ISSN 2409-9988

Inter Collegas

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2021

N4(8)

INTER COLLEGAS

2021

Vol. 8 No.4

OFFICIAL JOURNAL OF
KHARKIV NATIONAL MEDICAL UNIVERSITY
ISSN 2409-9988

EDITORIAL BOARD:

Recommended for publishing
by Scientific Council of Kharkiv National Medical University

16 – Dec. – 2021

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

Periodicity:
4 times a year

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CENTER OF PALLIATIVE MEDICINE AT KHARKIV NATIONAL MEDICAL UNIVERSITY: PRESENT-DAY CHALLENGES AND DEVELOPMENT STRATEGIES

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https://doi.org/10.35339/ic.8.4.196-200

Abstract

In the majority of the countries, palliative care is an integral part of quality medical care, which includes comprehensive medical, social, psychological, and spiritual support for critically ill patients and their relatives. According to the WHO, every year about 20 mln people worldwide need palliative care at the end of their lives. There are many more who need palliative care until the last year of their lives. Thus, the total number of people who need palliative care annually is about 40 mln. It is estimated that of the 20 mln people in need of end-of-life palliative care, 78% live in low- and middle-income countries; about 67% are elderly and about 6% are children. However, only 14% of people who need end-of-life palliative care receive it. Palliative care considers the principle of respect for patients' decisions and aims to provide practical support to their family members during illness and in the event of a patient's death to overcome grief over the loss of a loved one. The WHO's global strategy for health care, based on human approach and integration, is to strengthen palliative care programs for patients with various diseases. Despite the fact that some steps have already been taken in Ukraine towards the development of palliative care, there are still some problems, such as lack of qualified medical staff; lack of relationships between primary and secondary, tertiary care and coordination; imperfect system of informing medical workers about ensuring the right to anesthesia for seriously ill patients; lack of a sufficient number of pharmacies licensed to operate controlled medicines; lack of interagency programs in the field of palliative care.

Keywords: *medical care, palliative care, patients, quality of life.*

In the majority of countries, palliative care is an integral part of quality medical care, which includes comprehensive medical, social, psychological and spiritual support for critically ill patients and their relatives. In 2014, the first-ever global resolution on palliative care, WHA67.19, called on the WHO and Member States to improve access to palliative care as a core component of health systems, focusing on primary health care and community-based or home-based care [1].

Palliative care was first introduced in 1990 by the WHO and is defined as "an approach to care that improves the quality of life of patients and their families with life-threatening illnesses through the implementation of preventive measures, the assessment and treatment of of pain, and the prevention of physical, psychological and spiritual problems." In 2004, the WHO described palliative care for children in detail as active full care of the child, his/her physical condition, his/her state of mind and spirit, as well as measures to support the family. Recently, in 2013, the 18th edition of the WHO Model List of Essential Medicines and the 4th edition of the WHO Model List of Essential Medicines for Children were published. These papers included sections on the use of pain medications in the context of palliative care. The use of these medicines and the need to ensure the availability and accessibility of all medicines needed for optimal palliative care are described. In addition to opioid and non-opioid drugs intended for the treatment of pain syndrome, these lists also included drugs for the treatment of various general symptoms, such as anorexia, nausea, constipation, diarrhea, etc. [2-5].

WHO estimates that around 20 mln people worldwide need palliative care at the end of their lives every year. There are many more who need palliative care until the last year of

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their lives. Thus, the total number of people who require palliative care every year is about 40 mln. Of the 20 mln people who need palliative care at the end of their lives, an estimated 78% live in low- and middle-income countries; about 67% are elderly people (over 60 years old) and about 6% are children [6, 7]. However, only 14% of people who need palliative care at the end of life actually receive it [1].

According to the WHO, palliative care aims to improve the quality of life of patients and their families who experience all the clinical, psychological, ethical and spiritual problems associated with incurable diseases. Palliative care takes into account the principle of respect for patient decisions and aims to provide practical support to their family members during illness and in the event of a patient's death to overcome grief over the loss of the relative. Palliative care should be based on the principles of patient's autonomy, accessibility and continuity, with the obligatory consideration of all the rights of the patient and his/her family members. Within national health systems, palliative care should be involved in the ongoing care of children with life-threatening illnesses. There is a need to develop a strategic link between palliative care and prevention, early detection and treatment programs for these diseases.

With regard to palliative care and the right to health, the Committee on Economic, Social and Cultural Rights, in General Comment 14, noted that "...States have a duty to respect the right to health by refraining from taking measures that close or restrict equal access for all to preventive, curative and palliative health services" [8].

The main document regulating children's rights is the UN Convention on the Rights of the Child (1989) [9]. But the authors focus on another important document, which was published in 2013. This is the "Charter of the Rights of the Dying Child (Trieste Charter)" [10]. The death of a child is a devastating tragic moment for everyone involved in it. The Charter of the Rights of the Dying Child was created to highlight the rights of young patients, which should not be forgotten because of the age or condition of the child, nor because of cultural traditions, nor because of the place and time when it occurs. Each right has a number of responsibilities. The charter describes and defines them, seeking to combine all professional, moral, legal and scientific aspects. However, this knowledge often remains divorced from the real hospital, family and social conditions in which the child lives and dies and often does not correspond to the personal situation of the young patient [10].

To meet the needs of children with life-limiting or life-threatening illnesses, the International Children's Palliative Care Network (ICPCN) was established to bring together leaders and organizations from around the world, to improve childcare, to create global policy, research, education and technical assistance health care systems and governments. Also, the success of the ICPCN is the introduction of palliative care for children into the global health program [11].

Thus, the WHO global strategy for health care, based on a people-centered approach and integration, is to strengthen palliative care programs for patients with different diseases.

Despite the fact that some steps have already been taken in Ukraine towards the development of palliative care - mobile palliative care services have been created locally for both adults and children, inpatient beds are functioning, hospices have been opened, the state finances inpatient and mobile palliative care, a number of regulatory documents and so on, but the palliative care system is still in its infancy [12]. According to the authors, the problems are a critical shortage of qualified medical personnel; lack of effective methods of providing assistance; lack of opportunities to learn good practice in this area; lack of state policy and a common understanding of the philosophy of this type of medical care; lack of relationships between primary and secondary, tertiary health care and coordination; an imperfect system of informing medical workers on ensuring the right to pain relief for critically ill patients; lack of a sufficient number of pharmacies that have received a license to circulate controlled medicines; lack of interagency cooperation in the provision of palliative care (by the education sector, social services, confessors, lawyers, economists); lack of interdepartmental palliative care programs; lack of assessment of financing of palliative care measures.

Training palliative care professionals is an important component, while all health care professionals must have a basic knowledge of the principles of palliative care and proper pain management [13].

Despite this, most health care professionals do not receive training in palliative care at the start of their work, or take short courses that are insufficient. As stated in the WHO Planning and implementing palliative care services - a guide for program managers (2016), palliative care training should be provided primarily to physicians, clinical staff or physician assistants, who should receive at least 35 hours of theoretical and practical components. Nurses, community health workers or volunteers with 35 hours of training in basic palliative care are also not an exception. Volunteers and parents or relatives must be trained to provide some home care services, and must complete at least 6-16 hours of training. This will allow learning to recognize uncontrolled physical or psychological disorders or significant social problems and communicate this information to community health centers [6].

Kharkiv region is a favorable platform for development of palliative care because of its powerful educational component and scientific base, as well as opening and working of hospices for adults and children in recent years, a developed pharmaceutical base ("Health" factory and National Pharmaceutical University), creation of the Regional Clinical Center for Medical Rehabilitation and Palliative Care for Children, active media. As shown by a survey of the opinion of 378 pharmaceutical specialists conducted by the scientists from the National University of Pharmacy, only 67% of them demonstrated an average level of knowledge on the tasks of palliative care. The insufficient level of theoretical knowledge and practical skills on certain issues of palliative care was determined, namely, the basic definitions, principles and objectives, nosological forms of diseases in which palliative services are provided; the main provisions of the current regulatory framework for the organization of this type of medical care. The researchers came to the conclusion about the feasibility of introducing educational and scientific activities in order to increase the efficiency of palliative care in Ukraine, taking into account global trends in healthcare development, the implementation of scientific research in the system of providing palliative care with the definition of a socio-pharmaceutical component; development and improvement of educational and methodological cases at pre- and postgraduate levels of education for pharmaceutical specialists [14].

In the recent years, some basic aspects of palliative care have been included in the educational programs for preparation of bachelors, specialists and masters at Kharkiv National Medical University. Highly qualified personnel of the third level of higher education are trained thanks to the inclusion of the search for palliative care in the educational and scientific component of the educational and scientific program in the specialty "Pediatrics". Three theses for grade of candidates of medical sciences have been defended and 2 PhD theses on aspects of palliative care in pediatrics are being carried out [15].

Establishing palliative care services in a community involves either integrating care into the day-to-day work of existing health facilities or, where not existing, creating a new service.

The Center of Palliative Medicine was established at Kharkiv National Medical University in November 2021 to solve some of the pressing problems of palliative care, both at the regional and national levels.

The aim of the Center of Palliative Medicine is to improve the quality of palliative care for adults and children at the regional and national levels through the organization and conduct of educational activities; organizing, coordinating and conducting research in palliative medicine, popularizing research results; development of draft regulatory documents on palliative care; international cooperation in the branch of palliative medicine.

The main tasks of the Center of Palliative Medicine are:

- teaching students, graduate students, doctors, nurses, social workers, volunteers and the general public in the basic principles of palliative care;
- introduction of the philosophy and principles of palliative care in the process of professional development of medical workers, acquisition of new competencies and practical skills in the provision of palliative care to adults and pediatric patients;
- training of scientific and pedagogical workers of KhNMU in the basic principles of palliative care;
- conducting research in the branch of palliative medicine, including international projects;

- promotion and dissemination of knowledge on palliative medicine and care;

- cooperation with public authorities and local government, institutions and organizations of various sphere of activity, communal non-profit enterprises, volunteers, non-governmental public organizations, charitable foundations, domestic and international partners, church and religious organizations; participation in development of draft regulatory documents on palliative care.

Solution of the main tasks of the Center of Palliative Medicine will be realized by means of:

- creation of on-line educational platforms on pediatric and adult palliative medicine for students, graduate students, nurses, doctors, social workers, volunteers, and the public;

- cooperation with international experts in the branch of palliative medicine;

- collection of materials for research on palliative care, their generalization, publication of the results;

- creation of information resources on the problems of palliative care and dissemination of knowledge among the medical, academic community and the population;

- informing about the activities of the Center through the media; conducting information campaigns to advocate for development of palliative care;

- participation in scientific conferences and other forums on palliative care;

- preparation and holding of annual international events.

Conclusions.

Some results of the activities of the Center of Palliative Medicine will go beyond our vision and the established task. These are the so-called indirect consequences of the activity, because the Center will play a leading role in fostering a culture in which academic research thrives; children and their families will participate in the research and contribute their voice to increase the evidence base; leading role in supporting parenting organizations; a leading role in external work with the wider academic world; a leading role in the cost-effectiveness of palliative care provision and adaptation to demographic changes. That is, the main results of the activities of the Center of Palliative Medicine can be used by palliative care services, the media for the information space and the academic community for the cultivation of national experts.

Declarations

Statement of Ethics

The author has no ethical conflicts to disclosure.

Consent for publication

The author gives her consent to publication.

Disclosure Statement

The author has no potential conflicts of interest to disclosure.

Funding Sources

There are no external sources of funding.

Data Transparency

The data can be requested from the author.

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Received: 30-Oct-2021
Accepted: 13-Dec-2021

INSUFFICIENT CONTROL OF OUT-OF-OFFICE BLOOD PRESSURE: THE PROBLEM OF MASKED UNCONTROLLED HYPERTENSION (REVIEW)

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https://doi.org/10.35339/ic.8.4.201-210

Abstract

Despite significant advances in the diagnosis and treatment of arterial hypertension (AH), the problem of insufficient blood pressure (BP) control in hypertensive patients is quite acute. According to current guidelines, the effectiveness of antihypertensive therapy is mainly assessed by reaching the target levels of office BP, while masked uncontrolled hypertension (MUCH), which is diagnosed on the basis of insufficient control of out-of-office BP, increases the risk of cardiovascular events. Patients with insufficient out-of-office BP control have an increased risk of cardiovascular events compared to patients with both office and out-of-office BP control, therefore MUCH requires timely diagnosis and correction. This mini-review summarizes the understanding of the nature of MUCH. A particular attention is paid to risk factors and ways of influencing the out-of-office BP control. The article also assessed the important contribution of ABPM to the control of out-of-office BP and to determining the overall risk of MUCH.

Keywords: *masked hypertension, masked uncontrolled hypertension, risk factors, office and out-of-office blood pressure.*

Arterial hypertension (AH) has been and remains the most common non-communicable disease in the world associated with the world's highest rates of cardiovascular morbidity and mortality. It is known about numerous factors contribute to poor blood pressure (BP) control: lack of disease awareness, lifestyle, non-adherence to medication, inadequate treatment, drug hypertension, undiagnosed secondary causes [13, 18, 55].

According to current guidelines, the effectiveness of antihypertensive therapy is mainly assessed by reaching the target levels of office BP, while masked uncontrolled hypertension (MUCH), which is diagnosed on the basis of insufficient control of out-of-office BP, increases the risk of cardiovascular events [58, 62, 67].

As for masked hypertension in general, on the basis of the relationship between office and out-of-office BP, three of the subtypes can be distinguished: masked effect (BP in an untreated subject measured with ambulatory or home BP monitoring (ABPM and HBPM, respectively) is higher than the corresponding normal office BP but within the target), masked hypertension (in an untreated subjects office BP less than 140/90 mm Hg, however at least one of the indicators of out-of-office BP exceeds the diagnostic values for hypertension) and MUCH (in some treated patients in whom the office BP appears controlled to recommended BP targets, but BP is elevated and thus uncontrolled according to out-of-office BP measurements) [38].

It should be noted that patients with masked hypertension and MUCH have an increased risk of cardiovascular events compared to patients with both office and out-of-office BP control [2, 13, 19, 60, 61].

That is why modern guidelines for the diagnosis and treatment of hypertension emphasize the importance of measuring out-of-office BP to confirm the diagnosis of hypertension, as well as indicate the possibilities of this method for assessing the control of antihypertensive therapy [16].

Risk of cardiovascular events in MUCH

Several studies have shown that the presence of MUCH negatively affects the prognosis in patients, but studies that have assessed the global effect of MUCH on cardiovascular outcomes and mortality deserve special attention [3, 5, 8, 11, 40].

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A meta-analysis of six studies using ABPM (12,610 patients with 933 events) and five studies using HBPM (17,742 patients with 394 events) demonstrated a significant effect of MUCH on increased risk of cardiovascular events and mortality from all causes in all ethnic groups (with the highest hazard ratio in studies with Black patients). Therefore, regardless of the cause of MUCH, it is very important to diagnose it on time and then control out-of-office BP, including correcting the risk factors for MUCH [40, 41].

It should be noted that an increased cardiovascular risk in MUCH (compared with normotension and full controlled hypertension) was also confirmed in various single studies and meta-analyses [12, 17, 20, 23, 26, 28].

Results of the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) study (8,000 untreated subjects from 12 populations) that masked hypertension was associated with similarly increased risk of cardiovascular events as compared to normotensive subjects [7, 14, 38].

Due to the fact that masked hypertension is associated with an increased risk of cardiovascular disease, target organ damage, stroke, and mortality (compared to sustained normotension), 2017 ACC/AHA guidelines, 2018 ESH/ESC guidelines and 2020 ISH guidelines recommend prescribing ABPM to screen for masked hypertension [62, 66, 67].

Data from the Shi Xiaoyang study in the Chinese patient population also confirmed a higher incidence of cardiovascular disease with MUCH compared with patients without masked hypertension [54].

At the same time, compared with non-masked hypertension, patients with MUCH already had significantly more concomitant diseases at the initial level. However, since the cross-sectional design of the study did not allow the authors to confidently answer the question of whether MUCH contributed to these comorbidities or vice versa, additional studies are needed to answer this question, as well as to assess the cardiovascular benefits of patients in improving the control of out-of-office BP [54, 60, 61].

Risk factors of MUCH

Despite the fact that it is not possible to single out any one dominant factor that affects the development of MUCH, the studies have shown that, compared with hypertensive patients with complete control of both office and out-of-office BP, patients with MUCH have a higher constellation of traditional risk factors for cardiovascular diseases and hypertensive target organs damage [31, 35, 49, 68].

Among the factors that affect the MUCH formation, it is possible to distinguish lifestyle features, gender and racial differences, the presence of one or another variant of comorbidity, disturbances in the circadian rhythm of BP, excessive sympathetic activity, an increase in transferrin receptors, as well as factors associated with the choice of antihypertensive therapy and adherence to treatment [40, 41].

Lifestyle and MUCH formation

MUCH formation can depend on various lifestyle factors including psychological stress, smoking and alcohol consumption [13, 41, 42].

In particular, in older people, soon after a heavy meal, there may be a postprandial decrease in BP, so if the measurement of office BP is at this time, then it is likely that masked hypertension is present [39]. At the same time, those who are exposed to mental stress, with office measurements of BP can have normal BP levels, and only with ABPM and in stressful situations, they have an increased BP. Studies show that masked hypertension occurs more often in smokers and people who consume excessive amounts of alcohol [17, 40].

It is noteworthy that people with a sedentary lifestyle, who are obese, usually do not tolerate physical activity during the day, and when the office measurement of blood pressure at rest, BP levels often correspond to prehypertension [29].

In addition, in older people (especially males), masked hypertension occurs due to a decrease in the sensitivity of baroreceptors and an increased BP variability. 15. Whereas shortened sleep time (beginning in adolescence) and obstructive sleep apnea are also risk factors for masked hypertension [13, 53].

Sex differences in MUCH formation

Male gender is not only an unmodifiable risk factor for cardiovascular disease in general, but studies show that it is also associated with an increased risk of MUCH in particular [9, 22, 24].

Although the mechanisms underlying sex

differences in MUCH are not fully understood, a number of studies have explained these differences. The study by Siddiqui et al. showed that in MUCH, the level of extraclinical catecholamines and metanephrines in urine was higher than in complete BP control [57]. Since men have higher sympathetic activity than women, this may in part explain high-er prevalence of MUCH in men [22, 24, 57].

The CARDIA cohort, conducted on dif-ferent age groups of patients, showed that male gender was an independent predictor of masked hypertension [45].

Race and MUCH

A number of studies have shown that the prevalence of masked hypertension and MUCH in particular varies significantly depending on the ethnicity of the patients [9, 22, 24, 30, 43, 50].

It should be noted, that in high-normal office BP and additional use of ABPM, masked hypertension was found in more than one third of untreated African Americans and more than 40% of low-income South Africans [13-15, 65].

In particular, the Negroid race is considered as one of the risk factors for masked and MUCH. The results of the Jackson Heart Study of African Americans suggested the presence of isolated nocturnal hypertension in 19% of participants with the mean office BP 124/76 mmHg. In a more recent Jackson Heart Study, in 34% of untreated subjects with normal office BP masked hypertension was established [13-15].

Comorbidities and MUCH

Currently it was proven that the risk of masked hypertension and MUCH, in particular, increases in the presence of a number of comorbidity in patients [6, 9, 13-15, 25, 26].

It should be noted that in one third of Korean adolescents with type 1 diabetes mellitus, an increase in the intima-media thickness of the carotid artery was associated with the development of masked hypertension [25].

In the Brazilian population of patients with type 2 diabetes mellitus and prehypertension, in contrast to sustained normotension, one third of patients had untreated masked hypertension with significant left ventricular hypertrophy and macroproteinuria [26].

The IDACO study found that masked hypertension was present in 29% of patients with type 2 diabetes compared to 19% in the nondiabetic population (adjusted for age, sex and risk factors). It should be noted that 42.5% of diabetics had MUCH [14-15].

The study assessed the prevalence of insufficient out-of-office BP control in chronic kidney disease (CKD) showed that MUCH was observed in 66% of patients with high normal office systolic BP, 33% with normal office systolic BP, and 17% with optimal office systolic BP. This indicates the need for screening ABPM in patients with CKD and prehypertension [14-15].

A Spanish patient registry, which included 2,115 treated hypertensive patients followed for 4 years for cardiovascular events, showed that night BP was the single most important predictor of cardiovascular risk. At the same time, MUCH using ABPM was established in 31% of patients. The clinical characteristics of these patients were advanced age, male gender, smoking history, obesity, diabetes, a longer history of hypertension, which together increased the risk of cardiovascular events in the future [13-15].

Urinary albumin excretion and albumin-creatinine ratio (ACR) are not only markers of glomerular endothelial dysfunction, but have been proven to be associated with the development of MUCH. In particular, the Agarwal study [1] found that MUCH is strongly associated with ACR in CKD, and Verdalles et al. [63] found that albuminuria (measured by ACR) influenced the formation of resistant hypertension. The study of Sung J.H. [59] showed that the ACR was higher in MUCH than in patients with full controlled hypertension, even after controlling cardiovascular disease and CKD.

Another comorbidity that affects the MUCH formation is dyslipidemia. Prejbisz A. et al. [44] found that in MUCH, levels of total cholesterol, LDL-cholesterol and triglycerides were higher than with full controlled hypertension. At the same time, in the studies of Jafar T. et al. [21], differences were shown only in the levels of total cholesterol and LDL-cholesterol in MUCH and controlled AH. In the study of Sung J.H. [59] it was established that all lipids (including total cholesterol, HDL, LDL, triglycerides, and apolipoprotein B) were higher in MUCH compared to full controlled hypertension.

Circadian rhythm disorders and MUCH

Several studies have show that masked

hypertension is associated with a variety of circadian rhythm disturbances [15, 42, 48, 52]. In particular, those patients who smoke, consume excessive alcohol, are exposed to mental stress and do not tolerate physical activity are more likely to have a daytime variant of masked hypertension, whereas with lack of sleep, obstructive sleep apnea, metabolic syndrome, diabetes and chronic kidney disease, nocturnal variant of masked hypertension is most often observed [15].

The meta-analysis of Salles G.F. [48] established that a blunted nocturnal BP decline (as a mean nighttime sleep entity and as a categorical non-dipping subgroup), was a predictor of worse cardiovascular events.

The African American Study of Kidney disease and Hypertension (AASK) trial demonstrated the prevalence of nocturnal non-dipping or reverse-dipping pattern in 70% of patients with MUCH as compared to full BP control [13-15, 42].

The results of our study suggested that as compare to both office and out-of-office BP control in MUCH, circadian rhythm disorders (with a predominance of the non-dipper rhythm) were significantly more common [52].

Sympathetic activity and MUCH

Despite advanced our knowledge on uncontrolled hypertension thanks to the clinical benefits of decrease in BP with renal denervation, central arteriovenous anastomosis, baroreflex activation therapy and carotid body denervation, the variable BP response needs further studies of pathophysiology of poor BP control [18].

The results of the study of Siddiqui M. et al. have shown that patients with MUCH have a higher out-of-clinic sympathetic activity compared with well-controlled hypertension. These data indicate the influence of increased out-of-clinic sympathetic activity on the MUCH formation. Therefore, the question of the possible benefits of drugs and interventional procedures aimed at the activity of the sympathetic nervous system in MUCH remains debatable [55-56].

Another study by these authors showed that patients with MUCH have higher out-of-clinic levels of aldosterone in urine compared with patients with truly controlled AH (this may indicate a higher extraclinical tone of the sympathetic nervous system, that an increase in aldosterone secretion and a higher out-of-clinic BP). It has also been shown that elevated aldosterone levels in MUCH were independently associated with an increased risk of diabetes, suggesting that aldosterone blockade may play a role in lowering high BP and hyperglycemia in these patients [57].

Transferrin receptor and their role in MUCH formation

It is well known that the transferrin receptor plays an important role in the transport of cellular iron, and an increase in transferrin levels can be observed in the presence of iron deficiency. In addition, the association of an increase in transferrin receptors has also been established in a number of cardiovascular diseases (in particular, chronic left ventricular heart failure and pulmonary hypertension) [34, 46, 47, 51].

The study of Sung J.H et al. [59] showed that in MUCH, the transferrin receptors was higher than in patients with full controlled AH (even taking into account demographic variables and comorbidity). Thus, this study showed that the transferrin receptor, along with other factors (such as albumin-creatinine ratio, levels of total cholesterol, high-density lipoproteins, low-density lipoproteins, triglycerides, and apolipoprotein B), is associated with an increased risk of MUCH formation, while MUCH is associated with a very high risk of cardiovascular vascular disease and/or CKD. The results of this study partially explain the lack of efficacy of antihypertensive therapy in certain patient populations [59].

The role of patients and physicians in MUCH prevention and treatment

Considering the fact that in modern recommendations, control of out-of-office blood pressure in patients receiving antihypertensive therapy is not an obligatory component of monitoring the effectiveness of treatment, therefore, MUCH very often remains unrecognized and, accordingly, untreated.

At the moment, under the leadership of the Italian hypertensiologist G. Paratti, a MASTER study (multicenter, multinational study including around 40 clinical centers from different continents) is being carried out in which the strategies for controlling office BP and out-of-office BP (according to ABPM data) are being compared, which in the next few years will be able to answer the question of the effectiveness of one or another variant of BP control in influencing on the prognosis in hypertensive patients [37].

In addition to the fact that MUCH often remains undiagnosed, its high prevalence may be due to the fact that many doctors prescribe “suboptimal" antihypertensive treatment (due to both the doctor’s inertia and his inability to select long-acting antihypertensive drugs, and also due to confusion in optimal levels BP with high in patients cardiometabolic risk) [13-15].

Poor adherence of patients to therapy is considered one of the reasons for the development of MUCH. At the same time, there are controversial data on its effect on poor control of out-of-office BP. In particularly, in the study of Siddiqui M. et al [55], it was shown that patients with masked uncontrolled arterial hypertension did not have significant differences in adherence to therapy compared with patients with good control of office and out-of-office BP.

The results of nine studies with a total of 14,729 participants (11,245 normotensives patients, 3,484 participants with MUCH, 1,984 participants with white-coat hypertension, and 5,143 participants with sustained hypertension) showed that among patients receiving antihypertensive therapy, masked hypertension was associated with a higher the incidence of cardiovascular events than in patients with normal blood pressure and white coat hypertension, and a similar incidence of cardiovascular events in patients with sustained treated hypertension. Therefore, it is important to consider the benefits of early screening and detection of patients with masked hypertension, as well as to assess the goals of BP control in this category of patients based on HBPM and ABPM [36].

It remains not fully understood how the choice of antihypertensive therapy affects the MUCH formation. Despite the fact that a number of studies claim that there is no connection between the MUCH formation and the option of antihypertensive therapy [55, 56], nevertheless, the results of most studies confirm the effect of the choice of antihypertensive therapy on the risk of its formation [4, 10, 27, 29, 32]. In particularly, our recently published study found that in 86.5% of patients with previously established MUCH, strengthening antihypertensive therapy contributed to the achievement of both office and out-of-office BP control [52].

Interesting data on the effect on the prevalence of masked hypertension, sustained hypertension and MUCH in the nondiabetic population was obtained in the recent IDACO study, which compared patients on antihypertensive therapy with those patients who did not receive treatment [14]. It has been shown that both treated patients with MUCH and sustained normotensive patients, there was an increased cardiometabolic risk compared to untreated patients with either masked hypertension or stable normotension. This can be explained by the epidemiological principle that normalization of BP on antihypertensive therapy does not eliminate the burden of life from a previous increase in BP and does not eliminate other cardiometabolic risk factors associated with the hypertensive state. However, at the same time, antihypertensive therapy initiates the transition from stable hypertension to MUCH and then to stable normotension [14-15].

Thus, the analysis of the literature data showed that further research is needed to study the causal biomarker pathways of MUCH and its associations with lifestyle, existing comorbidities, and an antihypertensive therapy option.

Conclusions

Due to superiority of out-of-office BP over clinic BP in predicting prognosis, it is very important to provide ABPM (or HBPM) not only for AH confirmation and also for the control of antihypertensive therapy.

The results of most studies and meta-analyzes have shown that when starting antihypertensive therapy based only on office BP, many patients with sustained hypertension can be converted into the category of MUCH, while not achieving the desired therapeutic result - sustained normotension. At the same time, ABPM is the preferred method for monitoring out-of-office BP, since it provides recording of BP at night time and can determine the overall risk of MUCH (HBPM can be an addition to ABPM).

Given this fact, it is very important that guidelines for the diagnosis and treatment of hypertension, which currently focus on office BP, should reconsider their positions and for patients with elevated office BP it is recommended to receive additional ABPM (or, if not available, HBPM) for determining the true level of BP and improving indicators of poor control of hypertension around the world.

Declarations

Statement of Ethics

The author has no ethical conflicts to disclosure.

Consent for publication
The author gives her consent to publication.
Disclosure Statement
The author has no potential conflicts of interest to disclosure.
Funding Sources
There are no external sources of funding.
Data Transparency
The data can be requested from the author.

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Received: 16-Oct-2021
Accepted: 13-Dec-2021

INFLUENCE OF INSULIN-LIKE GROWTH FACTOR-I LEVELS ON THE COURSE OF ACUTE MYOCARDIAL INFARCTION

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https://doi.org/10.35339/ic.8.4.211-216

Abstract

Over the recent years, cardiovascular disease has reached epidemic proportions among chronic noncommunicable diseases worldwide. According to the latest tendencies, cardiovascular diseases play the leading role in formation of current negative health and demographic trends in Ukraine and all over the world: they significantly affect the main health indicators: morbidity, mortality, disability, life expectancy and quality of life. The recent 20 years, are characterized by triplication of the prevalence of CVDs among the Ukrainian population, the mortality rate from them has risen by 40%. This review analyzes serum level of insulin-like growth factor-I (IGF-I) in patients with acute myocardial infarction and his role in left ventricular remodelling. The scientific data regarding the neurohumoral component of acute myocardial infarction pathogenesis have been expanded by increasing levels of the angiogenesis marker IGF-I, which can be explained by his properties as markers of the acute phase of inflammation. An analysis of the relationship between troponin I and IGF-I, a marker of myocardial damage, showed a direct relationship, indicating an increase in troponin I concentration with rising serum IGF-I levels. This indicates that the activity of the angiogenesis marker IGF-I may be associated with the severity and depth of myocardial damage.

Keywords: *coronary heart disease, acute myocardial infarction, cardio markers, insulin-like growth factor-I.*

BACKGROUND

Among the many forms of coronary heart disease (CHD) today, the most life-threatening is acute myocardial infarction (AMI) [1-4]. According to various sources, every year more than 16 million new cases of AMI are recorded in the world, and its consequences can be observed in a few days or in months and years. According to the American Heart Association, within six years of undergoing AMI, 18% of men and 35% of women have a recurrence of AMI, and 22% of men and 46% of women become disabled due to severe chronic heart failure. 30-40% of patients have left ventricular dysfunction [5].

Preventive focus of modern cardiology is the search for fundamentally new risk factors and early diagnosis and prognosis of cardiovascular disease [6-8]. Thus, protein growth factors and damage in acute coronary syndrome were identified: pregnancy-associate IGF-I plays an important d plasma protein-A (PAPP-A) and IGF-I. PAPP-A and IGF-I are protein complexes circulating in the blood, the increase in the concentration of which in CHD indicates the instability of atherosclerotic plaques [9, 10].

The purpose of the review was to highlight the effect of the serum level of insulin-like growth factor-I on the pathogenetic features of endothelial dysfunction in patients with acute myocardial infarction.

Association of IGF-I serum levels with acute myocardial infarction

IGF-I is a protein from the family of insulin-like growth factors, similar in structure and function to insulin. It helps to repair damaged tissues, stimulate neoangiogenesis and vasodilation. It is synthesized mainly by the liver and kidneys, but also by the paracrine and autocrine pathways, vascular endothelial and smooth muscle cells, and cardiac myocytes [11, 12].

PAPP-A is a zinc-containing matrix metalloproteinase secreted by fibroblasts when atherosclerotic plaque is damaged.

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The molecular structure of IGF-I is very similar to the structure of insulin. IGF-I plays an important role in cell survival and growth by binding to a specific receptor (IGF1R), which is present in many cell types, including cardiac myocytes. IGF1R receptor activation has been shown to reduce apoptotic and necrotic cell death induced by ischemia as well as reperfusion injury by stimulating the intracellular phosphoinositide 3-kinase, protein kinase B and extracellular signaling-regulated signaling pathway [13-15].

Researchers such as Buerke M et al. [16] administered IGF-I 1 hour before rat myocardial ischemia for 20 minutes, followed by reperfusion. IGF-I maintained the state of ischemic myocardium due to inhibition of cardiac necrosis by polymorphonuclear-induced leukocytes and inhibition of reperfusion apoptosis of cardiac myocytes.

Davani EY et al. [17] caused isolated ischemia in the rat myocardium for 20 minutes, followed by reperfusion for 2 hours with a modified Krebs cycle or Krebs cycle with the addition of IGF-I. IGF-I, administered immediately after reperfusion, protected the ischemic myocardium from further injury through mitochondrial-dependent mechanisms that support the mitochondrial-to-nDNA ratio within the heart tissue.

Interventions are also known, O'Sullivan JF et al. [18], which caused ischemia/reperfusion in pigs by balloon occlusion of the middle left anterior descending coronary artery for 90 minutes, followed by reperfusion for 2 hours. After 2 hours of reperfusion, IGF-I was delivered to the ischemia via the intracoronary route. Thirty minutes after IGF-I treatment, it caused an increase in IGF-I receptor activation, as well as protein kinase B activation and glycogen synthase kinase-3, which are signaling pathways for IGF-I receptor activation.

Within 24 hours after IGF-I treatment, the apoptosis of cardiomyocytes in the area of myocardial infarction was significantly reduced compared to pigs that were not treated with IGF-I. Two months after IGF-I treatment, myocardial infarction decreased, myocardial collagen, and decreased fibrotic markers decreased; increase in the number of cardiomyocytes in the area of infarction; improved movement of the walls of the left ventricle; global reperfusion and left ventricular function have improved.

Padin-Iruegas ME et al. [19] suggested that the mechanism of cardioprotective effects of IGF-I was due to the activation of receptors for IGF-I, which flow into the caspase pathways. Another key-note conclusion of the mentioned work is the presence of defensive features of IGF-I, even when it was administered relatively late after reperfusion.

Other researchers who have studied myocardial ischemia [20] have suggested that if reperfusion injury exists, the window for improving myocardial reperfusion may be much wider than previously thought. Evidence that low doses of IGF-I reduced necrosis and at least partially reduced apoptosis suggests that apoptosis by reperfusion may result in significantly greater cardiac cell death than previously thought. This finding also raises the question of whether early administration of IGF-I (during or within minutes of reperfusion) would lead to an even greater degree of improvement in the affected myocardium.

It is known that exogenous IGF-I increases myocardial contractility in the short and long term [21-23]. In healthy subjects, IGF-I increases insulin sensitivity and increases plasma glucose loss and tissue glucose utilization [24]. Thus, significant data suggest a possible cardioprotective role of IGF-I.

According to another study, patients with a favorable course of acute myocardial infarction had significantly lower concentrations of IGF-I compared with those with an unfavorable course. One year later, IGF-I values returned to normal [25, 26].

Another study [27] found that low IGF-I levels in patients with CHD were associated with mortality over the next two years. Since there was no control group in this study [27], it cannot be compared with ours. Another previous study [28] of 122 people who underwent coronary angiography reported a significant reduction in IGF-I in patients with significant CHD (126±7 ng/ml) compared to people without it.

It is also unclear whether a marked decrease in IGF-I is a primary change or a secondary phenomenon for myocardial necrosis and associated neurohumoral environment [29, 30]. Given the physiological half-life of IGF-I circulating within 10 hours [31], a reduction in the risk of recurrence of myocardial infarction in patients seems unlikely. Neurohumoral changes following myocardial infarction, including elevated

cortisol, interleukin-1, and tumor necrosis factor-alpha (which inhibit IGF-I release) [32] or reduce IGF-I-binding proteins (which may prolong plasma half-life IGF-I) [33, 34], possibly would help reduce IGF-I. This is evidenced by the inverse relationship between IGF-I levels and the delay that separates the sample from the onset of symptoms.

In 2010, Japanese researchers published the results of a genetic study of case-control studies involving 320 patients with myocardial infarction and 307 healthy volunteers: they found proportions of IGF-I genes that probably differ in groups [35]. This study demonstrates that the specific nucleotide sequence of the IGF-I gene can be used as a genetic marker of high risk of myocardial infarction.

In recent years, there have been quite a few studies examining the IGF-I participation in the coronary atherosclerosis evolving in patients without pituitary disease. The first clinical study involving 218 individuals, which found a probable decrease in IGF-I levels in patients with myocardial infarction, was conducted in 1997 [36]. An inverse relationship between IGF-I and the risk of CHD and its complications, including cardiovascular mortality, as well as stroke, has been found in other, later studies [37]. It is also known that low levels of IGF-I correlate with the length of the QT interval regardless of heart rate, which indicates its effect on repolarization in the myocardium and the likelihood of developing threatening ventricular arrhythmias [38]. But there are also opposite data: people with high levels of IGF-I are more likely to develop CHD [39].

IGF-I as a marker of the acute phase of inflammation in AMI

The presence of AMI is followed through a growth in the level of IGF-I, which may be due to its properties as a marker of the acute phase of inflammation. Thus, according to several studies, IGF-I levels correlate with the risk of cardiovascular disease in the general population [40, 41]. It has been reported that low levels of IGF-I may be an independent risk factor for myocardial infarction and CHD, as well as prevent obesity, insulin resistance, impaired glucose intolerance [42]. According to Andrade D et al., (2020) Increased IGF-I activity is associated with cavity hypertrophy and myocardial wall thickening, as well as increased inotropic heart function, and increased IGF-I levels after AMI have been associated with increased PV and myocardial hypertrophy [43].

As it can be seen, some studies [44, 45] have shown an association between a known marker of myocardial damage, troponin I, and a marker of IGF-I angiogenesis, which also allows us to consider it as a marker of acute inflammation in AMI.

Conclusions

The numerous works demonstrate that IGF-I, a new highly sensitive biochemical marker of vascular inflammation and damage, can be used in the laboratory diagnosis of acute coronary syndrome in patients with and without obesity. In the aspect of the "cardiovascular continuum", the reparative role of IGF-I is systemic, having a beneficial effect on the kidneys, nevertheless, the pathogenetic, prognostic and therapeutic effects of IGF-I in patients with AMI requires further investigation.

Declarations

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Consent for publication

All authors give their consent to publication.

Disclosure Statement

The authors have no potential conflicts of interest to disclosure.

Funding Sources

There are no external sources of funding

Data Transparency

The data can be requested from the authors.

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Received: 03-Oct-2021
Accepted: 13-Dec-2021

THE VIEW OF THE CLINICIAN ON THE PROBLEM OF COVID-19

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https://doi.org/10.35339/ic.8.4.217-225

Abstract

The review article features the peculiarities in the epidemiological and clinical picture of a new coronavirus infection, COVID-19. The purpose of the review was to analyze the issues of the management. Pathogenetic relationships between SARS-CoV-2 virus, COVID-19 and angiotensin-converting enzyme 2 (ACE2) are assessed. Predisposing factors, which result in development of pneumonia and endothelial dysfunction, disorders in microcirculation, vasoconstriction, work of the renin-angiotensin system with subsequent development of ischemia in certain organs, inflammation and edema of tissues, are analyzed. Lung damage causes development of interstitial pneumonia, activation of the process of formation of fibrosis and decreased pulmonary function. Accumulation of anti-inflammatory cytokines, which break the blood-brain barrier, in the CNS can cause dysregulation of central structures, autonomic dysfunction and severe asthenic syndrome, which can maintain low-grade inflammation for a long time. Opportune diagnosis and treatment of concomitant diseases in post-COVID-19 patients are of paramount significance for achieving a positive clinical outcome. The plan of rehabilitation treatment should be individualized according to the patient's needs. In order to assess remote consequences of COVID-19 all patients require further follow-ups.

***Keywords**: SARS-CoV-2, post COVID-19, ACE2, cytokines.*

At the end of 2019 an outbreak of a new coronavirus infection took place in the People's Republic of China with its epicentre in the City of Wuhan. On February 11, 2020 the World Health Organization gave an official name, COVID-19 (CoronaVirus Disease 2019), to the infection caused by the new coronavirus [1]. The International Committee on Taxonomy of Viruses named the causative agent of this infection as SARS-CoV-2. The peculiar epidemiological and clinical picture of the new coronavirus infection, COVID-19, necessitates the analysis of the information about the pathogenesis of the above infection that is important because of absence of any etiotropic therapy at present and forced use of pathogenetic treatment [2]. Similar to other respiratory coronaviruses, the primary transmission of COVID-19 is via droplet spread, the fecal-oral route is not excluded [3].

SARS-CoV-2 is an RNA-containing virus, which together with SARS-CoV and MERS-CoV belong to β-coronaviruses. Angiotensin-converting enzyme 2 (ACE2), which participates in the functioning of the heart muscle and regulation of blood pressure, is the receptor of SARS-CoV-2 in people. In cases of COVID-19 the spike protein (protein S) with the crown-like form of the viral membrane is bound with the ACE2 receptor, and after that the viral RNA enters the cell [4, 5]. A number of researches and observations have demonstrated absence of any general consensus concerning the role of ACE2 receptors in the pathogenesis of this disease. ACE2 receptors are present on the cells of the respiratory tract, kidneys, esophagus, bladder, intestines, heart and central nervous system [6, 7].

In order to penetrate into a cell the virus cooperates with an ACE2 receptor and membrane-bound serine protease 2 (TMPRSS2), which is necessary for priming protein S. The binding of protein S with ACE2 is followed by direct fusion of the viral and cellular membranes; after that the protein is subjected to partial breakdown and becomes active. Viral RNA enters the cytoplasm, where translation is followed by an active replication of the viral genome; their cooperation with the Golgi apparatus makes it possible for viral particles to release themselves into the plasma, thereby continuing the cycle of the virus spread in the

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organism [8, 9]. Taking into consideration a decreased expression of ACE2 against a background of COVID-19, we may suppose a subsequent violation in the work of the renin-angiotensin system that can affect regulation of blood pressure and hydroelectrolytic balance [10]. Meanwhile, we cannot exclude that this change in the expression of ACE2 receptors plays an important role in the pathogenesis of COVID-19 itself. Statistical analysis of COVID-19 cases in individuals, who lived in high lands, revealed a milder course of disease versus inhabitants from even lands. The authors believe that the above fact can be caused by both a reduced period of life of the virus in conditions of a decreased atmospheric pressure and an induced decline of the ACE2 level against a background of hypoxia [11, 12]. Experimental data in mice, mutant by ACE2, revealed lower viral load and replication; on the other hand, proceeding from similar lung damages in COVID-19 and "avian influenza" virus H5N1, we may suppose a protective effect of exogenous introduction of ACE2 on the development of acute respiratory distress syndrome (ARDS) [13,14].

For a long time the ability to bind the human ACE2 receptor as well as some peculiarities in the structure of ORF3 and ORF8 genes, which are supposed to play a certain part in the pathogenesis of the virus, were regarded to be unique properties of SARS-CoV. Large-scale studies of Chinese populations of bats resulted in isolation of several viruses, which are similar to SARS-CoV by the structure of their receptor-binding domain. It has been shown that in order to penetrate into a cell these strains are able to use receptors of both people, bats and civets. A number of other strains had a similar structure of ORF3 and ORF8 genes [15]. Hence, among the viruses that circulate in colonies of bats there are variants, which already have the required tropism and ability to infect people without any necessity for an additional adaptation in an intermediate host [16, 17].

Type II alveolocytes are the main and rapidly achieved target for ACE2 receptors; their lesion with the virus results in diffuse alveolar damage that manifests clinically with development of ARDS in 41.8% of patients with lethal outcome in more than 50% of cases [18].

It is well known that in order to penetrate into a cell the virus uses ACE2 receptors, expressed on alveolar pneumocytes, thereby causing lung damages. However, ACE2 receptors are also widely expressed on endotheliocytes, which line the vessels of many organs. It has been proven that SARS-CoV-2 can directly infect epitheliocytes of human blood vessels in vitro. Vascular endothelium is an active paracrine, endocrine and autocrine organ, which participates in the regulation of vascular tone and maintaining of vascular homeostasis [19, 20]. By now there is evidence for direct contamination of endothelial cells with SARS-CoV-2 virus and resultant diffuse endothelial inflammation [21, 22]. Studies of molecular markers, which characterize the functional state of the vascular endothelium, reveal that endothelitis is one of key syndromes in COVID-19 and later a trigger for post-COVID syndrome. Direct lesion of endotheliocytes with the virus or their indirect damage with immune cells, cytokines and free radicals can result in significant endothelial dysfunction. The latter, which develops in COVID-19, causes disorders in microcirculation and vasoconstriction with subsequent development of ischemia of organs, inflammation and edema of tissues, procoagulation [23, 24]. Endothelitis can explain systemic impairments of microcirculatory function in different vascular beds and their clinical consequences in patients with COVID-19.

Oxidative stress plays a significant role in the pathogenesis of COVID-19, aggravating the consequences of cytokine storm, blood coagulation and hypoxia that cause damages of tissues and organ failure. It is hypothesized that there is a cross connection between cytokine storm and oxidative stress. These disorders can play an important role in the severity of signs and symptoms in patients with COVID-19 [25, 26]. Hence it is quite logical to present a model of the pathogenesis of coronavirus infection with a primary lung damage and late hematological tissue hypoxemia (cytopathic hypoxemia) and mitochondrial dysfunction caused by participation of oxidative stress. This fact is confirmed with reliable experimental data [27].

Dysregulatory activation of monocytic phagocytes, development of generalized thrombosis in the microcirculatory bed and interstitial pneumonia in COVID-19 [28]. In response to penetration of SARS-CoV-2 virus,

T-cell immune reactions prevail during the exudative and proliferative stages. In the fibrotic stage, the total amount of T lymphocytes is sharply reduced, whereas cells of humoral immunity are not revealed. The prevalence of CD8+ T suppressor lymphocytes over CD4+ T helper lymphocytes may be associated with mechanisms of autoimmune damage [29].

Lung damage as consequence of the direct injury of the vascular endothelium and alveolar complex (alveolocytes and interalveolar septa, when the radiological sign of "clouded glass" develops) with the coronavirus and cytokines causes development of interstitial pneumonia, activation of the process of formation of fibrosis as well as decreased pulmonary function [30].

Different aspects of patho- and morphogenesis of coronavirus infection are thoroughly studied; in particular, morphological changes in the pulmonary tissue of patients, who died within different time periods after appearance of the first clinical signs of the disease, are comparatively analyzed [31]. Analysis of macro- and microscopic changes in the respiratory tract with use of immunohistochemical studies has made it possible to assess the state of their lungs in patients with COVID-19 in 80 cases of lethal outcome [32]. The peculiarities of diffuse alveolar damage have been revealed and therefore make it possible to distinguish 3 phases in the pathomorphogenesis of interstitial pneumonia in COVID-19: fulminant (up to 10 days; it corresponds to the exudative and proliferative stages of ARDS), persisting (11-20 days; it corresponds to the proliferative stage of ARDS) and fibrotic (revealed in patients, who died on the 21st-45th days; it corresponds to the stage of organization of ARDS) [33].

An evidence base for a relation of ACE2 gene with sex dimorphism of mortality in COVID-19 (a lower death rate was detected in women) is presented. This fact may be caused by either genetic dimorphism, as ACE2 gene is located on X chromosome, or different immunoregulatory effects of estrogens and testosterone [34].

Accordingly, development and progression of the disease most frequently occur in two directions: lung damages and coagulation disorders, which often remain undetected. Coagulation disorders both result in the appearance of clinically significant thrombotic complications and play the role in the pathogenesis of coronavirus infection, including cases with lung damage. Disorders of microcirculation resulting from microthromboses can significantly aggravate the course of acute respiratory failure in patients with COVID-19 [35].

Many patients, who survived acute manifestations of COVID-19, are only in the beginning of their way to recovery. What consequences should be expected after the acute stage of coronavirus infection? It depends upon the spread and severity of viral damages in different types of cells and organs. Despite a vast number of scientific publications, the picture of long-term consequences of COVID-19 remains unclear. Without large-scale prospective observational studies, which are only in the beginning of their performance, clinicians cannot obtain any certain information about cases of post-COVID complications or small studies [36, 37].

Within the framework of the study with participation of 150 noncritical patients with COVID-19, conducted by researchers from the University of Tours (France), it was revealed that on the 30th or 60th days after appearance of signs and symptoms of COVID-19 the patients, who had survived a noncritical stage of the disease, still had the following signs and symptoms (at least one of them): loss of body weight (≥5%), severe dyspnea or asthenia, pain in the chest, palpitation, anosmia/ageusia, headache, skin manifestations, arthralgia, myalgia, digestive disorders, elevation of body temperature. At least one symptom was present in 68% of cases (n=103/150) on the 30th day and in 66% (n=86/130) on the 60th day. The commonest signs and symptoms were as follows:

• anosmia/ageusia: in 59% at the onset of the disease, in 28% on the 30th day and in 23% on the 60th day;

• dyspnoea: in 36.7% on the 30th day and in 30% on the 60th day;

• asthenia: in 50% on the 30th day and in 40% on the 60th day;

• persistent signs and symptoms on the 60th day were most frequently observed in individuals aged 40-60, they were associated with hospitalization and changes in the auscultation picture at the onset of the disease; a severe

course of COVID-19 and dyspnea at the onset of the disease were associated with presence of persistent signs and symptoms on the 30th day [38].

According to the information from the World Health Organization in February of 2020 (on the basis of preliminary data), the period from the onset to clinical recovery in mild cases of COVID-19 is approximately 2 weeks, in severe or critical cases it lasts from 3 to 6 weeks. But many patients have certain signs and symptoms for much more weeks and even months. Persistent damages of many organs and systems (lungs, heart, brain, kidneys, vascular system, etc.) have been documented in post-COVID-19 patients [39].

Different mechanisms in the development of these states are under investigation. Such damages may be caused by severe inflammatory reactions, thrombotic microangiopathy, venous thromboembolism, oxygen deficiency, autoimmune processes, pathological consequences after the acute period (pneumofibrosis) or persistence of the causative agent [40, 41].

The diagnosis, monitoring of the patient's state, prognostic criteria and treatment have been insufficiently studied and require improvement [42].

Clinical guidelines of the National Institute for Health and Care Excellence of Great Britain "COVID-19 rapid guideline: managing the long-term effects of COVID-19" (NG188) use the following clinical definitions for the primary disease and duration of COVID-19 depending upon the time when they appeared and during which they exist:

- acute COVID-19 – signs and symptoms of the disease are present up to 4 weeks;
- ongoing symptomatic COVID-19 – signs and symptoms of the disease are present from 4 to 12 weeks;
- post-COVID-19-syndrome – signs and symptoms develop during or after the infectious disease, which corresponds to COVID-19, are present longer than 12 weeks and not explained by an alternative diagnosis.

In turn, the Infectious Diseases Society of America (IDSA) distinguishes "long-lasting COVID-19", "post-COVID syndrome" and "post-acute COVID syndrome". Harvard Medical School uses such a definition as "long haulers". The concept "chronic" or "long-lasting" course of an infectious disease takes into consideration persistence of the causative agent. It is known that other coronaviruses have a potential to persist in the nervous system for a long period of time; it is possible, SARS-CoV-2 as well [43, 44]. If the pathological state after the survived disease remains, but the causative agent is not revealed, these facts point out consequences of the disease that can be rightfully termed post-COVID syndrome [30]. Post-COVID long-hauler is any patient with COVID-19 caused by SARS-CoV-2, who has not returned to his/her level of health and functioning in 6 months after the survived disease. According to different data, from 10 to 50% of post-COVID-19 cases become long-haulers [45]. Two groups of such patients are isolated: cases with irreversible damages in the lungs, heart, kidneys or brain that affect their ability to function; patients who go on suffering from devastating symptoms despite absence of any visible damages of their organs. No matter how natural the changes caused by long-term persistence of clinical manifestations or appearance of new signs and symptoms after survival of acute disease are, their presence necessitate rehabilitation of such cases [46].

Many patients develop severe asthenic syndrome, which significantly aggravates their quality of life and appreciably decreases capacity for work. For a long period of time such cases may preserve low-grade inflammation in the brain, reduced blood flow to it, its autoimmune damage or a combination of these abnormalities. Accumulation of pro-inflammatory cytokines, which penetrate the blood-brain barrier, in the CNS can cause dysregulation of central structures and cause autonomic dysfunction (elevated body temperature, sleep cycle disorders, cognitive disorders, rapid fatigue) [47].

Post-COVID asthenic syndrome most frequently manifests with mental problems and general exhaustion of the patient. The commonest manifestations of asthenia in post-COVID syndrome are as follows: rapid fatigue, irritable weakness (hyperexcitability, which rapidly changes into exhaustion), affective lability with traits of capriciousness and discontent, increased tears, memory defects. Possible causes for the development of asthenia in post-COVID syndrome include: massive drug load during therapy for COVID-19 (in particular, administration of dexamethasone,

which has the catabolic direction of its effect), long and devastating course of the disease with respiratory failure and hydroelectrolytic disorders, concomitant severe and/or uncompensated systemic diseases such as diabetes mellitus [48].

Important directions in rehabilitation treatment, for example for post-COVID-19 patients, were pointed out by a group of experts from the Defence Medical Rehabilitation Centre in Stanford Hall (Great Britain), who developed a relevant document, the Stanford Hall consensus statement, which contains the following general recommendations after COVID-19 for a target population of active individuals:

- rehabilitation treatment plans should be individualized according to the patient's needs, taking into consideration his/her comorbidities;
- in patients with COVID-19, rehabilitation should be aimed at relieving symptoms (dyspnea), improving psychological state, physical function and quality of life;
- patients should be periodically examined during their rehabilitation;
- patients should receive information about their condition and strategies of recovery after COVID-19.

Nevertheless, these are primarily general recommendations, which describe examination of patients with post-COVID syndrome and care for them. These guidelines do not elucidate drug treatment for such patients. In order to understand more clearly the direction of rehabilitation measures and their possible drug supplementation it is reasonable to examine the morphology and pathogenesis of post-COVID changes in more detail.

The main directions of treatment in post-COVID asthenic syndrome are as follows:

- optimization of drug treatment and early withdrawal of drugs with the catabolic effect (dexamethasone);
- organization of the diet, which should be optimum in amount and balanced by its components;
- psychological support in family and at work;
- revealing and control of hydroelectrolytic and metabolic disorders;
- monitoring and correction of disorders in presence of concomitant diseases (diabetes mellitus, arterial hypertension);
- prevention of metabolic disorders (fasting ketoacidosis and diabetic ketoacidosis);
- compensation for intracellular energy deficit.

According to the Stanford Hall consensus statement, the principles of pulmonary rehabilitation in post-COVID-19 patients are as follows:

- respiratory complications after COVID-19 may present with some degree of impairment and functional limitation, including (but not exclusively) due to decreased respiratory function;
- initial assessment of the patient's state is recommended in a timely manner, depending on the degree of dysfunction, normocapnic respiratory failure and the patient's physical and mental status;
- low intensity exercises should be considered initially particularly for patients who require oxygen therapy, while concurrently monitoring vital signs (heart rate, pulse oximetry and blood pressure). Gradual increase in the exercise should be based on severity of the patient's symptoms.

Respiratory rehabilitation in post-COVID-19 patients is aimed at decreasing manifestations of dyspnea, relieving anxiety and depression, preventing respiratory dysfunction, reducing disability rate, preserving the maximum volume of the respiratory function as well as improving the quality of life.

Recommendations for respiratory rehabilitation contain the following physical exercises:

- aerobic: walking, brisk walking, slow jogging, swimming, etc., beginning at a low intensity before progressively increasing in intensity and duration;
- training of strength: progressive trainings with load bearings;
- training of breathing: in presence of dyspnea, wheezing and difficult discharge of sputum it is necessary to use respiratory training techniques for improving sputum discharge and mode of breathing, including adjustment of breathing rhythm, thoracic activity training and mobilization of certain muscle groups.

Common signs and symptoms in hospitalized patients with COVID-19 include respiratory failure, dry cough, dyspnea and lung abnormalities on computerized tomography (opacity and/or thickening in the form of "clouded glass").

During the acute phase, physical exercise tolerance cannot be assessed with help of standard tests (e.g., 6-minute walking). Some patients still need oxygen therapy or have respiratory symptoms on discharge from hospital [49]. Follow-up of the respiratory system state is crucially important for assessing the pulmonary function, alveolar-arterial gas exchange and tolerance of physical exercise in patients, who recovered after COVID-19. At present, nothing is known about remote respiratory complications in post-COVID-19 patients.

Accordingly, a number of problems remain, which necessitate further study for developing methods of early diagnosis and more thorough prevention and effective rehabilitation of post-COVID-19 patients on the basis of innovation researches. Hence, having raised a huge number of fundamental questions concerning the pathogenesis of pneumonia, interactions of the virus with the lung microbiome and human immune system, heterogeneity and unpredictable severity of its course, the problem of SARS-CoV-2 virus-caused coronavirus infection of 2019, unprecedented in the human history, remains the main subject of the present-day life. Etiotropic and pathogenetic therapy of COVID-19 patients is now at the stage of development. Priority directions of research include development of a vaccine against COVID-19. The medical-organizational crisis,caused by the outbreak of COVID-19, also necessitates improvement of antiepidemic measures at the level of a medical establishment, a country and the world, modernization of health care systems and revision of their financing. Today a great army of specialists works tirelessly over solution of this difficult problem, thereby contributing to continuous updating and supplementing information about the above disease [50]. It is still urgent to develop comprehensive strategies for responding COVID-19 pandemic in order to decide in what way pathological states, caused by this infection, should be effectively controlled.

Declarations

Statement of Ethics

The author has no ethical conflicts to disclosure.

Consent for publication

The author gives her consent to publication.

Disclosure Statement

The author has no potential conflicts of interest to disclosure.

Funding Sources

There are no external sources of funding.

Data Transparency

The data can be requested from the author.

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Received: 17-Sep-2021
Accepted: 13-Dec-2021

MODERN METHODS OF DIAGNOSIS AND SCREENING OF NON-ALCOHOLIC FATTY LIVER DISEASE AND ITS STAGES (REVIEW)

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https://doi.org/10.35339/ic.8.4 226-231

Abstract

The review features the problem of diagnosing one of the most common pathologies of the contemporary world – non-alcoholic fatty liver disease (NAFLD). Data from experimental and clinical studies on the importance of various instrumental and biochemical methods of non-invasive diagnosis of non-alcoholic steatohepatitis (NASH) and liver fibrosis (LF) are presented. New non-invasive diagnostic methods of NASH and LF are discussed.

Keywords: *nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, liver fibrosis.*

In the structure of the overall morbidity in the economically developed countries of the world, nonalcoholic fatty liver disease (NAFLD) occupies one of the leading positions, pushing the hepatitis of viral and alcoholic origin [1, 2]. Despite the long period of study of NAFLD, timely diagnosis of its stages remains imperfect. This is mainly due to the diagnosis of NAFLD based on the history data, clinical and laboratory studies, and their interpretation, and much less often on the basis of the study of specific biomarkers of this pathology. The most common and adequate method of diagnosing nonalcoholic steatohepatitis (NASH) and liver fibrosis (LF) in patients with NAFLD is puncture liver biopsy [3, 4]. However, in most cases, a number of limitations for puncture liver biopsy should be considered. Such limitations include invasiveness of the procedure, its cost, diagnostic errors associated with the location of the sample, the presence of contraindications associated with the procedure, the risk of complications and mortality, etc. [5]. This number of limitations of liver biopsy does not allow the use of this procedure for the current screening of NASH and LF in patients with NAFLD.

Morphological examination of the liver allows to directly assess not only the stage of fibrosis but also a number of other indicators of liver damage: the presence of steatosis, inflammation, accumulation of copper, iron, and other histological changes. In complex diagnostic cases, histological findings are crucial for diagnosis verification. One of the major disadvantages of liver biopsy, which limits its use, is the presence of contraindications and the risk of complications. Absolute contraindications for liver biopsy are the presence of vascular malformations, obstruction of the extrahepatic bile ducts (biliary obstruction), uncompensated coagulation disorders, cystic changes in the liver [6]. Relative contraindications for liver biopsy are the presence of severe ascites, obesity, hemophilia, liver amyloidosis, right pleurisy or subphrenic abscess on the right, bacterial cholangitis [7].

Frequent complications of liver biopsy are pain in the right upper quadrant of the abdomen, intrahepatic or subcapsular hematoma, hypotension associated with the vasovagal reaction, intraperitoneal bleeding, biliary peritonitis. According to the data of the National Health Service of the United Kingdom, collected from 1998 to 2005, among 61,187 patients who underwent liver biopsy, the overall mortality rate was 2 cases per 1,000 biopsies (95%, confidence interval 1.8 – 2.5) [8].

Diagnostic errors in assessing the histological activity and degree of fibrosis due to uneven distribution of fibrous tissue are also possible. Thus, in the study of MD. Federica Vernuccio (2019), the diagnostic accuracy of liver biopsy performed among 389 patients was 89.4%, and the incidence of false-negative results was 6.5% [9].

In modern medical practice, ultrasound of the liver is most widely used in the diagnosis of NAFLD. Ultrasonographic signs of hepatic steatosis are an increase in its echogenicity compared

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with the parenchyma of the cortical layer of the kidneys, a bright pattern with vascular erosion, which is determined by deep attenuation of the wave, and focal hepatosteatosis [10]. The undoubted advantages of liver ultrasound are its safety and relatively low cost, which makes it possible to conduct repeated studies. However, with hepatic steatosis < 20% and BMI > 40 kg/m2, the sensitivity and accuracy of liver ultrasound to verify the diagnosis of NAFLD is limited [11]. Despite the fact that the quality of ultrasound diagnosis depends on the experience and qualifications of the specialist, ultrasound can reliably diagnose moderate and severe steatosis and provides additional information about the state of the hepatobiliary system [12].

Contrast-enhanced computed tomography (CT) of the liver is of high diagnostic value in the diagnosis of NAFLD due to its availability, ease of use, and accuracy in imaging hepatic steatosis [13]. Contrast-enhanced liver CT is a more complex method in terms of quantifying liver fat deposition due to the imposed parenchymal enhancement of the liver CT signal [14]. However, CT of the liver with vein contrast is a diagnostically valuable method of diagnosing moderate and severe steatosis in patients with NAFLD [187]. However, CT-scans cannot detect the initial LF. Also, the potential danger of ionizing radiation makes liver CT unsuitable for long-term follow-up of patients with NAFLD [15].

Another visualization method in NAFLD is magnetic resonance imaging (MRI) of the liver. Standard MRI of the liver, including chemical shift imaging with input and reverse phases, is diagnostically justified for the diagnosis of hepatic steatosis as a whole, but this method does not provide data on objective quantification of liver fat [16]. Until recently, MR spectroscopy was the reference standard for non-invasive imaging and quantification of liver fat. However, this method takes a lot of time and, as in the case of liver biopsy, is prone to errors in data interpretation [17].

Elastography is a very effective modern method of radiological diagnosis of NAFLD and its stages. Elastography has the ability to demonstrate increased stiffness of the liver parenchyma as a result of inflammation or fibrotic changes in the liver [18]. One of elastography types is transient elastography (TE). TE is a non-invasive technique recommended as an alternative method of morphological examination of the liver, which allows quick assessment of the presence of LF, including in the dynamics [19]. Also, TE is a method of imaging that allows non-invasive assessment of the stage of LF in patients with NAFLD, especially in patients with severe fibrosis and liver cirrhosis. However, the main disadvantage of TE is the unreliability of the results in patients with high BMI and/or significant thickening of the chest folds.

One of the leading methods of quantitative elastography of the liver is transitional elastography under the trademark "FibroScan". The method is based on the determination of liver fibrosis with the propagation of elastic waves from 20-30 ultrasonic pulses, followed by calculation of the average value of the deformation pressure in kilopascals (kPa) [20]. Maximum diagnostic accuracy of elastography was achieved in patients with LF stage F3 and F4 based on the results of semi-quantitative assessment of fibrosis (histological scale Metavir). Informativeness of the method by stages of liver fibrosis: F0-F1 – 88-90%, F2- F3 – 90-94, F4 – 94-98% [21].

However, the procedure is not recommended for patients with pacemakers and pregnant women due to the high acoustic power of the pulse. Also, this method has a high cost and does not give the exact location of the area of interest, as it is performed "blindly" and has a depth limit of 5 cm with a fixed size of the control volume of 4 cm [22]. A significant limitation of the method is the reduction in the significance of the results in overweight patients, and given that most patients with NAFLD have concomitant, this circumstance is a significant disadvantage [23].

Different scores and biomarkers are also used for the non-invasive diagnosis of NAFLD. One such biomarker for calculating hepatic steatosis is the fatty liver index. The liver obesity index has been reported to be a predictor of insulin resistance and is closely related to NAFLD [24].

Another scale for verifying hepatic steatosis is the NAFLD liver fat score. This scale is a reliable prognostic scale for predicting fat dep osition in the liver (AUROC 0.775-0.786) [25].

A hepatic steatosis index is also available to assess hepatic steatosis in NAFLD. The hepatic steatosis index has been reported to be an indirect marker of hepatic steatosis and metabolic syndrome in patients with NAFLD. In a study conducted by Jun Hyung Kim (2020), sensitivity of hepatic steatosis index was 90%; specificity – 74%; plausibility ratio – 3.46; positive prognostic value – 0.64; and negative prognostic value of 0.93 [26]. The result of calculating the index of hepatic steatosis in the range of 30 - 36 may indicate the presence of NAFLD in the stage of steatosis. Accordingly, at values < 30 or> 36 – NAFLD is not diagnosed [27].

According to the literature, there are also indirect biochemical markers of NAFLD – molecules that are released into the blood due to a pathological process occurring in the liver and are also able to reflect the presence of inflammation and its activity. They are represented by aminotransferases ALT and AST; molecules synthesized in hepatocytes by the liver, for example, alkaline phosphatase (AP), gamma-glutamyl transpeptidase (GGT), apolipoprotein A1, alpha-2-macroglobulin (A2M), ferritin, haptoglobin, coagulation factors.

The standard panel of a comprehensive study of the functional state of the liver includes measurements of AST, ALT, AP, total bilirubin and serum albumin. ALT and AST are liver enzymes involved in the transfer of the amino groups of aspartate and alanine to ketoglutaric acid and are markers of hepatocellular damage [28]. AST activity is most pronounced in the liver, heart muscle, kidney, and brain tissue, while ALT activity is predominant in liver tissue, making elevated ALT levels a more specific marker of hepatocyte damage. Numerous studies have shown that elevated ALT levels are associated with increased mortality in patients with liver disease, including NAFLD [29]. Also, a predictor of the severity of the liver disease is the ratio of AST and ALT, the so-called de Ritis coefficient, the value of which more than one (1), may indicate the presence of severe fibrotic changes in the liver in patients with NAFLD [30].

AP is a part of the family of enzymes of zinc metalloproteinases, which catalyze hydrolysis of esters of phosphoric acid under alkaline pH. This enzyme is found in hepatocytes on the tubular membrane, as well as in bone, placenta, intestine and kidneys. An isolated increase in AP levels can be observed after eating fatty foods, bile duct obstruction, pregnancy, and liver damage [31]. In the case of increased AP levels, to confirm the damage to liver tissue, it is necessary to further determine the level of tubular liver enzyme – GGT. Increased AP levels in combination with elevated GGT levels reliably indicate the process of hepatocyte damage, including NAFLD [32].

Total bilirubin is synthesized as a result of the physiological breakdown of erythrocytes and circulates in the unconjugated form. Unconjugated bilirubin, according to the Van den Berg reaction, is defined as indirect, accounting for about 70% of total serum bilirubin. There is scientific evidence that an increase in total bilirubin is associated with a risk of cardiovascular diseases (CVD), diabetes mellitus type 2 and metabolic syndrome [33]. Also, there are data associating with increase of circulating bilirubin with the development of NAFLD and the risk of NASH progression [34].

Apolipoprotein A1 is a 243-amino acid polypeptide that is mainly present in plasma as a component of HDL and is controversial as a marker of NAFLD and its stages. Elevated serum apolipoprotein A1 has been reported to be significantly associated with the development of NAFLD, regardless of the presence of metabolic syndrome [35]. However, a study by Reza Fadaei (2018) conducted among 50 patients with histologically confirmed NAFLD showed that circulating apolipoprotein A1 levels were lower in the NAFLD group compared to the control group [36].

Haptoglobin, first described by Polonowski and Jail, is a tetra-chain glycoprotein that normally circulates in blood plasma in the amount of 0.3 – 3 g/l. Haptoglobin is considered a marker of acute inflammation, which is synthesized in the liver and immune cells, including neutrophils and monocytes. Accumulated data on the function of this protein has established its close relationship with non-communicable diseases, which are based on the development of chronic systemic inflammation (obesity, CVD, arterial hypertension) [37]. It is well known that determination of haptoglobin is included in the panel of biochemical markers for determination of AF "FibroTest" and "Actitest" in patients with NAFLD. Chwist A. et al. (2014) reported that the level of haptoglobin

was significantly higher in the group of patients with NAFLD in the LF stage F2-F3 compared with the group of patients with NAFLD in the LF stage F0-F1and the control group [38].

Thus, there are a significant number of invasive and non-invasive methods for diagnosing NAFLD. However, the application of these methods presents certain difficulties due to their complexity, significant risk of complications, high probability of subjectivity and erroneous judgments in the interpretation of results, low patient compliance, inability to use in dynamics and high cost of research.

It should also be noted that as of today, the number of studies on diagnostic tactics in patients with NAFLD is insignificant, and the question of non-invasive diagnosis of NAFLD remains open.

Thus, the future of diagnostic hepatology is the use of non-invasive methods of diagnosing NAFLD using specific serum biomarkers with the possibility of early non-invasive diagnosis of NAFLD and differentiation of steatosis, NASH and LF.

Declarations

Statement of Ethics

The author has no ethical conflicts to disclosure.

Consent for publication

The author gives her consent to publication.

Disclosure Statement

The author has no potential conflicts of interest to disclosure.

Funding Sources

There are no external sources of funding.

Data Transparency

The data can be requested from the author.

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Received: 08-Oct-2021
Accepted: 13-Dec-2021

METABOLIC CHANGES / INSULIN RESISTANCE IN TUBERCULOSIS PATIENTS: CAUSE OR EFFECT (REVIEW)

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https://doi.org/10.35339/ic.8.4.232-237

Abstract

This review article contains current scientific literature data about the impact of infectious diseases, tuberculosis particularly, on the formation of systemic insulin resistance in patients. A number of immune reactions have been reported in the host body in response to tuberculosis infection, which may lead to the development of hyperglycemia in Tuberculosis (TB) patients. Some authors believe that such disorders are transient and disappear after a course of specific treatment, others are inclined to believe that tuberculosis can cause diabetes in people who have not previously suffered from it, and long-term impairment of carbohydrate metabolism that occurs under the time of active tuberculosis process forms a vicious circle in which insufficiently controlled blood glucose levels can lead to aggravated TB and provoke complications in the form of cardiovascular disorders. Also, we found data on the transformation of latent disorders of carbohydrate metabolism in manifest diabetes mellitus during 1-4 years of follow-up of patients with tuberculosis.

Key words: *tuberculosis, carbohydrate metabolism, insulin resistance*.

Tuberculosis (TB) is one of the most dangerous infectious diseases with high mortality rates. According to the World Health Organization (WHO), global efforts to combat this formidable disease since 2000 have saved approximately 53 million lives and reduced mortality by 37%. However, in 2018, TB was recognized as the infectious disease that caused the highest number of deaths. Thus, there were 10 million cases and 1.6 million deaths from TB in the world [1]. According to the literature data, mycobacterium tuberculosis (MTB) infects a third of the world's population, of which about 10% can develop active disease throughout life [2, 3, 4].

However, the risk of active TB increases significantly among people who have such risk factors as comorbidities, pathological conditions or harmful habits that weaken the body's defenses. The five most significant risk factors for TB, according to the WHO experts, include: HIV infection, malnutrition, diabetes mellitus (DM) and harmful habits (smoking and alcohol abuse). Thus, HIV-infected people suffer from TB 20 times more often than the population without comorbidities, people with malnutrition have TB on average three times more often, and patients with DM are 2.3 - 4 times more likely to develop TB [5, 6, 7, 8, 9]. At the end of 2017, there were about 36 million people living with HIV in the world, while the number of people with DM was almost 13 times higher - 460 million people [1, 10]. The incidence of DM is growing every year. Thus, according to experts of the International Diabetes Association (IDA), in 2045 the number of patients with DM may reach 629 million [1, 10, 11]. Therefore, despite the fact that the individual risk of TB in patients with DM is much lower than the risk in people with HIV/AIDS, in countries with a high burden of DM, this disease plays a key role in controlling the incidence of TB.

Comorbidity of TB/DM is no less important issue for our country. According to the Center for Public Health of the Ministry of Health of Ukraine, in 2016 the incidence of combined TB/DM in Ukraine reached 2.5 per 100 thousand

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population (detected 1 044 cases), which is about 3.1% of the total number of detected TB cases, and in 2015 this percentage was 2.7%. Also, the number of cases of combined pathology among patients with multidrug-resistant TB has increased: DM as a concomitant disease was detected in 4.2% of patients in 2016 as opposed to 3.7% in 2015 [10, 11].

Diabetes mellitus is a recognized risk factor and background disease that complicates the course of TB and its treatment process, reduces the effectiveness of therapy and causes early relapses of TB [5, 7, 12, 13]. There is an opinion about the two-way relationship between these two diseases [14, 15, 16], but there is no consensus on whether TB can cause DM.

From the time of infection with MTB to the development of active disease, the patient's body undergoes a number of immunological reactions aimed at destroying the foreign infectious agent. These include the synthesis of proinflammatory and anti-inflammatory cytokines, the release of nitric oxide and reactive oxygen species by macrophages [17, 18]. The pathogenesis of DM associated with obesity is also due to increased secretion of proinflammatory cytokines, formation of reactive oxygen species and nitric oxide, which cause insulin resistance and hyperglycemia [19]. Therefore, identical immune reactions that occur in the host body in response to the penetration of the MTB, may be the basis for the development of hyperglycemia in TB patients [4]. Some authors believe that such disorders are transient in nature, disappearing after a course of specific treatment [20]. Other authors are of the opinion that TB can cause DM in people who have not previously suffered from it, and longterm disruption of carbohydrate metabolism during active tuberculosis creates a vicious circle in which insufficiently controlled blood glucose levels can lead to aggravated TB and provoke complications in the form of cardiovascular disorders. There are data on the transformation of latent disorders of carbohydrate metabolism in manifest DM in 22% of cases during 1-4 years of follow-up of TB patients [21].

Another risk factor for TB is prediabetes, which is also associated with a high risk of developing DM with an annual progression of 510% [22, 23]. Prediabetes is a disorder of carbohydrate metabolism that precedes the manifestation of diabetes and is defined as an intermediate state of hyperglycemia with a glucose level higher than normal, but lower than the diagnostic level of DM. This term was introduced by the American Diabetes Association (ADA) in 1997 and has been officially used since 2005. This condition contains several levels: fasting blood glucose disorders, impaired glucose tolerance and prediabetes itself [24]. Diagnostic criteria for prediabetes vary in different countries, thus the data on its prevalence can vary widely [25]. But despite these differences, estimates suggest that the number of people with prediabetic carbohydrate metabolism is growing rapidly in all parts of the world. According to the CDC (US Centers for Disease Control and Prevention), in 2016 there were nearly 86 million adult prediabetic adults in the United States alone, 90% of whom were unaware of the problem. Unfortunately, there are no statistics on prediabetes in Ukraine, although, according to the maximum forecasts of the International Diabetes Association (IDF 2017), its prevalence is about 10% among the adult population. In total, about 7.8 million people in Ukraine suffer from DM and prediabetes [10, 24, 26]. Scientists around the world are increasingly recognizing prediabetes as a serious metabolic condition that not only predicts a high probability of DM in the future, but also increases the risk of many diseases that often accompany diabetes: diabetic retinopathy, neuropathy, nephropathy and macrovascular complications [27, 28]. Prediabetes is included in the International Classification of Diseases, 10th revision and assigned the code R 73.09, which indicates "prediabetes" as a separate pathological condition [29]. In the vast majority of people (70%) suffering from prediabetes, the risk of DM persists for life and only in 25% of cases there is a transformation of prediabetes into type 2 DM within the next 3-5 years [30, 31]. Prediabetes is associated with coexisting insulin resistance and pancreatic β-cell dysfunction, which usually develop before the onset of dysglycemic disorders [32, 33].

Today, the problem of carbohydrate metabolism disorders in TB patients is the subject of study by many scientists around the world. According to the modern scientific literature, disorders of carbohydrate metabolism in the form of prediabetes are diagnosed in 27.0% -

37.5% of TB patients [34, 35, 36, 37]. The authors point to the important role of glycosylated hemoglobin as a prognostic marker of the clinical course of pulmonary tuberculosis and the results of its treatment [38].

Under physiological conditions, the body of a healthy person strictly controls the fluctuations in glucose levels during the day. The concentration of glucose in plasma depends on the relative rate at which glucose circulates in the blood, as well as the rate of its distribution at the level of target cells [39, 40]. The processes of regulation of glucose homeostasis on an empty stomach and in the postprandial period are under multilevel multihormonal control and have a number of significant differences. About half of the glucose that enters the systemic human bloodstream on an empty stomach is formed by glycogenolysis (breakdown of glycogen deposited in the liver), the other half is newly synthesized (during gluconeogenesis) glucose molecules. The substrate for the formation of such glucose is lactate, glycerin, alanine and other amino acids, and the only organs capable of gluconeogenesis in humans are the liver and kidneys (due to the fact that they contain significant amounts of the enzyme glucose-6-phosphatase). Studies in recent years have shown that in the post-absorption period, the human liver and kidneys synthesize almost the same amount of glucose. Thus, after nocturnal fasting, 75-80% of glucose synthesized by the liver and 20-25% of glucose synthesized by the kidneys enter the systemic bloodstream. Glycogen stores in the liver are quite limited and after 48 hours of fasting almost all the glucose circulating in the bloodstream is the result of gluconeogenesis. It is important to note that the liver and kidneys use different substrates that are precursors of gluconeogenesis and have different hormonal regulation of de novo glucose synthesis. Although lactate is the main substrate of gluconeogenesis in both organs, the kidneys use mainly glutamine and the liver uses alanine [40]. Insulin inhibits glucose synthesis by both organs, while glucagon stimulates glucose production only by the liver, due to glycogenolysis. Catecholamines directly affect the production of glucose by the kidneys, although they may indirectly affect the synthesis of glucose by both the kidneys and the liver by increasing the availability of gluconeogenic substrates and suppressing insulin secretion. Cortisol, growth hormone, and thyroid hormones have a long-lasting stimulating effect on hepatic glucose production (within a few days) [40]. Suppression of endogenous glucose synthesis prevents the development of hyperglycemia after meals. Insulin plays a leading role in suppressing glucose production in the liver, which is responsible for disposing of more than a third of the oral glucose load in healthy individuals [41]. The rest of the glucose coming from the intestines enters the general bloodstream. About 2/3 of its amount is absorbed by muscles and adipose tissue, due to increased permeability of muscle and fat cell membranes for glucose under the influence of high concentrations of insulin. Glucose in the muscles is stored in the form of glycogen, and in fat cells it is converted into fat. The rest of the glucose from the general bloodstream is absorbed by other (noninsulin-dependent) cells. Hepatic gluconeogenesis is also slowed down and glucose molecules obtained as a result of this transformation pathway usually do not enter the systemic circulation, but largely go to the synthesis of glycogen in the liver. Renal gluconeogenesis is approximately doubled after a meal and accounts for about 60% of endogenous glucose production [42].

Acute infectious diseases lead to deep metabolic disorders of the macroorganism. All types of metabolism are involved in the pathological process: carbohydrate, lipid, protein and amino acid metabolism. One of the manifestations of the impact of an infectious agent on the human body is stress hyperglycemia.

Against the background of severe hyperglycemia, the process of glycosylation of proteins is activated, including transport proteins and insulin receptor proteins, which leads to their dysfunction. In addition, there is also a decrease in the absolute number of receptors on the cell membranes of insulin-sensitive tissues. Thus, despite the presence of hyperglycemia, insulin-dependent tissues lack energy substrates. The predominance of anaerobic breakdown of glucose over aerobic leads to depletion of glycogen stores in the liver, hyperlactataemia and increased oxidative stress, which, in turn, helps maintain hyperglycemia [43]. It has been experimentally proven that airway inflammation, which occurs during a number of lung diseases, even in patients

without overweight and manifestations of systemic hypoxemia, can lead to systemic insulin resistance (IR) [43]. The definition of insulin resistance was first proposed in 1998. According to experts of the association, IR is a violation of the biological response (metabolic and molecular genetic) to insulin (exogenous and endogenous); disorders of metabolism of carbohydrates, fats, proteins; changes in DNA synthesis, regulation of gene transcription, processes of differentiation and growth of cells and tissues of the body [43].

Hyperinsulinemia of any origin leads to the formation of insulin resistance. In conditions of excess insulin, all tissues that have insulin receptors, including β-cells of the pancreas, are involved in the pathological process. Defective transmission of insulin signal in β-cells disrupts glucose-stimulated insulin release. Hyperinsulinemia generates and maintains insulin resistance regardless of the underlying pathology. Hyperinsulinemia, insulin resistance, and impaired glucose-stimulated insulin release are biologically related. In this case, one process (hyperinsulinemia) can generate all three others simultaneously [44, 45]. It has been proven that hyperinsulinemia and IR have a detrimental effect on the body, even in people without impaired glucose tolerance. Thus, a number of researchers reported that fasting plasma insulin levels above 39 μg IU/ml or more were associated with an increased risk (31%) of cardiovascular events in people without diabetes. IR is the initial link in the process of transition from normal glycemia to impaired glucose tolerance and diabetes [45]. As long as the β-cells of the pancreas are able to produce enough - insulin and maintain a state of hyperinsulinemia, hyperglycemia will be absent. However, depletion of β-cell reserves causes a state of relative insulin deficiency, which is manifested by an increase in blood glucose levels. As a result, the main metabolic processes in the body - carbohydrate, lipid and protein metabolism, growth, differentiation, DNA synthesis, regulation of gene transcription, and so on - are disrupted. Glycemic parameters have a steady upward trend. First, the level of glycemia increases after a meal (postprandial hyperglycemia), then - the level of fasting blood glucose. Impaired glucose tolerance (latent diabetes) can progress and lead to the development of overt DM [46].

Conclusion.

Thus, the data of scientific literature showed that tuberculosis violates carbonhydrate methabolism, causing insulin resistance and in some cases may even provoke the development of diabetes mellitus in patients.

Declarations

Statement of Ethics

The author has no ethical conflicts to disclosure.

Consent for publication

The author gives her consent to publication.

Disclosure Statement

The author has no potential conflicts of interest to disclosure.

Funding Sources

There are no external sources of funding.

Data Transparency

The data can be requested from the author.

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Received: 08-Oct-2021
Accepted: 13-Dec-2021

ADHESIVE OBSTRUCTION OF THE SMALL INTESTINE: FEATURES OF DIAGNOSIS AND TREATMENT IN THE CONTEXT OF MINIMALLY INVASIVE TECHNOLOGIES (REVIEW)

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https://doi.org/10.35339/ic.8.4.238-246

Abstract

The review presents a modern view on the features of the course and treatment of adhesions of the small intestine, based on modern epidemiological data, accepted guidelines for the diagnosis and nature of the treatment of different categories of patients. It is noted that adhesive intestinal obstruction is a symptom complex due to violation of the movement of contents through the intestines due to the presence of adhesions in the abdominal cavity after operations and injuries. Attention is drawn to the peculiarities of diagnostics of various forms of the disease, which include the leading clinical symptoms, data of X-ray methods (X-ray and CT of the abdominal cavity), MRI, assessment of various biomarkers, indicators of the severity of the patient's condition. It is noted that at present the primary task in solving this problem is to study several controversial issues in this area. The main provisions of measures for the treatment of adhesive obstruction of the small intestine, based on the principles of non-surgical treatment in a certain category of patients, the use of surgical interventions strictly according to indications, especially in patients who require repeated operations, were highlighted. Among them, special attention is paid to the features of open and minimally invasive surgical interventions. It is emphasized that at present, minimally invasive surgical interventions perform the main tasks of surgical treatment for adhesive ileus of the small intestine and significantly reduce surgical trauma in comparison with "open" methods of treatment, but these interventions have not widespread in the world yet.

Keywords: *adhesive obstruction of the small intestine, epidemiology, diagnostic, surgical treatment, open surgery and laparoscopy.*

Introduction.

Adhesion disease (AD) is the most common disease of the small intestine and according to 87 studies involving 110,076 patients, the incidence of adhesive obstruction of the small intestine (ASBO) after all types of abdominal surgery was 2.4% [1]. There are more than 300,000 ASBO hospitalizations in North America each year, amounting to 850,000 days of inpatient care, costing more than $ 1.3 billion in medical expenses and contributing to more than 2,000 deaths per year. The first data on the induction of adhesions was in the animal model von Dembowski published in 1889, and in the following, more than 120 years, extensive research was conducted both in vitro and in vivo on the causes of its occurrence [2,3]. Over the last decade, the availability of limited clinical trials has caused some uncertainty in the world regarding best practices with further international differences in the assessment of treatment outcomes in patients with hypertension. Nowadays, there is a diagnostic dilemma as to how to distinguish between ASBO and its other causes, as well as how to distinguish between ASBO, which requires urgent surgery, and ASBO, which can be successfully treated conservatively.

It should be noted that ASBO after abdominal surgery and trauma is a well-known disease that still has problems in terms of prevention, diagnosis and treatment, despite the overall improvement in treatment. Good surgical techniques, such as laparoscopy and anti-adhesive barriers during the initial operation,

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seem to reduce ASBO, but reports have conflicting results and provide only general (CT) has improved the diagnosis of SBO in general, but it cannot be performed on every patient with severe vomiting and dehydration, shock, renal failure, etc., and it often fails to accurately identify adhesions as the cause of obstruction. In addition, the world is discussing the issue of predicting what treatment should be established at the beginning for the success of treatment of patients after contrast-enhanced CT without strangulation of the small intestine. As it is well understood that in patients with strangulation it is necessary to perform emergency surgery. In terms of surgical treatment, laparoscopy has become popular but is also associated with an increased risk of iatrogenic complications. In particular, it is difficult to identify patients who may benefit from laparoscopic adhesiolysis and who should use open surgery nowadays.

Epidemiology

Intra-abdominal adhesions after abdominal surgery and trauma are a serious unresolved problem worldwide: in patients with abdominal pain, ASBO is a common cause, accounting for about 4% of all admissions to emergency departments and 20% of all emergency surgical procedures [4]. Currently, it is estimated that fibrous cords in the abdominal cavity are found in 93% of patients who underwent abdominal surgery and significantly complicate the operation for SBO [5]. According to some data, adhesions are the cause of SBO in 74% of adults with this pathology and in about 30% of patients with readmission after intra-abdominal surgery after four years after surgery [6]. Today, it remains unclear whether the increase in the number of laparoscopic intra-abdominal operations led to a decrease in postoperative complications such as ASBO, although there were some reports of a decrease in adhesion formation after laparoscopy, these studies were controversial [7, 8]. In particular, some of the available data indicate that this reduction in adhesions does not necessarily mean a decrease in small bowel obstruction associated with adhesion. A recent randomized multicenter study comparing laparoscopic versus conventional approaches in colorectal cancer surgery indicated that there was no difference between the two groups for complications associated with obstruction during the 3-year follow-up consultation and study [9]. In a study on the frequency of hospitalizations for ASBO patients and operated with suspected acute appendicitis, the laparoscopic approach led to significantly lower rates than open surgery. However, it was noted that the incidence of ASBO after surgery was low in both groups [10].

Diagnosis

Since small bowel obstruction (SBO) occurs in about 5 cases per 100 thousand of the population, diagnostic errors at the prehospital stage reach about 51%, and in the hospital up to 19%, the relevance of the diagnosis of its is beyond doubt. With mechanical ASBO, occlusion of the lumen of the intestinal tube occurs at some level, which leads to a violation of the transit of intestinal contents. With strangulation ASBO, the blood circulation of the person involved in the pathological process suffers first of all [11]. A section of the intestine, which is associated with compression of the mesenteric vessels due to infringement, volvulus or nodulation, and which causes a rather rapid, within several hours, development of necrobiotic processes in the wall intestines. Timely diagnosis is essential to prevent mortality from late surgical treatment [12], as the causes for the death of patients in 24 - 58% of them are the development of necrosis of the intestine, severe pathological changes in water-electrolyte metabolism, multiple organ failure and sepsis.

The variety of forms and pathogenetic features of SBO cause polymorphism of clinical symptoms and create the basis for diagnostic difficulties and delayed treatment. In this regard, a huge role, along with clinical and laboratory data, belongs to instrumental diagnostic methods, the reasonable and timely use of which provides successful resolution of treatment issues. Since up to 80% of SBO cases are resolved with conservative treatment [13], it is important to identify patients in diagnostic procedures who can be treated conservatively for the resolves of obstruction to prevent unnecessary surgery and the risk of a new disease associated with it and developing. Moreover, such an approach aims to prevent new adhesions in the abdominal cavity after surgery [14]. Technological advances in diagnosis have significantly improved the ability to identify such patients for whom conservative treatment is likely to be more effective, but the accurate and early identification of those patients

who will ultimately require surgery remains a challenge, especially if the clinical symptoms of the disease are not entirely clear.

The 2010 Bologna Guidelines for the Diagnosis and Treatment of ASBO indicate that all patients with suspected disease should be evaluated with abdominal x-rays (level 2b). X-ray polypositional examination allows, in the shortest possible time and with high efficiency, to ascertain obstruction and, in some cases, diagnose its cause. The effectiveness of the method is high and according to numerous studies it reaches 87% in ascertaining the fact and the level of obstruction. For small bowel obstruction, it is typical to have swollen bowel loops of more than 3 cm above the obstruction, containing gas and fluid levels (Kloyber's bowls; fluid levels are usually wide with a low gas bubble), transverse striation corresponding to the Kerkring folds, and the absence of contents in the colon. The sensitivity of the method in solving this diagnostic problem is 60-85% [15]. According to the Bologna Recommendations of 2013, the use of X-ray examination of the abdominal cavity as soon as possible will allow paying attention to those patients who require conservative treatment upon admission to the hospital since there are currently several tools to improve the effectiveness of NOM, as well as to clarify the indications and timing for surgery [16]. On the contrary, W. Laméris et al. [17] showed that the assessment of patients with acute abdominal pain using standard radiography is useless to improve the above sensitivity and specificity, suggesting that it does not play any role in the diagnostic examination or its role is not so important.

Ultrasound of the abdominal organs allows you to effectively supplement the diagnostic program and ascertain AIO in 72-94% of patients, its level in 66.7-80%, the cause in 48-63% of patients and assess the functional state of the intestine. Typical ultrasound signs of intestinal obstruction are: 1) expansion of the bowel diameter more than 25 mm, associated with the deposition of fluid in its lumen; 2) thickening of the intestinal wall due to its edema; 3) visualization of the folds of the mucous membrane of the small intestine; 4) availability free fluid in the abdominal cavity; 5) pendulum movement of the contents of the intestine.

In cases with suspected SBO, using ultrasound, one can distinguish between partial intestinal obstruction and complete mechanical obstruction, since peristalsis can be visualized using this method, among other things [18]. The detection of fluid in the abdominal cavity from the intestinal lumen by ultrasound is of great clinical importance since this instrumental sign is usually used to make clinical decisions, including which surgical approach will be most tolerable and useful for a particular patient [19]. Contrary to the findings of this study, the Bologna Guidelines state that the value of ultrasound is limited (level 2c) because the accumulation of air in the digestive tract in ASBO limits the transmission of ultrasound, making it a useful diagnostic tool only when used by technical experts [16].

The use of computed tomography (CT) as an additional imaging modality to evaluate all patients after inconclusive use of simple radiological techniques has been very helpful in diagnosing SBO [20]. Computed tomography with double (oral and intravenous) allows to determine the localization and cause of obstruction, the diameter and pneumatosis of the intestine, the presence and amount of effusion in the abdominal cavity, to assess the arterial blood supply to the organ (celiac trunk, superior mesenteric artery, inferior mesenteric artery), to diagnose other abdominal pathology. CT has high sensitivity and specificity for SBO (> 92% and 93%, respectively); in addition, additional information provided by CT can help detect signs of ischemia or bowel perforation [21]. D. Maglinte et al. [22] reported that CT can be as sensitive as conventional abdominal x-rays to distinguish small bowel obstruction and strangulation in SBO, and this has been shown (detection rates 86% versus 82%). It is important to note that patients with possible signs of ischemia remain a major clinical problem for diagnosis [23].

Evidence suggests that magnetic resonance imaging (MRI) plays a role in the diagnosis of ASBO, but the method has not yet found a definite place in the diagnostic algorithm for SBO. According to some researchers, it is comparable in efficiency with computed tomography and ultrasound - the sensitivity in the detection of AIC is 86-100%, and the specificity is 90-100%. Although MRI provides approximately the same sensitivity and specificity for diagnosing all causes of SBO in patients as CT, the current recommendations for MRI in standard clinical practice have not been applied in patients

with SBO. The main advantage of the method is its high resolution, the ability to capture morphological changes in the wall of the small intestine, characteristic of a tumor, inflammation, ischemia andnecrosis, as well as to determine the motor activity of the small intestine. However, MRI, despite its low invasiveness and potentially high efficiency in the diagnosis of AIO, has not yet found wide application in clinical practice. This is due not only to the high cost of the equipment and the study itself, the complexity of its implementation in an urgent situation, but also, most importantly, lack of sufficient clinical material and experience to determine the place of these studies in the diagnostic algorithm for intestinal obstruction [24].

Interestingly, the combination of a dynamic X-ray approach with assessing the passage of contrast through the small intestine with a water-soluble contrast agent can help predict whether they can be treated conservatively if clinical signs of ASBO are present or whether surgery is required [25]. This study is indicated in all cases of small bowel obstruction in the absence of signs of strangulation and peritonitis. The method allows you to confirm with high accuracy the fact of intestinal obstruction, determine the severity, level of obstacle (high, low), the nature of intestinal obstruction (mechanical, functional) and the dynamics of the course of the disease. It should be noted that water-soluble contrast is not only a useful diagnostic tool, but also a therapeutic tool, which, due to its hyperosmolarity, has a therapeutic effect due to its ability to "absorb" fluid into the lumen, reduce swelling of the intestinal wall, eliminate obstruction and hyperperistalsis [26]. A randomized controlled trial J. Burge et al. [13] also showed a noticeable therapeutic effect when using gastrographin as a contrast agent for evaluating patients with ASBO: accelerated elimination of obstruction was observed in 75% of patients within 24 hours after contrast using. Although the precise benefits of contrast agents in reducing the need for surgery have not yet been systematically proven, a study has shown a link between their use and reduced length of hospital stay [27]. There is no doubt that ASBO patients, whose contrast does not penetrate the colon, require urgent surgical treatment.

Conservative therapy aimed at resolving SBO is carried out in patients with an obstructive form of SBO when the absence of pronounced introductory electrolyte disturbances and short (up to 36 hours) terms of the disease. Type of conservative therapy, its duration depends on the cause, the severity of the disease, the level of obstruction, features clinical picture. Very often in these situations it is difficult to distinguish obturation with strangulation of the small intestine, despite the use of many instrumental diagnostic methods in these cases. In recent years, several serum markers have been identified that can be detected in small bowel entrapment [28, 29]. These markers include factors released by damaged enterocytes, such as intestinal fatty acid-binding protein (I-FABP) and α-glutathione S transferase (α-GST). Enterocytes are rapidly damaged in the early stages of intestinal health and these biomarkers can be easily detected in both urine and plasma, which opens up promising opportunities for their use as markers of early detection of small bowel strangulation. Several studies on the equation of the cytosolic protein α-GST in plasma have shown the level of this protein gave various results as a diagnostic tool with a sensitivity of 20% to 100% and a total specificity of 85% [29, 30]. Because of this, α-GST might be also useful as an indicator for an effective treatment, as were evidenced by the authors of the study. Another biomarker I-FABP is a cytosolic protein found in tissues that are involved in the absorption. It was shown that I-FABP is a good and early indicator for damage to the small intestine, making it a very useful indicator in patients with suspected strangulation of the small intestine [31]. According to some studies, patients with obstruction of the small intestine had lower levels of I-FABP in serum or urine compared to patients with strangulation [32, 33]. Perhaps, I-FABP may be a significant indicator in the selection of candidates to continue to conservative treatment and choice those of patients to surgery of the small intestine. Also, the intestine includes D-lactate and Claudine [34, 35], but the low specificity of D-lactate and absence of important evidence of the role of claudin-3 in the diagnosis of different types of SBO made it difficult to determine the clinical potential of these biomarkers. However, the diagnostic model for the diagnosis of SBO, where in addition to these markers for prediction to include older age, large-volume drainage through of the nasogastric tube after three days

of the treatment was considered.

Laboratory assessment of patients with suspected small bowel obstruction should include a complete blood count and metabolic panel, taking into account the development of hypokalemic, hypochloremic metabolic alkalosis in all forms in patients during the progression of the disease. Increased levels of leukocytes in the blood, hemoglobin and hematocrit, blood urea nitrogen correspond to the degree of dehydration of patients. Unfortunately, all these data do not help to identify patients with small bowel strangulation. It should be noted that the evaluation of complete analysis of blood, electrolytes, blood urea nitrogen and creatinine, C-reactive protein, serum lactate, lactate dehydrogenase (LDH) and creatine kinase CC) is of great importance in this category of patients and systemic signs of fever, arthritis, tachycardia hypothesis, change in mental state, etc.) additional laboratory tests should include arterial blood gases together with the assessment of clinical symptoms of ASBO [36]. Unfortunately, the treatment of ASBO is less consistent transmissions for the differentiation of intestinal compression, which require immediate medical treatment [37]. Laboratory tests may be more useful for assessing the level of systemic response than confirming clinical results. The types of markers chosen as the number of key factors and the level of cardiovascular resuscitation cannot distinguish between choices caused by ASBO and those caused by other inflammatory conditions [28]. In the case of intestinal diseases due to suffocation of markers, there can be no variety of useful conservative treatment and those who need treatment [39]. However, when there are intestines, the level of serum lactate, LDH and CC may increase due to intestinal hypoperfusion. However, therefore LDH and CPK increase in any average condition, they, therefore, are nonspecific. Instead, the level of another status, the number of which is not enough to spread the intestine, is already well established to increase lactate is very sensitive, not specific to my intestines, but in the case of ASBO [40, 41]. As a result, studies can simply indicate the overall severity of the disease and can be used to support or link inappropriate treatment choices only in the context of several other clinical and instrumental data to detect the location of obstructions and complications of further NOM: the presence of ascites, CT such as ischemia, necrosis, and perforation [42].

Treatment. For patients on ASBO without signs of small bowel strangulation, peritonitis, or severe intestinal insufficiency, there is strong evidence to support the effectiveness of non-surgical treatment (NOM). The presence of free intraperitoneal fluid, oedema of the mesentery and its increase, signs of devascularized small intestine during CT, frequent vomiting in the anamnesis, severe abdominal pain on a visual analogue scale > 4, the presence of protective abdominal tension on palpation, increased white blood cell count predicts the need for laparotomy [16]. The authors point out that the selection of patients who may benefit from early surgery should be done with caution, especially in patients with recurrent episodes of ASBO, many previous laparotomies for adhesions and long-term conservative treatment [16]. Data from many studies have shown that NOM can be successful in approximately 90% of patients without peritonitis and small bowel ischemia [43]. In contrast, delayed surgery in patients with signs of small bowel ischemia creates an increased risk of intestinal resection for many patients. A retrospective analysis by the authors showed that only 12% of patients underwent bowel resection with conservative treatment time or waiting time before surgery ≤ 24 hours, and with waiting time before surgery ≥ 24 hours, 29% of patients required bowel resection [44]. D. Schraufnagel and co-authors [45] showed that in their large cohort of patients, the incidence of complications, resections, prolonged stay and death was higher in patients admitted with ASBO and who was operated on after some time≥ 4 days. The recommendations of the World Society of Emergency Surgery in 2013 stated that NOM in the absence of signs of strangulation or peritonitis can be extended to 72 hours in most patients, and after 72 hours of NOM without positive dynamics, surgery was recommended [16]. It should be noted that currently there are no objective criteria to determine those patients who are likely to respond only to conservative treatment because less clear is the way to predict disease progression to strangulation of the small intestine, or improvement in conservative treatment ASBO. To improve our understanding of this, some authors suggested using the following signs as fairly objective predictors of the impossibility

signs of complete ASBO (no signs of air in the colon), increased serum creatine phosphokinase, and an increase ≥ 500 ml of the liquids from the nasogastric tube on the third day of NOM [16]. It is clear that at any time if there are signs of strangulation of the small intestine, peritonitis or severe intestinal damage due to intestinal ischemia and perforation, NOM was recommended to stop with further surgery. Randomized clinical trials have shown that there are no differences in clinical efficacy between the use of nasogastric tubes compared with the use of long bowel decompression using a long tube [46]. In any case, early decompression of the digestive tract is useful for the initial treatment of these patients together with intravenous fluid and correction of electrolyte imbalance [47]. The introduction of gastrografin into the lumen of the small intestine to study the level of its obstruction was positive in treatment, as it activates the movement of water in the lumen of the small intestine, reduces swelling of the small intestine and can increase smooth muscle activity, which can create effective peristalsis and overcome obstruction [48]. The use of gastrografin and its positive therapeutic effect has been demonstrated in several randomized trials and meta-analyses. However, three recent meta-analyses did not show an advantage in waiting longer than 8 hours after administration and showed that contrast in the colon for 4-24 hours is a precursor and a sign of positive dynamics in the treatment of ASBO patients. Moreover, for patients who underwent HOM, the introduction of gastrografin reduced the need for surgery and length of hospital stay [49]. However, the use of gastrografin did not affect the recurrence rate of ASBO or recurrences that required surgery. Oral therapy with magnesium oxide and simethicone can be considered as helping patients with partial ASBO with positive results in reducing hospital stay [50], and the use of hyperbaric oxygen therapy may be an option for treating patients at high anaesthesia risk who should avoid surgery [51]. Current studies and guidelines do not agree on the risk of recurrence of obstruction, but factors associated with a higher risk of recurrence include age < 40 years, adhesion disease, and postoperative surgical complications [52].

Open operation

Until recently, open surgery was the best method for surgical treatment of ASBO in case, of suspected strangulation of the small intestine or after unsuccessful conservative treatment, and laparoscopy was offered only to a selected group of patients (preferably in the first episode of ASBO). More recently, the use of laparoscopy has become widespread and has become the best choice in treatment centres. Jacek Szelig and Marek Jackowski [53] in the review wrote that there was no statistically significant difference between open and laparoscopic adhesiolysis in the number of intraoperative bowel injuries, wound infections, or overall mortality. Conversely, there was a statistically significant difference in the incidence of general and pulmonary complications and a significant reduction in long-term obstruction. The authors concluded that in patients with SBO, laparoscopy is a technique showing its advantages resulting from a minimally invasive approach but SBO is still a condition where the use of laparoscopy is limited mainly to selected cases such as SBO caused by single adhesions or foreign bodies. A basic limitation of using this technique is advanced and complicated SBO and lack of sufficient technical skills of the surgeon. However, to date, no randomized controlled trials are comparing open-label laparoscopic adhesiolysis, and both the exact indications and the specific results of laparoscopic adhesiolysis in ASBO remain poorly understood. The only randomized controlled trial to provide evidence of level Ib evidence to assess the use of laparoscopy in the treatment of adhesive obstruction of the small intestine is currently ongoing, the main endpoint of which is the duration of postoperative hospital stay, and duration of hospitalization, frequency of ventral hernia and recurrence of small bowel obstruction during long-term follow-up are secondary and tertiary endpoints [54].

Laparoscopy

Laparoscopic adhesiolysis in small bowel obstruction has several potential benefits, including less postoperative pain, faster recovery of bowel function, shorter hospital stays, shorter recovery times, allowing you to return to full activity earlier, fewer wound complications, and reduced postoperative adhesions [15].

A recent extensive population-based analysis of selected indicators involving 6,762 patients showed [55] that laparoscopic treatment of ASBO was associated with lower rates of postoperative complications, including infectious,

and intraoperative transfusion, and an overall reduction in resource utilization compared to laparotomy and length of stay. hospitals. Laparoscopic treatment of ASBO was not associated with a significant difference in surgery duration, recurrence rate, or mortality within 30 days of surgery. Subsequent reports have confirmed that laparoscopic surgical treatment of ASBO is associated with faster recovery of the gastrointestinal tract, shorter length of stay (LOS) and reduction of overall complications compared to open surgery, without significant differences in the duration of surgery [56]. In addition, after the exclusion of bowel resection as a stage of surgery, secondary results continued to favour the use of laparoscopy over laparotomy. Although laparoscopic adhesiolysis requires a certain set of skills and may be unacceptable to all patients, it demonstrates a clear advantage in 30-day morbidity and mortality (lower incidence of serious complications and local infectious complications after incisions), as well as shorter postoperative LOS and surgery. In an analysis of the treatment of more than 9,000 patients in the United States, the authors concluded that increasing the use of laparoscopy may be a possible way to reduce costs and improve outcomes in this patient population [57].

The selection of patients for laparoscopic treatment of ASBO is still a controversial issue nowadays. At a recent consensus conference [58], a group of experts recommended that the only absolute criteria for excluding laparoscopic adhesiolysis in ASBO were those related to the use of pneumoperitoneum (eg, hemodynamic instability or cardiopulmonary disorders); all other contraindications are relative and should be evaluated in each case depending on the laparoscopic skills of the surgeon. In addition, it is necessary to take into account the research results, which indicate that the immune response correlates with markers of inflammation associated with the severity of the injury, and as a result, the extent of surgery may affect clinical outcomes due to adverse action of molecular factors that may eventually cause systemic inflammation reply. Therefore, the benefits of using minimally invasive surgery and avoiding laparotomy in ASBO are even more relevant in weak patients [59].

Conclusion.

Despite significant advances in the diagnosis of ASBO, the problem of determining how to most effectively and safely treat patients in all cases of manifestation of this disease remains. Objective instrumental or laboratory indicators that would allow the surgeon to reliably select the most appropriate tactics in each situation in the analysis of existing literature are not found. Through numerous efforts, the ability to identify patients in clinical practice who require conservative treatment has improved significantly. At the same time, there remain the problems of early identification of patients who require urgent surgical intervention. The choice of an adequate volume of intervention is made intraoperatively and based on visual evidence of intestinal viability. Data analyzing prognostic markers of adverse treatment outcomes are contradictory and dictate the need for further research, as well as the use of various markers, which may improve the diagnosis and early detection of patients with small bowel strangulation in the opinions of lots of surgeons

Declarations

Statement of Ethics

The author has no ethical conflicts to disclosure.

Consent for publication

The author gives her consent to publication.

Disclosure Statement

The author has no potential conflicts of interest to disclosure.

Funding Sources

There are no external sources of funding.

Data Transparency

The data can be requested from the author.

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Received: 28-Sep-2021
Accepted: 20-Nov-2021

MEDICINE OF BORDERLINE CONDITIONS AS AN INNOVATIVE DIRECTION FOR THE DEVELOPMENT OF PREVENTIVE MEDICINE (REVIEW)

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https://doi.org/10.35339/ic.8.4.247-253

Abstract
Reformation of domestic health care must take place not only on the basis of introduction of world experience but also taking into account the own experience received during realization of innovative developments in medical science. Medicine of the borderline conditions belongs to similar innovative developments that received priority financing of Ministry of Health of Ukraine, appreciation by the customers of the applied researches and support of European medical community.Medicine of the borderline conditions is scientifically justified direction of realization of primary purpose of health care, namely prevention of diseases, which is widely approved in practical activity. Thus, prevention of diseases takes place on the basis of determination of risks of development of certain diseases on individual and population levels, with establishment of orientation of this action on the certain systems and organs and body on the whole, that creates founding for directed correction of the educed pre-nosological states, averting their possible transformation into abnormal states. Acceptance of conception of medicine of the borderline conditions by a medical association can influence the revision of today's paradigm of health care, associated with definition of primary prophylaxis, as dominant direction in maintenance of individual health and health of population. Identification of a causal relationship between the action of unfavorable factors of various origins (professionally determined, educational process, environmental, etc.) with the definition of the acting force (substance, energy, information) and the likelihood of damage to the body of the corresponding etiology, is a prerequisite for the planned correction of the functional state of a person.
Keywords: *medicine of the borderline conditions, preventive medicine, occupational medicine, pre-nosological diagnosis, new paradigm of health care.*

Today, the reform of domestic health care sector is one of the most acute problems of our time. This is due to the complexity of the reform process, when the implementation of the "Western" model of health care must also take into account domestic achievements in medical science and practice [1, 2]. First of all, it concerns the generalization and comprehension of medical experience in the field of preventive medicine in order to introduce effective innovative measures to preserve health of the population, ensure adequate conditions for human growth, maturity and life expectancy. At the same time, occupational medicine is a separate branch, which takes care of the safety of the most problematic period of human life [3, 4]. Occupational medicine specifically combines two mandatory components of medical science and practice – preventive and clinical directions.

In recent years, developed states have begun to recognize the intersectoral nature of public health. The current health care paradigm, as well as the factors and conditions that led to its crisis, were formed within the framework of these strategies [5].

The results of many years of research conducted at Kharkiv National Medical University, as well as representatives of other universities that took their origin from Kharkiv school of hygiene, including department of hygienic and clinical specialties, gave a new understanding of the patterns of pathogenesis. They allowed to see health and disease as critical manifestation of on process – sanogenesis,

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between which lies a wide range of pre-nosological conditions and processes that have a borderline nature [6].

The ancient Roman physician Claudius Galen knew about borderline conditions, but systematic research on this problem was conducted by representatives of Kharkiv Scientific Medical School only in our time. According to the results of this study in the context of solving the problem of preserving health of young students working in hazardous conditions, as well as the population living in adverse environmental conditions, ***medicine of borderline conditions***, a fundamentally new scientific direction, found theoretical justification and practical confirmation and awareness of its methodology resulted in a revision of the existing health care paradigm [7, 8]. In addition, medicine of borderline conditions, as an innovative direction in health care, is a concept whose methodology is based on the millennia-tested axiom of Hippocrates, who defined that "the disease is easier to prevent than to cure", which has nowadays acquired not only personal, but also socio-economic sense [9, 10].

Medicine of borderline conditions is a field of medical science dealing with general patterns of formation of pre-nosological conditions and the transient processes of their transformations. The purpose of medicine of borderline conditions is to prevent somatic and mental diseases of different origin, by diagnosing their primary signs and risks of development with subsequent adjustment of the functional state of the body.

The author's logos regarding the definition of borderline conditions and medicine of borderline conditions are shown in Figures 1 and 2, respectively.

Fig. 1. Logo "Borderline conditions".

Fig. 2. Logo "Medicine of borderline conditions".

Medicine of borderline conditions is an integral part of such an innovative direction of world science as *limitantology* (from the Latin *limitans, -antis* - borderline, boundary), the science of borderline (limitiary) conditions and the processes of their transition [11]. In addition to the medical field aimed at studying pre-nosological conditions, limitantology involves implementation of the following scientific areas: solid state physics (competitive behavior of crystals); thorns and other common features of animate and inanimate nature; water and its intermediate states; transitional life forms (viruses, prions); psychology (marginality, as a borderline form of existence of an individual); sociology (revolution and thermidor); chronobiology (transitional days of the year); age physiology (adolescence); evolution (transitional life forms), etc. [12 - 14]. Medicine of borderline states is based on methodological principles, which have found practical confirmation in the study of the health of different age, sex, place of residence and occupation of the population [15, 16].

The *first principle* is **health centrism**. It prioritizes health over all other components of a person's existence (educational, environmental, economic, legal, etc.). All these factors are considered only as separate health-forming components, each contributing to a certain aspect of health formation. Therefore, maintaining good health is an integral part of human life.

The health of different populations is directly affected by lifestyle, environmental living conditions, quality of care, and hereditary factors. In this case, the whole set of vital factors is divided by their direction into two

antagonistic groups: risk factors (which become the subject of elimination) and health factors (which become the subject of use).

For example, the most significant risk factors for different populations of young students include excessive information and emotional stress associated with unhygienic features of cognitive activity. Conversely, physiological capabilities of the nature of learning, which contributes to the emergence of work stress, is an indisputable health factor in the living conditions of young people [17, 18].

The second principle is **dialectic of transient processes**. It is based on the assertion that human life is built on objective laws inherent in transient processes, which combine a certain sequence of borderline conditions on the way to achieving a stable state of the body (adaptation).

1. General patterns of the adaptation process: staging, the presence of adaptive reactions (evolutionary and individual experience), limitation of adaptation capabilities and their compensation, dynamism and hierarchy of adaptation systems, the principle of achieving a new quality state, the phenomenon of self-regulation and "adaptation price".

2. The law of adaptive transition: transition of the body to a state of adaptability is due to energy and plastic resources accumulated in past adaptive experience, through the destruction of former useful links in the leading biological system, which previously provided a stable state, by forming a new dominant system [19].

3. The phenomenon of complementarity (mutual complementation): achievement of the desired result (education while maintaining health) is achieved under the categorical condition of compliance with the nature of the functional (adaptive) capabilities of the body, and the relationship between the subject of cognitive activity and its factors are complementary [20].

The *third principle* is **methodological sequence**. It determines that the procedure for the practical implementation of the principles of medicine of borderline conditions, aimed at maintaining the mental health of young students, includes hygienic pre-nosological psychodiagnosis, correction of functional and mental state of the body and evaluation of the effectiveness of these actions [21].

Stages of the program implementation: **Stage I** – determination of the level of health of the studied contingent with emphasis on the prevalence of certain diseases, probably related to the impairment of systems and organs that belong to the "targets" of adverse environmental factors or heredity; **Stage II** – identification of environmental factors that belong to the risk factors in relation to deterioration of health of the studied contingent due to the general and targeted pathogenic effects on the body and individual systems and organs; **Stage III** – determination of indicators of the functional state of the body, which belong to the criteria of the pre-nosological state, on the basis of measuring the level of realization and stability of psychophysiological and physiological functions, paraclinical indicators of homeostasis; **Stage IV** – determination of psychodiagnostic indicators, which belong to the signs of conditions and periods of increased risk of mental health disorders; **Stage V** – elaboration and implementation of preventive measures, including individual and group measures of psychohygienic, adaptogenic, sanogenic and regime-organizational nature, aimed at disease prevention on the basis of hygienic pre-nosological diagnosis data; **Stage VI** – assessment of the effectiveness of the implemented measures based on the analysis of the time course of health and functional status of the subjects according to the criteria of pre-nosological diagnosis (feedback principle) [22].

The *fourth principle* is **evidence**. It is claimed that the implementation of the program of medicine of borderline conditions in health care involves the inclusion of standardized methods for measuring indicators of mental and functional states and objective criteria for their evaluation.

Hygienic pre-nosological psychodiagnosis involves the use of generally accepted and widely tested research methods. Assessment of living conditions of student youth implies identification of risk factors based on the measurement of sanitary indicators comparing them with existing state hygiene regulations, as well as the use of standardized questionnaires. Determination of the etiological relationship between risk factors and the consequences of their effects on the population of young students and specific individuals involves the use

of an epidemiological method to study the disease. Prospective analysis of the time course of mental and functional state is given on the basis of a comprehensive research program, which includes the most common and proven research methods [23].

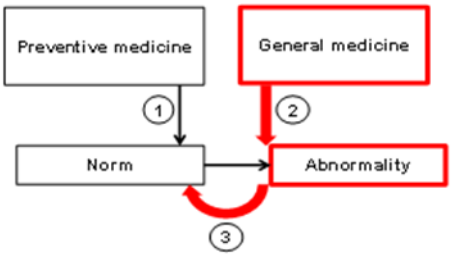
Common, interrelated criteria for the risk of adverse health effects in the "human being-environment" system are: 1) quantitative deviation of the environment and functional status from the norm (sanitary and physiological, respectively); 2) qualitative deviation of the state of the environment and the functional state of the body, which is manifested in the nature of external influence (separate, combined, complex, simultaneous action) and the corresponding reaction of the body, which is manifested in the formation of pathogenesis.

Standardized and evidence-based methods for quantitative assessment of pre-nosological states are based on the theoretical foundations of the adaptation theory, through the introduction of the most informative indicators of pre-nosological states and scientifically justified criteria for their qualitative and quantitative assessment, which include: 1) achieving a certain level of realization of psychophysiological functions (primarily those that determine productive cognitive and professional activity); 2) the ability of the body to maintain the achieved level of realization of psychophysiological functions during the generally defined educational cycle (daily, weekly, annual); 3) achieving a stable psycho-emotional state during the daily, weekly and annual training cycles.

The *fifth principle* is a **change in the paradigm of health care**. The prospect of implementing the principles of borderline medicine involves a revision of the set of values, methods, approaches, technical skills and tools adopted in the medical community within the existing scientific tradition.

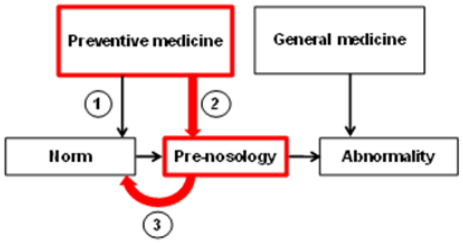
The traditional model of health care is based on a clear non-alternative understanding of the categories of "health" and "disease", as if the transition between these conditions is abrupt, without any previous qualitative and quantitative changes in the body (Fig. 3). But any doctor knows that this is not the case. Even the severity of the injury, and its very occurrence, is largely determined by the previous state of the body.

The new paradigm of health care, based on the theory of medicine of borderline conditions, states that the development of clinical forms of somatic and mental diseases is preceded by certain dysfunctional disorders of pre-nosological nature (Fig. 4). These deviations can be measured, estimated and systematized.



1 – 1 - identification and elimination of risk factors
2 - clinical diagnosis, treatment, rehabilitation
3 - restoration of health of patients

Fig. 3. The existing healthcare paradigm



1 - identification and elimination of risk factors
2 - pre-nosological diagnosis and correction of the functional stat
3 - prevention of the disease in healthy people

Fig. 4. A new paradigm of health care

Moreover, timely detection of these borderline conditions, detection and elimination of risk factors for their occurrence and their medical correction contribute to the preservation and promotion of health. And the cost of pre-nosological diagnosis is significantly lower than the whole range of medical-diagnostic and rehabilitation measures in case of a disease.

This is a new paradigm of medicine, which involves shifting the emphasis from the concepts of norm and abnormality to the concept of pre-nosology.

In addition, and perhaps most importantly, the proposed new health care paradigm focuses not on the patient but on the healthy person, and therefore fills the term "health care" with real meaning.

Thus, medicine of borderline conditions is scientifically justified, and widely tested in practice, the direction of the main goal of health care is disease prevention. The prevention of diseases is based on determining the risks of specific diseases at the individual and population levels with the establishment of the direction of this action on specific systems and

organs and the body as a whole, which creates a basis for targeted action to correct identified pre-nosological conditions, preventing their likely transformation in pathological conditions. The adoption of the concept of borderline medicine by the medical community can influence the revision of today's health care paradigm, which is associated with the definition of primary prevention as the dominant direction in maintaining the individual and population health of the population. Identification of the causal relationship between the action of adverse factors of various origins (professionally determined, educational process, environmental, etc.) with the definition of force (substance, energy, information) and the likelihood of damage to the body of appropriate etiology, is a prerequisite for planned correction of functional status.

Borderline medicine is one of the widely tested innovative branches of academic entrepreneurship on the basis of self-supporting activities. The commercial component of medicine of borderline conditions in recent years has been widely tested on the basis of current applied research in the field of occupational medicine in three interrelated areas: 1) hygienic studies of risk factors for occupational diseases; 2) occupational pathology studies on pre-nosological and clinical diagnosis of occupational diseases; 3) psychophysiological and psychodiagnostic studies to determine personal risk factors for health and life.

Perspective directions of development of preventive medicine on the basis of realization of innovative principles of medicine of border states include: 1) in the field of **public health** – revision of the current paradigm of health care on the basis of introduction of measures for definition of risk factors for human health (society) and correction of pre-nosological conditions; 2) in the field of **educational medicine** – hygienic pre-nosological diagnosis and correction of probable health disorders of students of different ages and educational groups; 3) in the field of **medical rehabilitation** – hygienic optimization of living conditions and disease prevention among children and adolescents suffering from congenital and acquired defects of vision, hearing, intellectual development, deviant behaviors.

Conclusions

1. Borderline medicine is scientifically justified, and widely tested in practice, especially in occupational medicine, the direction of the main goal of health care is prevention of diseases, including diseases of occupational origin. The prevention of diseases is based on determining the risks of specific diseases at the individual and population levels with the establishment of the direction of this action on specific systems and organs and the body as a whole, which creates a basis for targeted action to correct identified pre-nosological conditions, preventing their likely transformation into abnormal conditions.
2. Adoption of the concept of borderline medicine by the medical community, can influence the revision of the current paradigm of health care, associated with the definition of primary prevention as the dominant direction in maintaining individual and population health. Identification of the causal relationship between the action of adverse factors of various origins (professionally determined, educational process, environmental, etc.) with the definition of force (substance, energy, information) and the likelihood of damage to the body of appropriate etiology, is a prerequisite for planned correction of functional status.
3. Promising areas of implementation of the principles of borderline medicine are the fields of occupational medicine, public health, rehabilitation, school medicine, etc. Different areas of implementation of the proposed concept are combined on the basis of general patterns of formation of the adaptation process outside the type of external influence on the body. However, taking into account the peculiarities of the nature of the impact on certain functional systems of the body form a specific, complex of individual, group and population preventive measures, aimed at correcting a certain range of pre-nosological functional disorders, to correct the adaptation process.

Declarations

Statement of Ethics

The author has no ethical conflicts to disclosure.

Consent for publication

The author gives her consent to publication

Funding Sources

There are no external sources of funding.

Data Transparency

The data can be requested from the author.

Disclosure Statement

The author has no potential conflicts of interest to disclosure.

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Received: 01- Oct-2021
Accepted: 13-Dec-2021

ATTENTION AS A CRITERIONAL PROPERTY OF PROFESSIONAL FITNESS OF PERSONS WORKING IN HAZARDOUS CONDITIONS

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https://doi.org/10.35339/ic.8.4.254-259

Abstract

The purpose of the study was to improve methodological approaches to determination of attention as a criterion of professional fitness of persons working in hazardous conditions. To determine attention, we evaluated productivity index of information retrieval by "Numeric Square" method. When analyzing the data obtained during the study of attention (including its switching) on the productivity of information retrieval in persons who perform different types of hazardous work and the difference between the type of work performed. The vast majority of surveyed persons working in hazardous conditions were found to meet professional requirements (70%) by psychophysiological function "attention" (including its switching). The group of "conditionally fit" included (25%) subjects and "unfit" – 5%.

Keywords: *hazardous work, productivity of information retrieval, professional selection, psychophysiological functions, high risk activities, attention.*

Introduction

In Ukraine, as in the rest of the world, the problem of the impact of occupational hazards and peculiarities of the labor process on higher nervous activity and general health of the working contingent remains relevant. At the same time, the issue of the connection between changes in the psychophysiological state of the employee with his professional success, reliability and ultimately the results of professional activities in individual and social aspects, has been and remains extremely essential [1, 2].

Thus, on the one hand, employees under the stressful and frankly harmful effects of the labor process in the implementation of adaptive-compensatory mechanisms are subject to regular professional deformation and potentially are at risk of pathological changes in the body [3-8].

The issue of safety of workers, especially of hazardous, extreme risk professions is due to the extraordinary financial and economic [9], medical, social and psychological [10] urgency of the problem.

All this determines the need for special attention to health in general and psychophysiological parameters in particular, both at the stage of professional selection and employment, and throughout the period of professional activity [11].

In high-risk work, it is obvious that the clear organization of all components of psychophysiological support is extremely important for successful performance and maintenance of general and mental health [12,13].

It is important to take into account the peculiarities of psychophysiological support for becoming a specialist in professions where the key stressor is human interaction [14].

Purpose of the study: to improve methodological approaches to the definition of attention as a criterion of professional fitness of persons working in hazardous conditions.

Object and methods of the study

The object of the study was the psychophysiological state and health of employees working in hazardous conditions.

The study was conducted with the participation of persons working in hazardous conditions. According to the current legislation, a special criterion for attracting employees to the list of study participants was that they were subject to mandatory periodic (primary) medical check-ups [15] and psychophysiological examination [16]. The study group included representatives of 17 working professions that perform hazardous work. When studying such a psychophysiological indicator as attention, the following criteria were chosen: 1) the type of hazardous work performed; 2) a profession

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related to the performance of high-risk work; 3) the age of the employee; 4) the sex of the employee; 5) employment record of the employee.

To determine the attention, we studied the performance of information retrieval by "Numeric Square" method [17]. This method is based on detecting the amount of useful information that can be retained by the subject under conditions of active information retrieval in the shortage of time.

This technique is implemented as part of a self-developed computer software "Psychodiagnostic testing to determine the professional fitness of industrial employees for high-risk work by psychophysiological indicators "ProfRisk" [18]. Student's test in Excel was used to statistically process the results.

Results of the study and their discussion

Assessment of the data obtained during the study of attention (including its switching) on the productivity of information retrieval in persons who perform different types of hazardous work revealed the difference depending on the type of work performed.

Information retrieval productivity in employees who perform explosion-hazardous work was 7.17 ± 0.31 numbers, in employees with nervous and emotionally stressful work 6.96 ± 0.35 numbers, in those working with firearms 9.00 ± 1.22 numbers, in those maintaining oil and gas pipelines 3.17 ± 1.42 numbers, in persons performing fire-hazardous work 7.07 ± 0.47 numbers, in those working at height 6.12 ± 0.14 numbers, in those performing high-voltage work 6.30 ± 0.28 numbers, in those driving transport 6.14 ± 0.86 numbers, in those performing underground work 8.50 ± 0.99 numbers (Table 1).

A comparative analysis of the value of information retrieval performance showed that the optimal number was observed in employees who by type of job perform work using firearms and underground work. The largest deviation from the optimal value of information retrieval performance was found in employees who maintain oil and gas pipelines ($p < 0.05$- < 0.01), which requires attention from the representatives of these professions during psychophysiological examination and during direct implementation of their work. Maintenance of oil and gas pipelines is performed under the pressure of various gases, so employees who perform hazardous work in this field must be especially careful to avoid accidents and explosions. Nine of the studied types of work associated with increased risk were performed by representatives of 17 surveyed professions and specialties. Given that one of the main psychophysiological functions in the performance of high-risk work is attention, a study of the indicator of the "productivity of information retrieval" criterion was carried out for each of the 17 professions. The control group included employees whose job was not related to hazardous work, namely accountants and economists.

Observations in the study of the value of the productivity of information retrieval (Table 2) showed that in the representatives of management, whose work is associated with great responsibility and often requires nervous and emotional stress, it was 7.50 ± 0.37 numbers. In the following study groups, work was associated with other risk factors and the corresponding values were: technicians 6.23 ± 0.54 numbers, locksmiths 5.16 ± 0.34 numbers, shop assistants 6.52 ± 0.52 numbers, painters 5.65 ± 0.37 numbers, engine-drivers 7.00 ± 0.33 numbers, craftsmen 6.13 ± 0.43 numbers, engineers 7.28 ± 0.33 numbers, electric generator repairmen 5.91 ± 0.32 numbers, electromechanical technicians 5.91 ± 0.47 numbers, electric gas welders 4.68 ± 0.61 numbers, electricians 6.38 ± 0.82 numbers, drivers 5.50 ± 1.19 numbers, security guards 9.00 ± 1.22 numbers, utility operators 6.93 ± 0.35 numbers, fighters 7.67 ± 0.55 numbers. Representatives of the control group, which included accountants and economists, had an average of 7.60 ± 0.45.

Comparative analysis of the obtained data showed that none of these representatives had the highest productivity of information retrieval. Besides, significant differences were observed in locksmiths, electric gas welders and drivers where ($p > 0.05$-< 0.01) indicated a certain feature of this psychophysiological function in these subjects. This is an indicator of their inability to concentrate and switch attention to full speed, which is an essential requirement for successful and quality work in these professions.

The next step in conducting a comparative analysis of the value of the productivity of information retrieval was to study the dependence of concentration and speed of its switching on professional experience, age and sex of employees (Fig. 1, 2, 3).

Table 1

Information retrieval productivity in employees performing various types of high-risk work
($\bar{M} \pm m$, numbers; n = 810)

Types of work	Indices
Explosion-hazardous work	7.17±0.31
Nervously and emotionally stressful work	6.96±0.35
Work with the use of firearms	9.00±1.22
Maintenance of oil and gas pipelines	3.17±1.42
Fire-hazardous work	7.07±0.47
Work at height	6.12±0.14
High voltage work	6.30±0.28
Transport driving work	6.14±0.86
Underground work	8.50±0.99

Note: statistical significance of differences at p> 0.05 - <0.01

Table 2

The value of information retrieval productivity in representatives of various professions whose work is associated with high risk
($\bar{M} \pm m$, numbers; n = 810)

Profession	Indices	p
Management staff	7.50±0.37	>0.05 - <0.01
Technician	6.23±0.54	
Locksmith	5.16±0.34	
Shop assistant	6.52±0.52	
Painter	5.65±0.37	
Engine-driver	7.00±0.33	
Master	6.13±0.43	
Engineer	7.28±0.33	
Electric generator repairman	5.91±0.32	
Electromechanical technician	5.91±0.47	
Electric gas welder	4.68±0.61	
Electrician	6.38±0.82	
Driver	5.50±1.19	
Security guard	9.00±1.22	
Utility operator	6.93±0.35	
Fighter	7.67±0.55	
Accountant*	7.60±0.45	
Economist*	7.60±0.45	

Note: * – representatives of the comparison group

The study established that the value of "productivity of information retrieval" in persons with different experience in hazardous occupations ranged from 6.58 ± 0.13 numbers in the first group (employment record up to 10 years) to 5.53 ± 0.32 numbers in the group with experience of more than 30 years, which indicated a decrease in attention and switching attention with increasing professional experience, as an indicator of fatigue (Fig. 1).

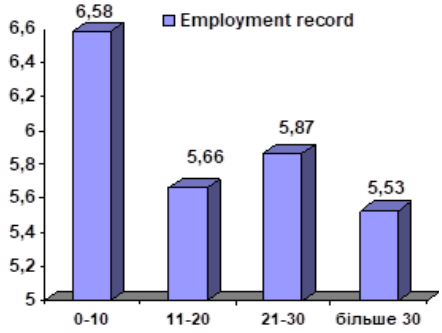

Fig.1. The value of information retrieval productivity depending on employment record ($\bar{M} \pm m$, numbers; n = 810).

However, the lack of significant differences between different groups of experience ($p > 0.05$), indicated stability throughout the whole term of work and leading functions that ensure efficiency and safety.

Evaluation of the dependence of indicators of key professionally significant functions of employees in hazardous professions showed a clear pattern on the age of workers.

The studied psychophysiological indicators tended to decrease. In employees aged 20 to 29 years, this figure was 6.77 ± 0.25 numbers, in the age group from 30 to 39 years 6.89 ± 0.23 numbers, in 40-49 years 6.47 ± 0.25 numbers, 50-59 years 5.61 ± 0.29 numbers, in 60 years and over 5.61 ± 0.31 numbers.

The absence of statistically significant differences between age groups ($p > 0.05$) indicated the normal physiological process inherent to older age groups and associated with reduced mobility of nervous processes on which the value of information retrieval productivity depends (Fig. 2).

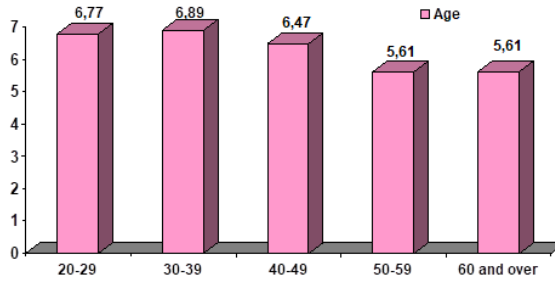

Fig. 2. The value of information retrieval productivity depending on age ($\bar{M} \pm m$, numbers, n = 810).

Indicators of the "productivity of information retrieval" criterion in women slightly exceeded its value than in men (6.30 ± 0.28 numbers and 6.27 ± 0.12 numbers, respectively), which indicated a slightly greater tension in the psychophysiological state of women who perform hazardous work.

But the lack of probable differences between the two groups of comparison showed a special role that belongs to professionally important functions in the performance of hazardous work, regardless of the sex of the employee (Fig. 3).

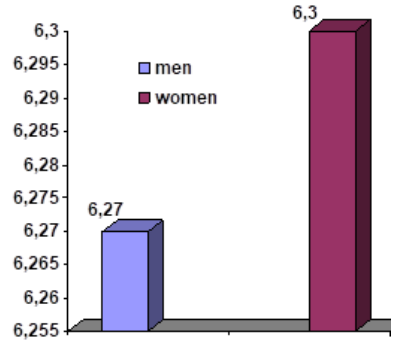

Fig.3. The value of information retrieval productivity depending on gender ($\bar{M} \pm m$, numbers, n = 810).

A generalized individual analysis of the material obtained during the study (9 types of work, 17 professions and specialties, 810 surveyed persons), allowed to establish quantitative parameters for assessing the professional fitness of persons performing hazardous work on the basis of productivity of information retrieval. The fitness to perform these works by the psychophysiological function of "attention" was determined by the value of this indicator from 12 numbers to 7 numbers. Conditional fitness to work was determined by the value of this indicator in the range from 6 to 1 number. Unfitness to perform these types of work was determined by the value of less than 1.

Based on this, it was found that among the total number of performers of various types of hazardous work, 70% of respondents met the requirements of professional fitness on the criteria of "productivity of information retrieval", 25% were conditionally fit, which determined a reduction in time for the next check-up from two (for unconditionally fit) to one year (Fig. 4). The number of professionally unfit among all the studied subjects was 5%.

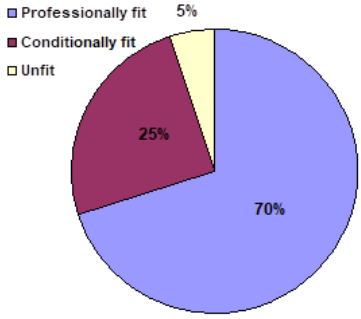

Fig.4 Professional fitness of employees who perform hazardous work on the basis of productivity of information retrieval ($P\% \pm p\%$, n = 810).

Conclusions

The following conclusions can be drawn according to the results of the study of attention (including its switching), as an important psychophysiological function, which an employee must have when performing hazardous work:

1. Quality and safe performance of hazardous work is ensured by the presence of attention and speed of switching attention.

2. According to the indicators of the "productivity of information retrieval" criterion the worst indicators were observed in employees who maintain oil and gas pipelines ($p < 0.05$-0.01), which requires attention from representatives of these professions during psychophysiological examination and in execution of the work itself.

3. Significant differences were observed in the representatives of the following professions and specialties: locksmiths, electric gas welders and drivers where ($p > 0.05$-<0.01). The set of preventive measures for the representatives of these groups of workers should include the improvement of the functional state by training professionally significant psychophysiological functions, as well as careful professional selection for these professions.

4. Experience, age, gender are signs in which the value of the "productivity of information retrieval" criterion directly depends on the physiological process of the population norm and are not reflected in the implementation of leading psychophysiological professionally important functions of persons performing hazardous work.

5. The vast majority of surveyed persons working in hazardous conditions meet professional requirements (70%) by psychophysiological function "attention" (including its switching). The group of "conditionally fit" included (25%) subjects and "unfit" – 5%.

Declarations

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Consent for publication

All authors give their consent to publication.

Disclosure Statement

The study was conducted at the Research Institute of Labor Hygiene and Occupational Diseases as part of the mandatory medical check-up and psychophysiological examination of employees who perform work in harmful and hazardous working conditions. Administrative settlement agreements were concluded with enterprises in accordance with the Order of the Ministry of Health of Ukraine No.246 of 21.05.2007 "On approval of the procedure for medical examinations of certain categories" and the Order of the Ministry of Health of Ukraine and the State Committee of Ukraine for Labor Protection No. 263/121 of 23.09.1994 "On approval of the list of jobs where with a need for professional selection".

Funding Sources

This study was not supported by any grants from public, commercial or other sectors.

Data Transparency

The data can be requested from the authors.

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Received: 11- Sep-2021
Accepted: 13-Dec-2021

OVERWEIGHT AND OBESITY IN YOUNG PEOPLE (REVIEW)

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https://doi.org/10.35339/ic.8.4.260-277

Abstract

Obesity in young people is one of the main problems of modern health care due to its high prevalence, complex adverse health effects, risk of complications and low effectiveness of existing treatments. The urgency of this problem is also increasing in low- and middle-income countries, including Ukraine. The article presents data on the medical and social significance of obesity at a young age, the prevalence of overweight and obesity among children of all ages in the world and in our country, key risk factors for overweight, as well as key WHO strategies and programs for the prevention of food-related diseases. In Ukraine, there is an insufficient level of registration of cases of obesity, which is due to the imperfection of the existing system of prevention of this pathology. Thus, important measures on this issue in our country, according to modern strategy, are the study of the environment where the child is, the lifestyle of families, the health of overweight children, followed by the organization of prevention and treatment.

Keywords: *obesity, adolescents, epidemiology, overweigh, alimentary-dependent diseases, eating behavior, physical activity, childhood, eating disorders, risk factors, lifestyle, diet, prevention, strategy.*

Obesity is one of the most common chronic diseases in the world. Currently, every fourth person on our planet is already overweight or obese. In all countries there is a progressive increase in the number of obese patients among both adults and young people. The World Health Organization has recognized obesity as an epidemic of the XXI century. Epidemiologists estimate that 40 % of men and 50 % of women will be obese by 2025 [1]. With the spread of obesity on the planet, the associated severe somatic diseases are multiplying and deepening - type 2 diabetes, hypertension, coronary heart disease, cancer and others that lead to poor quality of life, early disability and premature death [2]. But in clinical practice, the negative impact of obesity on the occurrence, course and effectiveness of treatment of diseases that have developed against the background of overweight is often underestimated.

Patients with complicated obesity, as a rule, receive medical care only for pre-existing comorbidities, they do not receive treatment aimed directly at weight loss and thus to prevent complications.

Today, the issue of overweight and obesity among young people is becoming more common: sedentary lifestyles, unbalanced diet, fast food and many other aspects that affect the change of dietary preferences and contribute to obesity.

During the Covid-19 pandemic, the issue of overweight became extremely important. Online training, delivery of anything to the door of the house, quarantine restrictions on movement and the absence of even the need to move do a great "service" to our body and contribute to the development of socially significant disease called "obesity".

Young people from different countries talk about the aggravation of overweight problems and that the habit of eating well is part of the national culture (United Arab Emirates, Nigeria, Israel, etc.)

Obesity is a multifactorial disease. In most cases (90 %) at a young age are exogenous-constitutional obesity. Other forms of this pathology are associated with medical problems: the use of certain drugs (eg, glucocorticoids, some antidepressants, antipsychotics, antiepileptics) or the presence of diseases (tumors of

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the hypothalamus or brain stem and its treatment, radiation therapy of brain tumors, hemorrhoids or hemobra skull, stroke, hypercorticism, hypothyroidism or other neuroendocrine diseases, monogenic obesity, chromosomal or other genetic syndrome) are quite rare and usually have a morbid course and the presence of specific symptoms [3, 4, 5, 6, 7, 8, 9, 10, 11, 12].

Obesity in young people is one of the main problems of modern health care due to its high prevalence, complex adverse health effects, risk of complications and low effectiveness of existing treatments [13, 14, 15, 16].

Being overweight in childhood and adolescence causes both short-term and long-term adverse effects on physical and psychosocial health. [17, 18, 19, 20, 21, 22, 23, 24, 25] Systemic hormonal and clinical disorders associated with childhood obesity are combined into metabolic syndrome. [26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42] Manifestations of this syndrome are insulin resistance and the manifestation of type 2 diabetes, dyslipidemia , arterial hypertension and ovarian hyperandrogenism. [43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 31, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63] In addition, obesity causes digestive [64, 65, 66, 67, 68, 69, 70, 71, 72], endocrine [73], orthopedic [74] and other disorders [75, 76, 77, 78], apnea in a sleep [79, 80], reduces resistance to colds and infectious diseases [81, 82, 83] and dramatically increases the risk of complications from surgery and trauma. Psychological aspects of overweight and obesity in childhood are also very important. They are associated with low self-esteem, dissatisfaction with your body, depression, up to suicidal thoughts. Such young people are stigmatized by peers and have fewer friends than people with normal body weight. This, in turn, can affect academic performance. In the future, obese young people are more prone to social exclusion, early school leaving, exacerbations of eating disorders, alcoholism and drug addiction, and have lower marriages and overall life satisfaction. [84, 85, 86, 87, 88, 89, 90, 91, 92] Thus, the problem of obesity is at the intersection of different branches of medicine - pediatrics, therapy, endocrinology, gastroenterology, nutrition, gynecology, andrology, neurology and psychiatry. It is known that overweight in childhood is a significant predictor of obesity in adults: 50% of children who were overweight at age 6 become obese in adulthood, and in adolescents this probability increases to 80%. It should be noted that often obesity and metabolic syndrome, which manifest in childhood and adolescence, lead to cardiovascular morbidity and mortality in adults, even at the stage of subclinical manifestations [93, 94, 95, 96, 97, 98, 99, 100].

Every year the problem of overweight in Ukraine becomes more urgent. According to statistics, only 39.6 % of Ukrainians were normal weight in 2019, while 59.1% of the population was overweight and 24.8% were obese. This is evidenced by the results of the STEPS study on the prevalence of risk factors for noncommunicable diseases in Ukraine [101].

Numerous negative consequences of obesity create a number of social and economical and medical problems that need to be addressed using integrated approaches [102, 103, 104, 105].

General trends in the epidemiology of overweight and obesity among young people

The high prevalence of obesity in the modern world is considered a global non-infectious epidemic, which was declared by the WHO in 1997. Thus, the growth of overweight and obesity is observed in both adults and children regardless of gender, age, race, place of residence and social status. The problem of overweight has become relevant even for countries where a large part of the population is constantly starving. Such a sharp increase in this incidence is largely due to negative changes in the lifestyle of the modern population of the planet. According to the WHO, up to 60 % of deaths are related to destructive behavior. At the same time, the leading positions are occupied by excessive and irrational nutrition, which accounts for 25 % of deaths, 11.9 % of deaths are related to alcohol use, 17.1 % - to tobacco smoking and 6% - to low physical activity [106, 107, 108, 109, 110, 111].

In 2016, the WHO, together with experts from Imperial College London, conducted a study of the prevalence of overweight and obesity in the world. This study is the most comprehensive in the last 40 years. According to the results, more than 1,9 billion adults over the age of 18 were overweight and obese. Thus, the number of adults suffering from obesity increased from 100 million in 1975 to 671 million in 2016. It is noted that the country with the largest number of overweight people

is the United States (38,2 %), and the smallest - Japan (3,7 %). At the same time, WHO experts predict a further significant increase in the number of obese people by 2025 [112, 113, 114, 115].

The most worrying situation is the growing number of overweight and obese children and the shift in the peak of childhood obesity in the early ages compared to previous years. According to a 2016 study, the total number of overweight and obese children was about 41 million children under the age of 5 and 340 million between the ages of 5 and 19. Thus, the prevalence of overweight and obesity among children aged 5 to 19 years increased sharply from 4% in 1975 to 18 % in 2016. In 1975, slightly less than 1% of children and adolescents aged 5 to 19 were obese. 19 years old, and in 2016 their number reached 124 million (6 % of girls and 8 % of boys). This trend exacerbates the epidemic of obesity in adults and poses a growing threat to the health of the next generation [2, 111, 112,113, 114, 116].

According to national epidemiological studies, up to 40 % of children in developed countries are overweight or obese. For example, in the United States, the average body weight of a child has increased by 5 kg over the past 30 years, and one in three people are overweight or obese in the pediatric population [112, 117, 118, 116]. In Europe, the incidence of overweight, including obesity, varies from 7-8% in Norway to 36 % in Italy and 40 % in Greece [2, 111,112, 113, 119, 120, 121, 116].

Despite the ongoing fight against hunger, an increase in the number of overweight and obese children is also observed in some developing countries (Southeast Asia, a number of countries in Africa). Foreign researchers (Popkin B.M., Adair L.S., 2012) associate this phenomenon with the gradual transition to Western life. As a result, these countries face a double problem: infectious diseases as a result of malnutrition and a sharp increase in the number of chronic diseases associated with obesity. WHO experts emphasize that, according to forecasts, in 2022 the number of obese children and adolescents will exceed the number of their peers suffering from malnutrition [2, 112, 122, 116].

The importance of obesity for modern health care is determined by the threat of disability of young patients and reduced overall life expectancy due to the frequent development of severe comorbidities. Overweight and obesity lead to diseases such as type 2 diabetes in 80% of cases, in 35 % of cases to coronary heart disease and in 55 % of cases to hypertension in the adult population. It has been found that every third premature death in the world is associated with diseases that are the result of obesity and physical inactivity [123, 124, 125, 126, 127, 100].

Obesity-related diseases are generally the cause of a significant share of the overall burden of disease in the WHO European Region: the Region accounts for more than 1 million deaths and 12 million years of poor health each year. Thus, every 13th death in the EU is due to being overweight. It is proved that this pathology significantly reduces life expectancy: on average from 3 to 5 years with a slight excess of body weight and up to 15 years - with severe obesity. It is determined that if humanity managed to solve the problem of obesity, the average life expectancy would increase by 4 years. For comparison: if the problem of malignant neoplasms were solved, the average life expectancy would increase by 1 year [128, 129, 130, 61, 131, 132].

Being overweight and obese have economic consequences. Numerous studies have been conducted in recent years and attempts have been made to estimate the economic losses due to obesity. Most of these studies looked at cases of medical expenses related to illness (direct costs), while some studies looked at costs associated with loss of productivity (indirect costs).

There is much less scientific data on the individual costs of obese people and their families, such as the cost of home care, special clothing or weight loss products. According to a WHO study, direct spending on obesity care accounts for a total of 2-4 % of national health spending. In line with the steady growth of this problem, health care expenditures are projected to increase to 6 % of national expenditures in the WHO European Region [132, 133, 134, 135, 136, 137, 138].

The health care of economically developed countries is just beginning to develop approaches to the prevention and treatment of obesity that correspond to modern ideas about the origin of this disease. Thus, the main directions for the complex solution of the problem were formed and the corresponding programs were adopted [139, 140, 115, 141].

In 2004, the World Health Assembly adopted the WHO Global Strategy on Nutrition, Physical Activity and Health. The strategy lists the necessary measures to support healthy eating and regular physical activity and calls on all stakeholders to take action at the global, regional and local levels to improve nutrition and physical activity. The political declaration adopted in September 2011 at the high-level meeting of the UN General Assembly on the prevention and control of noncommunicable diseases recognizes the importance of reducing the prevalence of unhealthy diets and low physical activity. The declaration reaffirms its commitment to the further implementation of the WHO Global Strategy on Nutrition, Physical Activity and Health, including through policy action and action to promote healthy eating and physical activity among the general population, as appropriate. WHO has developed a "Global Plan of Action for the Prevention and Control of Noncommunicable Diseases 2013-2020" in the framework of the commitments made in the UN Political Declaration on Noncommunicable Diseases (NCDs), approved by the Heads of State and Government in September 2011. The Global Plan of Action will contribute to progress towards the 9 global targets for noncommunicable diseases by 2025, including a 25 % reduction in premature deaths from NCDs and a stabilization of the global obesity rate in 2010. The World Health Assembly approved the report of the Committee on the Elimination of Childhood Obesity (2016), which contains six recommendations for combating conditions that contribute to obesity and critical periods of life that should be addressed. In 2017, the World Health Assembly reviewed and approved a plan to implement the commission's recommendations, prepared as a guide for further action at the country level. Regular physical activity is key to the prevention and treatment of non-communicable diseases, including heart disease, stroke, diabetes and cancer. At the same time, according to the WHO, every fifth adult in the world and 4 out of 5 adolescents aged 11-17 are not physically active. That is why the World Health Organization has developed a "WHO Global Plan of Action to Increase Physical Activity for 2018-2030" [142, 143, 144, 115, 145].

In order to implement programs in some countries around the world, studies have been conducted to study the incidence of overweight and obesity, diet and physical activity among the general population and its subgroups, depending on age, sex, social and economic status and place of residence, and interventions were also carried out at various levels [146, 147, 148, 149, 150, 151, 152,153].

Solving the problem of obesity in the world is to increase the quality and length of life, reduce morbidity and mortality, save huge amounts of money that society now spends on obesity and its complications [154, 155].

The urgency of this problem is also increasing in low- and middle-income countries, where the incidence of overweight and obesity in children is much lower than in developed countries. Until recently, there were virtually no large-scale epidemiological studies of obesity among children and adolescents in Ukraine. Despite the fact that in recent years in some regions significant progress has been made in studying the epidemiology of alimentary-dependent diseases, including obesity in children and adolescents, the diagnostic process for this type of pathology is ineffective. Thus, the prevalence of obesity in Ukraine in 2017 was 13.4 %, with a negative trend over the past 2 years. According to official statistics, in our country the highest incidence of pathology is observed among adolescents, with a moderate tendency to annual growth in this age group (from 21,9 in 2010 to 28,3 in 2015 per 1 thousand children aged 15-17 years inclusive) against the background of a gradual decrease in the prevalence of obesity among adolescents (from 11,4 in 2010 to 10,8 per 1 thousand children aged 0-14 years inclusive) [156, 157, 158, 159, 160].

Insufficient level of registration of obesity in Ukraine is due to the imperfection of the existing system of prevention of alimentary-dependent diseases and its information and communication support, lack of unified and standardized programs for early detection of overweight in children and related health disorders, accounting such children and medical supervision of them. This is the reason why the awareness and vigilance of the population of our country on this issue is low. In many families, obesity is not considered a disease, but rather a sign of children's health, especially boys. Therefore, children and adolescents often have complications due to premorbid conditions associated with obesity and the reason for seeing

a doctor is not overweight, but complaints related to the development of obesity complications: headache, shortness of breath, dizziness, thirst, pain in legs, sexual dysfunction. It was found that only 5,5 % of children with obesity of the I degree see a pediatrician, while among all obese patients they make up at least 65 % [161, 162, 163].

The International Consensus on Childhood Obesity states that early intervention, including diet, change in eating behavior and physical activity, is recommended to prevent the development of complications. It is known that the effectiveness of techniques used to treat this disease is low, and drugs are practically not used in children under 12 years of age. [164, 165, 166, 3, 139, 167, 6, 168] Important measures to address this problem in Ukraine in accordance with the current strategy are the study of the child's environment and lifestyle of families with children, statistics on the health of children with EBM with further organization of prevention and treatment using health technologies that affect on the lifestyle and health of children [169, 170, 95, 155, 172, 173, 174, 175].

Features of the formation of excess body weight in children and adolescents

It is known that the basis for the development of exogenous constitutional obesity is an energy imbalance, which is a mismatch between the number of calories that come with food and energy expenditure of the body [176].

Among the causes of childhood obesity are genetic (defects of certain genes that affect the rate of metabolism), metabolic, hormonal and external factors that cause failure of the mechanism of regulation of energy balance and disease development. When assessing the risk factors for obesity, it is necessary to take into account the child's belonging to a certain age, sex, race and ethnic group. [177, 178, 179, 180, 181, 182]

Leading factors in overweight and obesity in children are eating disorders and sedentary lifestyle. Numerous eating disorders include unbalanced diet, overeating, eating fast food, eating disorders and irregularities, lack of breakfast or the so-called "night" eating syndrome and eating disorders. Because the modern market is full of foods not recommended in children's diets, children often consume too many calories due to lack of vegetables and fruits. In addition, parents do not always monitor the child's diet during the day or encourage delicious food [182, 183, 156, 184]. An additional factor of social influence is an active advertising campaign with the promotion of high-calorie products [185]. Sedentary lifestyle in most cases is due to the fact that today children and adolescents widely use electronic devices necessary not only for entertainment but also for learning [186, 187, 188, 189, 190, 191].

Socio-economic factors play a very important role in the development of obesity, even in young children. These include low level of education and profession of parents, social status, single-parent family, number of children in the family (the frequency of overweight is much lower in large families). Obesity is more common among people with low socio-economic and educational levels. These factors determine dietary preferences, physical activity, family traditions, awareness of healthy lifestyles, the dangers of obesity to health and methods of prevention, and others. Low family incomes can be one of the barriers to a healthier diet and active recreation, sports [192, 193, 194, 195, 196].

The development of the disease can also be influenced by psychological factors: stressful situations, mental trauma, negative emotions and lack of interesting activities. Such circumstances can provoke excessive eating, lack of exercise and excessive weight gain [88, 197].

The "intrauterine programming" of the energy balance of the organism is determined. In the perinatal period, the following markers of obesity are distinguished: acute and chronic diseases, threats of abortion at different stages of gestation, preeclampsia, fetoplacental insufficiency, as well as other causes of chronic fetal hypoxia during pregnancy, overweight and inadequate maternal nutrition, burdened obstetric anamnesis [70, 198, 199, 200]. Predictors of obesity in neonatal and infant age are insufficient or overweight of the child at birth [201, 202], the duration of breastfeeding and others [203, 204]. Studies have shown that breast milk contains hormones that potentially prevent obesity in children. At the same time, artificial feeding, on the contrary, has a negative impact. Thus, according to research, it was found that the level of protein in the diet of infants was significantly correlated with an increase in body mass index. Based on this, the

mechanism of possible action of excessive protein intake was suggested: high nutrient levels are accompanied by increased plasma levels of insulin-induced amino acids, which stimulate insulin secretion and insulin-like growth factor 1, which increases the proliferation and differentiation of adipocytes and causes the development of obesity in the future. Other studies have shown that eating unadapted dairy products in infancy leads to higher values of body weight and length, from 6 months to 4-9 years of age. According to some data, the addition to the child's diet of any solid foods in the absence of grain-based foods up to 6 months of age is a risk factor for obesity in the future, especially for children with a burdened anamnesis. Thus, the detection of markers of obesity in the neonatal period and early childhood is important for the timely assessment of predictors of obesity in adolescents [205, 206, 207, 208].

Data from a nationally representative German study to identify possible determinants of childhood obesity have shown a direct link between overweight in children and parental obesity. The risk of developing obesity is doubled in children if both parents are obese. At the same time, the results of studies of familial predisposition such as childhood obesity indicate a lack of consensus on the importance of genetic factors. The child's body weight depends on the complex interaction of the genetic background with environmental factors. It is estimated that the genetic background explains about 40% of the differences in body weight. The factor of parental obesity is one of the main factors in the formation of excess body weight in children, primarily due to the similarity of the food stereotype [209, 210, 211].

Recently, there has been a steady increase in the number of patients suffering from various types of eating disorders. It was found that in 30-40% of cases of obese patients, certain disorders are registered, among which the most common are: hyperphagic reaction to stress, compulsive hyperphagia, carbohydrate thirst and premenstrual hyperphagia. Therefore, an important role in the prevention of overweight belongs to the identification and elimination of factors that cause these disorders. These include genetic, dietary, endocrine, psychological, psychiatric factors and inadequate physical activity. Eating disorders are often combined and in one patient to some extent may be expressed some of them or even all. The latter may indicate close mechanisms of their origin and development. Thus, with a hyperphagic response to stress and compulsive hyperphagia, patients periodically consume large amounts of food, often high-calorie, sweet and fatty. However, in the first case, the cause of the stress is realized, and in the second - no. Because the stress factor can last for a long time, excessive food intake can gradually lead to obesity. As a type of compulsive hyperphagia, nocturnal hyperphagia is considered, so-called carbohydrate thirst or food thirst - an imperative increase in appetite in the evening and at night. The term "carbohydrate or food thirst" is used if patients need to eat both sweet and fatty foods - chocolate, ice cream, cream, etc. In this case, the brain releases large amounts of endorphins and food is similar in effect to a drug. In its absence, patients develop a severe depressive state, reminiscent of abstinence, while the consumption of sweet foods, these phenomena disappear. Premenstrual hyperphagia is also characterized by a predominance of sweet and fatty foods and can occur in some women for 4-7 days before menstruation. It is important to note that the presence of eating disorders is one of the significant predictors of weight gain after its successful reduction [212, 213, 214].

Today, the EAT-26 Adaptation Questionnaire and the Dutch Food Behavior Questionnaire (DEBQ) are widely used to diagnose eating behavior. However, it should be noted that the reliability of the relationship between such conditions and the development of obesity in most cases is observed in adults. Adolescents with normal body weight can often be overwhelmed by emotional and / or restrictive eating habits due to youthful maximalism and the influence of fashion and the media. Children under the age of 12 almost never have significant increases in emotional overeating, as they usually find a more direct way to express their emotions [215].

The peculiarity of studying the mechanisms of development and formation of obesity in children is that, in addition to the main causes of overweight, it is necessary to take into account the age periods: children and adolescents.

Critical periods of overweight in children are actively discussed in the literature. Thus, we can distinguish three main periods: early childhood, prepuberty and adolescence. In the 1st year of life, overfeeding is the cause of an

increase in the number of adipocytes, but not their size. With timely and competent correction of the diet during this period, a successful outcome is possible. In prepuberty (5-7 years), obesity can be recurrent and often persistent, because during this period the excessive number of adipocytes does not decrease and creates a reserve for fat depots. More than 60 % of overweight children before puberty will be overweight in early adulthood, reducing the average age of noncommunicable disease detection and increasing the burden on health services, which must provide treatment for the most part. Adult life of these children. During adolescence, the vast majority of overweight adolescents retain it in adulthood. This obesity is largely due to the restructuring of the neuroendocrine system associated with puberty and often forms the so-called hypothalamic syndrome of puberty. Puberty is a transitional period between childhood and puberty. It is during this period that a number of changes occur that lead to physical, psychological and reproductive maturity of the organism. Biological changes during puberty are regulated by neurosecretory factors and hormones that accelerate somatic growth, development of the gonads, their endocrine and exocrine functions. Excess adipose tissue leads to dysfunction of the hypothalamic-pituitary-gonadal system in adolescence, and this disrupts the formation of reproductive function. Periods of critical weight gain in girls - 9, 10 and 12 years, in boys - 7, 13 years, which corresponds to the age of initiation of sexual development. Both girls and boys have a maximum prevalence of overweight at 12-13 years of age.

As you grow older, the number of overweight children decreases, which is associated with the physiological peak of growth in 14-16 years, but formed and rooted at this age, the nature of nutrition and lifestyle can later lead to obesity [216, 114, 218].

The medical and social significance of obesity and overweight determines the need for research in this area. At the same time, the official documentation of medical institutions does not reflect the actual prevalence of obesity and overweight among young people today, so identify the true prevalence of obesity among young people in the Kharkiv region, with further study of potential risk factors and quality of life, the organization of medical care for young people is relevant. Addressing these challenges will help improve the quality and effectiveness of prevention among young people.

In this regard, research is devoted to one of the most important scientific and practical tasks of modern health care - the prevention of obesity and overweight among young people.

Declarations

Statement of Ethics

The author has no ethical conflicts to disclosure.

Consent for publication

The author gives her consent to publication

Funding Sources

There are no external sources of funding.

Data Transparency

The data can be requested from the author.

Disclosure Statement

The author has no potential conflicts of interest to disclosure.

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Received: 29-Aug-2021
Accepted: 07-Nov-2021

FLOW CYTOMETRY IN NANOTOXICOLOGY: A BRIEF OVERVIEW

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https://doi.org/10.35339/ic.8.4.278-289

Abstract

The paper deals with the role of flow cytometry in assessing the biocompatibility and safety profiles of nanomaterials. Flow cytometry is a powerful tool to characterize the impact of various exogenous factors on different cell populations due to its ability to register optical and fluorescence characteristics of cells analyzing multiple parameters simultaneously. An overview of flow cytometry application for evaluating the redox state of cells, viability and cell death modes (apoptosis, necrosis, necroptosis, pyroptosis, autophagy), and pro-inflammatory effects of nanoparticles is provided. Flow cytometry offers rapid, informative, quite cost-effective and multi-angled analysis of safety profiles of nanomaterials taking into account the key mechanisms of their toxic action. Recent advances in flow cytometry technologies and the availability of commercial automated cell counters make flow cytometry a convenient research tool for in vitro nanotoxicology. However, the field requires the development of standardized flow cytometry protocols for nanotoxicity testing.

Keywords: *nanomaterials, nanoparticles, cytotoxicity, cell death, reactive oxygen species*.

Introduction

Nanomedicine is a rapidly growing field of medicine, which implies the application of nanotechnologies for medical purposes. In general, nanomaterials are defined as materials that have at least one dimension ranging from 1 to 100 nm [1]. Nano-sized materials possess unique physicochemical characteristics compared to the large-sized substances of the same composition due to quantum effects, higher surface area, which increases the surface-to-mass ratio, and higher reactivity [2]. These size-dependent effects of nanostructured materials make them promising agents in medicine. Over the recent years, a plethora of applications have been suggested for nanomaterials. In particular, nanomaterials are used as diagnostic and therapeutic agents [3-7], antibacterial agents [8, 9], drug delivery tools [10, 11], photodynamic and photothermal agents for the treatment of neoplasms [12], contrast agents for magnetic resonance imaging [13], gene delivery agents [14], wound healing nanodrugs [15, 16], etc. However, the field faces significant obstacles and challenges that have to be overcome to successfully translate the results of experimental research into clinical practice. The major issues that limit the progress of nanomedicine are targeted delivery, poor biocompatibility and safety of nanomaterials, pollution of environment with nanostructured materials, lack of cost-effectiveness and full-scale industrial production, and imperfect governmental regulations [17, 18].

Toxicity remains one of the major concerns and severe challenges to nanomedicine. It has been reported that toxicity of engineered nanomaterials is dependent on multiple factors, including composition, size, which affects the surface area, shape, surface chemistry and charge, dose, protein corona, exposure routes, environmental factors, etc. [19, 20]. Hazardous effects of nanomaterials are mediated via multiple mechanisms. However, it has been revealed that reactive oxygen species (ROS) generation and oxidative stress are key factors of their toxicity [20-22]. It is important to note that ROS generation is usually proportional to the surface-to-volume ratio, which is associated with a higher reactivity of nanostructured materials [23]. In turn, excessive ROS formation causes oxidative damage to phospholipids, promoting lipid peroxidation, DNA

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molecules, resulting in genotoxic and carcinogenic effects of nanomaterials, and proteins. Nanomaterials-induced ROS overgeneration can be indirect and mediated via NADPH oxidase-dependent or mitochondrial mechanisms [24, 25]. In addition to direct ROS-mediated damage to macromolecules, nanomaterials-induced oxidative stress triggers apoptosis, necrosis, necroptosis, autophagy, pyroptosis, mutations, inflammation, fibrosis, and cancer [24, 26].

ROS overproduction mediated by nanomaterials can trigger mitogen-activated protein kinase (MAPK) and the c-Jun-N-terminal kinase (JNK) signaling, initiating apoptosis [27]. Moreover, there is accumulating evidence that nanoparticles can enhance apoptosis not only via intrinsic, but also extrinsic pathways, in particular, through FAS-mediated mechanisms [28]. Both pathways result in activation of caspases.

Oxidative stress-mediated pathway has been stated to be a key mechanism of nanoparticles-induced necrosis and necroptosis [29]. The latter is referred to as a regulated form of necrosis. Both necrosis and necroptosis lead to similar morphological changes, rupture of cell membranes and release of strongly pro-inflammatory damage-associated molecular patterns (DAMPs) [30].

Nanomaterials have been demonstrated to induce autophagy [31], which is a cellular degradation process crucial for the maintenance of homeostasis in response to nutritional and metabolic dysregulation [32]. Changes in the redox status induced by nanostructured materials inhibit the PI3K/Akt/mTOR signaling pathway, which results in activation of autophagy [33]. The feature of nanoparticles to affect authophagy makes them a promising anticancer therapeutic agents, given the role of autophagic cell death in cancer.

Another cell death mode regulated by nanomaterials is pyroptosis, which is a strongly pro-inflammatory form of caspase-1-dependent cell death of mainly macrophages associated with pore-mediated leakage of pro-inflammatory cytokines interleukin-1β (IL-1β) and IL-18 through the cell membrane with the subsequent influx of ions and cell lysis [34, 35]. Nanomaterials have been shown to induce pyroptosis [36, 37]. Increasing evidence demonstrates that NLRP3 inflammasome, which plays a key role in pyroptosis, responds to changes in the redox status, in particular, nanoparticles-mediated ROS overgeneration [37, 38], which implies the importance of ROS-mediated mechanisms in nanomaterials-induced pyroptosis activation.

In addition to pro-oxidant action and induction of various cell death modes, nanoparticles are characterized by immunotoxicity [39, 40]. Nanoparticles-triggered ROS-mediated activation of signaling pathways and transcriptional factors, including NF-κB (nuclear factor κB) and activator protein (AP)-1, upregulates cytokines such as TNF-α (tumor necrosis factor-α), IL-2, IL-6, and IL-8 [26]. It is worth mentioning that the pro-inflammatory cytokines enhance ROS generation in cells, which causes secondary oxidative stress and exacerbation of toxic effects [41]. In addition, IL-1β and IL-18 can be secreted by cells via ROS-associated NLRP3 inflammasome pathway activation [38].

Furthermore, ROS-mediated pathways are involved in the development of nanoparticles-induced fibrosis. TGF-β (transforming growth factor-β) is known to be a key driver of fibrosis, which can act via canonical (Smad-associated) and non-canonical (non-Smad-associated) pathways. TGF-β signaling activates fibroblasts, epithelial-mesenchymal transition, production of extracellular matrix (ECM) components, downregulating of ECM-degrading metalloproteinases and upregulation of tissue inhibitors of metalloproteinases (TIMPs) [42]. TGF-β is known to be upregulated in oxidative stress [43], which provides evidence that nanoscale materials can induce fibrosis via ROS/TGF-β pathways. The ability of nanoparticles to induce fibrosis via oxidative stress/TGF-β signaling pathway has been proven experimentally [44, 45].

The mechanisms of oxidative stress-mediated nanotoxicity are summarized in Fig. 1.

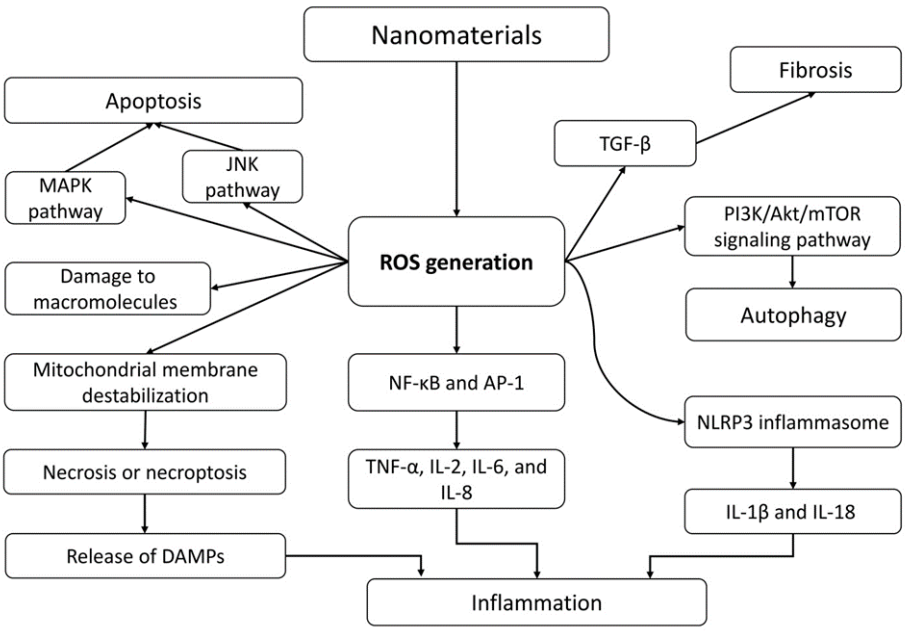

Figure 1. ROS-mediated pathways of nanomaterials-induced toxicity.

All the parameters outlined above can be assessed by flow cytometry. Flow cytometry is a sophisticated technology, which is used to separate and characterize populations of cells suspended in a fluid based on their morphology, size, granularity and fluorescent parameters using fluorescent dyes and labeled antibodies [46]. Flow cytometry is widely used in immunophenotyping, analyzing the expression of both surface and intracellular antigens, ROS generation, cytokines, the content of intracellular ions, and various cell death forms [47, 48]. In addition, flow cytometry can be used to detect proteins underwent post-translational modifications, including phosphorylation, which is crucial for analyzing cellular signaling [49]. Flow cytometry has been widely used to test the toxicity of various xenobiotics in vitro [50-52].

In this paper, we want to highlight the flow cytometry-based approaches to detect major toxicity factors of nanomaterials, including oxidative stress, apoptosis, necrosis, necroptosis, pyroprosis, autophagy and inflammation.

The major flow cytometric assays used for testing nanotoxicity are available in Table 1.

Cell redox homeostasis and flow cytometry

Flow cytometry is a common tool to assess ROS generation in cellular populations. It has been reported that several ROS-sensitive probes can be used for this purpose [53]. The most common oxidative stress-detecting probes are: 2',7'-dichlorodihydrofluorescein diacetate (H2DCFDA), DHE (dihydroethidium), and CellROX green.

In particular, H2DCFDA is a ROS sensor, which is catabolized into H2DCF (dichlorodihydrofluorescein) by esterases inside the cells. In turn, H2DCF is converted to a highly fluorescent DCF (dichlorofluorescein) whose fluorescence is registered by flow cytometry. One of the advantages of H2DCFDA staining is the fact that this dye is sensitive to multiple ROS, such as H2O2, hydroxyl radicals, peroxy radicals, and reactive nitrogen species (RNS), such as ·NO and ONOO- [54]. H2DCFDA staining is used to assess ROS generation in cells exposed to nanoscale materials [55-61]. It is important to note that H2DCFDA is less sensitive to superoxide ion compared to DHE [62]. When DHE enters a cell, it interacts with superoxide ion to produce fluorescent ethidium and 2-hydroxyethidium [63]. Redox status of cells has been reported to be assessed by DHE staining with the registration of fluorescence by flow cytometry [59, 61, 64, 65]. CellROS green dye is used to distinguish oxidatively stressed viable cells from the non-stressed ones. It is used primarily to detect hydroxyl radical. The use of this dye for evaluating the impact of nanomaterials on the redox status of cells has been reported [66, 67]. Our analysis suggests that H2DCFDA staining is more commonly used due to the fact that it is less specific

Table 1

Flow cytometry-based approaches used to assess nanotoxicity

Mechanisms of nanotoxicity	Techniques used	Reports on the use in nanotoxicology
Oxidative stress induction	H2DCFDA staining	Onishchenko et al., 2021 Tkachenko et al., 2020 Kermanizadeh et al., 2018 Zhang et al., 2018 Gu et al., 2016 Han et al., 2014 Zhao et al., 2013
	DHE staining	Sadhu et al., 2018 Gu et al., 2016 Lehman et al., 2016 Zhao et al., 2013
	CellROX staining	Quan et al., 2020 Sabido et al., 2020
Apoptosis	Annexin V/7AAD staining (both apoptosis and necrosis)	Azizi et al., 2017 Wu et al., 2017 Kumar et al., 2015
	Annexin V/PI staining (both apoptosis and necrosis)	Vuković et al., 2020 Yang et al., 2019 Kai et al., 2011 Lu et al., 2011
	Cleaved caspase-3 staining	Plackal Adimuriyil George et al., 2018 Ma et al., 2015 Kai et al., 2011
	Mitochondrial transmembrane potential ($\Delta\psi_m$) detection	Plackal Adimuriyil George et al., 2018 Zhao et al., 2018 Kai et al., 2011
Necroptosis	Combination of PI staining with other methods	Niu et al., 2019 Sonkusre & Cameotra, 2017
Pyroptosis	FLICA caspase 1 assay	No data available
Autophagy	MDC staining	Liu et al., 2020
	LysoTracker dyes	Liu et al., 2020 Wang et al., 2018
Inflammation	Changes in leukocyte subpopulations	Michelini et al., 2021 Hazan-Halevy et al., 2019 Gamucci et al., 2014 Hardy et al., 2013 Kourtis et al., 2013 Hanley et al., 2009
	Changes in intracellular cytokine production	Brzóska et al., 2018 Bancos et al., 2015 Strehl et al., 2015

and covers more ROS types. Thus, CellROS and DHE can be used as additional dyes in combination with H2DCFDA to figure out the role of particular ROS types in nanomaterials-induced oxidative stress.

Cell death modes and flow cytometry

Flow cytometry is routinely used to detect apoptosis of cells. Several types of staining have been proposed, which focus on different hallmarks of this suicidal cell death mode. The commonly applied cytometric assays to analyze apoptosis are a combined staining with annexin V and 7-aminoactinomycin D (7AAD) or propidium iodide (PI), detection of the content of intracellular active caspases and the mitochondrial transmembrane potential (Δψm) [68].

The cytofluorimetric staining of cells with annexin V and 7AAD or PI is based on the ability of annexin V to bind phosphatidylserine (PS) located on the surface of cells and the capacity of 7AAD or PI to interact with DNA and become fluorescent upon binding. The former is used to detect PS externalization, which is a hallmark of apoptosis, while the latter indicates the loss of membrane integrity, which occurs in late apoptosis or necrosis. Thus, this staining can be used to discriminate viable, early apoptotic, late apoptotic/necrotic and dead necrotic cells [69]. Both techniques are convenient for analyzing nanoparticles-induced apoptosis [70-76].

Caspases are intracellular proteases that are involved in orchestration of apoptosis. They are widely used as markers of apoptosis, especially active caspase-3 produced both in intrinsic and extrinsic apoptotic pathways, including for flow cytometry [77]. Identification of cleaved caspase-3 in cells treated with nanostructured materials is the most common and informative approach to detect caspases by flow cytometry [76, 78, 79].

In normally functioning mitochondria, the mitochondrial transmembrane potential (Δψm) is created by constant proton pumping from matrix to intermembrane space by electron transport chain complexes I, III and IV and is used to generate ATP by oxidative phosphorylation [80]. The depolarized mitochondrial membrane is a sign of apoptosis [81], which is used as a marker for assessing the influence of nanomaterials on apoptosis by flow cytometry using primarily a mitochondrial transmembrane potential-sensitive JC-1 probe [76, 78, 82]. According to our estimates, other methods to detect apoptosis by flow cytometry such as analysis of cytochrome c release or DNA fragmentation are less frequently applied.

The major technique to detect necrosis is 7-AAD (or PI) staining, which indicates the loss of cell membrane permeability to impermeable fluorescent probes. Usually it is combined with annexin V staining, since there are no specific markers for necrosis, in contrast to necroptosis, a programmed lytic cell death. Canonically, necroptosis is mediated by RIPK1 (receptor interacting protein kinase 1)–RIPK3 (receptor interacting protein kinase 3)–MLKL (pseudokinase mixed lineage kinase domain-like protein) axis [83]. In particular, TNFα signaling recruits RIPK1 and RIPK3 involved in MLKL phosphorylation. MLKL compromises the cell membrane integrity forming pores, which results in lytic cell death [84].

Flow cytometry can be used to detect necroptosis in several ways, including with the help of a combination of imaging flow cytometry and annexin V/PI staining, labeled antibodies to RIPK1 and caspase-3 plus cell viability dye staining, and using fluorescently labeled antibodies to phospho-MLKL [85, 86]. Data on the impact of nanomaterials on necroptosis are scarce. In particular, selenium nanoparticles were reported to induce it in a ROS-dependent manner [87]. In addition, necroptosis-inducing features of nanomaterials can be detected by a combination of flow cytometry with other methods, e.g., western blotting [88].

Pyroptosis, a pro-inflammatory caspase-1-mediated cell death mode, is detected by flow cytometry using mainly fluorescent-labeled inhibitors of caspases (FLICA) caspase-1 assays [89]. However, this approach is not widely used in nanotoxicology researches due to the prevalence of immunobloting-, confocal microscopy- or ELISA-based detection of pyroptosis-associated proteins.

Several flow cytometric assays have been developed to assess autophagy. They include determination of the microtubule associated protein LC3B and the use of LysoTracker dyes or monodansylcadaverine (MDC) staining [90, 91]. There is accumulating evidence that nanomaterials can modulate the autophagic process in cells [92, 93]. However, confocal microscopy

is a preferential method for autophagy-detecting assays.

Inflammation markers and flow cytometry

Flow cytometry is widely used to assess inflammation markers [94, 95]. Flow cytometry can be applied for evaluating nanomaterials-mediated changes in leukocyte subsets and intracellular cytokine production. Expectedly, both approaches have been reported to be used for testing nanotoxicity [96-104], since flow cytometry is a generally recognized approach to assess inflammation-associated cells and intracellular cytokine expression.

However, due to the heterogeneity of nanomaterials there are no standard guidelines for testing nanotoxicity. In addition, novel screening methods to assess biological effects of nanoparticles are required [105]. Recent advances in flow cytometry, including the application of more lasers and development of novel fluorochromes, multiplexed analyses and the availability of new commercial dyes and florescent-labeled antibodies increase the scope of opportunities for flow cytometry in nanotoxicity testing. Thus, flow cytometry has become an essential tool in nanotoxicology and since the field is expanding this instrument seems promising.

Declarations

Statement of Ethics

The author has no ethical conflicts to disclosure.

Consent for publication

The author gives her consent to publication

Funding Sources

There are no external sources of funding.

Data Transparency

The data can be requested from the author.

Disclosure Statement

The author has no potential conflicts of interest to disclosure.

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Received: 01-Oct-2021
Accepted: 13-Dec-2021

FRACTAL DIMENSION IN MORPHOLOGY AND MEDICINE: THEORETICAL BASES AND PRACTICAL APPLICATION (REVIEW)

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https://doi.org/10.35339/ic.8.4.290-297

Abstract

Morphometry is an integral part of most modern morphological studies and the classic morphological morphometric methods and techniques are often borrowed for research in other fields of medicine. The majority of morphometric techniques are derived from Euclidean geometry. In the past decades, the principles, parameters and methods of fractal geometry are increasingly used in morphological studies. The basic parameter of fractal geometry is fractal dimension. Fractal dimension allows you to quantify the degree of filling of space with a certain geometric object and to characterize the complexity of its spatial configuration. There are many anatomical structures with complex irregular shapes that cannot be unambiguously and comprehensively characterized by methods and techniques of traditional geometry and traditional morphometry: irregular linear structures, irregular surfaces of various structures and pathological foci, structures with complex branched, tree-like, reticulated, cellular or porous structure, etc. Fractal dimension is a useful and informative morphometric parameter that can complement existing quantitative parameters to quantify objective characteristics of various anatomical structures and pathological foci. Fractal analysis can qualitatively complement existing morphometric methods and techniques and allow a comprehensive assessment of the spatial configuration complexity degree of irregular anatomical structures. The review describes the basic principles of Euclidean and fractal geometry and their application in morphology and medicine, importance and application of sizes and their derivatives, topological, metric and fractal dimensions, regular and irregular figures in morphology, and practical application of fractal dimension and fractal analysis in the morphological studies and clinical practice.

Keywords: *morphometry, size, dimension, fractal dimension, fractal analysis, lacunarity.*

Morphometry (from the Greek μορφή – form, shape and μέτρον – measure, size) is the basis of numerous modern morphological methods and is an integral part of most modern morphological studies. Despite the fact that traditional morphology is based on classical fundamental descriptive studies of the structure of various organs and structures, modern morphology is gradually moving from qualitative-descriptive to quantitative-morphometric studies, and morphometry and statistics have become its evidence base. In most modern studies, the quantitative parameters of the studied structures are determined. There are many methods and algorithms of morphometry, which are used in classical morphology, but also are often borrowed for research in other fields of medicine and clinical practice. The diagnosis of diseases of various organs and systems often involves morphometry: determining the size of cells, organs, structures, etc. The choice of methods and algorithms of morphometry primarily depends on the features of the spatial configuration of the studied structures and the aim of the study [1-3]. The majority of morphometric techniques are derived from Euclidean geometry and allow the quantification of anatomical structures by determining simple geometric parameters: linear measurements, area and volume. Thus, morphometry usually involves measuring of the size of anatomical structures or pathological foci. In addition, the derivatives of the certain sizes are calculated: relative or specific sizes, ratios, indices, etc. [1-3]. These quantitative characteristics provide a lot of useful information and in most cases allow to achieve the aim of the study. Such morphometry tech niquesare the

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most informative in the studies of regular structures with a geometrically simple shape (for example, spherical or prismatic), determining the size of which is simple and unambiguous. However, irregularity is much more common among anatomical structures. Irregular anatomical structures are difficult to assess using traditional morphometric techniques, and simple quantitative characteristics (sizes and their derivatives) do not allow to comprehensively characterize the spatial configuration of these structures.

Thus, traditional quantitative characteristics are not enough to give a comprehensive morphological characteristics of irregular anatomical structures, as it is necessary to assess the qualitative characteristics – shape and spatial configuration. Can these qualitative characteristics be quantified? The answer to this question depends on features of studied object. Different indices and indicators are quite useful and informative in the studies of objects with a simple shape. For example, the cranial index (the ratio of width to length of the skull) allows us to determine the craniotype – an indicator that describes the shape of the neurocranium [4] and is quite informative (if we know that a skull is brachy, meso- or dolichocranial, we clearly and unambiguously understand the features of skull shape).

However, it is quite difficult to describe the shape of irregular anatomical structures using derivative indices calculated on the basis of size values. For example, the shape factor (SF) may have the same values for structures whose spatial configuration differs significantly (Fig. 1).

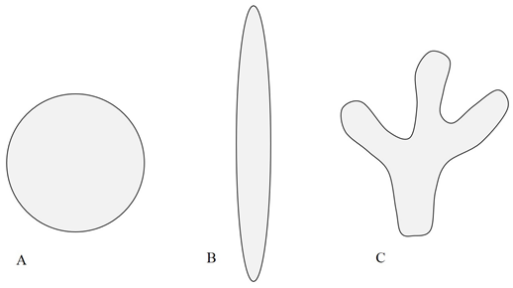

Figure 1. Figures of different shapes. The values of the shape factor (SF): A – circle, SF = 1; B – oval, SF = 0.25; C is an irregular branched structure, SF ≈ 0.25.

Therefore, in some cases it is not enough to determine *the sizes and their derivatives* for morphometry alone. In these cases, another characteristic of geometric shapes and space – *space dimension or dimensionality* – comes in handy.

Spatial dimension (D) is a parameter that characterizes the spatial configuration of a geometric figure (object, structure) and the degree of filling of space with this figure. There are topological and metric dimensions [5, 6]. Most often, when we mention the spatial dimension, we mean the topological dimension, which belongs to the traditional (Euclidean) geometry [6].

The topological dimension (Euclidean dimension, Lebesgue dimension) of various geometric objects has only integer values – 1, 2 or 3. The topological dimension is equal to the minimum number of parameters (coordinates) required to unambiguously characterize the point of the object in space. For example, in order to characterize a point of a straight line, it is enough to specify one coordinate, a point of a plane – two coordinates, a point of a cube – three coordinates. In Euclidean geometry, the topological dimension usually coincides with the minimum number of linear parameters (n) that are needed to characterize an n-dimensional object (for example, length, width, and height for three-dimensional objects). Thus, the topological dimension of lines that can be characterized by only one linear dimension – length (one-dimensional linear objects), is equal to 1; the dimension of surfaces (planes), which in addition to the two linear dimensions (length and width) also have their derivative value – area (two-dimensional flat objects or planes), is equal to 2; and the dimension of three-dimensional objects, which in addition to the three linear dimensions (length, width and height) and area also have a volume, is equal to 3 [5-11].

The terms "one-dimensional" (1D), "two-dimensional" (2D) and "three-dimensional" (3D) come from the topological dimension. Two-dimensional or three-dimensional images can be used for morphometry [1-3], and when we say that the image is two- or three-dimensional, it means the topology of the images: two-dimensional or three-dimensional (Fig. 2, Fig. 3). Any anatomical structure can be represented in a two-dimensional or three-dimensional topology (the topological dimension of the space in which a certain structure is represented is 2 or 3, respectively) [12].

There is also a *metric dimension*. The values of metric and topologic dimensions may be the same or different. The metric dimension of ideal geometric figures coincides with the topological dimension. The metric dimension (D) of an ideal line is equal to one, D of the ideal plane (surface) is equal to 2, D of the filled cube is 3. Such structures fill all available space in the corresponding coordinate system: one-dimensional, two-dimensional or three-dimensional [5-12].

However, among anatomical structures and pathological foci, such figures are extremely rare. Most anatomical structures and different foci are irregular, and their metric and topological dimensions differ [6]. For example, some anatomical structures and their parts are linear objects – the outer linear contours of various structures and foci, vessels, nerves, fibers, etc. But these structures are almost never ideal lines with a metric dimension of 1. Much more often, linear structures are represented by curves that can be wavy, coiled, zigzag, etc. These objects are not ideal straight lines, so they have a metric dimension greater than one. At the same time, they are not planes, so they have a dimension less than 2. Thus, they fill more space than a straight line, but less than a plane (Fig. 2). Taking into account this feature, we can conclude that the value of the metric dimension of irregular lines can be in the range from 1 to 2 [8, 10].

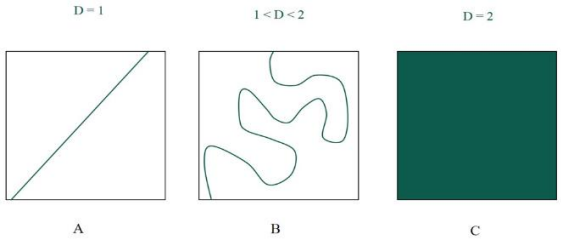

Figure 2. Geometric figures with different degrees of space filling, two-dimensional topology of images. A is an ideal line that practically does not fill the space, B is an irregular curve, C is an ideal plane that fills all available two-dimensional space.

Ideal planes (perfectly flat surfaces), the metric dimension of which is 2, are also usually non-existent in organisms of humans and animals. Much more often the surfaces are not smooth (they are wavy, rough, etc.) and fill more space than the ideal plane, but less than the filled cube (Fig. 3). By analogy with irregular curves, we can conclude that the value of the metric dimension of irregular surfaces will be in the range from 2 to 3 [8].

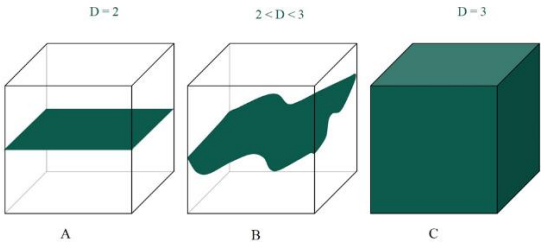

Figure 3. Geometric figures with different degrees of space filling, three-dimensional topology of images. A is an ideal plane (regular surface), B is an irregular surface, C is an ideal filled cube that fills all available three-dimensional space.

Thus, the metric spatial dimension can be not only an integer but also a fractional number. This dimension is called fractal or fractional (from the Latin fractus – fractional) [5-15]. Fractal dimension allows you to quantify the degree of filling of space with a certain geometric object and to characterize the complexity of its spatial configuration. Among natural objects, including anatomical structures, in addition to irregular curves and surfaces, there are also many objects with complex shapes that cannot be unambiguously and comprehensively characterized by methods and techniques of traditional geometry and traditional morphometry [6]. These are structures with complex branched, tree-like, reticulated, cellular or porous structure, etc. [3, 16, 17].

Fractal analysis is used to determine the fractal dimension of geometrically irregular objects, including anatomical structures and pathological foci [16, 17].

In the study of linear structures, the fractal dimension characterizes the degree of spatial complexity of their shape (how twisted, tortuous or wavy these linear structures are), so it is an informative indicator for quantitative assessment of spatial complexity degree of various fibers and other linear structures.

In addition to irregular linear structures, fractal analysis and fractal dimension are relevant for the quantitative characterization of irregular surfaces. These include surfaces formed by various membranes, the surfaces of the brain cortex and white matter, the outer and

inner surfaces of various organs and pathological foci (tumors, foci of necrosis, fibrosis, gliosis, etc.). In this case, such surfaces can be represented both in three-dimensional topology (on three-dimensional reconstructions) and in two-dimensional topology (on two-dimensional images) as an anatomical, histological, or tomographic sections, projections, etc. Irregular surfaces in two-dimensional images often look like linear objects, such as linear contours of structures and foci and cross-sections of various membranes. Therefore, it is informative to estimate the spatial configuration of linear contours of three-dimensional structures on two-dimensional images. Determining the complexity (tortuosity and irregularity) of the contour of tumors can provide information about the degree of tumor invasion into the surrounding tissues. Thus, fractal analysis was used for quantitative research and interpretation of mammography results [18]. Determining the complexity of the spatial configuration of the cerebral cortex (entire surface on 3D images and its linear contour on 2D images) can quantify the degree of atrophic changes in the brain [19]. In ophthalmology, fractal analysis was used to analyze the configuration of the Bowman's membrane of cornea [20].

Among irregular anatomical structures, tree-like branched structures are quite common [21] (vascular network of internal organs, bronchial tree, duct system of exocrine glands, dendritic trees of neurons, cerebellar white matter). Fragments of such structures may have a network-like, or reticulated configuration (for example, the vascular network is essentially a tree-like structure, but its fragment may have a reticulated structure). In addition, some structures may have a reticulate structure without tree-like branching (for example, a network of fibers in fibrous connective or reticular tissue, myeloarchitectonics of the brain white matter, etc.). The fractal dimension makes it possible to quantify the degree of branching of the branched structures and the density of the network of the reticulated structures.

Fractal analysis in morphology and medicine was often used in the studies of the vascular network [22, 23]. The fractal dimension of the vascular network allows to characterize the degree of branching of blood vessels and the degree of filling of the space with blood vessels within the studied organ. This method was used in the studies of the retinal vessels [24], the kidneys arterial tree [25], vessels of lungs [26], heart [27] and pituitary gland [28]. The vascular network of the brain also has fractal properties [29]. A quantitative assessment of the superficial vascular network of the cerebellum was performed using fractal analysis of anatomical preparations [30]. Fractal analysis of brain vessels is used in neuroimaging with diagnostic purpose, for example, for analysis of the shape complexity degree of arteriovenous malformations [31].

Fractal analysis was used in the studies of the bronchial tree, and the pattern of bronchial branching and lung morphogenesis was considered fractal [32].

Fractal analysis was also used to characterize the arborization (branching) of the dendritic trees of neurons. Various types of neurons were studied by fractal analysis, including Purkinje cells [33], pyramidal cells [34], spinal cord neurons [35], and retinal nerve cells [36]. Fractal analysis was used to classify retinal nerve cells according to the degree of branching of their dendritic tree and functional characteristics [6, 36].

Fractal analysis was used in the studies of glia cells. This method was used to analyze astroglia and revealed morphological changes in astrocytes in stroke and dementia [37], revealed significant differences in the fractal dimension of different types of astrocytes – protoplasmic and fibrous [38]. Fractal analysis revealed changes in microglia in inflammation of nerve tissue, and fractal dimension values were used to develop a classification of glia by the degree of its activation [39].

Fractal analysis was informative in the studies of the human cerebellum white matter ("arbor vitae cerebelli"), which has a complex branched tree-like configuration. The cerebellar white matter was studied by fractal analysis in our previous work [40, 41] and the works of other scientists [42-44].

Fractal analysis is also informative and appropriate method for the study of *cellular, porous or spongy objects* and allows you to quantify their porosity and density by assessing the degree of filling of the space by the studied structures. For example, fractal analysis was used to study the density of the spongy bones (most often – the spongy bone tissue of the skull, mainly in dentistry and for the diagnosis of osteoporosis) [45], dental images [46].

Porous structures also include the tissue of the respiratory portion of lungs (lung alveoli), so the fractal dimension can be an informative parameter for the quantitative assessment of the lung tissue density.

In some cases, fractal analysis includes two quantitative parameters: in addition to the fractal dimension, the *lacunarity index* may be determined. The classical fractal analysis determines the degree of filling of space with a certain structure and determines fractal dimension (areas of space which are occupied by the studied structure are taken into account). But lacunarity index characterizes the degree of *filling of space with empty areas* (*lacunae*, or areas of space which *are not* occupied by the studied structure are taken into account). In other words, fractal analysis is performed and the fractal dimension is calculated, but for the lacunae – space around and inside studied structure. The lacunarity index usually is determined during fractal analysis (two parameters are determined at the same time – fractal dimension and lacunarity index) and makes it possible to characterize the "hollowness" of the studied structure [47, 48]. Thus, the lacunarity index was used in the studies of cellular, porous or spongy structures or structures, an important characteristic of which is the density: bone tissue [49], tooth tissue [50] and tumors [51, 52].

Different *methods, techniques and algorithms of fractal analysis* are used in morphology. The box counting method or grid method is most often used. Less commonly used methods are caliper method, dilatation method, mass-radius method, cumulative intersection method, grid intercept method and some other methods [6, 13-17]. A detailed description of the methods of fractal analysis is given in the review of the methodology of fractal analysis in morphology [53] and in other reviews related to the use of fractal analysis in various fields of medicine [6, 16, 17, 36].

Thus, techniques and parameters derived from fractal geometry can be used in morphometric studies of various anatomical structures of human and animal organisms alongside with traditional techniques and indicators derived from Euclidean geometry. Fractal dimension is a useful and informative morphometric parameter that can complement existing quantitative parameters to quantify objective characteristics of various anatomical structures and pathological foci. Fractal analysis can qualitatively complement existing morphometric methods and techniques and allow a comprehensive assessment of the spatial configuration complexity degree of irregular anatomical structures.

Declarations

Statement of Ethics

The author has no ethical conflicts to disclosure.

Consent for publication

The author gives her consent to publication

Funding Sources

There are no external sources of funding.

Data Transparency

The data can be requested from the author.

Disclosure Statement

The author has no potential conflicts of interest to disclosure.

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Received: 28-Sep-2021
Accepted: 07-Dec-2021