitochondrial electron transport chain, elevation of NADH-dehydrogenase oxidation level (decrease of NADH-dehydrogenase FeS-centers EPR signal intensity) and suppression of the energogenesis. As result placental ischemia, intensive generation of the reactive oxygen species and intensification of oxidative stress are developed. This is supported by intensive EPR signal of lipoperoxides detected in preeclampsic placenta.

The placenta performs endocrine function durinf pregnancy - it synthesizes steroid hormones (estradiole and progesterone), necessary for the normal development of pregnancy. During the third trimester of pregnancy level of progesterone usually increases approximately 10 times. Progesterone synthesis initiates on the inner membrane of the mitochondria in desmolase reaction converting side chain of cholesterol into pregnenalon, catalysed by placental cytochrome P-450 [9]. Cytochrome P-450 also participates in the hydroxylation of steroids in 11-β-position. Cytochrome P-450 is paramagnetic in oxidized (low spin) state. During the intensification of steroidogenezis EPR signal intensity of ferricytochtom P-450 (g_1=2,42, g_2=2,25, g_3=1,92) decreases as a result of its joining substrate ad convertion in high-spin isoform (g=8.0), or one-electron restoration. In these reactions adrenodoxine plays the electrons donor role and intensity of its FeS-centres EPR signal increases.

During PE decrease of intensity of adrenodoxin FeS-centres and increase intensity of ferricytochrome P-450 EPR signals were detected. This data indicate on the disregulation of mitochondrial electron transport and disorders of steroidogenesis processes in placenta.

During the physiological pregnancy nitric oxide involves in the regulation of balance between oxygen supply and mitochondrial respiration in placenta, which is necessary for the maintenance of normal metabolism of the cells. Vasodilatative activity of nitric oxide is potentiated due to its ability to produce S-nitrosothiols, which possesses many NO-like biological functions. S-nitrosylation alters enzyme activity regulates functions of trophoblasts and plays an important role in the regulation of physiological pregnancy. Numerous studies indicate on the important role of NO in pathogenesis of PE. The data according intensity of NO synthesis during PE are controversial. Some authors indicate on the intensification of nitric oxide synthesis (due to oxidative stress induced overexpression of iNOS in placenta), or adaptative activation of eNOS at at conditions of low perfusion, hypoxia and increase of blood vessel resistance. The other data indicate on the decrease of nitric oxide synthesis as a result of iNOS gene mutation and decrease level of its mRNA [1]. Biological degradation of nitric oxide in oxidative stress conditions and its transformation to toxic peroxinitrite also is possible [3]. Peroxinitrite involves in peroxidation mebrane lipids, oxidation proteins, nitrosilation of amino acids residues with following disorders of their structure and functions.

During pregnancy complicated with PE in the EPR spectrum of placenta a significant ecreace of free nitric oxide content and increase intensity of nitric oxide complexes with hemic and nonhemic iron (FeSNO, HbNO) were detected. These complexes indicate on the nitrosilation of mitochondrial electron transport chain proteins with following alterations of their activity and disorders of energo- and steroidogenesis processes in placenta during PE. These data therefore show that nitrosilation is crucial mechanism by which NO regulates placental proteins activity linked to various biological pathways. The alteration of placental nitrosilated complexes content during PE suggests that NO plays an important role in the regulation functions of placenta during PE.

REFERENCES

1. Christopher W. Redman and Ian L. Sargent Latest Advances in Understanding Preeclampsia. Science 2005; 308:1592-2005.
2. Hladunewich M., S. Ananth Karumanchi,Richard Lafayette. Pathophysiology of the Clinical Manifestations of Preeclampsia. Clin J Am Soc Nephrol 2007; 2:543-549.
3. Huang W.M., Foulk R., Clauer K., Burlingame A., Gibson B.W., Fisher S.J. Functional proteomics examining the effects of hypoxia on the cytotrophoblast protein repertoire. Biochemistry 2001; 40: 4077-4086.
4. Klimek J., M Woźniak; G Szymańska; L Zelewski Inhibitory effect of free radicals derived from organic hydroperoxide on progesterone synthesis in human term placental mitochondria. Free radical biology and medicine 1998;24(7-8):1168-75.
5. Redman CW, Sargent IL Latest advances in understanding preeclampsia. Science 2005; 308: 1592-1594.

6. Roberts JM, Cooper DW Pathogenesis and genetics of pre-eclampsia. Lancet 2001; 357: 53-56.
7. Strauss I.H., Grafrols J.F., King B.F. Placenta influenses in endoctinology. In: Degroot L.J., ed. Endocrinology. v. 3. Philadelphia: W.B. Saunders; 1995: 2171-2206.
8. Sanyal M, Nag TC, Das C Localization of nitric oxide synthase in human trophoblast cells: role of nitric oxide in trophoblast proliferation and differentiation. Am J Reprod Immunol 2000; 43: 70-77.
9. Zhang H., Wang Y., Chen D., Analysis of Nitroso-Proteomes in Normotensive and Severe Preeclamptic Human Placentas. Biology of Reproduction 2011; 84(5): 966-975.

SUMMARY

THE EPR STUDY OF NITRIC OXIDE IN PLACENTA DURING PREECLAMPSIA

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The aim of the study was to establish alteration of nitric oxide (NO) metabolism in placenta and its role in pathogenesis of physiological and complicated with preeclampsia (PE) pregnancy.

Fifty women with preeclampsia and 30 control pregnant women were studied. The control group was selected from healthy pregnant women; the preeclamptic group consisted of women who were normotensive before pregnancy and during the first 20 weeks of gestation, and developed hypertension associated with new onset proteinuria. NO content in placenta was studied by Electron paramagnetic Resonance (EPR) method.

During pregnancy complicated with PE intensity of EPR signal of adrenodoxin FeS-centres reduced (by 60%), of cytochrome P-450 increased by 60% - compared to the same parametres during physiological pregnancy; intensive EPR signal of spin-trapped Lipoperoxide (LOO.) was also detected; in the EPR spectrum of placenta a significant reduction of free nitric oxide content and intensive signals of of nitric oxide complexes with hemic and nonhemic iron were detected. These complexes indicate on the nitrosilation of mitochondrial electron transport proteins with following alterations of their activity and disorders of energo- and steroidogenesis processes in placenta during PE. Alterations of placental nitrosilated complexes during PE suggests that NO plays an important role in the regulation its functions.

Key words: Nitric oxide in placenta, preeclampsia.

РЕЗЮМЕ

ЭПР ИССЛЕДОВАНИЕ СОДЕРЖАНИЯ ОКСИДА АЗОТА В ПЛАЦЕНТЕ ВО ВРЕМЯ ПРЕЭКЛАМПСИИ

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Оксид азота (NO), вследствие взаимодействия с белками плаценты, с образованием S-нитрозотиолов, потенциирует функциональную активность плаценты. Однако механизм регуляторной активности оксида азота до конца не установлен.

Целью исследования явилось определение нарушений метаболизма оксида азота в плаценте и их роли в патогенезе преэклампсии.

Обследованы 50 женщин с преэклампсией (основная группа) и 30 женщин с физиологической беременностью (контрольная группа). В группу преэклампсии были включены женщины, у которых в третьем триместре беременности выявлена артериальная гипертензия и сопутствующая протеинурия.

Содержание NO в плаценте определяли методом электронного парамагнитного резонанса (ЭПР).

Установлено, что при преэклампсии в плаценте интенсивность ЭПР сигналов FeS-центров адренодоксина уменьшилась на 60%, в то время как цитохрома Р-450 увеличилась на 60% в сравнении с аналогичными показателями в контрольной группе. В спектре ЭПР плаценты зафиксированы также интенсивный сигнал липопероксида, значительное уменьшение содержания свободного оксида азота, резкое увеличение интенсивности ЭПР сигналов нитрозильных комплексов оксида азота с гемовым и негемовым железом. По заключению авторов статьи, полученные данные свидетельствуют о нитрозили-

ровании белков цепи электронного транспорта митохондрий при преэклампсии, способствуя нарушению энерго-генеза и стероидогенеза в плаценте. Вынесен вывод, согласно которому оксид азота играет весьма значимую роль в регуляции метаболизма плаценты при преэклампсии.

რეზიუმე

პლაცენტაში აზოტის ჟანგის შემცველობის კვლევა ელექტრონული პარამაგნიტური რეზონანსის მეთოდით პრეეკლამფსიის დროს

მ. თორთლაძე, ნ კინტრაია, თ. სანიკიძე

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, საქართველო

აზოტის ჟანგი (NO) პლაცენტაში ცილების ნიტროზილირების მეშვეობით მონაწილეობს პლაცენტის მეტაბოლიზმის რეგულაციაში. სადღეისოდ NO-ს პლაცენტის მეტაბოლიზმის რეგულაციის მექანიზმი ჯერ კიდევ სრულყოფილად დადგენილი არ არის. კვლევა ჩატარდა 50 პრეეკლამფსიით გართულებულ და 30 ფიზიოლოგიურ ორსულებზე. პრეეკლამფსია დადგინდა ორსულობის მესამე ტრიმესტრში. აზოტის ოქსიდის შემცველობა პლაცენტაში ისაზღვრებოდა ელექტრონული პარამაგნიტური რეზონანსის (ეპრ) მეთოდით.

დადგინდა, რომ პრეეკლამფსიით გართულებულ ორსულობის დროს პლაცენტაში ადრენოდოქსინის FeS ცენტრების ეპრ-სიგნალის ინტენსიობა 60%-ით მცირდება, ხოლო ციტოქრომ P-450-ს - 60%-ით იზრდება, ფიზიოლოგიური ორსულებისათვის დამახასიათებელ ანალოგიურ მაჩვენებელთან შედარებით; გამოვლინდა, აგრეთვე, ლიპოპეროქსიდების ინტენსიური ეპრ-სიგნალი, აზოტის ჰემურ და არაჰემურ რკინასთან კომპლექსების ეპრ-სიგნალის მკვეთრი მატება და თავისუფალი NO-ს მნიშვნელოვანი შემცირება. მიღებული მონაცემები მიუთითებენ მიტოქონდრიული ცილების ნიტრირებაზე, რაც განაპირობებს პლაცენტაში ენერგოგენეზისა და სტეროიდოგენეზის დარღვევას. ყოველივე ზემოაღნიშნული უფლებას გვაძლევს დავასკვნათ, რომ NO მნიშვნელოვან როლს ასრულებს პლაცენტის მეტაბოლიზმის რეგულაციაში.

PREVALENCE OF MYCOPLASMA HOMINIS AND UREAPLASMA UREALITICUM IN PREGNANT AND WOMEN WITH REPRODUCTIVE PROBLEMS

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Mycoplasma and ureaplasma are the two genera in the family Mycoplasmataceae and belong to class of Mollicutes. They are widely spread in humans, mammals, birds, reptiles, fish and other vertebrates [9,12]. The species of Mycoplasma hominis and Ureaplasma are commensal organisms which house in the urinary systems and genitals of sexually active teenagers and adults. The majority of the authors indicate that these microorganisms play main roles in the pathologies of the genital system like Inflammation of the pelvic organs, urolithiasis, non-gonococcal urethritis, pyelonephritis, endometritis after delivery, and neo-natural infection (meningitis, respiratory system infections, septicemia).

The main way to transfer Mycoplasma hominis is sexual one. The frequency correlates with sexual activity; the agent causes urethritis and prostatitis in male while in female it causes colonization of vagina, and even more rarely uterus and urethra. It should be noted that this bacterium was identified in clinically healthy women [1,8,10]. There is threshold concentration of this bacterium (less than 10 000 in 1 ml or $<10^4$). The amount beyond it causes pathogenicity.

Urogenital Mycoplasma is especially dangerous during pregnancy as it commonly causes early labors or infection of fetus that is the often reason of sepsis.

Ureaplasma Urealyticum contacts with the cylindrical epithelium cells of urethra and causes diseases of the Urogenital system.

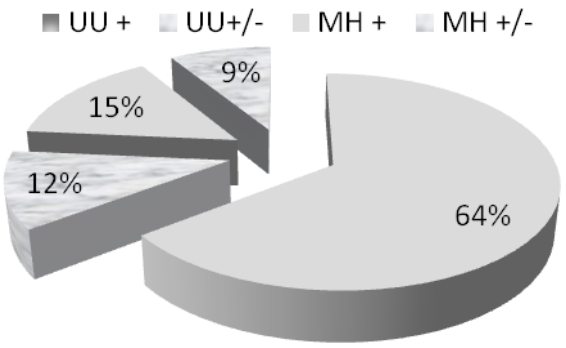
The aim of the research was to explore women with reproductive problems and pregnant women on Mycoplasma and Ureaplasma as well as to investigate spread of these microbes in the women of reproductive age.

Material and methods: The samples of 196 patients were investigated.

The material taken from the cervix was used for research; it was placed in feeding area and then incubated during 48 hours at 37^0 C. The method is based on hydrolyze principle of Urea and arginini as a result of metabolism of Bacterium. It results in color change and the outcome of visual observation is interpreted. The Micoplasma DUO reactives of BioRad (France) were applied in research. Titer material was placed in two parallel holes (10^{-1}; 10^{-2}).

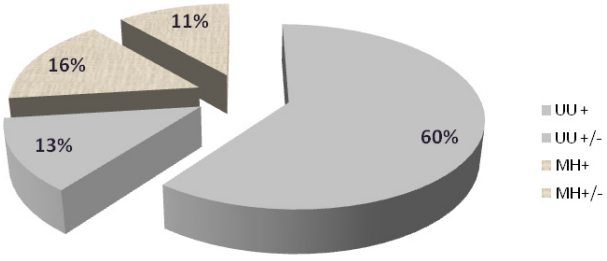
Results and their discussion. In total 196 patients were investigated. In 2008-2009 100 patients with reproductive problems were examined, and 96 pregnant women were examined in 2010-2011.

64% of the investigated people were positive on Ureaplasma with high titer $\geq 10^4$ (UU+), or more than 10000 cells in 1 ml; carrier of Ureaplasma (or low titer) was discovered in 15% of the examined women (UU+/-). As for Mycoplasma, high titer was found in 12% (MH+) of the investigated women; carrying of mycoplasma was less low and equaled 9% (MH+/-) (Fig. 1).



64 %- high titer of Ureaplasma, or ≥104; 15%- Ureaplasma carrying low titer, or <104;
12% - High titer of Mycoplasma, or ≥104; 9% - Mycoplasma carrying low titer, or <104;
Fig. 1. Dissemination of UU and MH (%) in women with reproductive problems (2008-2009)

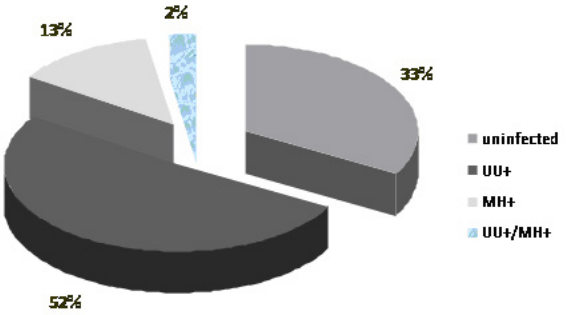
Only pregnant women were investigated in 2010-2011; high titer ($\geq 10^4$) of Ureaplasma (UU+) was found in 60% of women, while carrying found in 13% (UU+/-). Mycoplasma with high titer was discovered in 16 % (MH+), while carrying of mycoplasma was almost analogous and reached 11% (MH+/-) (Fig. 2).



60%- high titer of Ureaplasma or ≥104; 13% - Ureaplasma carrying low titer or <104;
16% - High titer of Mycoplasma, or ≥104; 11% - Mycoplasma carrying low titer, or <104;
Fig. 2. Dissemination of UU and MH % in pregnant women (2010-2011)

There were patients in the investigated ones who were infected with high titer both of Ureaplasma and Mycoplasma (Fig. 3).

In the investigated pregnant women and women with reproductive problems the indicator or infection with high titer of Ureaplasma reached 51 %, the infection with mycoplasma equaled 13% while both mycoplasma and Ureaplasma with high titer was found at 3% of the examined women.



51%- high titer of Ureaplasma or ≥10^4; 33%- uninfected;
13% - High titer of Mycoplasma, or ≥10^4; 3% - high titer of Ureaplasma and Mycoplasma
Fig. 3. Infection indicator (%) of UU and MH in pregnant women and women with reproductive problems

As research displayed the figure of Ureaplasma infection was higher (60%) in women with reproductive problems than in pregnant women. Almost analogous result is shown in the researches of the different authors 37-50% non-pregnant women with reproductive problems [4,7,11]; on the other hand, percentage of infection with mycoplasma is substantially different in women with reproductive problems: 2,3%-4,8%-16,5% [2,6,7]. According to our researches it is vice versa as mycoplasma titer was higher in pregnant women and reached 16%, while it was 12% in non-pregnant women. Carrying of Ureaplasma both in pregnant and non-pregnant women was almost the same, while carrying of mycoplasma in non-pregnant women was less found than in pregnant ones (9% in women with reproductive problems, and 11% in pregnant women). Keane and co-authors indicate that 53% of women with reproductive problems caused by infection with Ureaplasma. It is also underlined that women having bacterial vaginosis I more often infected by mycoplasma than women not having the stated disease [2].

The high percentage of infection by Ureaplasma (51%) both in non-pregnant women with reproductive problems and pregnant ones indicate at high indicator of dissemination of this microorganism in population of Adjara-Guria. Moreover, the higher figure (64%) in women with reproductive problems proves the concept that this microbe is one of the pathogens of this problem. Therefore, it would be much effective if the research on this pathogen would be carried in women of reproductive age before marriage and not after the registration. It would avoid complication during pregnancy.

In addition, it would be interesting to screen women for these microbes at reproductive age of Adjara – Guria Region in order to identify figure of dissemination of microbes.

REFERENCES

1. Deguchi T, Maeda S. Mycoplasma genitalium: another important pathogen of non-gonococcal urethritis. J Urol. 2002; 167:1210-1217.
2. Di Bartolomeo S, Rodriguez FM, Sauka DH, Alberto de Torres R. Prevalence of associated microorganisms in genital discharge, Argentina. Rev. Saude. Publica. 2002; 36: 545-552.
3. Keane FEA, Thomas BJ, Gilroy CB, Renton A, TaylorRobinson D. The association of Mycoplasma hominis, Ureaplasma urealyticum and Mycoplasma genitalium with bacterial vaginosis: observation on heterosexual women and their male partners. Int. J. STD. AIDS. 2000; 11: 356-360.
4. Khan J., Farzand R. Prevalence of mycoplasma hominis and ureaplasma urealyticum among women with unexplained infertility, with and without vaginitis and cervicitis. African Journal of Microbiology Research 2011; 5(8): 861-864.
5. Maeda S, Deguchi T, Ishiko H, Matsumoto T, Naito S, Kumon H, Tsukamoto T, Onodera S, Kamidono S.Detection of Mycoplasma genitalium, Mycoplasma hominis, Ureaplasma parvum (biovar 1) and Ureaplasma urealyticum (biovar 2) in patients with non-gonococcal urethritis using polymerase chain reaction-microtiter plate hybridization. Int J Urol. 2004; 11(9):750-4.
6. Rodriguez R, Hernandez R, Fuster F, Torres A, Prieto P, Alberto J. Genital infection and infertility. Enferm. Infect. Microbiol. Clin. 2001; 19: 261-266.
7. Stray-Pedersen B, Bruu A, Molne K. Infertility and uterine colonization with Ureaplasma urealyticum. Acta Obstetricia et Gynecologica Scandinavica 1982; 61: 21-24.
8. Taylor-Robinson D, McCormack WM. The genital mycoplasmas. N Engl J Med. 1980; 302:1003-1010.
9. Tully JG, Taylor-Robinson D, Cole RM, Rose DL. A newly discovered mycoplasma in the human urogenital tract. Lancet 1981; 1288-1291.
10. Tully JG, D Taylor-Robinson D, Rose L, Cole RM, Bove JM. Mycoplasma genitalium, a new species from the human urogenital tract. International Jour. of systematic Bacteriology 1983; 387-396.
11. van Belkum A, van der Schee C, van der Meijden WI, Verbrugh HA, Sluiters HJ A. clinical study on the association of Trichomonas vaginalis and

Mycoplasma hominis infections in women attending a sexually transmitted disease (STD) outpatient clinic. FEMS Immunol. Med. Microbiol. 2001; 32: 27-32.

12. Yoshida T, Maeda S, Deguchi T, Ishiko H. Phylogeny-based rapid identification of mycoplasmas and ureaplasmas from urethritis patients. J Clin Microbiol. 2002; 40:105-10.

SUMMARY

PREVALENCE OF MYCOPLASMA HOMINIS AND UREAPLASMA UREALITICUM IN PREGNANT AND WOMEN WITH REPRODUCTIVE PROBLEMS

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The aim of the research was to explore women with reproductive problems and pregnant women on Mycoplasma and Ureaplasma as well as to investigate spread of these microbes in the women of reproductive age. There were investigated 100 women with reproductive problem and 96 pregnant women. It was found that 64% of women with reproductive problem and 60% of pregnant women had Ureaplasma urealyticum with high titer (more then 1000 cells in ml), but Mycoplasma hominis was detected approximately in equal % of non-pregnant and pregnant women (12% - non-pregnant women; 16% - pregnant women). It is recommended to investigate women before planning pregnancy.

Keywords: ureaplasma urealyticum, mycoplasma hominis, pregnant women, reproductive problems.

РЕЗЮМЕ

РАСПРОСТРАНЕНИЕ MYCOPLASMA HOMINIS И UREAPLASMA UREALITICUM СРЕДИ БЕРЕМЕННЫХ И ЖЕНЩИН С РЕПРОДУКТИВНЫМИ ПРОБЛЕМАМИ

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Обследовано 100 женщин с репродуктивными проблемами и 96 беременных. Результаты исследования показали, что 64% женщин с репродуктивными проблемами и 60% беременных были инфицированы уреаплазмой с высоким титром (больше чем 1000 клеток в мл). Микоплазмоз как среди беременных, так и небеременных женщин выявлен примерно с одинаковой частотой: 12% у небеременных женщин с репродуктивными проблемами, 16% - у беременных, что свидетельствует о широкой диссеминации выявленных микроорганизмов среди женской популяции Аджарии.

Авторы рекомендуют обследование женщин на инфицирование уреаплазмой и микоплазмой до планирования беременности.

რეზიუმე

Mycoplasma Hominis და Ureaplasma Urealiticum-ის გავრცელება ორსულ და რეპროდუქციული პრობლემების მქონე ქალებში

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შესწავლილია 100 რეპროდუქციული პრობლემების მქონე და 96 ორსული ქალი. კვლევის შედეგად რეპროდუქციული პროლემების მქონე ქალების 64% და ორსულების 60%-ში

გამოვლინდა Ureaplasma urealyticum მაღალი ტიტრი (1000 უჯრედი/მლ-ზე მეტი); Mycoplasma hominis გამოვლინდა არაორსული რეპროდუქციული პრობლემების მქონე ქალების 12% და ორსულების 16%-ში.

ავტორების მიერ რეკომენდებულია გენიტალური ორსულობის წინ გამოკვლევების ჩატარება მიკოპლაზმოზითა და ურეაპლაზმოზით ინფიცირებაზე.

STUDY OF SOME BIOGERONTOLOGICAL FACTORS ASSOCIATED WITH WOMEN LONGEVITY IN AJARA POPULATION

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The search for the factors and mechanisms preconditioning longevity has actively been conducted for the last decades. As a multi-factorial process, longevity is preconditioned by hereditary as well as the combination of social factors and environment a man is destined to live [2]. Accordingly, complex gerontological researches are being conducted applying genetic, molecular, biological, cytogenetic, immunological and sociological methods [4-6,8,9].

According to the data from the Demography Department of the United Nations Organization, women prevail among the long-livers. In various countries of the world spinsters, bachelors, widows, widowers and the divorced live shorter than the married. For example, in Japan, men's mortality is 4,3 times more among bachelors, 3,9 times among widowers, 5,1 times among the divorced than among the married ones. In Germany the factors are 2,5; 4,0 and 2,1 respectively; in Hungary – 2,1; 3,5 and 2,3 [1]. Among the factors preconditioning the longevity phenomenon on which health and longevity more or less depend, the following can be singled out: reproductive system functioning, emotions management ability and presence of optimism [7], happy marriage, longtime coexistence of couples [1,3,10].

The aim of our research was to reveal the biogerontological factors associated with longevity among the long-lived women population living in Ajara region.

Material and methods. The study was conducted with the gerontological questionnaire compiled by us. The questionnaire comprised such questions as: marriage age and duration of marital period, number of children, reproductive data and long-livers' psychoemotional state. Through the randomization method 120 long-living women were selected (over 91 years of age) in Ajara. The obtained results were processed and studied with the method of percentage calculation. During the experiment the genealogical method of research was applied as well.

Results and their discussion. The results of the research showed that among the population under study there are very early as well as very late marriages, 66% of the long-livers created families between the ages of 18 and 30. With the consideration of the local traditions, this means their first sexual intercourse, especially among women. The rate of long-livers who married before the age of 18 is 21% while from the age of 30 till 40 – 12,7%. As the rates show, the marital age of the majority of long-livers is from 18 to 30 years of age (Fig. 1).

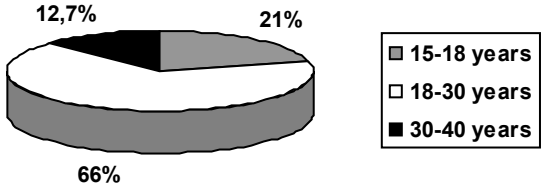

Fig. 1. Long-Livers' Marital Rate

It has been revealed that the majority of the respondents participating in the survey had a stable partner and was in long and happy marriage. They consider the death of a partner as the greatest stress in lifetime. As the research results show (Diagram 2) the rate of the long-lived women under study who spent most of their lifetime with their spouses is considerably high and comprises 74%.

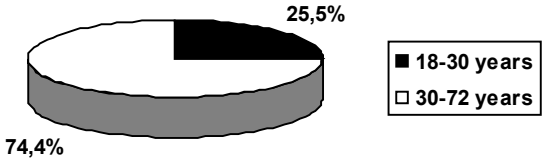

Fig. 2. Time Spent by the Long-Livers with their Spouses

120 women among the questionnaire participants have children, including the mothers of many children. At the same time it was shown that 32% of long-living women have over 3 children whereas 88% - two or three children (Fig. 3).

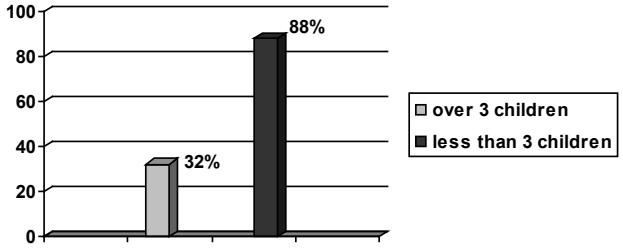

Fig. 3. Number of Children

The reproductive age of the surveyed is also different. Most of them had their last delivery (childbirth) after the age of 40. In two cases the long-livers had the delivery at the ages of 48 and 50. On the basis of the data analysis we can make a conclusion that among the long-livers under study 24% had their last childbirth from 25 to 30 years of age while 76% - from 30 to 50 years of age (Fig. 4).

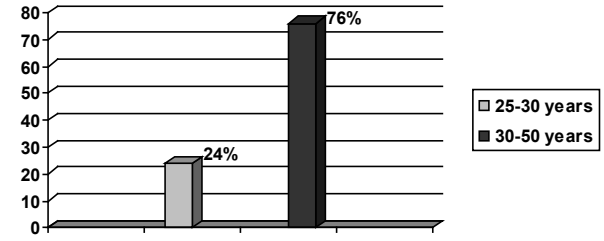

Fig. 4. The Age of Long-Livers' Last Childbirth

As it is known, premature biological aging is often provoked by nervous tension and stress [2]. The survey of the long-livers showed that they are mostly distinguished by calm nature, are able to master emotions and re optimists. The majority leads active physical activities.

Thus, among 120 women in Ajara studied with the purpose of revealing biogerontological factors associated with longevity everyone is married, their absolute majority was in happy and long marriage, most of them had stable partners and were in happy and long marriage. There are early as well as late marriages among the long-livers. However, the women who married at the age of reproductive puberty (from 18 to 30 years of age) considerably prevail among them. It seems that having many children is not directly associated with longevity. The correlation between late childbirth (over 40 years of age) and longevity was also shown. At the same time, the women having had their last delivery over 40 are distinguished by stronger health and high rate of longevity. The majority of long-livers are distinguished by balanced character, they are optimists and most of them lead lives of active physical labor.

REFERENCES

1. Anisimov V.N., Berstein L.M., Egormin P.A. et al. Exp. Gerontol. 2005; 40: 685-693.
2. Christensen K., Vaupel J.W. Determinants of longevity: genetic, environmental and medical factors-Journal of Internal Medicine 1996; 240: 333-341.
3. Harper J.M., Salmon A.B., Chang Y., Bonkowskiv, Bartke A., Miller R.A. Stress resistance and aging: Influence of genes and nutrition. Mechanisms of ageing and development 2006; 127(8): 687-694.
4. Khukhunaishvili R., Koridze M. Distribution of Eritrocyte Group Antigens (ABO, Rh-Hr,R,MN) in Long-livers of Adjara Region (Georgia,Caucasus). 6th European Congress of Biogerontology 2008 Ageing and individual life history. Netherlands: 2008.
5. Koridze M., Khukhunaishvili R., Zosidze N. at all. Biogerontological Study of Population in Some Districts of Ajara Autonomous Republic. Georgian Medical News 2009; 6(171): 53-56.
6. Koridze M., Khukhunaishvili R., Zosidze N., Akhvlediani L., Nagervadze M., Koiava T., Parulava I., Tskvitinidze S. Demographic Picture of Long-livers of the Mountain Region of Ajara(Georgia, Caucasus). Aging Clinical and Experimental Research 2011; 23(1).
7. Koridze M., Khukhunaishvili R., at. all. Some biogerontological peculiarities of long-livers in Ajara Region of Georgia. The Journal Nutrition, Helth and Aging. 2009; 13.

8. Kudryavtseva A., Zaichenko I.N., Efremov O.M., Abramov A.A., Rizhak G.A., Grigoryev E.I. Molecular Mechanisms of Ageing of Reproductive System. VII International Symposium Bilogical Mechanisms of Ageing. 24-27 May, Kharkov: 2006.
9. Lezhava T., Monaselidze J., Jokhadze T., Kakauridze N. Khodeli N., Rogava M., Bochorishvili T., Gorgoshidze M., Khachidze D., Lomidze E., Tkemaladze J., Chichinadze K., Koridze M., Khukhuneishvili R., Zosidze N., Nagervadze M., Buadze T., Gaiozishvili M. Gerontology research in Georgia. J. Biogerontology. Publisher Springer Netherlands. ISSN 1389-5729 (Print) 1573-6768 (Online). 2010.
10. Melzer D., Hurst A.J., Frayling T. Genetic variation and human aging: progress and prospects.the journals of gerontology series A: biological sciences and medical sciences 2007; 62:301-307.

SUMMARY

STUDY OF SOME BIOGERONTOLOGICAL FACTORS ASSOCIATED WITH WOMEN LONGEVITY IN AJARA POPULATION

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120 long-living women have been studied in Ajara with the purpose of revealing biogerontological factors associated with longevity. On the basis of special gerontological questionnaire survey and the genealogical research it has been revealed that the absolute majority of the long-livers was in happy and long marriage, most of them had stable partners and were in happy and long marriage.

There are early as well as late marriages among the long-livers. However, the women who married at the age of reproductive puberty (from 18 to 30 years of age) considerably prevail among them. It seems that having many children is not directly associated with longevity. The correlation between late childbirth (over 40 years of age) and longevity was also shown. At the same time, the women having had their last delivery over 40 are distinguished by stronger health and high rate of longevity.

Keywords: long-livers, longevity, life expectancy.

РЕЗЮМЕ

ИЗУЧЕНИЕ НЕКОТОРЫХ БИОГЕРОНТОЛОГИЧЕСКИХ ФАКТОРОВ, АССОЦИИРОВАННЫХ С ДОЛГОЛЕТИЕМ ЖЕНЩИН В АДЖАРИИ

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С целью выявления биогеронтологических факторов, которые ассоциированы с долголетием, в Аджарии исследовали 120 долгожительниц (старше 91 года). С помощью специального геронтологического анкетирования и на основе генеалогических исследований выявлено, что абсолютное большинство долгожительниц состояли в длительном и счастливом браке; у большинства из них был постоянный партнер. Среди исследованных отмечены как очень ранние, так и поздние браки, однако преобладали женщины, вступившие в брак в репродуктивном возрасте (от 18 до 30 лет). Согласно результатам исследования, многодетность не во всех случаях ассоциируется с долголетием. Установлена корреляция между поздними родами (старше 40 лет) и долголетием. Установлено, что крепким здоровьем и самой высокой продолжительностью жизни, выделяются женщины, которые рожают после 40 лет.

რეზიუმე

ქალთა დღეგრძელობასთან ასოცირებული ბიოგერონტოლოგიური ფაქტორების კვლევა აჭარაში

მ. ქორიძე, რ. ხუხუნაიშვილი, მ. ნაგერვაძე, ნ. ზოსიძე, თ. ქოიავა, ი. ფარულავა

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დღეგრძელობასთან ასოცირებული ბიოგერონტოლოგიური ფაქტორების გამოვლენის მიზნით შესწავლილია აჭარაში მცხოვრები 120 დღეგრძელი ქალი (91 წელზე მეტი ასაკის). სპეციალური გერონტოლოგიური ანკეტირებისა და გენეალოგიური კვლევების მეშვეობით

გამოვლინდა, რომ დღეგრძელ ქალთა აბსოლუტური უმეტესობა იმყოფებოდა ხანგრძლივ და ბედნიერ ქორწინებაში; უმეტესობას ჰყავდა სტაბილური პარტნიორი. დღეგრძელთა შორის გამოვლინდა როგორც ადრეული,ასევე გვიანი ქორწინების შემთხვევები. თუმცა, მათ შორის სჭარბობდნენ ქალები,რომლებიც დაქორწინდნენ რეპროდუქციული სიმწიფის ასაკში (18-დან 30 წლამდე). მრავალშვილიანობასა და დღეგრძელობას შორის უშუალო ასოციაცია არ გამოვლინდა. აღინიშნა კორელაცია ნაგვიანებ მშობიარობასა (40 წლის ასაკის ზემოთ) და დღეგრძელობას შორის. განსაკუთრებული ჯამრთელობითა და სიცოცხლის მაღალი ხანგრძლივობით გამოირჩევიან ქალები, რომლებმაც იმშობიარეს 40 წლის შემდეგ.

NITRIC OXIDE DEPENDENT SKIN AGING MECHANISM IN POSTMENOPASAL WOMEN

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In the aging process of living organism participitate the various internal and external factors [18]. These factors by the similar mechanisms affect the internal organs and skin tissues and cause alterations in there metabolism amd functions [2,3].

Exogenous factors (sunlight, ionizing radiation, contaminated air, smoking, alcohol, poor nutrition, impacts of various physical and psychological factors) play an important role in the skin aging [5].

Internal factors of the skin aging include genetic as well as hormonal (estradiol, testosteronis, melatoninis, insulin, thyroxine, etc.) factors [11,14,23,26], which induce in general age-related alterations of the hole body's metabolism (changes of hormones, their receptors and various signaling molecules content and/or their sensitivity, disorders of metabolic processes, intensification of the free radical oxidation, enhanced production of reactive oxygen species, membranes destruction, oxidative damage of DNA). These promote modification of the skin structure and deterioration of its functional state.

Subcutaneous blood flow is one of the factors, which determines the direction and intensity of the metabolic processes in the skin and its functional state. Skin blood flow is neurally controlled by two distinct branches of the sympathetic nervous system: an adrenergic vasoconstrictor system (acetylcholine), an active vasodilator system (vasoactive intestinal peptide (VIP) and histamine 1 (H1)) [1] and nitric oxide (NO), which is responsible for the 30% of the vasodilatation [1,8,9,15,20,24,25].

It is known that with age decreases functional activity of the reflexive regulation mechanism of subcutaneous blood flow [10], which causes an increase role of NO-dependent mechanism. Low stability of NO and dependence of its synthesis on vareious factors causes impairment of subcutaneous blood flow regulation, which contributes to violations of the oxidative processes, accumulation of the reactive oxygen compounds in the skin [12,13,16] and its rapid aging.

The goal of our study was to determine NO-dependent mechanisms of skin aging in post- and premenopausal women.

Material and metods. 23 women (age 40-50 year) were investigated. Women were divided into 2 groups: I group - reproducvtive age women (10 patients); II group - menopause age women (13 patients). For reasons of standartizaation women with cystic disease, ovarioectomy, or using hormone replacement therapy were excluded from studiing group. Patients were included in the menopausal group when they fulfill the following criteria: at least 12 month of amenorrhea.

All patients are subjected to a standart diagnostic protocol. In each group we investigated estradiole, free NO content in blood and lipid spectrum. Free nitric oxide (NO) was measured by Electron Paramagnic Resonance (EPR) method on the rediospectrometre РЭ-1307 (Rassia). For the detection of free NO spin-trap natrium diethildithiocarbamate (DETC) (Sigma) was used. EPR spectres of $NO\text{-}Fe^{2+}\text{-}(DETC)_2$ complexes are measured at the temperature of liquid nitrogen at microwave power 20 mVt.

Statistical analyses of the obtained results were performed by SPSS (version 10.0) program package. Result was obtained in form of standard deviation of average values. Difference between groups was assessed by student t+ criterion. In all cases statistical confidentiality was defined according to < 0.05 index. In order to determine the relationship between the obtained parameters correlation analyses were carried out.

The research complies with ethical standards and international best practice. The local ethics committee approved the protocol, and informed consent was obtained from all participants.

Results and their discussion. Skin of postmenopausal women as rule was pale, grayish, in some cases revealed pigmentation, which usually is due to insufficient supply of oxygen; skin around the eyes less flexible, wrinkled. As is known by subcutaneous blood flow to the skin cells are transported a variety of biologically active compounds; when this process is incomplete the violation of colagenesis is possible, which in turn contributes to reducing skin elasticity and wrinkle formation.

This alterations in skin of postmenopausal women were accompanied by significant reduction of the estradiol (22%) and HDL (20%) content, while the content of LDL (28%), triglycerides (16%) and total cholesterol (58%) were increased in comparison to the same parameters in the reproductive women (Table 1).

Table 1. Results of blood laboratory analyses in reproductive and menopausal women

Parameter		Age	
		Reproductive	Menopause
Estradiol (pg/ml)		0,52±0,034*	0,41±0,024
Lipid specter	LDL (mmol/L)	3,20±0,421*	4,11±0,214
	HDL (mmol/L)	1,09±0,0311*	0,90±0,053
	VLDL (mmol/L)	0,97±0,431	1,12±0,2
	TG (mmol/L)	1,84±0,132*	2,13±0,125
	Total Cholesterol (mmol/L)	3,28±0,251*	5,18±0,42

p<0,05

It was also revealed statistically significant changes of the free nitric oxide (NO) EPR signal in blood of postmenopausal women (Table 2).

Table 2. Intensivity of free nitric oxide (NO) EPR signal in blood of reproductive and menopausal women

	NO (mm/mg)
Reproductive	2,26±0,112
Menopause	1,89±0,050*

p<0,05

As follows from the results of our investigations in postmenopausal women moderate hypercholesterolemia and reduced levels of nitric oxide in the blood were revealed. Decrease free NO content in postmenopausal women' blood may be due to the decrease of NO synthesis (at the expense of the reduction constitution eNOS-ase activity), as well as the oxidative degradation of NO (its transformation to peroxinitrite in the oxidative stress conditions).

There are several facts indicating to the participation of hypercholesterolemia in the regulation activity of

NO-dependent vasodilation system. The three type isoforms of NOS, eNOS, iNOS, and nNOS, produce NO from the substrate L-arginine. Hypercholesterolemia favors the accumulation of asymmetrical dimethyl-L-arginine (ADMA), which interferes with L-arginine in the production of nitric oxide by eNOS. Modified LDL to oxidized LDL (oxLDL) increases the activity of the S-adenosylmethionine-dependent protein arginine methyltransferases, which generate ADMA from L-arginine. Moreover, oxLDL decreases the ADMA-degrading dimethylarginine dimethylaminohydrolase activity [22]. OxLDL also increases caveolin I expression (interaction of NOS with this protein impairs NO formation [4,6]) and modulates PKC activity and expression (this family of kinases has been shown to acutely attenuate eNOS-dependent NO production [6]).

The substrate of NOS, L-arginine, is able to be converted to L-ornithine and urea by the action of arginase. It's concepted that arginase is the enzyme that sharecrops L-arginine as a substrate and reciprocally regulates NOS activity by competing for the substrate. OxLDL increases arginase II activity by early post-translational event involving the release of the enzyme from microtubule association, resulting in activation and transcriptional upregulation [19].

Thus as follows from the above mentioned, hypercholesterolemia can cause failure of the NO-system and NO-dependent vasodilatation.

Many facts indicate on the important role of estrogens in the regulation of endothelium-dependent vasodilatation [27]. It is known that estrogen causes stimulation of eNOS enzymatic activity mediated by plasma membrane estrogen receptors [21], but inhibits indusible NO-sinthase (iNOS) [17]. It was shown also that supplementation of estrogens led to reduced expression of both iNOS and arginase I and II, increase activity of eNOS, accompanied by attenuation of atherogenesis [7].

Conclusion

This study demonstrate that in menopausal women insufficiency of estrogen's content is the main factor, which stipulates insufficiency of NO-dependent vasodilatative mechanism, and disorder of subcutaneous vasodilation in aged (postmenopausal) women, which contributes to violations of the oxidative processes in the skin and its rapid aging.

REFERENCES

1. Bennett LA, Johnson JM, Stephens DP, Saad AR, and Kellogg DL Jr. Evidence for a role for vasoactive intestinal peptide in active vasodilatation in the cutaneous vasculature of humans. J Physiol 2003; 552: 223-232.
2. Berneburg M, Plettenberg H, Krutmann J. Photoaging of human skin. Photodermatol Photoimmunol Photomed. 2000;16:239-44.
3. Dewberry C, Norman RA. Skin cancer in elderly patients. Dermatol Clin. 2004;22:93–6.
4. Everson WV, Smart EJ. Influence of caveolin, cholesterol, and lipoproteins on nitric oxide synthase: implications for vascular disease. Trends Cardiovasc Med. 2001;11:246–250.
5. Fan GB, Wu PL, Wang XM. Changes of oxygen content in facial skin before and after cigarette smoking. Skin Res Technol. 2011.
6. Fleming I, Mohamed A, Galle J, Turchanowa L, Brandes RP, Fisslthaler B, et al. Oxidized low-density lipoprotein increases superoxide production by endothelial nitric oxide synthase by inhibiting PKCalpha. Cardiovasc Res. 2005;65:897-906.
7. Hayashi T., Teiji Esaki, Daigo Sumi, Tapan Mukherjee, Akihisa Iguchi, Gautam Chaudhuri. Modulating role of estradiol on arginase II expression in hyperlipidemic rabbits as an atheroprotective mechanism. Proc Natl Acad Sci USA 2006; 103;27.
8. Holowatz LA, Thompson CS, and Kenney WL. L-Arginine supplementation or arginase inhibition augments reflex cutaneous vasodilatation in aged human skin. J Physiol. 2006; 574: 573–581.
9. Kellogg DL, Crandall CG, Liu Y, Charkoudian N, and Johnson JM. Nitric oxide and cutaneous active vasodilation during heat stress in humans. J Appl Physiol 1998; 85: 824-829.
10. Kenney WL, Morgan AL, Farquhar WB, Brooks EM, Pierzga JM, and Derr JA. Decreased active vasodilator sensitivity in aged skin. Am J Physiol Heart Circ Physiol 1997; 272: 1609–1614.
11. Kim B, Choi J, Park K, Youn S. Sebum, acne, skin elasticity, and gender difference - which is the major influencing factor for facial pores? Skin Res Technol. 2011.
12. Kohen R. Skin antioxidants: their role in aging and in oxidative stress—New approaches for their evaluation. Biomed Pharmacother 1999; 53: 181-192.
13. Leveque N, Muret P, Makki S, Mac-Mary S, Kantelip JP, and Humbert P. Ex vivo cutaneous absorption assessment of a stabilized ascorbic acid formulation

using a microdialysis system. Skin Pharmacol Physiol. 2004; 17: 298-303.
14. Makrantonaki E, Zouboulis CC; German National Genome Research Network 2. The skin as a mirror of the aging process in the human organism--state of the art and results of the aging research in the German National Genome Research Network 2 (NGFN-2). Exp Gerontol. 2007; 42(9):879-86.
15. McCord GR, Cracowski JL, and Minson CT. Prostanoids contribute to cutaneous active vasodilation in humans. Am J Physiol Regul Integr Comp Physiol 2006; 291: 596-602.
16. Munzel T, Daiber A, Ullrich V, and Mulsch A. Vascular consequences of endothelial nitric oxide synthase uncoupling for the activity and expression of the soluble guanylyl cyclase and the cGMP-dependent protein kinase. Arterioscler Thromb Vasc Biol 2005; 25: 1551-1557.
17. Pfeilschifter J., Ditz R., Pfohl M., Schatz H. Changes in Proinflammatory Cytokine Activity after Menopause. Endocrine Reviews. 2002; 23(1):90-119.
18. Puizina-Ivi. N. Skin Aging Acta Dermatoven. APA 2008; 17(2): 47-54.
19. Ryoo S, Lemmon CA, Soucy KG, Gupta G, White AR, Nyhan D, et al. Oxidized low-density lipoprotein-dependent endothelial arginase II activation contributes to impaired nitric oxide signaling. Circ Res. 2006;99:951-960.
20. Stanhewicz AE, Bruning RS, Smith CJ, Kenney WL, Holowatz LA. Local tetrahydrobiopterin administration augments reflex cutaneous vasodilation through nitric oxide-dependent mechanisms in aged human skin. J Appl Physiol. 2012;112(5):791-7.
21. Stirone C., Boroujerdi A., Duckles S.P., Krause D.N. Estrogen receptor activation of phosphoinositide-3 kinase, akt, and nitric oxide signaling in cerebral blood vessels: rapid and long-term effects. Molecular Pharmacology. 2005; 67(1):105-113.
22. Sungwoo Ryoo, Dan E. Berkowitz, and Hyun Kyo Lim. Endothelial arginase II and atherosclerosis. Korean J Anesthesiol. 2011; 61(1): 3–11.
23. Verdier-Sévrain S. Effect of estrogens on skin aging and the potential role of selective estrogen receptor modulators. Climacteric. 2007;10(4):289-97.
24. Wilkins BW, Chung LH, Tublitz NJ, Wong BJ, and Minson CT. Mechanisms of vasoactive intestinal peptide-mediated vasodilation in human skin. J Appl Physiol 2004; 97: 1291–1298.
25. Wong BJ, Wilkins BW, and Minson CT. H1 but not H2 histamine receptor activation contributes to the rise in skin blood flow during whole body heating in humans. J Physiol 2004; 560: 941–948.
26. Yan W, Zhao Z, Zhang L, Wang D, Yan L, Yin N, Wu D, Zhang F. Identification of estrogen-associated intrinsic aging genes in Chinese Han female skin by cDNA microarray technology. Biomed Environ Sci. 2011; 24(4):364-73.
27. Yanes L.L., Reckelhoff J. F. Postmenopausal hypertension. Am J Hypertens. 2011; 24(7):740-749.

SUMMARY

NITRIC OXIDE DEPENDENT SKIN AGING MECHANISM IN POSTMENOPASAL WOMEN

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The goal of our study was to determine nitric oxide (NO)-dependent mechanisms of skin aging in post- and premenopausal women.

23 women (age 40-50 year) were investigated. Women were divided into 2 groups: I group - reproducvtive age women (10 patients); II group - menopause age women (13 patients). Patients were included in the menopausal group when they fulfill the following criteria: at least 12 month of amenorrhea. All patients are subjected to a standard diagnostic protocol. In each group we investigated estradiole, lipids and free NO content.

Skin of postmenopausal women as a rule was pale, grayish, in some cases revealed pigmentation; skin around the eyes less flexible, wrinkled. Moderate hypercholesterolemia and reduced levels of nitric oxide and estradiole in the blood of studed postmenopausal women (in comparison reproductive aged women) was revealed. Decrease free NO content in blood may be due to the decrease of NO synthesis, as well as the oxidative degradation of NO in the oxidative stress conditions. N artcle the mechanism of dependence of NO-vasodilatative system activity on rhe level of hypercholesterolemia and estrogen content in blood are discussed.

It was concluded that in menopausal women insufficiency of estrogen's content is the main factor, which stipulates insufficiency of of NO-dependent vasodilatative mechanism, and disorder of subcutaneous vasodilatation in aged (postmenopausal) women which contributes to violations of the oxidative processes in the skin and its rapid aging.

Keywords: skin aging, premenopausal women, postmenopausal women.

РЕЗЮМЕ

РОЛЬ ОКИСИ АЗОТА В МЕХАНИЗМЕ СТАРЕНИЯ КОЖИ У ЖЕНЩИН В ПОСТМЕНОПАУЗАЛЬНОМ ВОЗРАСТЕ

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Целью исследования явилось установление NO-зависимых механизмов старения кожи у женщин репродуктивного и постменопаузального возраста.

Обследование проводили 23 женщинам в возрасте от 40 до 50 лет. Обследованные подразделены на 2 группы: I составили женщины репродуктивного возраста (n=10), II - в возрасте менопаузы (n=13). В группу менопаузы были включены женщины минимум с 12-месячной аменореей. Все пациенты подвергались стандартному обследованию; дополнительно исследовали содержание эстрадиола, липидов и свободного NO в крови.

Кожа у обследованных женщин постменопаузального возраста - бледная, с сероватым оттенком, в некоторых случаях выявлялась пигментация; вокруг глаз - малоэластичная. морщинистая. Изменения сопровождались умеренной гиперхолестеринемией, низким уровнем оксида азота и эстрадиола в крови в сравнении с женщинами репродуктивного возраста. Уменьшение свободного NO в крови, по всей вероятности, было связано со снижением синтеза NO, а также с его окислительной деградацией в условиях окислительного стресса. В статье обсуждаются механизмы зависимости активности NO-вазодилатационной системы от уровня холестерина и содержания эстрогенов в крови.

По заключению авторов, у женщин постменопаузального возраста низкий уровень эстрогенов в крови является основным фактором, определяющим недостаточность NO-зависимого вазодилятационного механизма и нарушения кровоснабжения организма в целом, в том числе и кожи, что способствует возникновению окислительного стресса в коже и ее быстрому старению.

რეზიუმე

NO-ს როლი კანის დაბერების მექანიზმში პოსტმენოპაუზის ასაკის ქალებში

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თბილსის სახელმწიფო სამედიცინო უნივერსიტეტი, საქართველო

კვლევის მიზანს წარმოადგენდა კანის დაბერების NO-დამოკიდებული მექანიზმების დადგენა რეპროდუქცული და პოსტმენოპაუზის ასაკის ქალებში.

კვლევა ჩაუტარდა 40-დან 50 წლამდე ასაკის 23 ქალს. ქალები გაყოფილი იყო ორ ჯგუფად: I ჯგუფი გაერთიანდა რეპროდუქციული ასაკის ქალები (n=10), II ჯგუფი - პოსტმენოპაუზის ასაკის (n=13). პოსტმენოპაუზის ჯგუფში ჩართვა ხდებოდა მინიმუმ 12-თვიანი ამენორეის არსებობისას. პაციენტებს ჩაუტარდათ სტანდარტული გამოკვლევები, დამატებით კი შესწავლილია თავისუფალი NO-ს, ლიპიდების და ესტრადიოლის შემცველობა სისხლში.

დადგინდა, რომ პოსტმენოპაუზის ასაკის ქალების კანი,როგორც წესი,ფერმკრთალია, დაჭკრავს მორუხო ფერი, ზოგიერთ შემთხვევაში შეინიშნება პიგმენტაცია; თვალების ირგვლივ კანი ნაკლებად ელასტიური და დანაოჭებულია. სისხლში გამოვლინდა ზომიერი ჰიპერქოლესტერინემია, თავისუფალი NO-ს და ესტრადიოლის დონე შემცირებულია, რეპროდუქციული ასაკის ქალებთან შედარებით. სავარაუდოა,რომ თავისუფალი NO-ს შემცველობის შემცირება პოსტმენოპაუზის ასაკის ქალებში განპირობებულია მისი სინთეზის ინტენსივობის დაქვეითებით, ან ოქსიდაციური დეგრადაციით ჟანგვითი სტრესის პირობებში. განხილულია NO-დამოკიდებული ვაზოდილატაციური სისტემის აქტივობა და სისხლში ქოლესტეროლისა და ესტრადიოლის შემცველობას შორის კორელაცია.

გამოტანილია დასკვნა: ესტროგენების დაბალი დონე სისხლში წარმოადგენს ძირითად ფაქტორს, რომელიც განსაზღვრავს NO-დამოკიდებული ვაზოდილატაციური მექანიზმებისა და სისხლის მიმოქცევის უკმარისობას ორგანიზმში, კერძოდ კი - პოსტმენოპაუზის ასაკის ქალების კანშიც.

THE ROLE OF ESTROGENS IN PATHOGENESIS OF AGE-RELATED ARTERIAL HIPERTENSION

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Several studies have examined menopausal age and related factors in women; the association of menopause status with hypertension is widely discussed in literature [5,11]. Many authors reported about gender-related differences in the pathophysiology of hypertension; literature data suggest that hypertension and cardiovascular complications are more severe in men and post-menopausal women than in pre-menopausal women [15] and in the seventh decade of life the blood pressure in women is even higher than in men [7]. It is generally assumed that several factors contribute to postmenopausal hypertension; the estrogens play a complex role in the pathogenesis of hypertension [11]. A lot of studies reveal effects of estrogens on regulation of cardiovascular system [3,12]. These effects connected with endotelium-dependent and independent vazodilatation. It is well known, that estrogen inhibits vascular smooth muscle proliferation (via blocking collagen secretion), reduce permeability of potassium-dependent calcium channels [1], resulting in antihypertensive activity.

To our knowledge there is little published information on processes that underline pathogenesis of hypertension in menopause. In this respect the aim of our investigation was to study some aspects of the role of estrogens in the pathogenesis of hypertension during menopause.

Material and methods. 93 women with hypertension, who are referred to the Central Clinic of Tbilisi State Medical University (Georgia) during 2009-2011 were investigated. All patients are subjected to a standart diagnostic protocol. Women were divided into 2 groups : I - reproducvtive age group – 43 patients; 2 - menopause age group – 50 patients. Patients were included in the menopausal group when they fulfill the following criteria: at least 12 month of amenorrhea. For reasons of standartization women with cystic disease, ovarioectomy, or using hormone replacement therapy were excluded from studing group.

Subjects were undergone preliminary screening for body mass index, dislipidemia, history of arterial hypertension, diabetes mellitus, myocardial infarction or stroke, angina pectoris, family history of coronary artery disease. Extensive data were collected regarding smoking, alcohol intake, diet, physical activity, lifestyle factors, exposure to toxic materials, etc.

In each group we investigated estradiole, oxygen (O_2^-) and lipid (LOO^-) reactive species, NO and endoteline content and antioxidant enzymes superoxidismutase (SOD), catalase, glutaTionreductase (GR) activity in blood.

In order to determine activity of antioxidant enzymes packed red blood cell lysate of patients' blood was prepared. The activity of antioxidant enzymes (SOD, catalase, GR) was measured according standard methods described in [8]. Free nitric oxide (NO), free oxygen (O_2^-) and peroxil radicals ($LOO^·$) was measured by Electron Paramagnic Resonance (EPR) method on the redio-spectrometre РЭ-1307 (Rassia). For the detection of free NO spin-trap natrium Diethyldithiocarbamic acid (DETC) (Sigma) was used. EPR spectres of $NO\text{-}Fe^{2+}\text{-}(DETC)_2$ complexes are measured at the temperature of liquid nitrogen at microwave power 20 mVt. Peroxil radicals ($LOO^·$) was measured with spin-trap α-phenyl-tertbutilnitron (PBN) (SIGMA). Free oxygen radicals (O_2) was measured with spin-trap 5,5-dimethyl-I-pyrolin-IV-oxide (DMPO) (Sigma). Spin-trapped O_2^- and $LOO^·$EPR spectres are measured at room temperature at microwave power 20 mVt. Endothelin-1 content in blood was measured by immunoenzymatic assay with "Cayman Chemical" standard - test reagents.

Statistical analyses of the obtained results were performed by SPSS (version 10.0) program package. Result was obtained in form of standard deviation of average values. Difference between groups was assessed by student t+ criterion. In all cases statistical confidentiality was defined according to $p<0.05$ index. In order to determine the relationship between the obtained parameters correlation analyses were carried out.

The research complies with the norms of the bioethics's foundations. The local ethics committee approved the protocol, and informed consent was obtained from all participants.

Results and their discussion. It was revealed statistically significant changes of the redox - homeostasis parameters in menopausal women (in relation to reproductive age): activity of catalase increased (50%), GR reduced significantly (38%) and SOD wasn't significantly changed; lipoperoxide- (LOO.) and superoxide-radicals (O_2^-) content increases, a free nitric oxide (NO) content decreases and endotheline content increases (Table).

Table. Activity of pro- and antioxidant system and free nitric oxide (NO) and endothelin content in blood of reproductive and menopausal aged women

	$LOO^·$ (mg/ml)	**O_2^- (mg/ml)**	**Cat (units)**	**SOD (nmolNADPHmin /1 mg peot.)**	**GR (nmolNADPHmin /1 mg peot.)**	**NO (mg/ml)**	**Endothelin (pg/ml)**
Reproductive	0,36± 0,039	0,06± 0,016	12,08± 0,711	2,34± 0,471	9,03± 0,421	2,26± 0,112	5,4± 0,2
Menopause	0,63± 0,073*	0,26± 0,206*	18,02± 2,299*	3,02± 0,274	5,63± 0,387*	1,89± 0,050*	6,4± 0,5*

$p<0,05$

We have identified, as well decrease free nitric oxide and increase on endothelin content in the blood of menopausal women.

In some patients it was detected low intensity of HbNO EPR signal in blood (data is not shown). At the same time no statistically significant correlation was revealed between HbNO EPR signal intensity an estradiol blood concentration in reproductive ($r=-0,60$, $p=0.03$) and only tendency in the correlation between this two parameters in menopausal women ($r=-0,29$, $p=0,12$).

Free radicals including oxygen (O_2^-,·OH, H_2O_2) and nitrogen (NO) reactive species, are the products of normal cellular metabolism and exist in cells at low concentrations [9]. Imbalance in their generation and clearence induced by insufficiency of endogenous antioxidant system increases the content of free radicals in the body and promotes the development of oxidative stress. Oxidative stress plays a central role in the pathogenesis of numerous diseases.

Results of our investigation revealed the disbalance between pro- and antioxidant systems activity in blood of menopausal women, which manifested by increase content of oxygen and lipids free radicals ($LOO^·$, O_2^-), alteration in antioxidant enzymes (catalase, GR) activity and reduction in estrogen level. The important role of estrogens in regulation of women redox metabolism is well known. According to the results of numerous studies estrogens might protect tissue from oxidative demage by the receptor-dependent (increase expression and activity of endogenous antioxidant enzymes) and receptor independent (direct scavenging of reactive oxygen species) pathways.

Direct receptor-independent antioxidative effects of estrogens is due to existense in their structure specific unsubstituted A-ring phenolic hydroxyl group, which provides strongest antioxidant protection. It was shown that estrogens increase manganese SOD (MnSOD) and extracellular SOD (ecSOD) expression and enzymatic activity [10]. Significantly lower GR activity has been seen in blood samples from menopausal women compared with that in reproductive aging women. Prolonged oral contraceptive use, increased GR activity [10].

In our study it was revealed, that in menopausal women GR shows significantly lower activity, whereas activity of SOD didn't changed in comparision to the reproductive age women. These results appear to confirm findings regarding the stimulatory effect of estrogens on glutathione content [9] and the glutation cycle regulating enzymes [10]. Significant increase of catalase activity in menopausal women may be considered as a compensation against falling activity of GR. Therefore, estrogen deficiency in menopausal women causes the accumulation of free oxygen (O_2^-) and lipid ($LOO^\cdot$) radicals in blood due to the reduction of their scavenging potential and failure of antioxidant enzymes activity.

Many facts indicate on the important role of estrogens in the development of hypertension in postmenopausal women. There are numerous evidence indicating on the association between development of endothelial dysfunction and reduced endogenous production of estrogens [18]. Endothelial dysfunction is characterized by an impairment of endothelium-dependent vasodilatation, linked to imbalance between the endothelial-derived vasoactive factors, like nitric oxide and endothelin [2].

Nitric oxide (NO) is an extremely pleiotropic molecule, and there are many contradictory reports in the literature concerning its physiological and pathophysiological role. These may be due to the multiple cellular activity of this molecule, the level and site of NO production, and the redox milieu into which it is released. Decrease free NO content in menopaul-aged women' blood detected in our study may be due to the decrease of NO synthesis (at the expense of the reduction constitution eNOS-ase activity, or enzyme content), as well as the oxidative degradation of NO (transformation to peroxinitrite in the oxidative stress conditions), or deposition it in form of HbNO complexes. It is known that estrogen causes stimulation of eNOS enzymatic activity mediated by plasma membrane estrogen receptors [16], but inhibits indusible NO-sinthase iNOS. The inhibitory effects of estrogens on iNOS activity might be conditioned to their suppressive effects on proinflammatory cytokine activity [13], while long-term estrogen deficiency can cause development of the inflammation.

Endothelin-1 is a potent vasoconstrictor peptide and increases in its synthesis/release are associated with vaso-occlusive disorders in the blood vessel. Being an important mediator of vascular dysfunction in aging, endothelin has also been identified as one of the targets for estrogen action in the vasculature. Estradiol and its major endogenous metabolites inhibit endothelin-1 synthesis by an estrogen receptors-independent mechanism [4,8].

Conclusion

This study confirms that in menopausal women insufficiency of estrogens is the major factor, which causes imbalance between the endothelial-derived vasoactive factors (nitric oxide and endothelin) and development of hypertension. It was concluded, that in women of reproductive age probability and risk of hypertension grows in the presence of additional risk factors, such as oxidative stress and/or fluctuations in estrogen's level towards insufficiency, which leads to reduction of nitric oxide content due to its oxidative transformation in peroxinitrite, or enhanced inclusion in HbNO complexes, whereas development of hypertension in postmenopausal women may develop by different mechanisms, might including inflammation.

REFERENCES

1. Colditz GA, Hankinson SE, Hunter DJ, Willett WC, Manson JE, Stampfer MJ, Hennekens C, Rosner B, Speizer FE. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. N Engl J Med. 1995; 332: 1589-1593.
2. Dobarro D, Gómez-Rubín MC, Sanchez-Recalde A, Moreno R, Galeote G, Jimenez-Valero S, Calvo L, López de Sá E, López-Sendón JL. Current pharmacological approach to restore endothelial dysfunction. Cardiovasc Hematol Agents Med Chem. 2009; 7(3):212-222.
3. Dubey RK, Oparil S, Imthurm B, Jackson EK. Sex hormones and hypertension. Cardiovasc Res. 2002; 53: 688-708.
4. Dubey R. K., Jackson E. K. Keller P. J. Imthurn B., Rosselli M. Estradiol Metabolites Inhibit Endothelin

Synthesis by an Estrogen Receptor-Independent Mechanism. Hypertension. 2001;37:640-644.
5. Erdine S., Arslan E., Olszanecka A. Hypertension in women – pathophysiological and clinical aspects. Przegl Lek., 2012; 69(2): 72-75.
6. Halliwell B, Gutteridge JM Role of free radicals and catalytic metal ions in human disease: an overview. Methods Enzymol. 1990; 186:1-85.
7. Landahl S., Bengtsson C., Sigurdsson J. A., Svanborg A., Svardsudd K. Age-related changes in blood pressure. Hypertension, 1986; 8:1044-1949.
8. Lekontseva O., Chakrabarti S., Davidge S.T. Endothelin in the female vasculature: a role in aging? AJP - Regu Physiol. 2010; 298(3): R509-R516.
9. Liu H., Wang H., Shenvi S., Hagen T. M., Liu R.-M, Glutathione Metabolism during Aging and in Alzheimer Disease. Annals of the New York Academy of Sciences. 2004; 1019: 346–349.
10. Massafra C, D Gioia1, C De Felice1, E Picciolini, V De Leo, M Bonifazi and A Bernabei. Effects of estrogens and androgens on erythrocyte antioxidant superoxide dismutase, catalase and glutathione peroxidase activities during the menstrual cycle. Journal of Endocrinology. 2000; 167: 447–452.
11. Matthias B., Matthias R. M. Postmenopausal Hypertension: Mechanisms and Therapy. Hypertension, 2009; 54:11-18.
12. Pelzer T, de Jaeger T, Muck J., Stimpel M, Neyses L. Oestrogen action on the myocardium in vivo: specific and permissive for angiotensin-con-verting enzyme inhibition. J Hypertens. 2002; 20:1001-1006.
13. Pfeilschifter J., Ditz R., Pfohl M., Schatz H. Changes in Proinflammatory Cytokine Activity after Menopause. Endocrine Reviews. 2002; 23(1):90–119.
14. Ratiani L, Parkosadze G, Koptonashvili L, Ormotsadze G, Sulaqvelidze M, Sanikidze T. Correlation of atherogenetic biomarkers and estradiol changes in postmenopause. Georgian Med News. 2011; 195:100- 105.
15. Regnault V. , Thomas F., Safar M. E., Osborne-Pellegrin M., Khalil R. A., Pannier B., Lacolley P. Sex difference in cardiovascular risk: role of pulse pressure amplification. J Am Coll Cardiol., 2012; 59(20):1771 -1777.
16. Stirone C., Boroujerdi A., Duckles S. P., Krause D. N. Estrogen Receptor Activation of Phosphoinositide-3 Kinase, Akt, and Nitric Oxide Signaling in Cerebral Blood Vessels: Rapid and Long-Term Effects. Molecular Pharmacology. 2005; 67(1):105-113.
17. Strehlow K, Rotter S, Wassmann S, Adam O, Grohé C, Laufs K, Böhm M, Nickenig G. Modulation of antioxidant enzyme expression and function by estrogen. Circ Res. 2003;25; 93(2):170-177.
18. Yanes L. L., Reckelhoff J. F. Postmenopausal hypertension. Am J Hypertens. 2011; 24(7):740-749.

SUMMARY

THE ROLE OF ESTROGENS IN PATHOGENESIS OF AGE-RELATED ARTERIAL HYPERTENSION

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Several factors are contributing to menopausal hypertensión; the role of estrogens in patogénesis of hypertensión in menopausal women have not completely established. The aim of the present investigation was to study some aspects of the role of estrogens in the pathogenesis of hypertension during menopause. 93 women with hypertension, who are referred to the Central Clinic of Tbilisi State Medical University (Georgia) during 2009-2011 were investigated. Women were divided into 2 groups: 1 - reproducvtive age group (43 patients); 2 - menopause age group (50 patients). In each group we investigated estradiole, oxygen ($O_2^{\cdot}$), lipid ($LOO^{\cdot}$) reactive species, NO and endotheline content and antioxidant enzymes (SOD, catalase, GR) activity. The results of study reveal increased of superoxide - and lipoperoxide - radicals, as well as of endothelin content in blood of menopausal women, while concentration of free nitric oxide decreased; at the same time activity of catalase increased (by 50%), GR reduced significantly (by 38%) and SOD's activity didn't change in comparision to reproductive aged group. Negative correlation between the HbNO and estradiole content in blood of reproductive aged women was established (r=-0,60, p=0.03); no dependence between these two parameters in menopausal aged women was revealed (r=-0, 29, p=0,12). It was concluded, that in women of reproductive age probability and risk of hypertension grows in the presence of additional risk factors, such as oxidative stress and/or fluctuations in estrogen's level towards insufficiency, which leads to reduction of nitric oxide content due to its oxidative transformation in peroxinitrite, or enhanced inclusion in HbNO complexes, whereas development of hypertension in postmenopausal women may develop by different

mechanisms, might including inflammation.

Keywords: menopause, nitric oxide, endothelin, oxidative stress.

РЕЗЮМЕ

РОЛЬ ЭСТРОГЕНОВ В ПАТОГЕНЕЗЕ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ У ЖЕНЩИН РАЗНОГО ВОЗРАСТА

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Роль эстрогенов в патогенезе гипертонии у женщин менопаузного возраста в современной научной литературе широко представлена, однако этот вопрос по сей день дискутируется. Целью настоящего исследования явилось установление роли эстрогенов в патогенезе менопаузной артериальной гипертензии.

Исследованы 93 женщины с артериальной гипертензией, которые обратились в Центральную клинику Тбилисского государственного медицинского университета в 2009-2011 гг. Женщины были подразделены на 2 группы: I группа - 43 женщины репродуктивного возраста, II группа - 50 женщин менопаузного возраста. Включение в группу постменопаузы происходило на основании как минимум 12-месячной аменореи. В каждой группе были исследованы содержание эстрадиола, реактивных соединений кислорода (O_2^-) и липидов ($LOO^\cdot$), содержание свободного оксида азота (NO) и эндотелина, активность антиоксидантных ферментов (супероксиддисмутаза - SOD, каталаза, глутатионредуктаза - GR) в крови. Исследования выявили увеличение содержания супероксид- и липопероксид-радикалов и эндотелина и уменьшение свободного оксида азота в крови у женщин постменопаузного возраста. В то же время активность каталазы увеличилась на 50%, GR - уменьшилась на 38%, а показатель SOD оставался в пределах, соответствующих значений у женщин в группе репродуктивного возраста. Обнаружена отрицательная корреляция между содержанием HbNO и эстрадиола в крови в группе репродуктивного возраста (r=-0,60, p=0.03); а у женщин менопаузного возраста зависимость между этими параметрами не установлена (r=-0,29, p=0,12). Сделано заключение, что у женщин репродуктивного возраста риск развития артериальной гипертензии возрастает в присутствии таких добавочных риск-факторов, как окислительный стресс и/или недостаток эстрогенов, что способствует окислительной трансформации оксида азота в пероксинитрит или его усиленному включению в HbNO комплексы и снижению уровня NO в крови, а развитие гипертензии у женщин постменопаузного возраста возможно посредством различных механизмов, включая воспаление.

რეზიუმე

ესტროგენების როლი არტერიული ჰიპერტენზიის განვითარებაში სხვადასხვა ასაკის ქალებში

ლ. რატიანი, მ. ხორავა,მ. დგებუაძე,ნ. ჟვანია, თ. სანიკიძე

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, თბილისი, საქართველო

თანამედროვე ლიტერატურაში ესტროგენების როლი მენოპაუზის ასაკის ქალების არტერიული ჰიპერტენზიის პათოგენეზში დეტალურადაა აღწერილი,თუმცა ეს საკითხი დღემდე დისკუსიის საგანია. წინამდებარე ნაშრომის მიზანი იყო მენოპაუზური ჰიპერტენზიის განვითარებაში ესტროგენების როლის ზოგიერთი ასპექტის დადგენა. გამოკვლეულია 93 ქალი ჰიპერტენზიით,რომელთაც მიმართეს თბილისის სახელმწიფო სამედიცინო უნივერსიტეტის ცენტრალურ კლინიკას 2009-2011 წლებში. ქალები გაყოფილ იქნა 2 ჯგუფად: I - რეპროდუქციული ჯგუფი (43 პაციენტი); II - პოსტმენოპაუზური ჯგუფი (50 პაციენტი). პაციენტების პოსტმენოპაუზურ ჯგუფში ჩართვა ხდებოდა მინიმუმ 12-თვიანი ამენორეის საფუძველზე. თითოეულ ჯგუფში გამოკვლეული იყო ესტრადიოლის,ჟანგბადის (O_2^-), ლიპიდების რეაქტიული ნაერთების ($LOO^\cdot$), აზოტის ჟანგის (NO) შემცველობა და ანტიოქსიდანტური ფერმენტების (სუპეროქსიდდისმუტაზა - SOD, კატალაზები, გლუტატიონრედუქტაზა - GR) აქტივობა სისხლში. კვლევის შედეგად პოსტმენოპაუზის ასაკის ქალების სისხლში გამოვლინდა სუპეროქსიდ- და ლიპოპეროქსიდრადიკალების,

ენდოთელინის შემცველობის მატება, თავისუფალი აზოტის ჟანგის შემცველობის შემცირება; კატალაზას აქტივობის მომატება 50%, GR-ს აქტივობის შემცირება 38%, ხოლო SOD-ს აქტივობა უცვლელი რჩებოდა რეპროდუქტიული ასაკის ქალებისათვის დამახასიათებელ პარამეტრებთან შედარებით. რეპროდუქციული ასაკის ქალებში გამოვლინდა უარყოფითი კორელაცია სისხლში HbNO-ს და ესტრადიოლის შემცველობებს შორის (r=-0,60, p=0.03), პოსტმენოპაუზური ასაკის ქალებში კორელაცია ამ 2 პარამეტრს შორის არ დადგინდა (r=-0,29, p=0,12).

გაკეთებულია დასკვნა,რომ რეპროდუქციული ასაკის ქალებში არტერიული ჰიპერტენზიის რისკი იზრდება ისეთი დამატებითი ფაქტორების თანაობისას, როგორიცაა ოქსიდაციური სტრესი და/ან ესტროგენების უკმარისობა, რაც ხელს უწყობს აზოტის ჟანგვის პეროქსინიტრიტად ტრანსფორმაციას, ან მის გაძლიერებულ ჩართვას HbNO-ს კომპლექსებში და სისხლში თავისუფალი NO-ს დონის დაქვეითებას. პოსტმენოპაუზური ასაკის ქალებში კი არტერიული ჰიპერტენზია ვითარდება განსხვავებული მექანიზმების მეშვეობით, ანთებითი პროცესის ჩათვლით.

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