Challenges of the current medicine

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Happiness lies in good health and a bad memory
Ingrid Bergman

Dear Colleagues

The monograph periodical *"Challenges of the Current Medicine - 8 Edition"* is a collection of works written by authors from many different medical centers.

Charles Baudelaire said *„Life is a hospital, in which every patient wants to change his bed"* , because, according to Bertrand Russel, "*Research in the field of medicine has made so much progress that today - practically speaking - no one is healthy anymore*."

The leading theme of the monograph applies patient. In the particular chapters are discussed various therapeutic care problems: of death and dying, of the old age, selected therapeutic and diagnostic

We hope that the monograph subjects allow demonstrating respect for the patient's dignity, because he claims Hanna Krall, *"in medicine, every life counts -every little chance to save a life".*

As the authors, we believe in the truth from words of Archibald Joseph Cronin – *„An ounce of preventive measures is better than a ton of medications* "and of Jonathan Swift *"The best doctors in the world are Doctor of Peace, Doctor Diet, and Doctor Joy".*

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The problem of death and dying

Levels of mortality and primary morbidity by cervical cancer as efficiency indicators of actions in the field of reproductive health preservation

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Introduction

Female's reproductive health preservation is a priority direction for the activities of the health care organizations in the Republic of Belarus.

Cervical cancer is the second most common oncological disease of the female population accompanied by severe deterioration of reproductive health: specialists register over than 500.000 new cases of this pathology every year [1].

Primary screening of cervical cancer is carried out at the primary health care level in most cases. High-quality assurance of medical care is the most critical indicator of the health care organizations' activities in this direction which can be objectively proved by decreasing mortality and primary morbidity by cervical cancer [2].

Objective

To study the levels of mortality and primary morbidity by cervical cancer and to evaluate the effectiveness of measures introduced in the Grodno region for prevention of this pathology.

Material and methods

This research was carried out within the framework of the research work of the Department of General Hygiene and Ecology at the Grodno State Medical University in 2015-2017 (Governmental registration number 20150651, approved 18.05.2015).

We have analyzed all cases of cervical cancer which were registered in the Grodno region of the Republic of Belarus in 2008-2017. On the basis of copying information from primary medical documentation: outpatient charts (form № 25/y), medical records (form №

003/y-07), notifications about newly diagnosed cases of malignant tumors (form № 090/y-16), protocols about case of malignant neoplasm in the III stage of visual localization and (or) in the IV stage of all localization (form № 027-2/y-13). Also, we have studied data on the cancer registry of the Grodno Regional Clinical Hospital for 2008-2017.

Assessment of cervical cancer's stages and the primary tumor's persistence was based on the International Clinical Classification TNM (6th edition, 2002) and FIGO (1994). Statistical processing of the data was done by the usage of the computer software STATISTICA 10.0.

Results

It was established that in 2008-2017 levels and dynamics of primary morbidity by cervical cancer in the Grodno region were differed from similar indicators in the country (Figure 1).

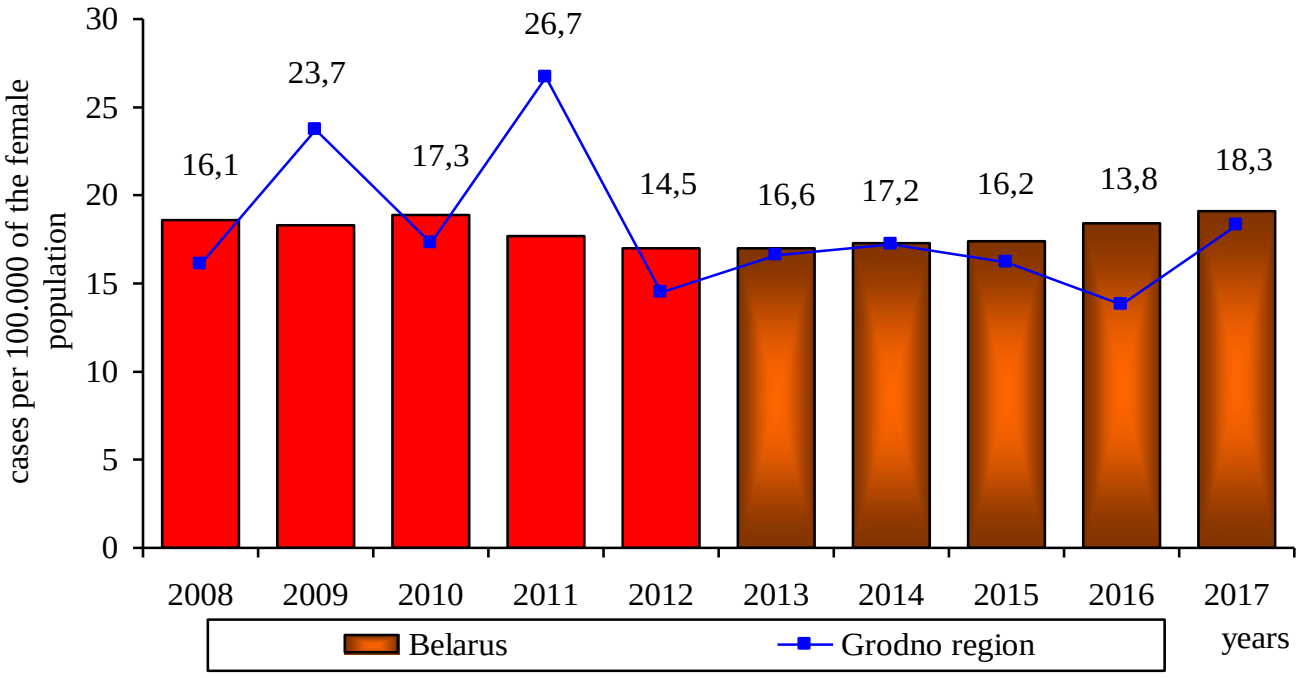

Figure 1 – Dynamics of the primary morbidity by cervical canser in 2008-2017

Thus, the average value of the primary morbidity level of this pathology (cases per 100.000 of the female population) in 2008-2012 in the Grodno region was 19.66±2.31, and that was slightly lower than in comparison to the whole country – 18.36±3.06. In the next five years, the average value of the indicator in the region was slightly decreased – to 16.42±2.07,

while the average value was almost unchanged in the Republic of Belarus – 17.84±2.68.

The dynamics of the primary morbidity by cervical cancer in the Grodno region and the country was multidirectional. However, there was a seasonal pattern of morbidity changes in 2008-2012 in the region: the maximum level was 26.7, and the minimum level was 14.5. In the next five years, the values of the indicator were not significantly changed.

According to the results of a ten-year assessment of the primary morbidity by cervical cancer in the administrative territories of the Grodno region, carried out by the signal deviation method. It was found that in the city of Grodno and three districts of the Grodno region the levels of the indicator was low, in 11 districts – medium, and in Dyatlovsky, Korelichsky and Novogrudsky districts – high, exceeding the average regional level from 2.5 to 4.9 times.

The results presented in Figure 2 indicate that if in 2008-2012 in the Grodno region among patients who lived in urban settlements, the average level of the primary morbidity of this pathology amounted to 17.64±2.64. It was not much different from the country's level (16.62±2.36), then in the subsequent five years, the differences became more significant due to decreasing in the region – to 13.54±2.21 (Republic of Belarus – 15.70±2.18).

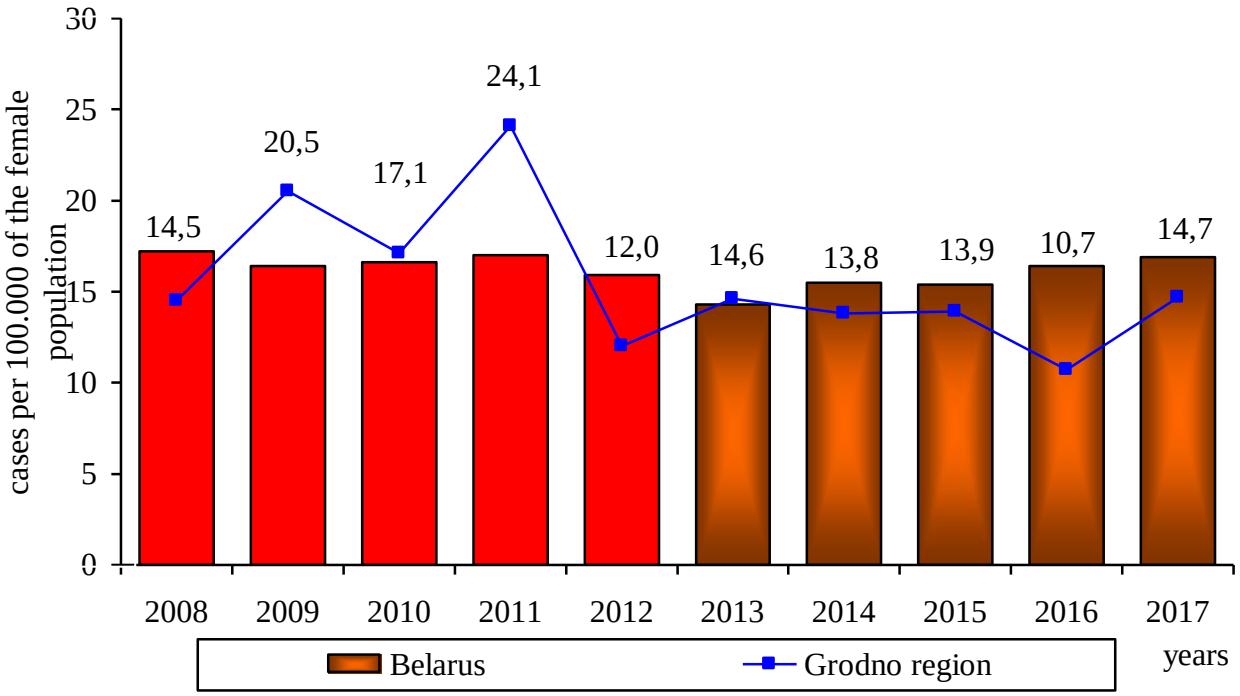

Figure 2 – Dynamics of the primary morbidity by cervical cancer among urban population in 2008-2017

The analysis of primary morbidity by cervical cancer allowed to establish that in 2008-2017 the dynamics of this indicator among patients which lived in rural settlements of the Grodno region and in the country was similar to established among urban residents. Moreover, the average values of the primary morbidity of this pathology in the region in 2008-2012 (24.52±3.53) and in 2013-2017 (24.84±3.87) practically weren't differ from those in the country – 23.64±3.39 and 25.32±3.84, respectively (Figure 3). It was established that cases of primary morbidity by cervical cancer were recorded in all age groups of women. At the same time, the peak of the morbidity among the population of the Grodno region in the considered decade was in the groups of women which were in active (30-39 years) – 21.7% and in late (40-49 years) reproductive age – 23.3% of all cases.

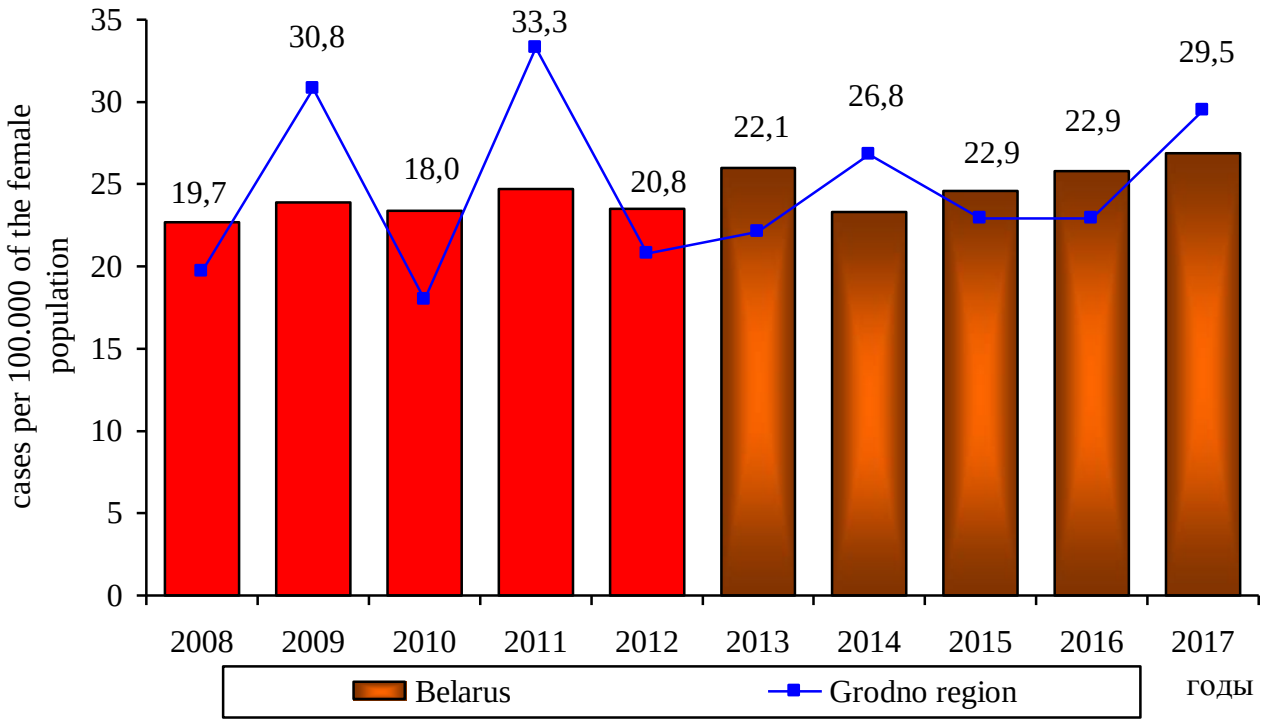

Figure 3 – Dynamics of the primary morbidity by cervical cancer among rural population in 2008-2017

The study of the structure of cervical cancer's stages taking into account tumor invasion allowed to establish that in 2008-2017 among patients which lived in the Grodno region, in 33.9% of cases was identified I stage of cervical cancer, in 37.4% – II stage, in 19.5% – III stage, in 8.1% –- IV stage, in 1,0% – it wasn't possible to determine the stage of the process. Moreover, the structure of the tumor process' stages was not significantly changed in the

compared five-year periods. This, in turn, determined the levels and dynamics of mortality from cervical cancer (Figure 4).

Thus, in the compared five-year periods, the average mortality rates of the population (cases per 100.000 of the female population) from cervical cancer in the region with a slight decreasing from 6.72±0.91 to 6.08±0.61 were not significantly changed in comparison with the same indicators for the country – 6.84±0.72 and 6.54±0.79, respectively.

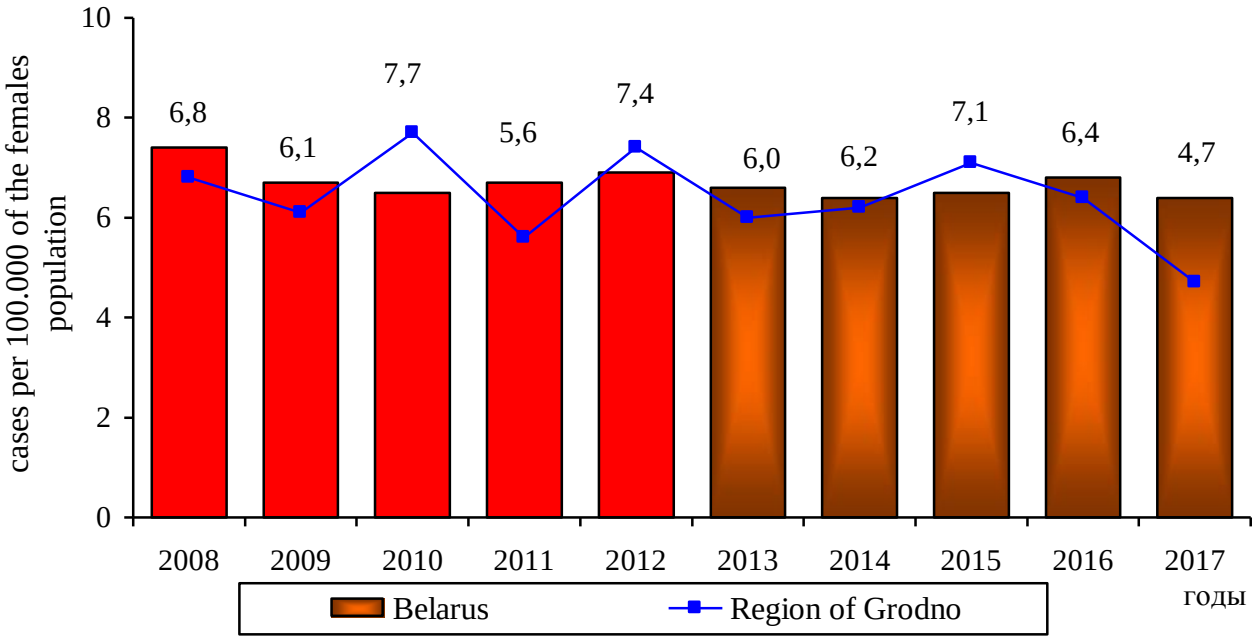

Figure 4 – Dynamics of the mortality from cervical cancer in 2008-2017

While the in-depth analysis, it was established that deaths from cervical cancer at the early (15–19 years old) reproductive age were not recorded during the decade under consideration in the health care organizations of the region. So, the age contingent of those who died from this pathology was distributed as follows: women at the age of 20-29 – 2.9% of patients, at the age of 30-39 – 9.4%, at the age of 40-49 – 30.9%, at the age of 50-59 – 26.9%, at the age of 61-70 – 13.2%, at the age of 71 and older – 16.7%.

Discussion

As follows from the data presented in Figures 2 and 3, in the compared five-year periods in the Grodno region, as well as in the whole country, the average values of primary morbidity by cervical cancer among the urban population were significantly lower than

among the rural population. However, the current situation is typical not only for the Republic of Belarus, but also for many countries in Europe and Asia [3] because of the greater availability of medical care in urban settlements and the possibilities of modern clinical and laboratory examination of patients [4].

The notion about cervical cancer as a disease of women of predominantly late reproductive age is quite widespread in the literature [5]. However, data which we have obtained while this research shows that the peak of primary morbidity by cervical cancer among the population of the Grodno region was registrated in the groups of women which were in active (30-39 years) and in late (40-49 years) reproductive age, that comes into a certain contradiction with the results of previous studies and possibly reflect regional specificity of the epidemiological situation.

Due to the fact that one of the main prognostic factors determining the course of the disease and the further fate of a patient with cancer is the extent of the tumor process at the time of diagnosis [6], the very high rate of cervical cancer incidence at the I and II stages of invasion describes the corresponding the quality and timeliness of preventive and diagnostic activities carried out in the health organizations in the region.

Conclusions

1. Stable levels of primary morbidity and mortality by cervical cancer with a tendency of decreasing in the period 2013-2017 indicated the quality and timeliness of preventive and diagnostic measures introduced in the health organizations of the Grodno region.
2. Lower levels of primary morbidity and mortality among women of active reproductive age, as well as consistently high rates of early detection of oncopathology in the health organizations of the Grodno region showed the effectiveness of the work of obstetrician-gynecologists at the level of primary health care in the field of preservation of the patients' reproductive health which suffer from cervical cancer.

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Death full of life and life full of death – two images of antiquity

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Introduction

The two patterns towards death known in thanatology were formulated by Philippe Aries [1]. These are tamed death and forbidden death. The modern times are dominated with the forbidden death attitude, that means dying in the hospital bed, being unconscious and eschewing end to the last moment. Other people also do not let themselves think about death and be with dying persons. This attitude is the opposite of the tamed death pattern. To tame the death process is to gain a deeper consciousness, to become familiar with it and to give it some space at home and in everyday life. Death is painful but not horrifying thanks to being in the natural environment shared by humans, animals, and plants. When people naturally regard death, their death terror and panic are reduced. Although nowadays the Western world is permeated with the forbidden death attitude the development of thanatology inquiries and scientific branches dealing with thanatology diminishes trying to avoid death and the dying persons. People are again being brought up towards death. This bringing up involves gloomy mood and forms the polarised reality of the end which excludes life and the life which excludes death. Some ancient civilizations are the treasure of experiences, feelings, and thoughts on the tamed death. This text is an introduction to this treasure of the past.

On Supplementing Thanatology Education

Thanatology education gained importance in the health, psychology and pedagogy studies curricula. Its primary focus is death. Biological, medical, social and psychological definitions of death are presented during classes, workshops, lectures, and seminars. Lecturers explain philosophical approaches to death. They attempt to do anthropological and cultural analyses of the phenomenon of death and mortality awareness. They present psychological concepts of death and data on death anxiety. They discuss symbolism, tradition, and customs related to death and dying, as well as mortuary rites in religions and cultures. They compare

representations of stern, yet grave and dignified Mors of old with contemporary media images of death which is hasty, or pushed aside, hidden behind a curtain. They teach students how to work with persons experiencing loss and mourning, and various kinds of psychological assistance that should be offered to adults, children, and youths. They educate teachers making them aware of the necessity to develop intervention procedures for students and teachers in case of death, as well as postvention procedures. The latter is of particular importance as they are used in suicide cases – the kind of death which is even more traumatizing, than other ones [2].

Thanatology education tames death which is often repressed in the public and the private domains. It gives an impulse for an individual realization of the existential meaning of death. It provides knowledge and skills to psychological and medical assistance professionals.

However, those important and necessary subjects shape a paradigm of the polarised reality with life ruling out death and death ruling out life. Contrary to educators' intentions, the polarisation may discourage, breed despair and terrify. What is missing is a certain kind of thinking and a presentation of life so wide that it encompasses death. Life images and experiences captivating and uplifting at the same time that does not necessarily involve neither religion nor divine knowledge. This means that those images and experiences respect the diversity of people's attitudes and choices, as not everybody is a part of a church or practices religious rites of this kind or another.

The purpose of my deliberation is to present experience, which could be more appropriately termed a visual experience and the traces of which may be found in the oldest civilizations. The interpretation of the original experience enables a deeper understanding of death and life and a thanatology education broadened in such a way, as to highlight life transcending death alongside existential and axiological meanings of death. The interpretation uncovers not only the bios referring to individual (i.e., mortal) existence but also the zone including all living and feeling beings. Evoking the experiences I see to the understanding of myth, not as a mind-meddling illusion, but rather a tool enabling individuals to understand themselves and their life events in the context of culture and cultures [3]. Carl Gustav Jung recognised this context as a spiritual space [4].

Dionysian Experience

Experiences full of vision contents were available to people from the end of the Palaeolithic, through Neolithic and Antiquity, so perhaps it would be a good idea to start with

storytellers' favourite line: Once upon a time… Especially that fairy-tale chronology is more useful (than a scientific one) to let the mind perceive poorly visible, or even hidden aspects of the reality.

Once you experience abundant, unspoiled nature you continue to be under its impression and significant influence. Persons with more lively imagination may realize how its charm impressed people when the Earth was younger. Even today, in spite of being separated from it by various objects allegedly improving comfort, some still feel accosted by nature. They feel that nature speaks to them clearly, even if its message is not always obvious. A live experience of a being slightly mysterious and separate from humans makes one wonder. The mind starts to see the additional dimension existing in nature. People of ancient cultures understood that it might be grasped through visionary skills as it constitutes the content of a vision.

In the distant past, visionary talents were more common than now and were not treated as a manifestation of a mental disorder. Initially, fasting and isolation were enough to generate visions. Later, as the abilities got weaker, people supplemented themselves with plants. Depending on culture, geographic location, climate, and flora people would use poppy, Salvia divinorum, peyote (Lophophora williamsii) or Erythroxylum coca, the plant used to make cocaine. The Minoan civilization from Crete had extensive knowledge of dosage, mixing and ingestion of farmakon which was opium [5]. It corresponded with the divinity of Demeter, whose name in the linear B script meant "poppy fields." The knowledge was gone with the Minoan culture. Fasting, isolation, silence (not necessarily combined with isolation), darkness, dancing or running until a trance, the abovementioned plants, and in colder climate zones tansy, Artemisia and Amanita muscaria (fly agaric) infusions, small quantities of fermented honey or wine – all those methods and substances induced an experience of timeless being and bliss.

The oldest mythical stories – fragmentary and not the same as Greek and Roman myths taught at school – preserve the belief of continuity and indestructibility of this being. Aristaeus, son of Apollo, taught people bee-keeping thus making them independent of wild bees. Honey, which previously was being found only through lucky coincidence, became an accessible component of diet. Mythical stories of Aristaeus – scarce as they are – talk about the indestructability of life manifesting itself through the act of rousing the bees. Sacrificial animal – bull or cow – had to be killed. At least one animal would be killed. Virgil says that

Aristaeus killed four bulls and four cows [6]. Dead animals were left for a time – between nine and forty days – sometimes with all of their body orifices blocked. They would wait for entrails to come out. Once the entrails were gone, bees appeared. Bees would swarm above sacrificers' heads like golden rain of holiness, as bees were considered sacred. The belief of the sanctity of bees was reflected in a strong prohibition to kill those insects which survived in rural Europe until the 1950s. The evocative image of motionless black or white animal bodies, first steaming, then rigid, and finally transformed into a golden swarm represents the continuity of life in its awe and beauty.

Death, acutely painful as it was, did not terrify ancient Greeks, Thracians, Minoans or Phoenicians in the same way as it terrifies most of us today. They were protected by rituals dedicated to a deity whose cult originated perhaps in Lydia (today's Turkey), or Thrace, or maybe – as Karl Kerenyi believes [5] – from Minoan Crete. We know the mature version of the cult under the name of Dionysus – god of wine, bull, and women. Women were his enthusiastic devotees, by the etymology of the word "enthusiasm" from entheos meaning the state of "being taken over by God." Cult acts performed in honour of Dionysus not only mirrored the myth of suffering, body being torn apart, voyage across the land of the dead and regaining bodily integrity but also expressed the reality. The indestructibility of life construed as zone, as opposed to individual and mortal bios, was the reality. In the flux of the ever-changing life cycle the soul was linked both with life and death.

Two important acts were performed in the Dionysian myth. Firstly, the ritual consumption of the body of God (who was still a child), and secondly the enthronement of Dionysus as the king of the world. Conception, development stages from embryo until birth and regaining corporal integrity were regarded as zoe acts. Dionysus protected life in those phases in particular, when life is left on its own; therefore all (not only human) fetuses were spared in Dionysian rituals.

Non-reducible life was expressed at its fullest in several plant and animal forms. A snake represents the first one. Resilient, moving without limbs through the strength of muscles, rising in different poses. Cool and moist it slithers through dark recesses. It can survive the scorching heat and winter frost. It is linked with the element of earth and the underworld. It is vitality itself. Before Christianity imposed on it a bad reputation in the Satan allegory, it had symbolized fertility. That is how Hindus know it, that is how ancient Slavs knew it; the latter believed that when a snake settles near a household, it protects home and brings good luck to its residents.

In the plant world, life was reflected in ivy and grapevine devoted to Dionysus. Grapevine is the shrub of the sun, while ivy – a shoot of the shade. Grapevine issuing sweet fruits is linked with the god of wine and vineyards, but it is kissos – meaning ivy – which is the god's nickname. When in autumn, as part of the vegetation cycle, grapevine loses leaves, ivy blossoms. It bears fruit in spring, and it brings joy to human eyes throughout severe winter. It is the plant echo of the snake – it is linked with everything cool, resilient and climbing. Tirelessly entwining itself around tree trunks and branches, ivy weaves curtains and tents for birds to rummage about. Invisible as Thyiades in the dark they sound as if flute voices of Dionysus' retinue.

Ivy is a vivid backdrop for a cloth-wrapped column on top of which a mask is swinging – a non-phallic attribute of god who suffers and returns from the underground land of the dead. The phallic idol of the god was hidden in liknon (basket) and carried during ritual processions of Dionysian festivities. Either a dried penis of a black sacrificial goat, or a phallus carved out of fig wood was used. Fig wood was chosen for its symbolism. This friendly and nourishing tree was linked with the chthonic world [5]. The conviction of the ivy chthonic nature continues until today, and ivy is often planted in cemeteries.

Dionysian festivities were taking place in winter months when days are short. Women-god worshippers would roam dangerous mountain passes during winter nights. They would use torches to illuminate the darkness hard to imagine for inhabitants of today's too intensely glowing Earth. They would be silent, lost in the dance. They were not inebriated. Rituals required the utmost concentration and probably murderous physical effort. Intoxication with psychoactive substances could be significantly harmful. Women summoned Dionysus from the underworld whence he returned renewed and full of power. Worshippers were called Thyiades. This name may be associated with the Greek word thyione – running in amazement. Thyiades' trance had a different source, namely the ecstatic experience of life as such. In the incredible images, a strong conviction is rooted, that a dying person goes on a love adventure, that the person shares certain features with dying Dionysus and that – like Dionysus – the person will return reborn.

Life Power Experience in Cybele Rites

According to contemporary archaeologists and ancient languages experts, Phrygians

arrived in Asia Minor between the 10th and the 11 the centuries BC [7]. They grew in strength and built a state that had capital in Gordium, and that encompassed the majority of the Anatolian plains, up to Cappadocia, and bordered the lands of Lydians and Tabal to the north of Cilician Gates. They developed a great culture. Ancient Greeks admired the frieze – the Phrygian architectural invention – so much that no temple could be built without it. Midas, a Phrygian king ruling the state at its peak of development, became one of the symbolic personifications of richness.

Phrygia may be regarded as a bridge between cultures of the Orient and the West, both present in ancient Greek civilisations. Phrygians worshipped Cybele, an ecstatic mother of all living beings. Cybele was not an expression of Phrygians' religious talents, but rather a continuance of Kubaba, the ancient goddess of the North-Syrian city of Carchemish, which was also worshipped in the Lydian city of Sardis as Kuvava. She also had its counterpart in the world of Hittites whose power fell and their abandoned settlements were, with time, taken over by Phrygians again.

Cybele was a deification of the Earth Mother having been worshipped in Anatolia since Neolithic times. The Cybele cult employed the practice of taurobolium, the slaughter of a bull whose blood dripped through a grate down onto the worshiper who stood beneath. The taurobolium was a baptism, and a sacred bull represented dying god Attis, who was a consort of Cybele. The taurobolium was practiced in ancient Rome after the Cybele cult had been brought to Rome from Phrygia around 204 B.C. The temple of Cybele stood on the Vatican Hill where St. Peter’s basilica stands today. The cult of Cybele became the universal one in whole Roman Empire. The male worshipers of Cybele sometimes castrated themselves in the frenzy of her rites. The goddess was given something what symbolised the powerful vitality. This power is so mighty that it can afford to be destructive.

Cybele had its ancient predecessor. A magnificent sculpture originates from Çatal Höyük (near today's Konya), one of the oldest human settlements. It is kept at the Anatolian Civilisations Museum, Ankara where it is called the Seated Woman from Çatal Höyük. A talented artist gave her an astonishing form of a woman-goddess giving birth. Large breasts, thighs, abdomen, buttocks, strong arms. An apotheosis of robust corporeality – life power, which is fertility. Woman seats on a throne. Her hands are rested on lions (or panthers) standing on both sides of her royal seat. Her gesture shows that she is also a fearless ruler of wild animals. Her power was echoed in the mature form of Cybele of the Roman period with

the goddess – now much slimmer – being presented as a woman in a rich gown, seated on a throne, with lions at her side and a lion cub in her lap. Both forms of the personified sacrum point to a mother – "matar", as Phrygians referred to her. This is the mother of all living beings. Lions, panthers, snakes, cereals, people – all that are the epiphany of life are her children. They are equal among themselves and blessed with goddess' attention with nobody and nothing being favoured, nor excluded. Rich vigour, as the abundance and excess bordering wastage, accepts all. Since it is indestructible and cyclically reborn, it may afford destruction and prodigality.

Conclusions

Psychological researches show that an individual's profound existential experiences influence their temporal orientation [8]. The time starts flowing in a different way than it did before. The present direction is actively evaluated. The present is more important than the past events and the will projects which always focus on the future. Inward persons (concentrate on the present) plan their actions within a few weeks or months not being concerned about the future years and the past as well. The inwards also highly estimate good relationships with others. They are engaged in their friendships, marriages and loving relations more than their professional successes and career development.

Elisabeth Kübler-Ross [9] thinks that children, who have overcome the fear of separation/fear of abandonment and physical pain start speaking about death as the transition situation. She cites children's storytelling as they express their feelings and visions more willingly than adults — the experience of profound suffering changes human consciousness. The time is flowing differently as it did before. The changed consciousness opens an individual to the bliss that emotionally echoes the potential of the other being. Mysticism is thought to be an individual's bond with the separated being elusive but always whispering to a person. The ardent experience witnessed by the rites of Cybele and Dionysos is the mystic ones in this meaning. They express an individual's relationship with life itself. Then the life power and its real continuity (not duration) are revealed for individuals who become aware of intertwining of death and life.

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Brain death as a death of whole body in a context of social perception and organ donation

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Introduction

Human death determined by neurological criteria occurs when the function of the brain stem stops. The definition is specific and was elaborated by a group of specialists, but still arouses controversy, especially in the area of organ donation [1].

In this report, as the proper understanding of the concept of "brain death" and organ donation is the basis of good end-of-life care and successful organ donation, we would like to raise the issue of brain death and its social perception [2].

The issue of death, especially brain death, is very complicated. After many years of research and definition updating, on 17th July 2007, the Minister of Health issued an announcement which regulates the criteria and method of determining the permanently irreversible cessation of brain function. The announcement says that death is a dissociated phenomenon, which means that it covers tissues and organs at different times. The nature of this phenomenon is particularly visible when death has already covered the brain, while circulation is still preserved. In such cases, we should use the "new" definition of death. In its view, the criterion for qualifying for the death of a human is brain death. Both human deaths based on the "classic"- circulatory criterion or the criteria of brain death does not mean that with its occurrence all tissues and cells are dead. In the death of the brain as a whole, the qualifying factor is the death of the brainstem. Its statement is necessary, but also sufficient

condition to recognize the death of the brain as a whole, and thus the death of a human being.

The diagnosis of brain death is a specialized procedure based on the finding of irreversible loss of its function. Before the procedure is started, the initial observation is carried out - depending on the clinical situation; it ranges from 6 to 12 hours. The procedure of adjudging on the death of the brain is composed of two stages:

- I - suspicion of brain death
- II - confirmation tests. In the first stage, several statements should be made, e.g., that the patient is in a coma, artificially ventilated, there have been primary or secondary damage to the brain that is irreversible to the use of available therapeutic agents and the passage of time.

It is also necessary to exclude poisoning, hypothermia, and metabolic or endocrine disorders. Stage II consists of a series of tests and trials showing the absence of reflexes and persistent apnea. A critical issue, also included in the announcement, is the awareness that facial muscle movements or the shoulder joints movement with flexion in the elbow joints do not exclude brain death (the so-called Lazarus symptom) - they come from the spinal cord, and therefore they can't question the brain stem death [3,4].

The fact that in the twenty-first century there are social controversies and problems in the reception of the phenomenon of brain death and its importance as human death when from a medical point of view there is no field for any doubts and discussions in this regard is a matter of concern for the medical environment.

The purpose of the work

The aim of the work was a rating of the knowledge and social perception of people unrelated to the medical community about brain death and organ donation.

Methodology

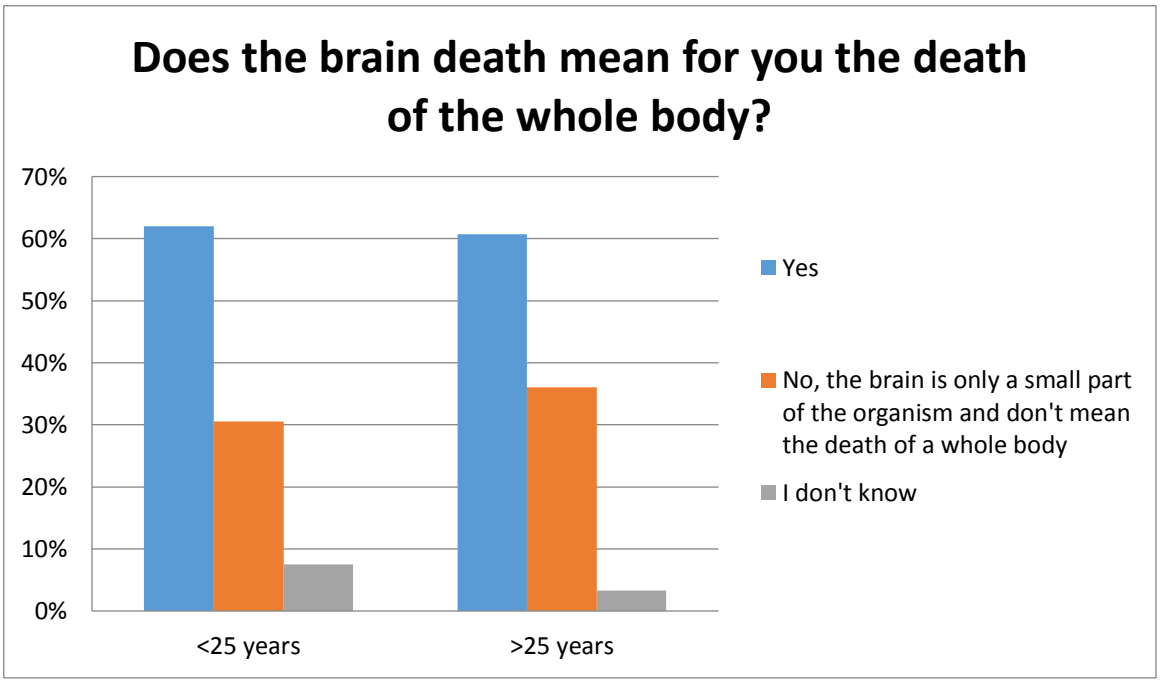
A group of 427 people not professionally connected with medicine was analyzed. The respondents completed a questionnaire consisting of 16 questions and defined their demographic data (age, sex, education, place of residence). Half of the respondents were people up to the age of 25, of which around 3% were under the age of 18. From among those over 25, 25-45 were found in 40.3% of respondents, aged 45-65 in 7.3%, while over 65 years

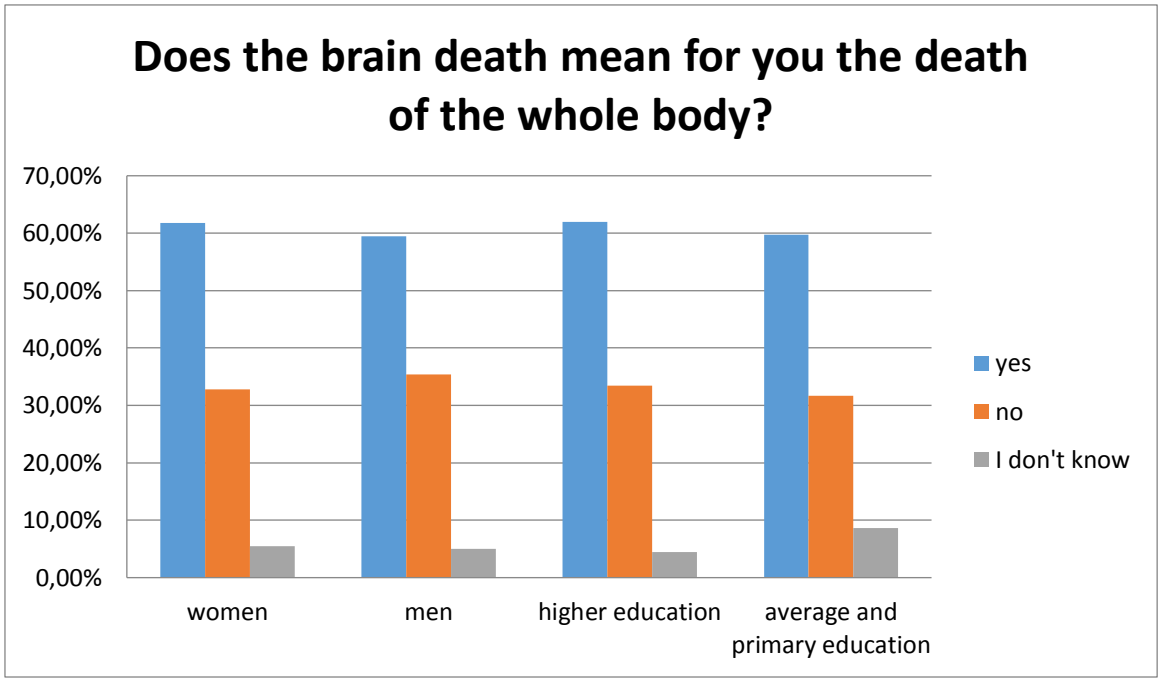
of age 2.6%. The vast majority of respondents were women - 81.5%, the remaining 18.5% men. In terms of education, people with higher education were dominant - 67.2%, followed by an average of 27.9%, primary - 4.2%, and vocational - 0.7%. 52.9% of the respondents came from a large city (> 100,000 inhabitants), 22.7% from the village, 14.5% from a small town (20,000-100,000 inhabitants), 9.8% from the town (<20,000 inhabitants).

The survey was carried out using the author's questionnaire. The survey was conducted online using Google Forms.

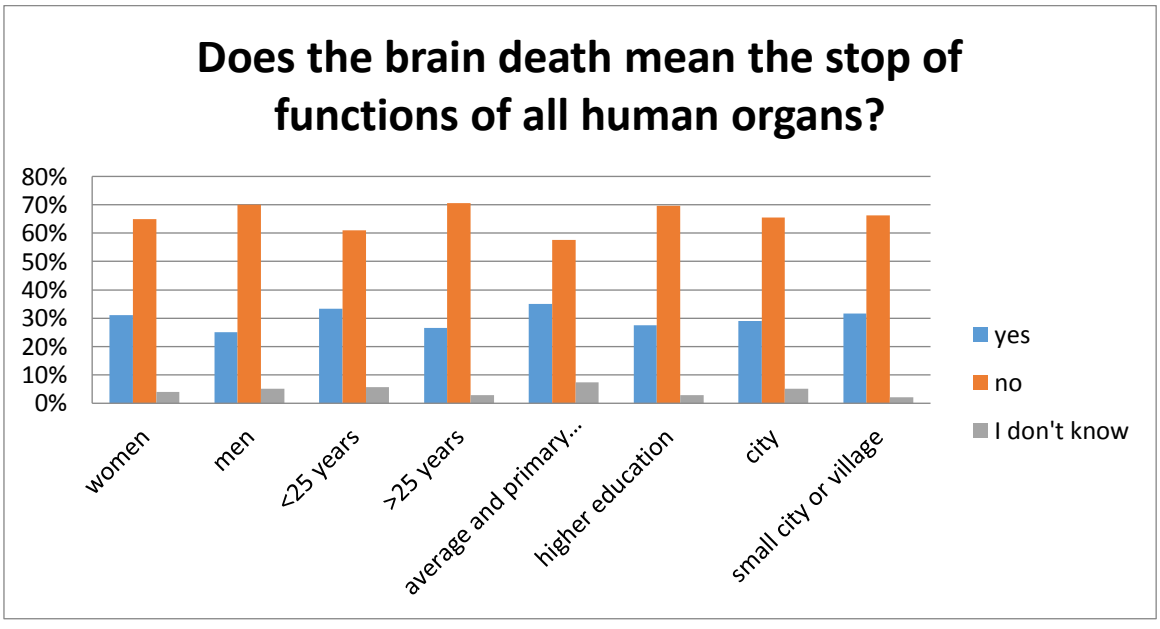
Results

This part of the work will discuss the results of the survey. The first two questions in the questionnaire concerned the knowledge of the definition and understanding of the concept of brain death. Just over half - 61.5% of respondents believe that brain death means the death of the whole body. A third (33.3%) of the respondents said that the brain is only a small part of the body, and therefore its death is not equivalent to human death. When analysing data for demographic characteristics, the distribution of "yes" and "no" responses irrespective of sex, age and education level and place of residence is almost the same (spread of about three percentage points).





The majority (65.8%) of the respondents are aware that the death of the brain does not have to mean the end of work of all organs of the body. In the percentage distribution of responses, also in this question, no significant differences are observed depending on the demographic criterion, as presented in the chart below.

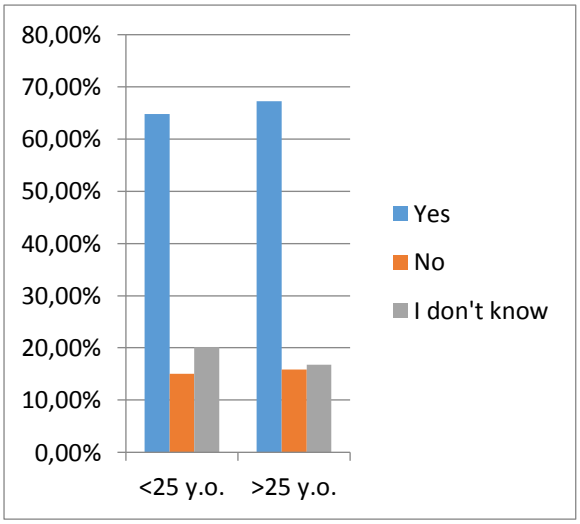


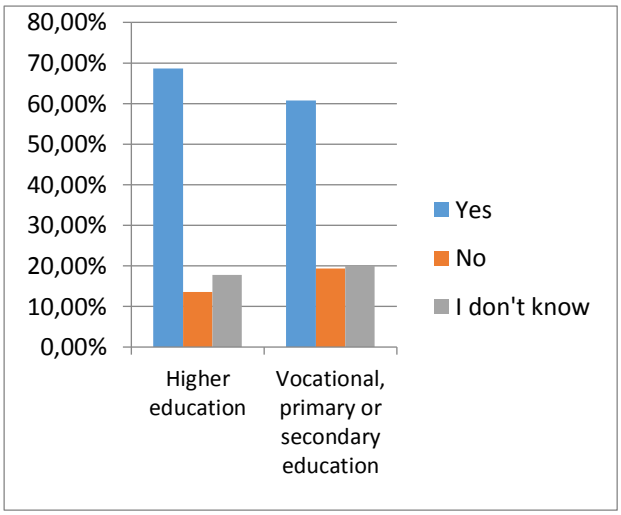
The respondents were asked, among others about whether they think determining brain death is problematic. As many as 2/3 of respondents - 64.8% in the age category below 25

years of age and 67.3% in the age category above 25 years of age - believe that diagnosing brain death often causes problems. Every fifth respondent admitted that he does not know if the procedure is problematic. Analyzing the results in terms of respondents' education, a similar distribution of responses can be stated, regardless of the level of education of the respondents. 68.6% of respondents with higher education gave an affirmative answer, slightly less in the group of people with basic vocational, primary or secondary education - 60.7% of respondents.

Answers of the respondents to the question: "Do you think that determining the death of the brain is often problematic?"

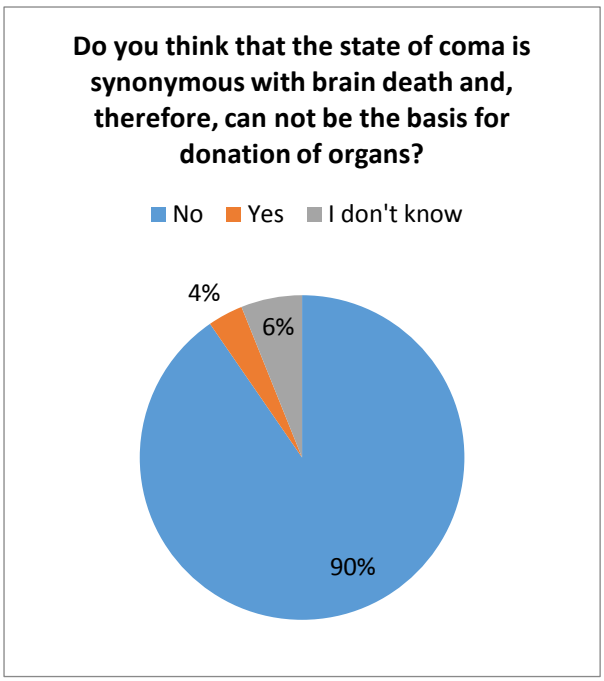
Brain death is sometimes erroneously identified with a coma. This aspect has also been studied, and the results clearly show that only every tenth respondent confuses these concepts. The share of negative answers amounted to 90.3%. Therefore there is an awareness of the difference of these two concepts in society.

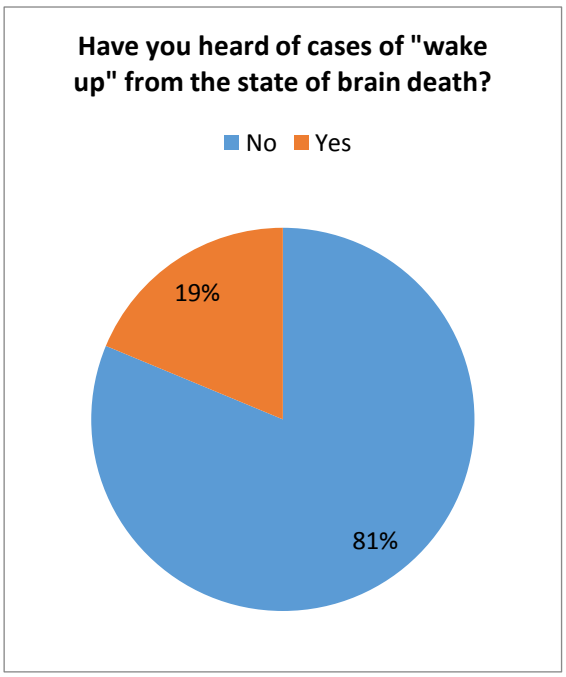




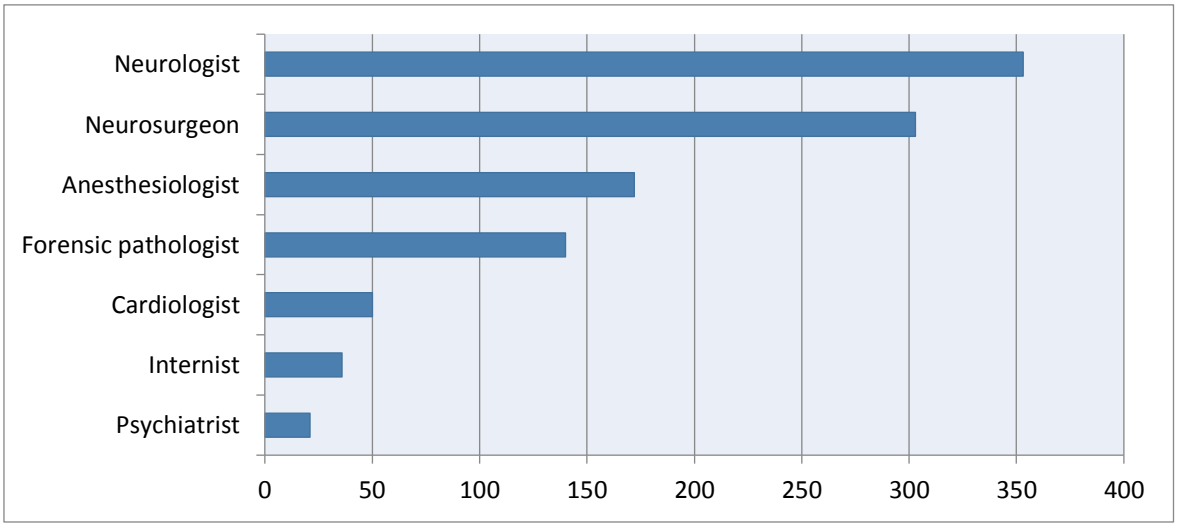
In the Republic of Poland under the provisions of art. 9 par. 6 of the Act of 1 July 2005 on the collection, storage and transplantation of cells, tissues and organs (Journal of Laws No. 169, item 1411) [6], the composition of the adjudicating committee is determined.

After the commencement of the qualification procedure, meeting all criteria, proper execution of tests, and in justified cases of instrumental examinations, a commission composed of three medical specialists, including at least one in the field of anesthesia and intensive care and one in the field of neurology or neurosurgery, can determine the death of the examined person as a result of brain death.





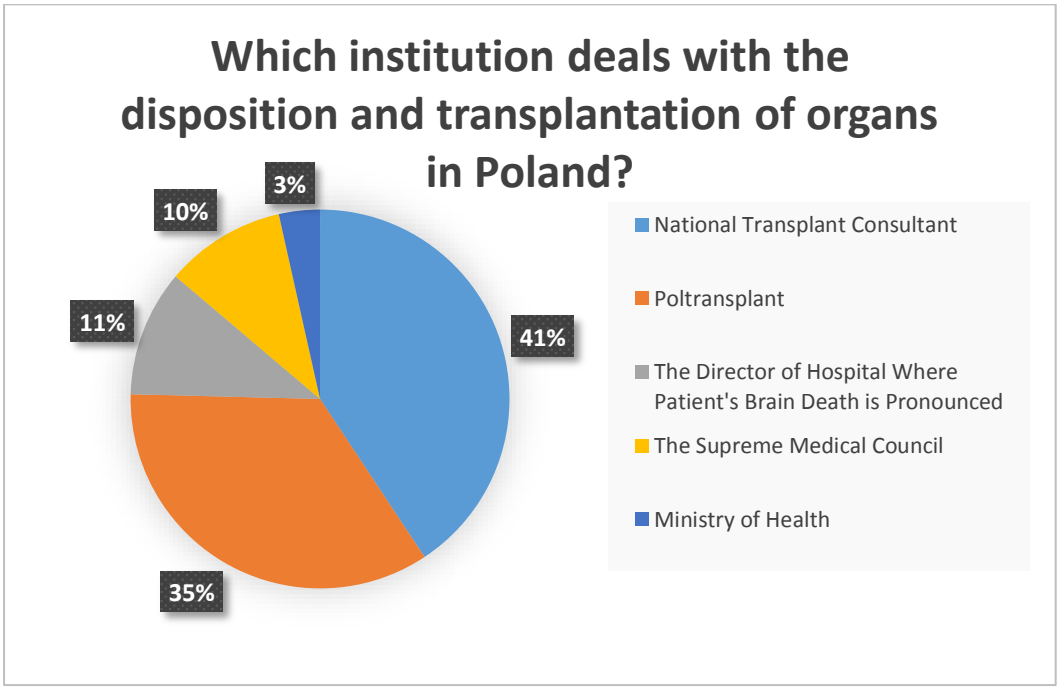
In order to study the knowledge about this issue, the respondents were asked to indicate which medical specialist is entitled to declare decease due to brain death. They could indicate more than one answer at the same time.



The distribution of votes indicates that there is an awareness in the public which physician is authorized to determine brain death. Interesting and noteworthy in this juxtaposition is the position of forensic specialist, indicated jointly by 30% of voters. The respondents were also asked in this context whether the procedure for determining the death of the brain can be performed by a single doctor. The vast majority (88.5% of respondents) answered that brain death can not be determined by only one physician. Compliance with

such a picture of the procedure existed to an equally high degree in all the studied groups, regardless of age, education or place of residence.

The respondents' answers should also be considered in the context of public belief about the actual death of a human being when his brain is determined to be dead. This fact is associated with some kind of dissonance - on the one hand doctors confirm brain death, on the other hand often other human organs function properly, which leads to wrong conclusions and belief that the patient is still alive. To examine the opinion of the respondents on this subject, they were asked a number of questions, including whether, according to their knowledge, there are frequent cases of misjudgement of brain death. Most respondents declared that they do not know if such cases exist - in both age groups it was about 60% of respondents. The answers to the question of whether the procedure for determining brain death is properly prepared, so that irregularities in the organ donation process can be ruled out, are standing similar. Also in this case, the significant majority of the respondents referred to the lack of knowledge - 57.3% of the answers "I do not know" in the age group under 25, 49% in the group of people older than 25 years. Comparable percentages also fell on groups depending on their education.

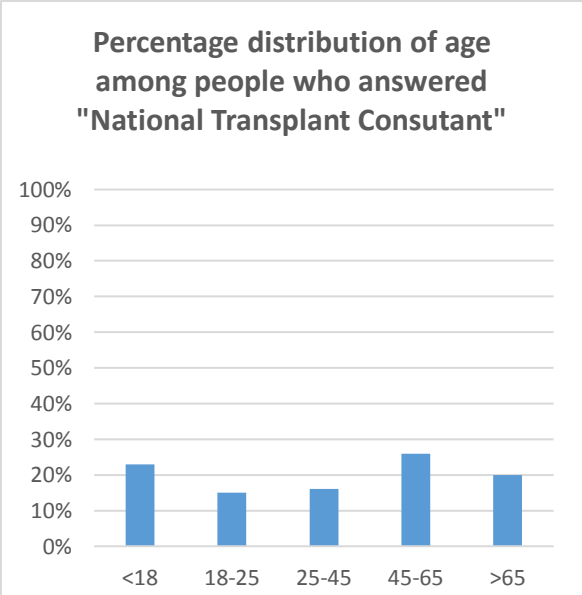


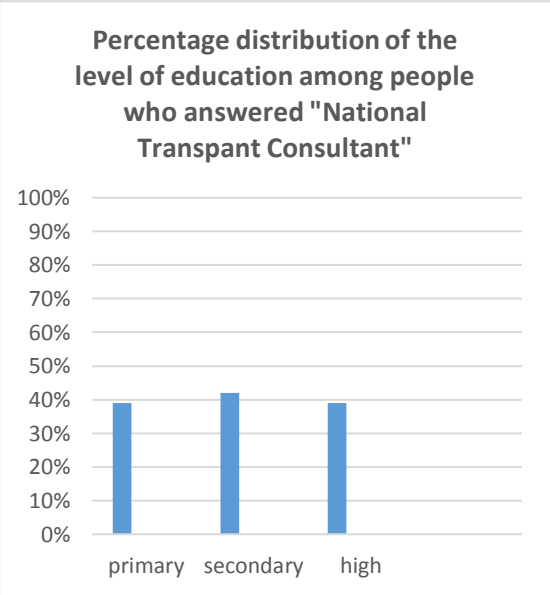
A big problem for the respondents turned out to be the question in which they had to determine the institution that in Poland deals with the disposition and distribution of donor organs. The most frequently answered response was a choice of the National Transplant

Consultant as the superior in making this decision. 40.7% of the respondents gave this incorrect answer.

The function of the National Transplant Consultant is, in fact, consultative and advisory, he has no possibility of making decisions independently. His role is to supervise the availability of medical services in specific regions of the country, which enables him to cooperate with the regional consultants subordinate to him. He verifies whether health care institutions perform their tasks in the field of education and professional development of medical personnel. He draws up opinions on staffing needs in transplantology.

Analysing the age distribution of persons choosing the above answer, it can be concluded that none of the groups dominates over others. The most significant difference occurs between respondents aged 18-25 and 45-65 and amounts to 11 percentage points. By analysing the distribution of education among those who gave this answer, we come to a similar observation. The most significant difference is between people with primary and secondary education and is only three percentage points.

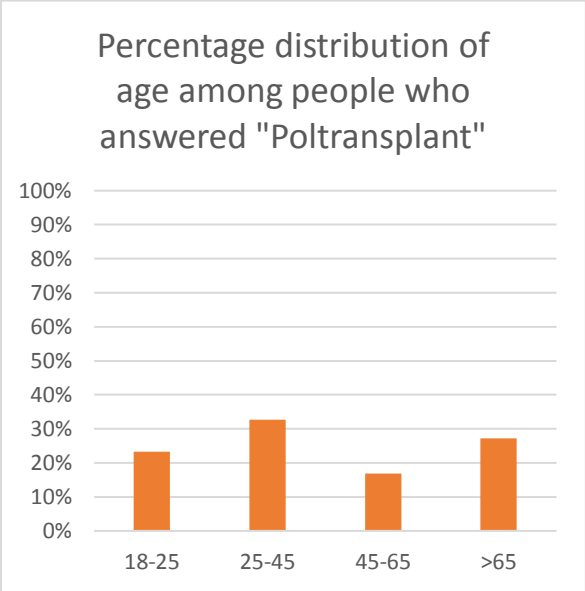


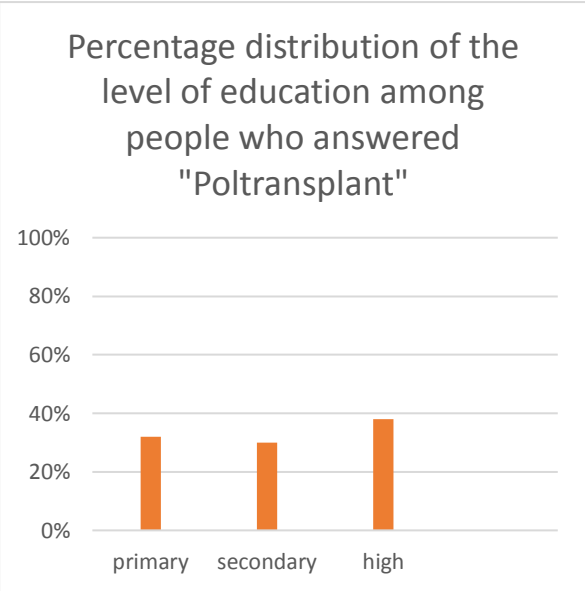


Turning to the analysis of the second, most popular answer (Poltransplant), which was selected by 34.7% of respondents, we discover that again differences in the distribution of age and education do not play a significant role. The most substantial difference in responses is between the age group 25-45 and 45-65 and is 12 percentage points, and when it comes to the distribution of education, the most significant difference is between the respondents with secondary and higher education and is eight percentage points.

The Poltransplant answer was the correct one. Poltransplant, or rather the Center for Organizing and Coordination for Transplantation were established in 1996. It operates under the Act of law "*The collection, storage, and transplantation of cells, tissues, and organs*" from July 1, 2005 [6].

In this document in article 38, the detailed scope of the institution's activity can be found. It includes coordinating the collection and transplantation of cells, tissues, and organs, creating a national list of people awaiting transplantation, keeping a transplant registry, keeping a register of living donors, coordinating the search for unrelated bone marrow donors, tissues and organs.

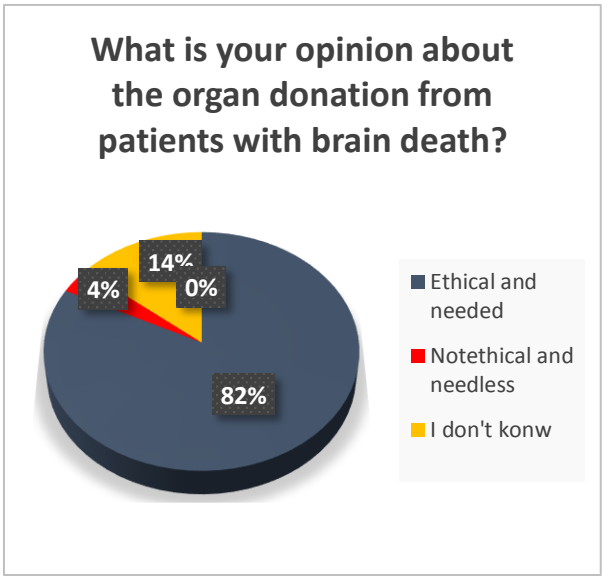


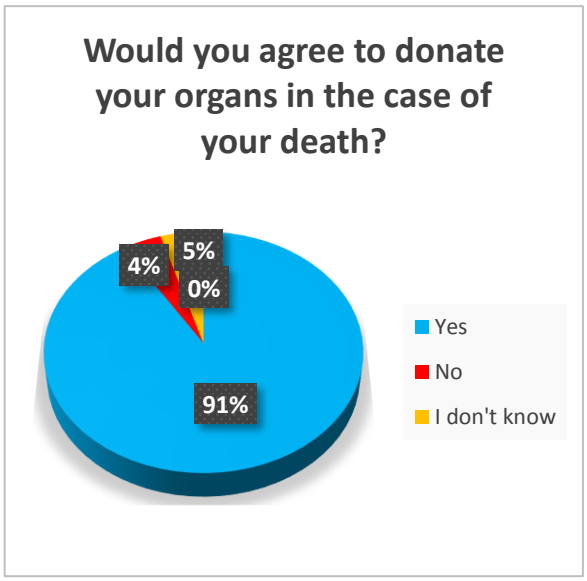


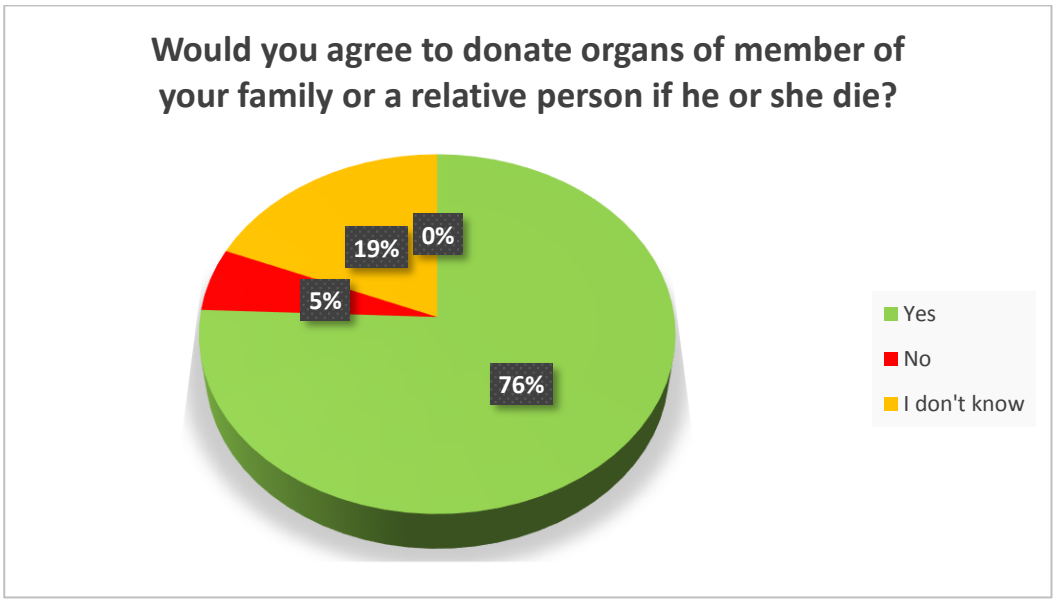
Lack of diversity in terms of age and education among people providing both correct and incorrect answers gives us information about a comparably low level of knowledge on the coordination of organs transplantation in Poland. This is supported by the lack of a dominating answer to this question.

This is very important information when we combine it with a very positive attitude to the organs transplantation in Poland. This is supported by the fact that 82% of the respondents consider donating organs from brain death donors to be ethical and necessary, and over 9 in 10 people would agree to donate their organs in the event of their death.

Slightly fewer respondents would agree to donate a family member organs (76%), which is due to the concern of family members to respect the will of the deceased. Particularly problematic will be when this will has never been determined.

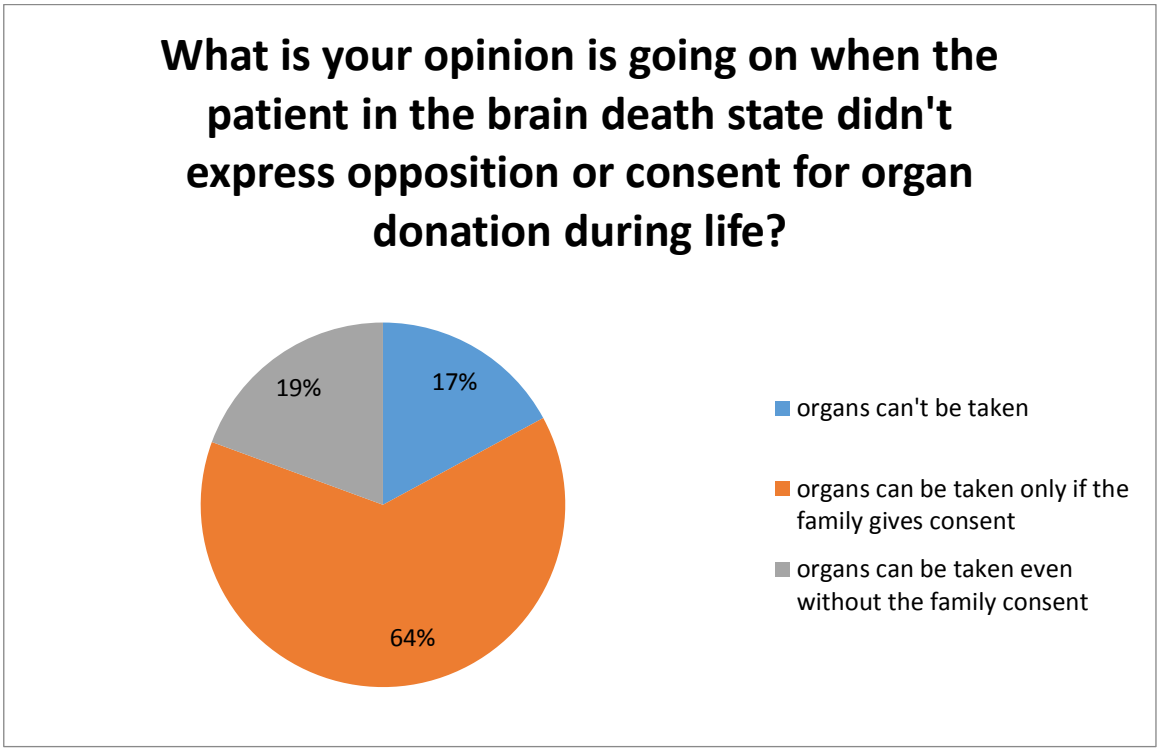






The next question in the questionnaire concerned the possibility of organ donation in the state of brain death when the donor did not express opposition or consent during his life. As many as 63.5% of respondents believe that organs cannot be taken without the consent of the family. This is obviously due to the common practice of asking for the consent of the family to take organs in the case of a patient in a state of cerebral death, related to expressing respect for this family and its tragedy. Less than one fifth (19.4%) of respondents are aware that organs in this situation can legally be taken even if the family does not express the consent [1].

17.1% of respondents believe that organs cannot be collected at all if the patient did not specify his consent during life.

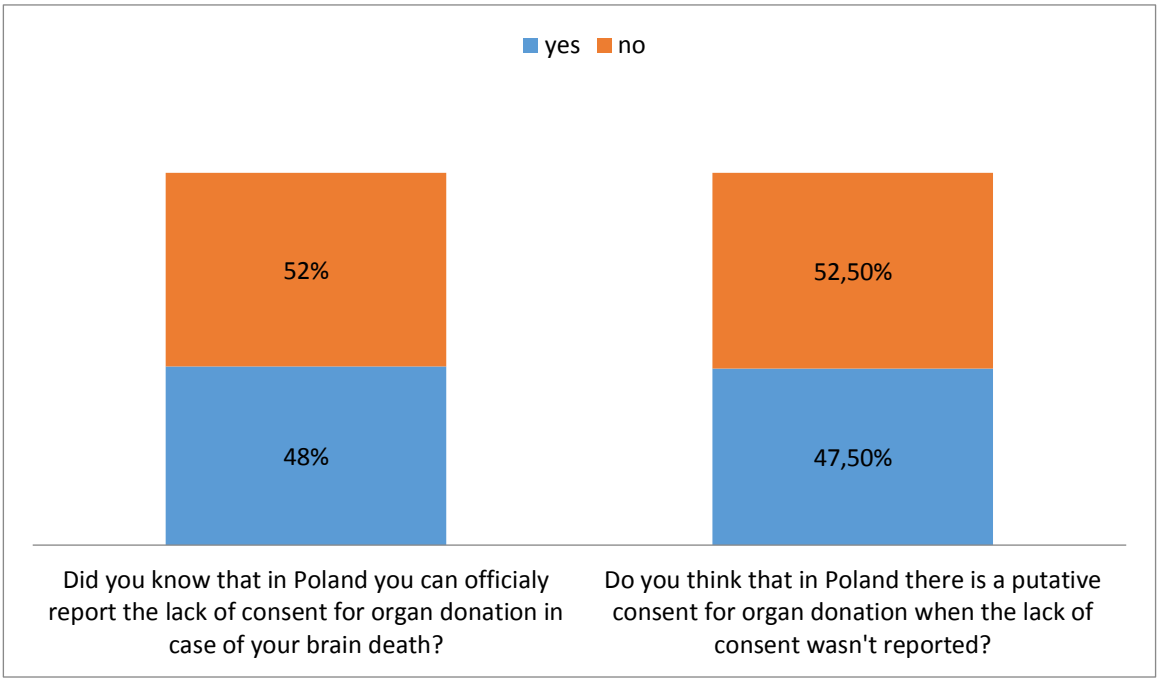


The respondents were also asked if they were aware of the possibility of expressing disagreement on organ collection in the case of brain death, which lack of consent has legal force. Answers to this question were spread in a ratio of 1: 1 - 48% of respondents knew about this possibility, 52% did not.

Very similar percentage distribution of responses concerns the last question about the putative consent to organ collection when the lack of consent was not reported through official documentation. 52.5% of respondents believe that the putative consent does not exist.

There is a correlation between the answers to the above three questions - over 60% of respondents who think that the family must give consent to organ donation did not know about the possibility of not reporting consent and about 50% of the putative consent for the collection.

To sum up, 50-60% of respondents do not realize the rules, which transplanting physicians in Poland use, which may be the result of insufficient social education and media coverage of the issue of transplantology as well as the need and importance of ethical being a potential organ donor.



Discussion

Analysis of the answers provided indicates a relatively high level of knowledge of the respondents about the issue of brain death. Over 60% of respondents correctly indicated that brain death is synonymous with the death of a human being as a whole. This is in accordance with the state of medical knowledge and the globally accepted concept of human death at the moment of irreversible cessation of the function of the brain. Also, for the majority (over 65%), brain death is not equivalent to the death of other organs of the body, which can, therefore, be taken and implanted into the recipient.

However, on the other hand, every third respondent does not identify brain death with the death of the whole person, downgrading it only to the rank of death of a single organ. This can lead to not identifying the death of the brain as an irreversible process, which it undeniably is, and persevering in wrong hope of a "wake-up" of another person. This, in turn, has far-reaching consequences for reconciliation with the loss of a close relative. According to the five stages of grief model introduced by Elisabeth Kübler-Ross regarding the human response to the news of death, there are five psychological stages: denial, anger, bargaining (negotiation), depression and acceptance [5]. The lack of the latter prevents the completion of this process. This results in misunderstanding and frustration and the ongoing state of depression leads to the individual’s impairment of functioning in society.

Among those questioned, the awareness of the difference between brain death and coma is noticeable - the awakening of patients sometimes occurs from the vegetative state of coma, never from the irreversible death of the brain. Over 90% of respondents - people unrelated to the medical community who do not have medical education - recognize these two states as separate and independent. The result of the answers given to the question about brain death awakening seems to confirm this awareness - 81% of people did not hear of any cases of "wake up" from the state of brain death.

The relatively high level of respondents' knowledge may result from the image of brain death and organ transplantation shaped by mass media, including television, medical TV-series and the Internet. For many people, these are the primary and often the only sources to obtain information and shape the image of brain death, along with the procedure for its detection and donation of organs. Therefore, it is essential to focus on raising broad awareness of the society what death of the brain is, how it is determined and how the organ transplant system functions in Poland. This task could be pursued through the implementation of nationwide education campaigns, meetings organized throughout the country with doctors authorized to determine the death of the brain or transplantologists. Also, teaching children and young people in schools about these issues is a critical element of the broader society education process.

Actions that dispel doubts and refute myths are very much needed. As the results of this paper show, especially in the field of knowledge about the procedure of determining brain death, a large group of respondents expresses distrust or directly admit they do not know this issue. A large percentage (66.6%) recognizes that determining brain death is problematic and it is often difficult to make a precise diagnosis. Almost 20% even think that there are often misjudgments regarding this process. At the same time, more than half (53.2%) do not know whether the procedure for determining brain death in Poland is well prepared to rule out irregularities in the process of donation of organs.

Although the picture of a patient who is suspected of brain death sometimes happens to be ambiguous, in the vast majority of cases the death of the brain is correctly determined, in compliance with the factual situation, based on numerous statements, confirmed by examinations and observations mentioned in the introduction of this paper. A medical commission, consisting of three specialists in the field of neurology, neurosurgery, and anesthesiology, must unanimously adjudicate death of the brain. In the case of doubts of even one of its members, such a ruling cannot be issued. The respondents most often indicated these specialists as authorized to adjudicate, but there were also many incorrect answers.

Also, this element of the procedure should be brought closer to the public as part of activities promoting tanatoeducation.

Many myths have appeared on transplantology, and the fear of death and confrontation with it is essential for this fact. Fear of dealing with such topics has taken the form of a social taboo. Conscious education open to discussion enables understanding among all social groups. There are not many harder decisions in life than those that concern the transfer of one's own or the organs of the people closest to us in order to save a life for another person. Talks about death accompany conversations about transplantology. On the one hand, the fact of transplant is a confrontation of the recipient with his mortality, and on the other hand, the decision to be a donor (especially after his death) is an act of accepting his mortality [1].

However, the positive attitude of the respondents to the idea of donating organs fills us with optimism. As many as 82% of respondents declare that in their opinion organ procurement in a state of brain death is ethical and necessary, and 91% would agree to donate their organs in the event of their death. It is related to several factors that shape such a great attitude. The involvement of medical staff in communication and contact with future donors and recipients, political, religious and non-governmental activities contributes to the care of this attitude. The vast majority of religions and religions support donating organs for transplantation, pointing to the fact that it is the highest form of social solidarity and an act of mercy addressed to another human being. In Poland, the dominant religion is Catholicism, and it is in its discretion to increase the awareness of the faithful about the subject of transplantation. A clear position on transplants was repeatedly held by Pope John Paul II, among others in the Evangelium Vitae encyclical, writing that the donation of organs consists in the heroism of everyday life and is the highest form of selfless support for one's neighbor.

According to Polish law, in the absence of any objection to donation, the informed consent of the donor should be assumed. However, above all, in the case of knowing the will of the deceased, she should decide what will happen to the organs. However, what if the family did not recognize the will of the deceased? Opposition to organ donation expressed by the deceased's family causes that the lives of many patients cannot be saved. The issue of family consent for a transplant was shown by a question in which 76% of respondents voted in favour of organ donation in such a case. This number is satisfactory, but not entirely satisfying. Most likely, this is due to the concerns of those who are asked to make the wrong decision, which will be inconsistent with the will of the deceased. It may also result from questions that arouse anxiety among the family, which is to decide on the addition of organs

of a loved one. It is doubtful about the final state in which the donor is, and whether brain death can be misdiagnosed and are methods that would reverse it?

In order for such doubts not to occur, it is necessary to educate on the procedure of determining the death of the brain, managing donation and separation of organs. Respondents asked about who is involved in the coordination of transplants in Poland in the vast majority have given an incorrect answer. Analysing the distribution of education and the age of people providing wrong and right answers, we can see that there is no specific trend among a particular group. The whole society has little knowledge about the organization of donations. It is sad because a society with such a willingness to help in the form of organ donation should be well educated in this matter.

The results of organ transplantation are getting better, thanks to which the indications for treatment with this method are widening. The number of people waiting for transplantation is increasing and the time they are waiting for surgery is increasing, which may pose a threat to the patients' lives. The society's knowledge of the value of hundreds of deadly and waiting for transplantation of the human organ is insufficient. A permanent educational and information campaign about the needs and results of organ transplantation should be conducted, which will help convince the public about the effectiveness of this method of treatment and deprive the family of donors of doubts as to the justice, professional preparation and significance of this process.

Conclusions

A high percentage of incorrect and abstaining answers may indicate ignorance of procedures and lack of knowledge regarding the issue described in this paper. This conclusion is also reflected in the questions concerning the technical side of the procedure of adjudging on brain death, where too many answers were incorrect. In turn, in the context of recognition of the death of a patient diagnosed with brain death, the answers are given by the respondents - regardless of their age or education - indicate that a large percentage may not fully trust the diagnosis.

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Psychooncology as an important element of breast cancer treatment from diagnosis to convalescence

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Introduction

Psychooncology is a new field of medicine and psychology. Its significant development began about 20 years ago. Earlier, in the 1970s, the first research on the psychological aspects of an oncological patient, eg coping with the psychological effects of the disease, the role of social support, quality of life in the disease, the impact of lifestyle on health, relationships between personality traits and predispositions to get sick e.t.c. was conducted [1]. In the case of cancer, psycho-oncology deals with patients' emotional reactions to various stages of the disease, their families and caregivers - this is a psychosocial dimension of psycho-oncology. Also, there is an area of psycho-oncology that investigates psychological, behavioral and social factors that can affect cancer morbidity and mortality (psychobiological dimension) [2].

Currently, by increasing the self-awareness of patients, more accessible access to knowledge about diseases and the introduction of the Medical Profession Act and the Patient's Rights Act - patients are more aware of the seriousness of their illness, and at the same time, they have a stronger impact on their psyche.

Psychological problems of women with breast cancer

At the beginning of the 1990s, oncological patients began creating associations that were supposed to support each other's members in a similar situation. In 1987, the first in Poland Mastectomy Women Club was founded and called ,,Amazonki". This movement was developing rapidly, and women eagerly benefited from the help of the association. Many of them have enjoyed it today. There are about 20 000 members now [3].

The Amazonki movement plays the role of the psycho-oncologists group. Ladies who belong to this association know best what they need and how to help their friends after breast cancer treatment. As they say in the "Amazons" newspaper: "Mental support is a very serious task of our clubs, implemented thanks to our volunteers. Very difficult, very delicate. (...) Our women have a different mentality. All literalness is alien to them, any talk in the style of "maybe you would like to talk about it." I think that we often prefer to keep silent on a sensitive topic." [4].

Women living with an awareness of such a severe disease as breast cancer is, and those who have undergone mastectomy, struggle with several psychological dilemmas. These psychological aspects are often found to be utmost challenging for patients. Numerous studies show that cancer affects the human psyche negatively. It has been shown that over 40% of cancer patients simultaneously suffering from affective disorders [5].

In 1969, Elizabeth Kubler-Ross announced a theory that was a breakthrough in systematizing the stages of human adaptation to the perspective of death. This process starts with the initial stimuli (stressor) and the appraisal/perception of that as a threat (stage I) and continues with the reaction to the stressor if it is perceived as a threat (stage II). This is the time that, if manipulation of the stressor with appropriate interventions occurs, prevention of ineffective coping and/or maladjustment to illness is possible. The third stage refers to the coping with the disease (adaptive or maladaptive coping), followed by the degree of adaptation to illness and satisfaction with daily life (quality of life). Depending on interventions applied at this stage, the outcome can be either adjustment to illness or maladjustment and low quality of life (final step) [6]. As it turned out after many years, these stages do not have to happen in the given order, one of them often does not exist, or they overlap [5].

It is also known that a diagnosis of invasive breast cancer propels women into a time of uncertainty that brings fear and emotional work. This disease often challenges a woman's identity [7], self-esteem [8], body image [9] and relationships. Studies show that women with cancer are more often distressed than men [10]. Also, women experience much more psychological stress compared to men who mainly experience stress related to physical dimension [11]. The level of mental stress is also influenced by the type of therapy or lack of it. Patients who undergo treatment experience less stress than those who do not receive any treatment. This is probably due to the hope that any treatment is a chance for more prolonged survival and better health [10].

It is known that for younger women, the diagnosis of cancer is shocking [12] and it is an opportunity to consider mortality. Older women more often approach their diagnoses in a tangible way, related to the expected aging process and other accompanying chronic diseases. In the face of so many challenges for women who have breast cancer and subsequent consequences of treatment, e.g. mastectomy, 20% of patients struggle with depression. Depression has many substrates, and it results mainly from mental stress due to life-threatening situations, the occurrence of pain, dependence on drugs, dependence on other people, the need for repeated hospitalizations, loss of control over life and uncertainty about the immediate future. The patient is powerless and does not influence the course of the disease [13]. Besides, when a woman is diagnosed with breast cancer, and her breasts undergo a physical transformation, it is likely to affect her sexual identity, interpersonal relationships, and self-esteem. Breast cancer deforms the image of a woman's body in her mind, makes her feel unattractive in front of her husband, children, and friends [14].

Women with more confidence, more excellent emotional stability, positive thoughts, and higher self-esteem have higher psychological well-being during the fight against breast cancer [13]. Along with the positive attitude of the patient, the level of anxiety and positive thinking are reduced. Such an attitude of fighting spirit prolongs survival after 5 and ten years from diagnosis in comparison to negative attitudes with the domination of helplessness and hopelessness. Denying, minimizing or avoiding strategies, although often are the way of escape, isolation and spiritual crisis, are very valuable in the primary phase of treatment, especially after surgery - at that time they show strong mechanisms of defense and are a good prognosis for the long–term therapy. Therefore, it is essential to ensure psychological care from the moment of diagnosis. Precise monitoring of negative emotions, especially anxiety and depression, is a crucial element of healthcare, because their intensification may interfere with the results of the treatment [15].

What is the psychological support during treatment?

Psychological methods used during oncological treatment constitute a variety of techniques, sparsely described in the literature. One of them, most often cited by the authors, is cognitive-behavioral therapy, also known as CBT. Its main goal is broadly understood the improvement of the patient's quality of life, achieved primarily by modifying the patient's way of thinking and his behavior. It is based on the belief that emotions or behaviors affect physiological reactions, but this is a two-way action. This therapy includes a range of

therapeutic methods and systems. The vast majority of them using cognitive, multimodal and rational emotive behavior therapy. They are associated with skills that the assumes to help the patient with general copings, such as hypnotherapy, meditation or relaxation training [16,17].

Systemic therapy is another type of methods. Its essence is to focus not only on the patient but also on the functioning of his entire system, which is most often the family or friends. It has great importance for the course of treatment. As reported by literature, close relatives and acquaintances of cancer patients are a primary source of support. They are termed "the primary network," indicating the close emotional relationship maintained between them and the patient. Most often they are spouses or children. In this therapy, the basic idea is the interaction of the disease, the patient and other people in the family. In this case, the analysis of the impact of the current situation on the system and the degree and type of communication between individual members of the system are applied. It is also very important to analyze the willingness of accepting help and giving it [18,19]. During the visit, the participants share their history and the impact of the disease on themselves. A dying woman often concerns about the burden of his close ones, which should be mitigated by the spouse and children by expressing gratitude for what they have received from the patient in the past. Information is also gathered on emotional connections, family conflicts, and problems faced by members. Their solution is emphasized as the basis for improving the family's functioning. Factors complicating life inside the home must be clarified to ensure peace and mutual tolerance within a given system. Systemic therapy is considered to be the one of basic in palliative cancer treatment; however, there is no definitive research to determine how effective it is in improving family functioning, solving problems and preventing psychosocial morbidity [20].

Although oncological patients undoubtedly require and need an individual approach, group therapy is often an effective method. It can play an educational role, but it also helps relieve anxiety, because it allows meeting and conversation with people unrelated to the family who share the same problem. By exchanging experiences, they achieve a sense of mutual support and understanding and acquire friendships that can survive outside formal meetings. In the initial phase of therapy, patients are restrained in describing emotions, but rather they try focusing on medical aspects. But over time, the group reveals more profound thoughts, first of all about changes in the body, fear of death, fear of relapse or the fate of a family deprived of one member. The advantage of this method is its flexibility. The therapist can follow the issues raised by patients. However, it is not free from flaws. Due to the different structure of the group, its participants must abide by the principles of mutual tolerance. The group should be perceived

as a whole; therefore contacts outside the meetings are indicated, but not at the expense of excluding one of its members, which could ultimately worsen the patient's mental state instead of correcting it. The changes in the size and condition of the group, especially with the emotional bonding of its elements, which often takes place with time, play an important role. Therapists must face sudden deterioration of one patient's health and even death, which affects the progress in therapy in other patients [20].

A particular form is the Simonton method, mainly because of its popularity among patients who often identify the term "psycho-oncology" with this technique. This is a therapeutic program developed in 1971 by Carl O. Simonton for people with cancer and their relatives. This American oncologist doctor considered that it is necessary to supplement the traditional oncological treatment. This technique is based on the principles of neuropsychoimmunology and is mainly associated with the methods of "visualization of recovery." The patient during the therapy creates a recovery plan, which includes the closest and most beautiful areas of his life, and additionally analyzes the secondary benefits of the disease [18,21]. Also, the goal of this method is to improve the emotional function of the patient and to strengthen the commitment to treatment. Clinical trials have documented the effectiveness of this program, so it is widely used in oncology centers around the world, also in Poland, and is very popular. Thanks to the initiative of the propagator of this method in Poland, psychiatrist Mariusz Wirga, and Simonton, it is possible to take training in the field of the Simonton Program in several centers [22].

The Rational Behavior Therapy which mainly has the features of self-therapy is close to the previous one. Its basis is the concept that it is not the situation in which the patient is located that leads to the appearance of specific emotions, but his beliefs about these facts. During its duration, patients should focus on ensuring that their thoughts meet the five principles of rational thought defined by Maultsby, and according to the followers of this method, healthy thinking meets a minimum of 3 of them. It should be remembered that what seems to be fit for one patient does not always turn out to be for another. It also leaves the patient free what is healthier to think in a given situation, avoiding lecturing by the therapist. RBT is contained within the current Simonton Program and constitutes its most crucial component, and it is used as a critical procedure in emotional crisis [23].

Therapy based on the principles constructed by M. Erickson is less common. It refers to the conviction that the patient's attention should be focused on the future and the present, departing from the past that can not be changed. The therapist should give the patient hope and

faith in the possibility of changing for the better in the next time. And the patient should imagine how his life will look in the future. This is an original method [18].

The type of method adopted by the therapist should correspond to the needs and characteristics of the patient. During therapy, however, one should not forget about the primary goal, which is the release of emotions, understanding them and improving the mental state of the patient. One should take into account the individual approach, also depending on the type of cancer, phase of the disease (the therapist should have a different attitude towards a recently diagnosed, dying or chronic patient) and support that the patient receives from others.

Summary

With the increase in the awareness of cancer patients associated with increasing access to knowledge over the last 20-30 years, the impact of the disease on their psyche significantly increased. The need for psychological support is confirmed by establishing associations such as the Amazons due to stress occurring at various stages of the disease. It is known that the condition have a negative impact.

Breast cancer can be associated with mastectomy, which means a change in the appearance of the woman and the perception of her femininity. This may involve lowering self-esteem or a sense of lower attractiveness [24]. Depression is an important adverse effect resulting from a mastectomy.

Psychooncology comes to help women with breast cancer and their families. There are various possibilities of psycho-oncological interventions that have been effective in reducing stress and improving the quality of life of patients [25]. Cognitive-behavioral therapy (CBT) based on the interaction of emotions and physiology is one of the options for psycho-oncological treatment. There is also systemic therapy that assumes the functioning of the patient in a relationship with family and friends, where the disease also affects. This is the primary method in the palliative treatment of cancer. Another type of therapy is group therapy, in which participants have the opportunity to contact people in a similar disease situation. It is an opportunity to create friendship, which undoubtedly has a positive, supporting effect. The Simonton method, documented in tests, where the patient analyzes the secondary benefits resulting from the disease. The patient's convictions related to the fact of the condition, not his emotional approach, lies at the basis of Rational Behavior Therapy. Therapy based on the principles constructed by M. Erickson focuses on the patient's future.

It is emphasized that both the source of support and its type (e.g., emotional, material) are consistent with the needs of the individual. It is known that women after mastectomy expect significantly more social support of each type compared to the group of healthy women. Psychooncology as interdisciplinary science has a lot to offer women who need help fighting against breast cancer. The psychological strengthening of the patient is justified by the better results of the healing process. Recovery is the primary goal of modern psycho-oncology [26].

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Knowledge among medicine students from Poland about issuing death certificate

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Introduction

The profession of a doctor is inseparably associated with the phenomenon of death; therefore, the process of issuing a declaration of death is one of the doctor's essential duties. Nonetheless, currently, the medical environment is not proficient in the field of legal acts aimed at protecting relatives of the deceased against refusing or delaying the issuance of a death certificate, even if the exact cause of death cannot be precisely determined. These type of cases occur in practice, which we had the opportunity to observe during clinical work in the hospital wards. A delay in such difficult and demanding circumstances results in additional stress for the family and is undoubtedly an epidemiological and legal problem. Consequently, we decided to explore the subject and examine what the reason of ambiguity is in the scope of the competence to issue death certificates and whether students of medical universities in Poland have adequate knowledge in this matter.

In accordance with the law, doctor-binding regulations for above-mentioned duty are: *Act of 31 January 1959* refers to Ustawa z dnia 31.01.1959 r. o cmentarzach i chowaniu zmarłych - Dz. U. 1959) [1], to which there are several executive regulations. The most crucial of them are: *Ordinance of 3 August 1961* refers to Rozporządzenie Ministra Zdrowia i Opieki społecznej z dnia 03.08.1961 r. w sprawie stwierdzenia zgonu i jego przyczyny - Dz.U. 1961 nr 39 poz. 202) [2], *Ordinance of 11 February 2015* refers to Rozporządzenie Ministra Zdrowia z dnia 11 lutego 2015 r. w sprawie wzoru karty zgonu - Dz.U. 2015 poz. 231) [3]. In addition,

to the rules of death declaration also refer: *Act of 05 December 1996* refers to Ustawa z dnia 05.12.1996 r. o zawodach lekarza i lekarza dentysty) [4], in which it is indicated who can declare the death; *Act of 15 April 2011* refers to Ustawa z dnia 05.12.1996 r. o zawodach lekarza i lekarza dentysty) [5], which describes the steps taken after the patient's death in the hospital; *The Penal Code* refers to Kodeks postępowania karnego) [6], which contains provisions related to the proceedings in the events of the criminal cause of death.

The issue of patient's death is an integral element of the medical profession. Even at the very beginning of a professional career, a young doctor may encounter a situation that obligates him or her to issue a death certificate. Thus, a graduate of a medical university, starting the work as a physician, should have appropriate knowledge on this subject and understanding of its legal aspects.

Aim

The study aimed to compare the knowledge of students of Polish medical universities about issuing a death certificate.

Materials and Methods

The research group consisted of 203 students of medical and dentistry faculties from several universities in Poland. 44.4% of the respondents were students of the Wrocław Medical University, 13.3% of the Medical University of Warsaw, 11.3% of the Medical University of Bialystok, 10.3% of the Silesian Medical University, 9.4% of the Medical University of Lodz. The remaining 11.3% were students of other medical universities. The vast majority (98%) of the respondents were students of the Faculty of Medicine; the remaining 2% were students of the Faculty of Dentistry. 57.6% of the respondents did not yet have classes of medical law, while 42.4% declared that they had completed such a curse during their studies. The majority of the respondents were students of the third year- 37.9%, the second in terms of size were the second-year students - 20.2%, then 5th year - 16.7%, 4th year - 13.3% and 1st year - 6,4%, 6th year- 4.9%, the 1st- year-resident - 0.5%. The research was carried out using the original questionnaire created by the authors, containing 12 questions regarding the knowledge of students on the issuing of death certificates. The survey was conducted online using Google Forms. The criterion for inclusion in the survey was holding the status of a student of faculty

of medicine or dentistry in the medical university of Poland.

Results

This part of the work will present the results of the survey.

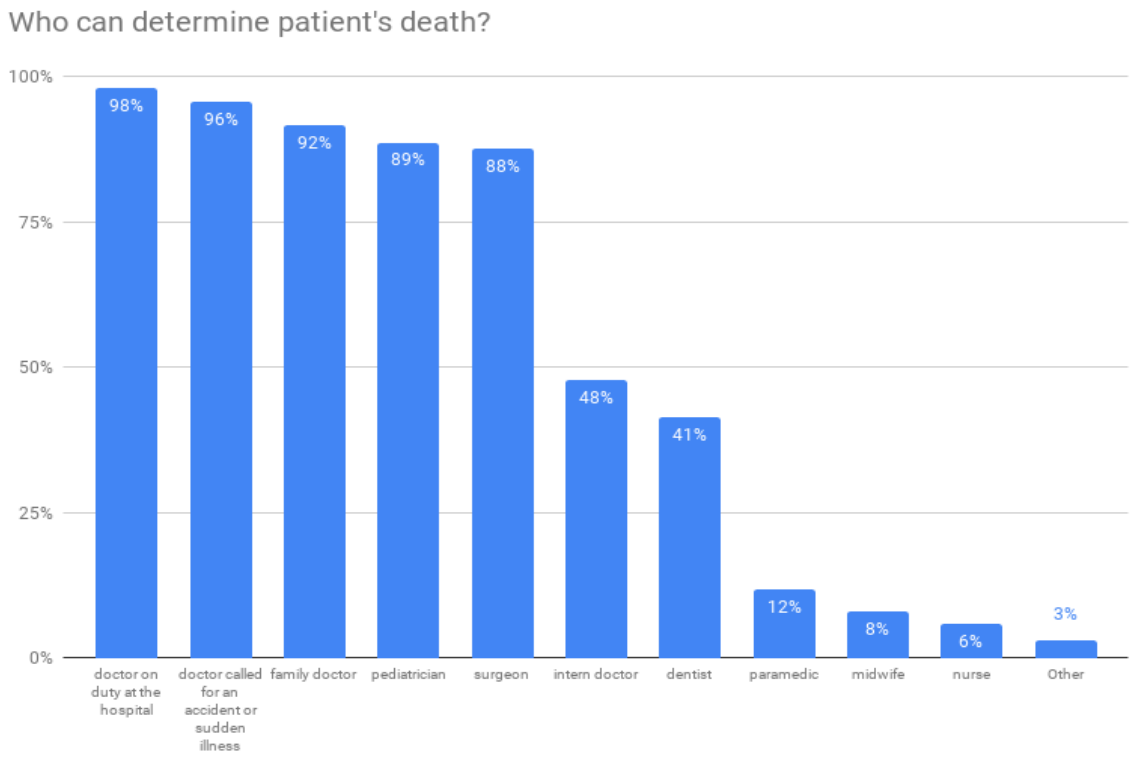

Figure 1. Students' knowledge about the obligation to issue a death certificate

Figure 1 shows the students' answers to the question of who can certify the death. 98% of people indicated the doctor correctly on duty at the hospital, whereas another correct answer - a doctor called for an accident, or sudden illness chose 95.6% of people, a family doctor - 91.6%, a pediatrician - 88.7%, a surgeon - 87.7% , intern doctor 47.8%, dentist - 41.4%. Among the wrong answers, respondents most often marked the paramedic (11.8%), midwife (7.9%) and nurse (5.9%). The remaining answers were chosen by less than 3% of the respondents. Among them, one examined person added the answer 'anesthetist,' which is also correct.

In the survey, we asked students whether the lack of establishing the cause of death or the need to conduct laboratory tests to determine it could be the basis for delaying the issuance of a death certificate. 43.3% of responders answered wrongly 'Yes' (Figure 2), only 32% indicated the correct answer, while as many as 24.6% admitted that they did not know.

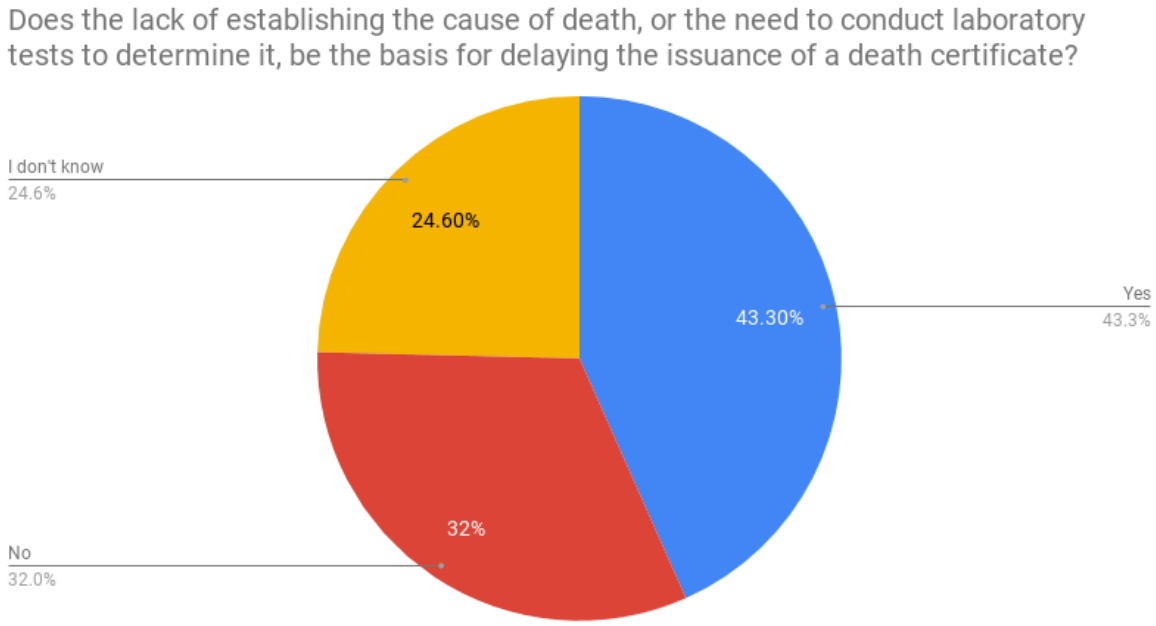

Figure 2. Students' knowledge about possible reasons for delaying the issuance of a death certificate

In the further part of the study, we asked whether, in the case of an autopsy needed, the death certificate is issued before or after the autopsy. Figure 3 shows that over half (50.2%) of the respondents indicated the correct answer (after the autopsy). However, an incorrect answer (before the autopsy) was 49.8%.

The graph presented in Figure 4 shows the students' answers to the question of which the doctor is obliged to issue a death certificate in the first place. More than half of the respondents (66%) correctly stated that this is a doctor, who last provided medical care to the patient in the last 30 days. 15% of the respondents incorrectly indicated the family doctor under whose care the patient is at the time, and 18% chose an emergency care physician.

Figure 5 shows the differences in the answers of students before and after the course in medical law to the question of which doctor is required to issue a death certificate in the first place. Among people after the course in medical law correctly responded as many as 80% of the respondents - a doctor who during the last 30 days gave medical services, and wrong answers were given by a total of 6% of the respondents in this group. In the case of students before the course of medical law, the number of correct answers was just over half (53%). 28% of the respondents answered the family doctor under whose care the patient is being looked after, and 19% - the emergency care physician.

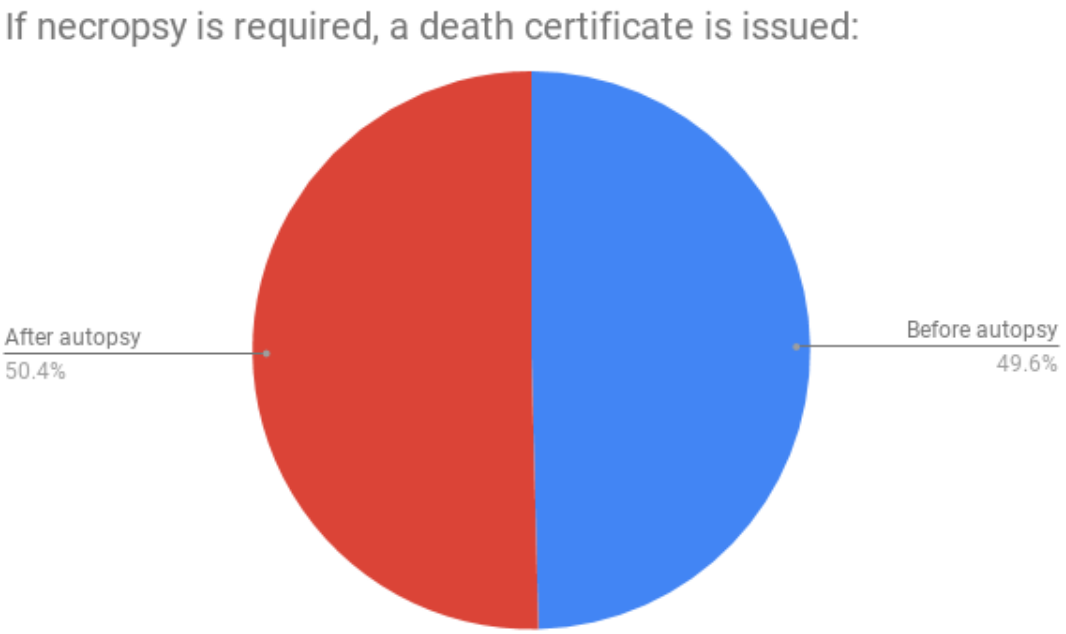

Figure 3. Students' knowledge about the legal connection of issuing death certificate and autopsy

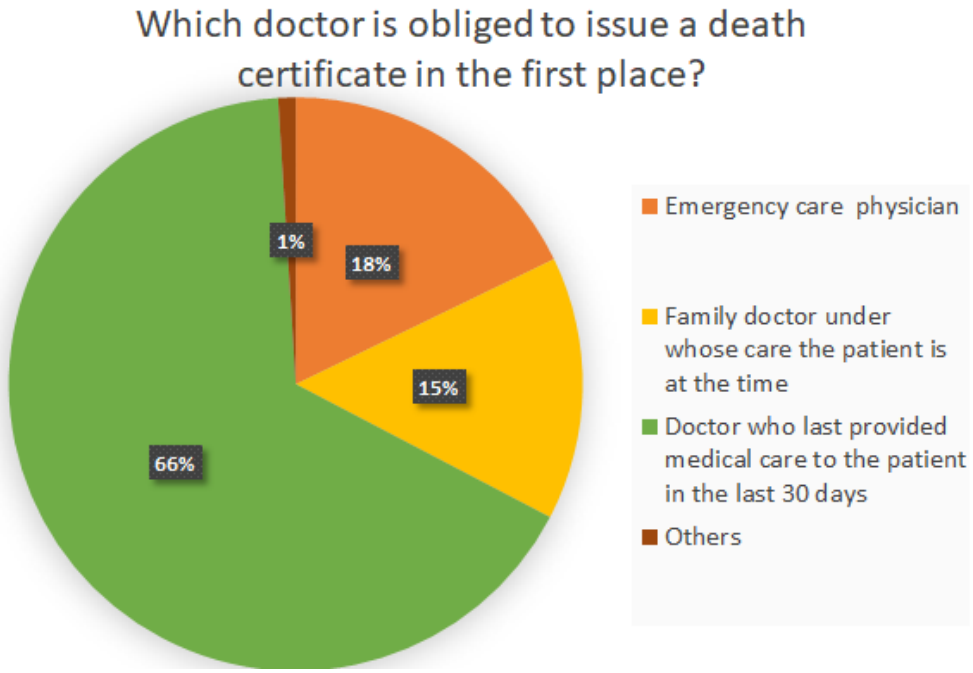

Figure 4. Students' knowledge about the physician obliged to issue a death certificate in the first place

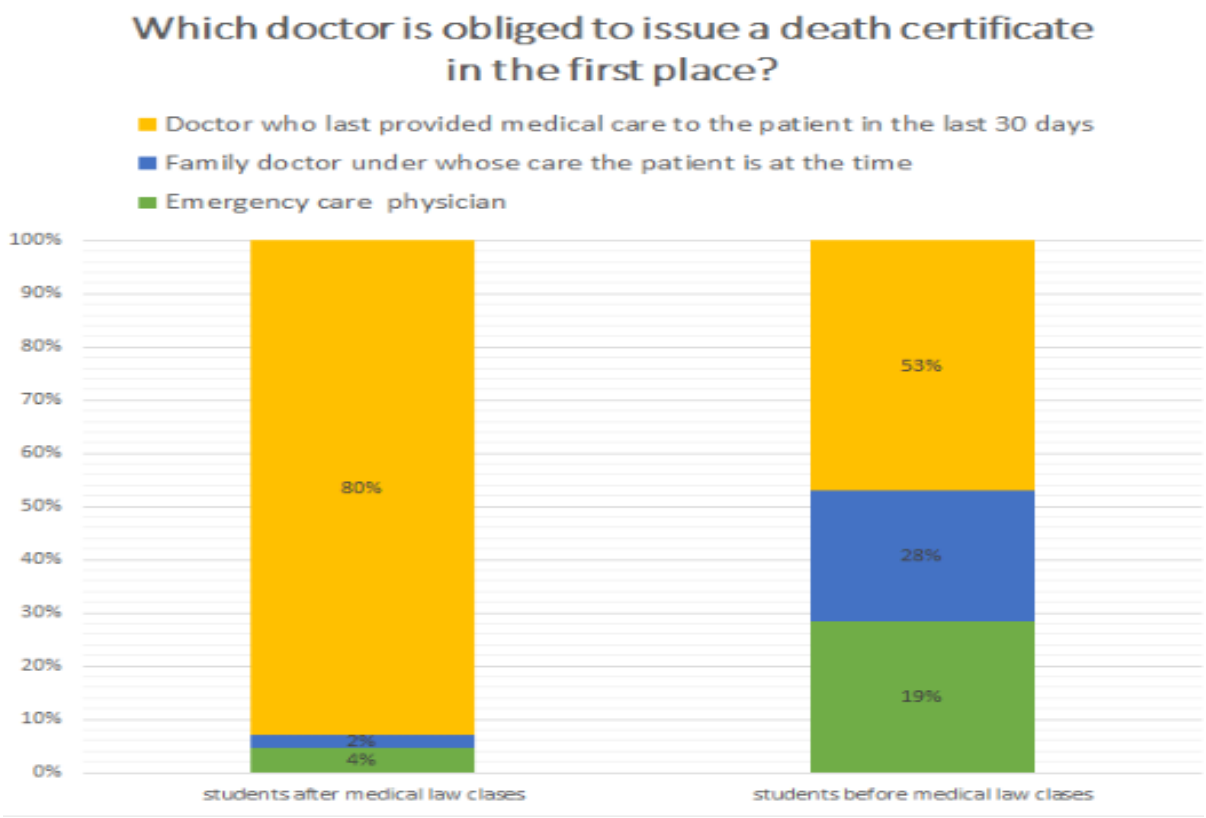

Figure 5. Students' knowledge before and after the medical law course about a physician obliged to issue a death certificate in the first place in case of finding certain signs of death

In the question presented in Figure 6, we asked who is obliged to issue a death certificate in the situation when there is no doctor responsible for that in the first place. The vast majority of the respondents indicated the incorrect answer - a doctor who stated death, being called to an accident or sudden illness (83.3%), as well as a policeman present at the scene - 2%. Correct answer: the coroner - a doctor appointed to declare death by a locally competent starost (is a Polish local government officer) - chose only 38.4%.

In the next question, the results of which are described in Figure 7, we asked whether the obligation to declare death automatically connects with the obligation to issue a death certificate. Just over half of the respondents (56.7%) correctly answered that the obligation to declare death was not automatically linked to the obligation to issue a death certificate. However, other respondents indicated an incorrect answer (22.2%), or admitted to lack of knowledge in this subject (20.7%).

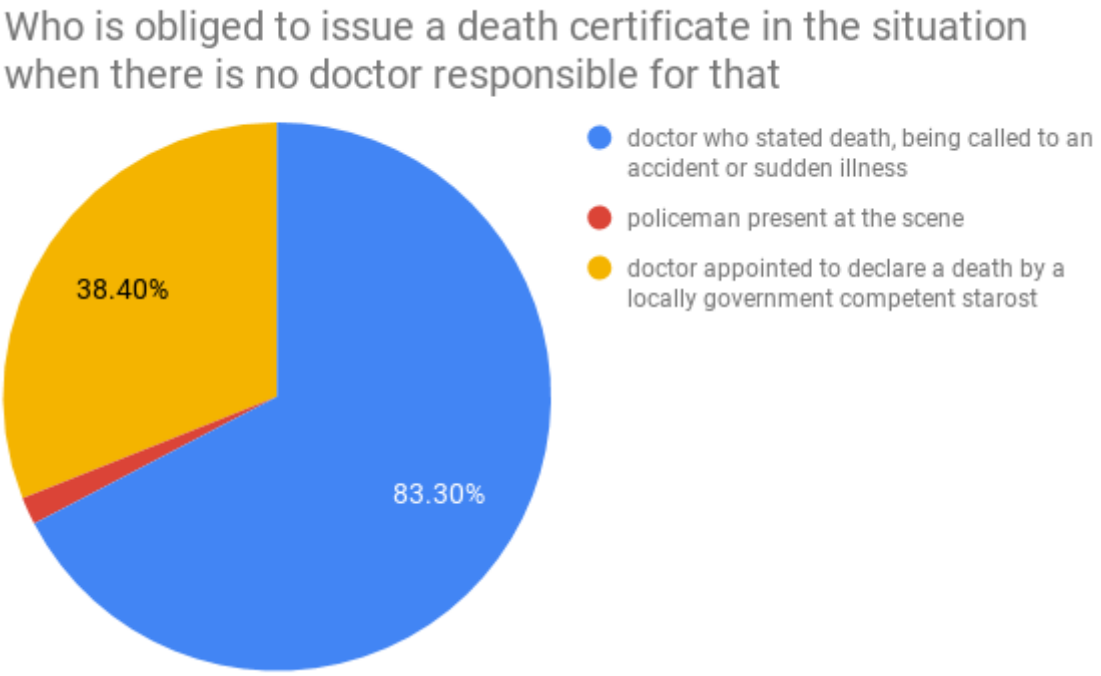

Figure 6. Students' knowledge about the order of doctors responsible for issuing a death certificate

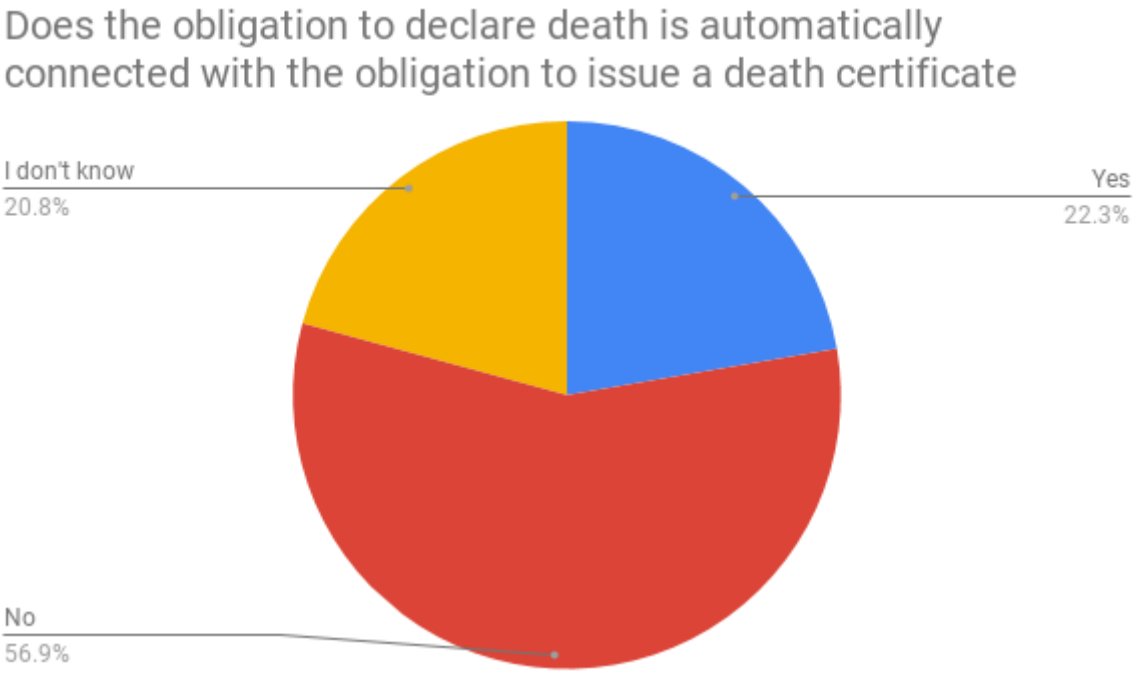

Figure 7. Students' knowledge about the connection between declaring the death and issuing a death certificate

The question presented in Figure 8 showed that 45.5% of people think wrongly that the National Health Fund is financially responsible for issuing a death certificate. Another opinion is tipped by 25.2% of respondents - 'ZUS' that is The Polish Social Insurance Institution. Only 22.3% of the respondents knew the correct answer - the district (that is *starost* - is a Polish local government officer - local government officer).

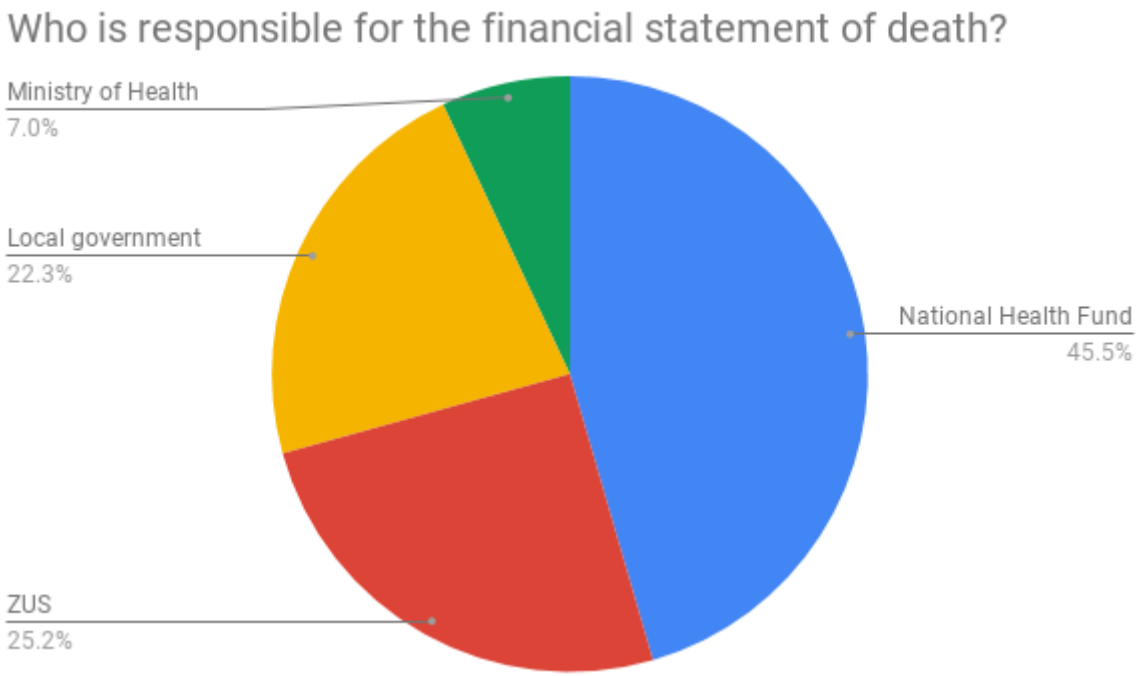

Figure 8. Students' knowledge about financing issuing death certificate

As it is presented in Figure 9, the majority of respondents - 91.6% - answered correctly that a paramedic does not have to carry out resuscitation activities for a person who is undoubtedly already dead (for example an accident with a victim without a head). 5.4% of the respondents answered that paramedics are obligated to start such proceedings . The other people did not know the answer.

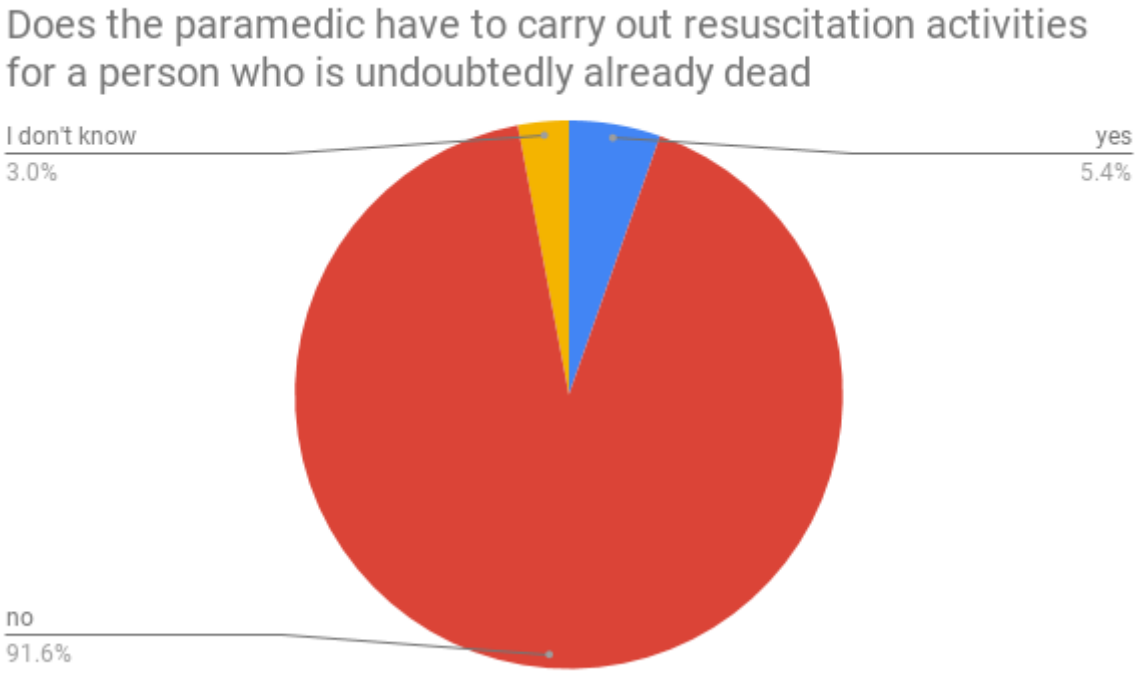

Figure 9. The students' knowledge about medical help in the case of undoubtedly dead patients

The next questions referred to individual cases. In Case No. 1: the emergency medicine doctor with the ambulance team was called to the patient who had a sudden cardiac arrest. A resuscitation action was undertaken, but the physician gives it up, stating that the criteria for ineffective resuscitation are met. The question was whether in this case the doctor is required to issue a death certificate. According to the answers presented in Figure 10, it appears that less than half of students correctly think that he is indeed required to do so - 45.8%, while 29.1% say incorrectly that he is not. 25.1% of respondents did not know the answer to this question.
In the 2nd case: the rescue doctor with the ambulance team was called to the victim of a road accident. Resuscitation action is not undertaken since the doctor has found certain signs of death. The question was as it follows: is the rescue doctor obliged to issue a death certificate in such a situation? As it is shown in Figure 11, only 38.9% of students chose the correct answer - he is not obliged to do so, but a similar number of people (37.9%) answered the opposite. 23.2% of respondents declared they did not know. Analyzing the answers to this question, we divided students according to the criterion of undertaking a medical law course during study. We presented the results in Figures 12 and 13.

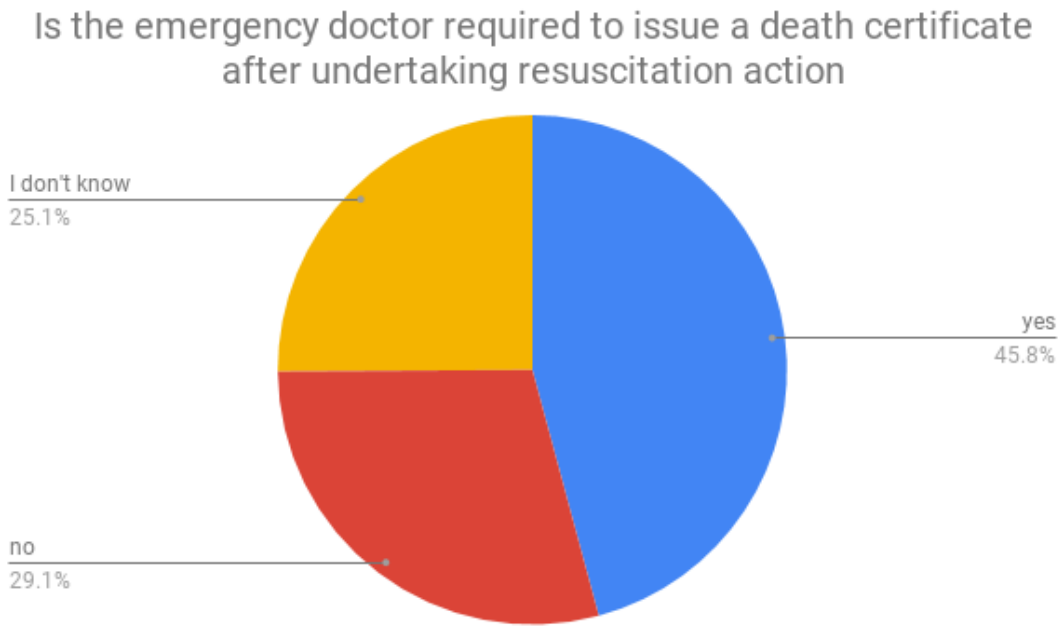

Figure 10.Students' knowledge of the obligation to issue a death certificate by an emergency medicine doctor in case of performing CPR

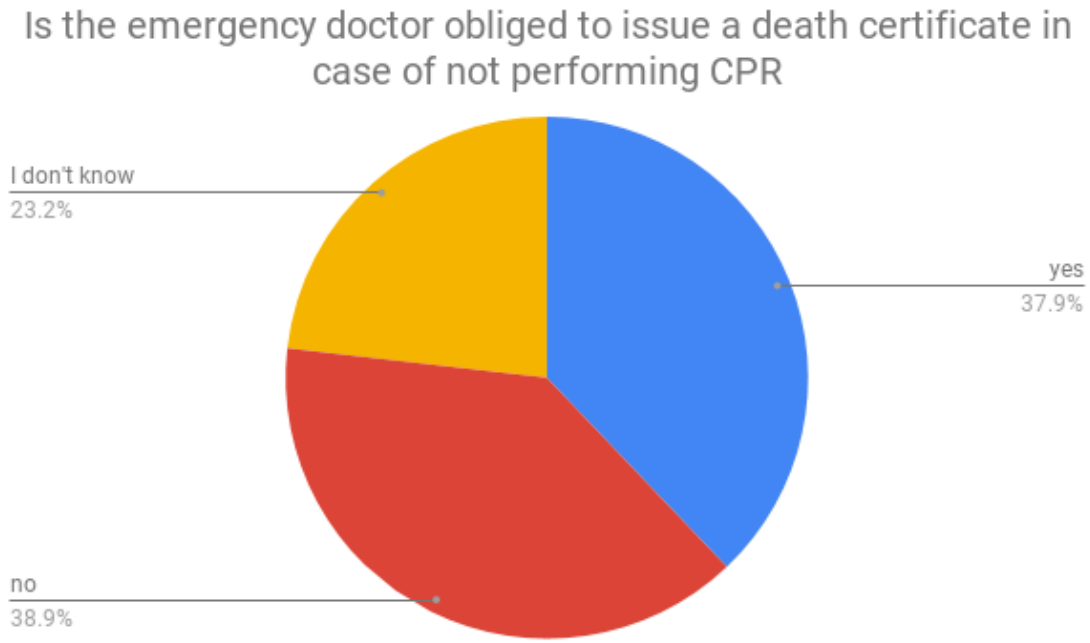

Figure 11. Students' knowledge about obligation to issue a death certificate by an emergency doctor in case of not performing CPR

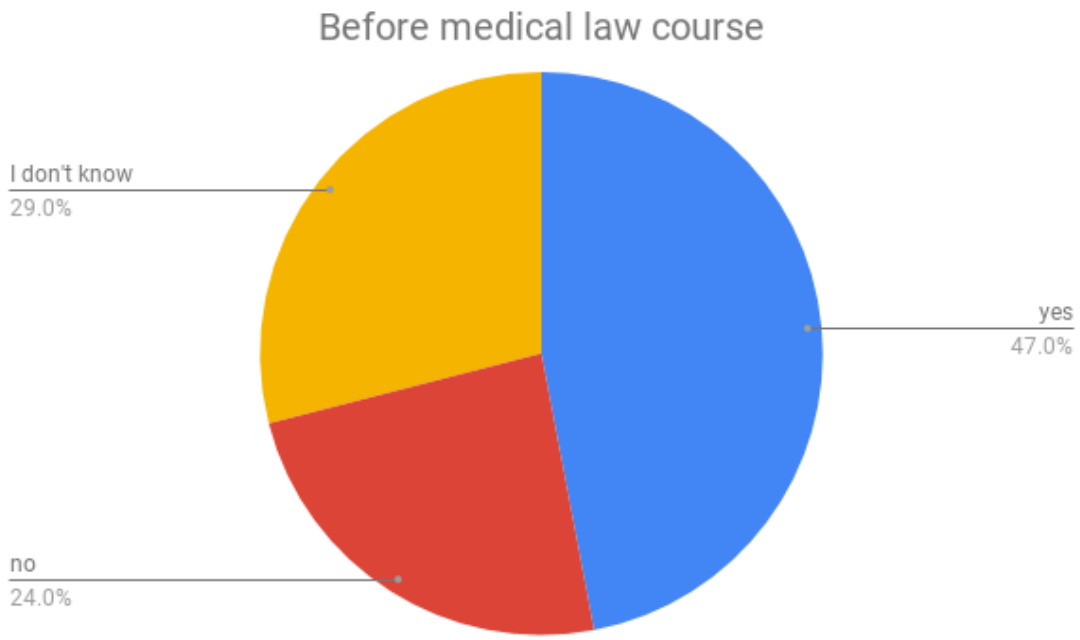

Figure 12. Students' knowledge before the medical law course about the obligation to issue a death certificate by an emergency medicine doctor if they find certain signs of death

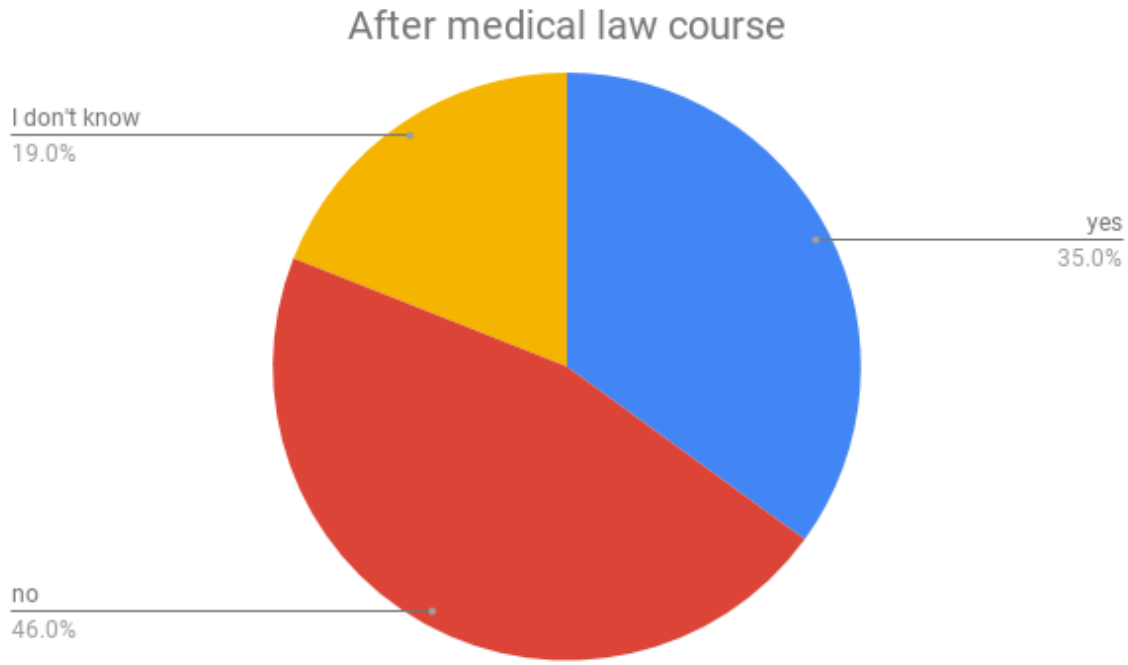

Figure 13. Students' knowledge after the medical law course about the obligation to issue a death certificate by an emergency medicine doctor if they find certain signs of death

Among people before the course in medical law, 24% of the respondents answered correctly, the wrong answer was 47%, while 29% of respondents did not know the answer to this question. In the case of students after a course in medical law, the number of correct answers was almost twice as high and amounted to 46%. 35% of the respondents gave an incorrect answer, and 19% admitted to lack of knowledge on the subject.

In the next question, we asked the students, whether in the situation presented in Case 2, the general practitioner, who has been taking care of the patient recently, can issue a death certificate on the basis of a post mortem examination performed by an emergency medicine doctor. Figure 14 shows that less than half (45.3%) of the respondents indicated the correct answer (yes). On the other hand, 23.2% responded negatively. As many as 31.5% of respondents admitted that they do not know the answer to this question.

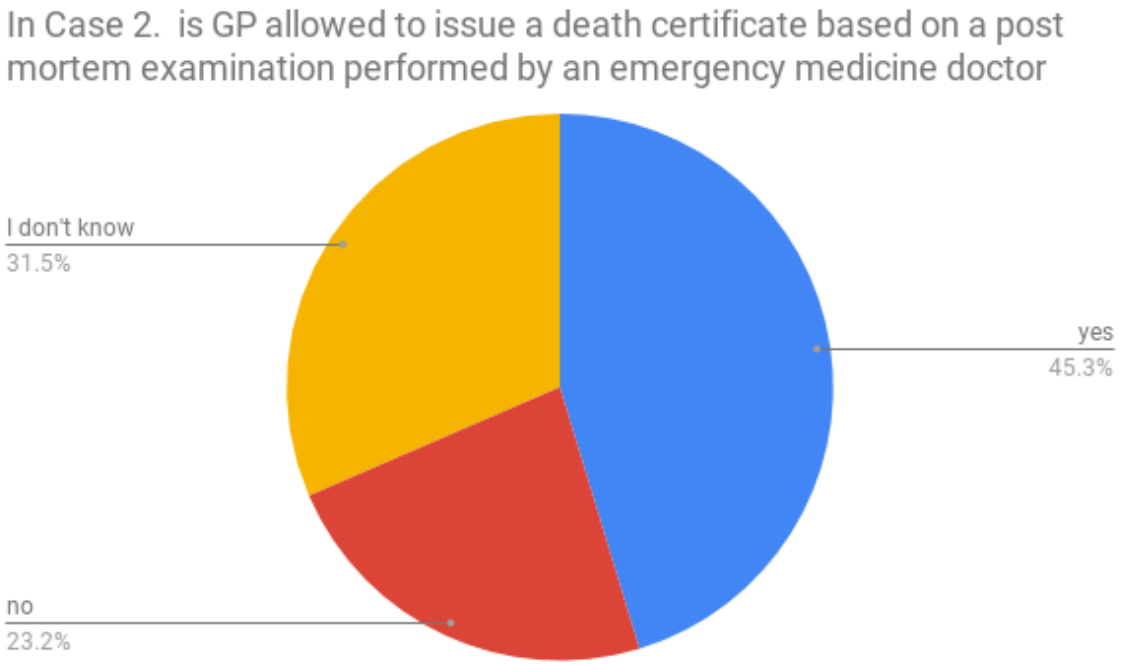

Figure 14. Students' knowledge about the possibility of issuing a death certificate by a general practitioner based on a post mortem examination performed by an emergency medicine doctor

Figure 15 shows students' answers to the question of who is required to issue a death certificate in the 2nd case, if there was no general practitioner taking care of the patient recently or the doctor was more than 4 km away from where the body is located or because of illness or for other important reasons or he could not fulfill this obligation within 12 hours of calling. Only 35.1% of people correctly marked a coroner - a doctor appointed to declare a death by a

locally competent staroste - is a Polish local government officer. Among the wrong answers, the respondents chose: another general practitioner / physician expert called to look after the corpse at the accident site - 39.6%, the emergency medicine doctor - 25.2%.

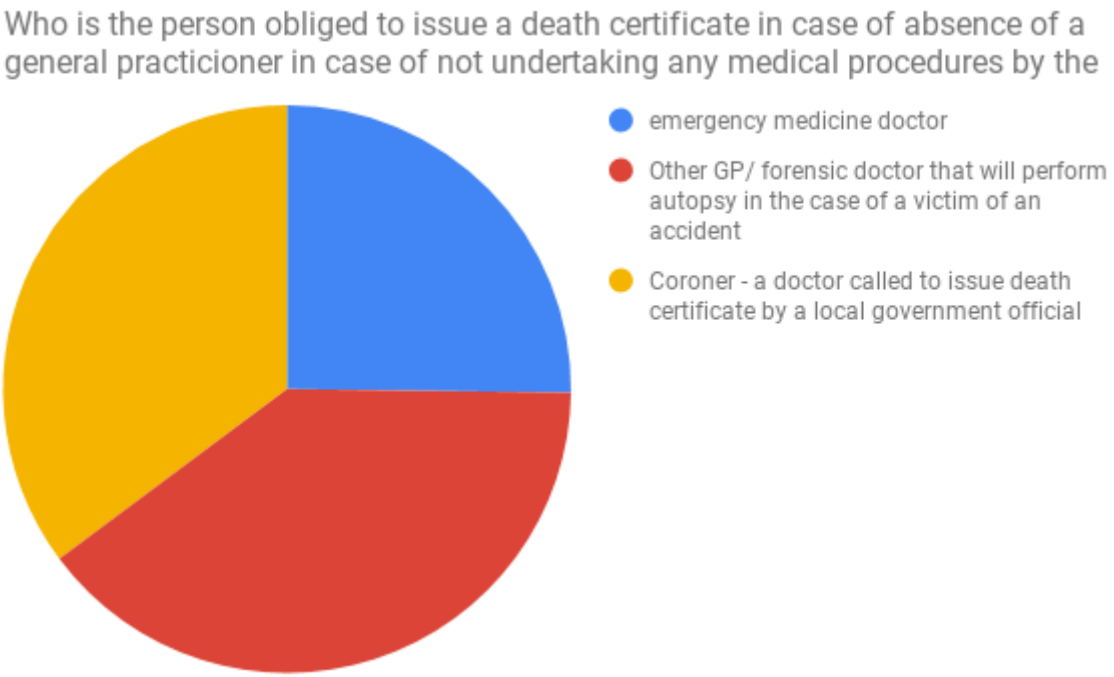

Figure 15. Students' knowledge about the person obliged to issue a death certificate in the absence of a general practitioner in a situation where the rescuer doctor has found some signs of death

Discussion

The subject of issuing a death certificate is currently a significant problem in the healthcare sector. Each doctor will encounter the patient's death and obligation to issue the death certificate during her/his medical practice. Therefore, it is essential that students, who graduate from medical universities, have sufficient knowledge on the subject, as they start their professional career in medical practice immediately after graduation. Ignorance of the law in situations related to the death of another person harms not only the doctor but also the family of the deceased. Knowledge of legal regulations, therefore, protects the doctor against misunderstandings, shame and, ultimately, the trial. On the other hand, the family of the departed is allowed adequate and appropriate mourning.

The aim of our work was to examine the level of knowledge of students of medical universities in Poland on the legal aspects of issuing a death certificate. The study covered 203 students from various medical universities in Poland.

The results of our survey showed that the majority of students correctly indicated which doctors can issue a death certificate. Only 2.5% of the respondents gave the wrong answer - a policeman. This indicates a satisfactory knowledge of the law in this area.

In the survey, the respondents were also asked whether the lack of establishing the cause of death or the need to conduct laboratory tests to determine it, may be the basis for delaying the issuance of a death certificate. As many as 43.3% of students gave an incorrect answer. On the other hand, 24.6% of respondents did not know the answer. This indicates bad knowledge about issuing death certificates in unclear, dubious situations that require additional tests to confirm the cause of death. Such tests cannot cause burial delays, which could be emotionally difficult for the deceased's relatives. However, in the next question, almost half of the respondents correctly answered the question whether the death certificate, if a necropsy is necessary, is issued before or after the section. This indicates a greater awareness of students about the connection between autopsy and issuing a death certificate. It may be connected with the fact that students take part in autopsy during classes.

34% of respondents mistake only answered the question of which the doctor is obliged to issue a death certificate in the first place. Essential for us was to compare students' knowledge depending on whether they had already completed a course in medical law. Among people after the course in medical law correctly answered up to 80% of the respondents - the physician obliged to issue a death certificate in the first place is a doctor who during the last 30 days gave medical benefits to the patient. In the case of students, who have not taken a medical law course yet, the number of correct answers decreased to 53%. Unfortunately, the lack of appropriate knowledge in this matter may be associated with moral problems. For example, the body of the deceased will have to 'wait' until the appropriate doctor issues a death certificate, and until that time the burial activities will not be allowed to begin. These situations usually have a negative impact on the deceased's family. There are stories in the media where, after the death of a loved one, the family was forced to wait for the appropriate doctor to fulfill this obligation [7]. This results in a bad reception of healthcare in society.

In the next question, the respondents were asked who is, in the absence of a doctor who in the last 30 days gave medical services to the patient, obliged to declare death and to issue a death certificate. Most of the students answered the question wrong, which may indicate that

they do not demonstrate legal knowledge in this area. Only 38.4% of the respondents chose the correct answer - a coroner - a doctor appointed to declare death by a locally competent staroste.

However, we are not surprised by insufficient knowledge of students on this subject, because doctors appointed as coroners function only in a few districts in our country.

Satisfactory is also the information that more than half of respondents (56.7%) correctly answered that the obligation to declare death does not automatically connect to the obligation to issue a death certificate. However, about 1/5 admitted to a lack of knowledge in this area. At this point, it should also be noted that there is no definition of death in Polish law. Therefore, there are many doubts as to whether a doctor diagnosing a death should be identified with a doctor only diagnosing death, or a doctor both declaring death and issuing a death certificate.

Another issue that we addressed in the survey was the problem of the financial aspect, which is connected with the declaration of death. Most people answered incorrectly. Only 22.3% of the respondents chose the correct answer - district, and that is a local government officer. Establishing death is an integral element of medical work, and every work should be paid. Therefore, education on this subject should not be neglected in medical law classes. Such knowledge lies in both the interest of the doctor and the medical student as a future doctor.

The vast majority (91.6%) of respondents correctly indicated that an emergency medicine physician is not obliged to help a person who is undoubtedly dead. This is a satisfactory result. Then we asked the two next questions in the form of cases to check the knowledge we study in specific situations the most properly. Both questions concerned situations that seemed almost identical - the rescue team along with the emergency medicine doctor is called to the patient. The only difference between cases is the fact of providing health services. In Case 1 the patient died during the resuscitation. However, the rescue team no longer attempts to resuscitate the patient; therefore the emergency physician will not be the last person providing health services. This results in a legal difference regarding the competence to issue a death certificate. In the first case, an emergency medicine doctor is obliged to issue it, while in the second case he prepares only a post-mortem examination document, based on which the physician, who had provided health services to the deceased within the last 30 days, issues a death certificate. Such a complicated situation can create many difficulties, take additional time and result in an additional bureaucratic obligation. As our survey showed, also for medical students the answer to the question, whether the emergency medicine doctor is obligated to issue a death certificate, was not visible. In Case 1 the correct answer was given by 45.8% of respondents, but about 25% admitted that they did not know. Only 38.9% of respondents marked the right answer regarding Case 2. We are however content that the medical law course, which students of

medical faculties take, apparently increases the number of correct answers. In Case 2, 24% of students who did not have classes in this subject answered correctly, and almost twice as many (46%) of respondents who have already taken the medical law course. Also, the number of respondents answering 'I do not know' decreased from 29% before the medical law course to 19% after it. Thus, we can see that although the level of knowledge in this matter is still not satisfactory, the education of future doctors is critical.

What is more, the students were not able to find out who in the situation of death, described in Case 2, should issue a death certificate. Only 45.3% of responders marked that it is the duty of the family doctor, whose patient has recently been the deceased, and almost ⅓ admitted that they did not know. If the general practitioner is not within 4 km or because of other reasons cannot fulfill this obligation within 12 hours from the moment of summoning, the coroner issues the death certificate - a physician appointed to declare death by the locally competent government officer. Only 35.1% of respondents answered this question correctly.

However, this should not come as a surprise, because coroners are appointed only in some districts in Poland. In the absence of a person holding the function of a coroner in a given poviat (administrative unit), the law does not specify who is required to issue a death certificate in the next step. In practice, this often results in a police officer searching for a doctor near the scene of the incident that will issue the death certificate. Our law on issuing a death certificate is, as we can see, intricate and raises doubts also among the practicing emergency and family doctors. For the last few years, there was an argument between the medical and political environment about finding out who is the 'last doctor' indicated to fulfill this obligation. There were many parliamentary questions to the Minister of Health with a request to clarify the mentioned issue and determine the current position [8]. We included the reached conclusions in the presented results.

Insufficient knowledge of law among medical students should not be surprising given the complexity of legal acts. The leading cause of misunderstanding and ambiguity is the fact that the available legal provisions that are said on this subject are non-uniform and outdated. This makes the issuing of a death certificate by a physician problematic. The most important legal act regulating the rules of issuing a death certificate is the Ordinance of 3 August 1961 Ordinance refers to Rozporządzenie Ministra Zdrowia i Opieki Społecznej z dnia 03.08.1961 r. w sprawie stwierdzenia zgonu i jego przyczyny (Dz.U. 1961 nr 39 poz. 202) [2], which is an executive regulation to the Act of 31 January 1959 refers to Ustawa o cmentarzach i chowaniu zmarłych) [1]. Both of these documents are obsolete: the first of them is from 03 .08. 1996, and the Act - 31. 01. 1959. As we can see, both documents are over 50 years old, and more and

more recent amendments introduced only minor changes, which caused only a lot of ambiguities. For example, in the Ordinance of 3 August 1961, 'rural midwife' (refers to the occupation of' położna wiejska") [8] is indicated as a person who can determine death. Also, there is a 'gromada' (is an obsolete administrative unit that existed in Poland in the past) in the legal files [9]. However, both 'gromada' and 'położna wiejska' are terms that do not exist today. 'Gromada' is the name of an administrative unit that has not existed since 1972 [10]. The uncertainties in the provisions above concern not only who has the rights or the obligation to issue a death certificate in a given situation, but also who bears financial responsibility for activities related to the declaration of death. Declaration of death does not belong to health services financed from public funds, so the National Health Fund ('NFZ') cannot be burdened with its costs. The deceased's family cannot be charged with them either. The Ministry of Health indicates the administration unit ('powiat'), that is, the proper local government officer ('starosta'), as the person has the obligation to cover these costs. At the same time, no uniform legal regulations are stipulating the principles and mode of financing the dying declaration, as well as the rules of remuneration for doctors in connection with the death declaration. Another problem is the situation in which a doctor who is obliged to declare the death is absent. The best solution would be a 'coroner,' that is, a doctor authorized to declare the death, which would work for the local government. Many institutions, including the 'Porozumienie Zielonogórskie' (is a federation of health care employers' associations in Poland) [8,11,12], repeatedly demanded the establishment of such an organ. However, this was not done. Some of the local government's organs and cities have appointed coroners themselves, but there are no sources for financing them [13]. In 2013, the Supreme Medical Council ('Naczelna Rada Lekarska' - is medical self-government associating and representing doctors in Poland) requested the then Prime Minister to update and harmonize legal acts in this matter [10]. However, this request has not been fulfilled so far.

Nowadays, thanks to the available possibilities and broad perspectives of work outside the country, more and more young doctors decide to emigrate. That is why knowledge of the law in other countries also becomes indispensable.

In England, the law related to issuing a death certificate and declaring a patient's death is relatively similar to the Polish one. In the case when the patient is suffering from a deadly disease, the doctor called to the deceased, as in Poland, is the doctor who provided him with the last health benefits. The difference has occurred since the last contact with the patient. In Poland, this period is 30 days, while in England it is 14. In England, the majority of death cards are issued by coroners [14,15].

The situation is similar in the Latin American countries, such as Mexico or Uruguay. There are three situations in which the clinician physician was caring for the patient is required to issue a death certificate. These are the following cases [16,17]:

- Death as a result of an emergency - when the doctor provided health services to the deceased in the last 24 hours;
- Death as a result of a chronic disease - when the doctor has provided health services to the deceased in the last seven days;
- If the death was the result of chronic illness and the attending physician provided health services to the deceased at any time, he may issue a death certificate, provided that there is no suspicion of a crime or sudden death resulting in additional illness.

This obligation applies to every doctor providing health services, both a specialist physician and a family medicine doctor, a doctor who conducts a patient or a doctor on duty. Ideally, when he is the medic who was the last to provide health services to the patient. In other situations, such as death as a result of an accident or the death of a patient, in which the authorized person (doctor) did not provide health services, a death certificate may only be issued by a forensic doctor.

In Spain, the law does not specify in detail who should issue a death certificate, which causes frequent misunderstandings and leaving this duty to family medicine doctors. According to the current regulation [18], it is supposed to be a doctor who provided health services to the deceased in his last illness or any other doctor who can examine the patient and declare the death. Despite everything, a physician abstains from issuing a death certificate, explaining that he had no professional contacts with the deceased, which leads to the case being taken over by the forensic physicians, exposing the organs responsible for the additional costs of autopsies and stress for the family. In order to prevent this, the relevant institutions came to an agreement defining the physicians' competence to issue death certificates in individual situations.

According to it, in the case of non-hospital death, emergency medicine doctor or emergency room doctor only assesses whether there are marks of sudden or suspected death. In the event of their absence, issue a document based on which the family doctor issues a death certificate within 24 hours. However, if a visit to the primary care practitioner is not possible during this period, the death certificate is issued by the rescuer, even if the first contact with the deceased was after his death. This detracts from Polish standards, especially in the sensitive situation that we asked about in the last points of our survey. As we can see, the separate approach used here and leaving more freedom to interpret the law can also bring positive effects to the patients.

The subject of death is reluctantly discussed, which may be the cause of ignorance of the law.

However, it should not be an excuse for ignorance. Everybody can encounter the death of another person - as a witness of an event, as a loved one of the person who died. Alternatively, just as a doctor in the future. That is why continuous education in the area of issuing death cards is so vital.

Conclusions

- Students of medical universities in Poland have some knowledge about the legal aspects of issuing death certificates, however, this knowledge is incomplete and insufficient.
- Universities should provide an appropriate level of medical law classes so that the graduate starts her/his professional career with sufficient knowledge that is necessary in medical practice.
- The intricacy and vagueness of legal acts regarding death certificates is a common problem not only among students, but also doctors.
- Ignorance of the law is harmful. Knowledge of legal acts not only protects the doctor against embarrassment and the possible legal process, but also allows the deceased's family to adequately go through mourning.
- Poland is not the only country struggling with the complexity of law in the field of issuing death certificates.

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Social responsibilities imposed during treatment of homeless patients in Poland

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Each of us has his or her idea of homelessness. Some associates it negatively; in others, it arouses empathy, many people in the homeless see the image of liver failure and defeated ambition, while others see in them the accumulation of problems and also helplessness. Whose assumption is the correct one and what is "homelessness"? Let us begin our reflection on homelessness by explaining the term.

Homelessness can be understood literally, and also metaphorically or symbolically, presenting the home as one's place in the world. It may also be describing a lack of a sense of bond, love or family. According to the PWN Encyclopedia, it is a social phenomenon which defines lack of a home or a place of permanent residence that guarantees an individual or family a sense of security; providing shelter from adverse weather conditions and satisfying basic needs at a level considered adequate in a given society [1]. An outstanding expert on the subject, prof. Andrzej Przymeński distinguishes the narrow and broad understanding of this concept. In a narrow sense, homeless people are permanently deprived of the possibility of satisfying housing needs in a given society; it includes so-called "street" homeless and those using different types of facilities for the homeless. It talks about people who have to reside in conditions considered below the universally accepted standard [2]. There is also a legal definition of homelessness contained in the "Act on Social Assistance." According to the above act, homeless is a person without a permanent home or flat, as well as a person with permanent residence; however, being unable to live there [3]. The topic of this work is the problems encountered by homeless patients

undergoing treatment process, and these problems, in the most significant and characteristic way, can describe the problem of homelessness - therefore to such a group we will limit our considerations.

Knowledge about the scale of the problem of homelessness is a necessary basis for taking further actions leading to the reduction of its adverse social effects and for providing a reference for the shaping of social policy. Due to the nature of this phenomenon, it is difficult to estimate its scale accurately. The Ministry of Family, Labor and Social Policy undertakes this effort cyclically. A nationwide survey of the number of homeless people was carried out on a winter night from 8 to 9 February 2017, when the vast majority of homeless people could be found in shelters for homeless people, stations and other places providing shelter and heat. This data estimates the number of homeless people in Poland at the level of up to about 500,000 people; however, these calculations may be not precise enough, especially as they lack a specifically defined definition of the phenomenon or counting method. The most reliable data give the number of homeless people to be around 33-35 thousand [4,5,6].

The vast majority are men (83.5%). The most numerous group represent people aged 41-60 (48%). The leading cause of homelessness was eviction/removal (45%) and family conflict (36%). 40% of homeless people are educated at the vocational level, and over 30% have had only primary education. During the study period, 80% of the homeless stayed in institutionalized places [6,7]. The most recent survey took place in February 2019. However, at the time of writing this article, detailed data was not yet available [8]. In the United States, the number of homeless people is estimated at around 550,000. This accounts for less than 0.17% of the population. For comparison, in the European Union it is about 0.08%, and in Poland less than 0.09% [9,10,11]. Reports FEANTSA (European Federation of National Organizations with Homelessness) underline the prevalence of men among homeless people [12]. It was observed at 65-85% depending on the country. The highest number was noted in Italy -at 87%, and the lowest in Sweden (62%) [13]. These statistics coincide with the situation in the US, where the ratio of homeless men exceeds 60% [11,14]. In Poland, as in the European Union and the USA, the largest age group is made up of people aged 31-50 [11, 12].

Regardless of geographical location, homeless people are representing the poorest social layer. Their primary sources of income are social support and material gathering (metal, glass, paper) [6,13].

Thinking about the causes of homelessness, it is easy to conclude that identification of

obvious causes is quite hard. Instead, it is the coexistence of many critical events in human life, which in turn lead to exclusion [15]. The professor mentioned earlier, Andrzej Przymeński emphasizes that factors causing homelessness to interact with each other, and in reality, they cannot be considered separately [2].

One of the more accurate definitions of the causes of homelessness is quite a distinctive macro and micro-social factors. Macro-social factors are a reflection of the socio-economic situation and therefore determine the existence of homelessness in general, while micro-social factors determine who is most vulnerable to it. The most frequently mentioned macro-social factors include the general socio-economic situation in the country, unemployment, the adverse situation in the labor market, poverty, inefficiency of the social welfare system, the lousy situation in the housing market, errors in the rehabilitation process and post-penitentiary care. The most critical micro-social factors include domestic violence, permanent breakdown of the relationship between people, divorce, being an orphan, rejection by close relatives, personality disorders, crime and substance addiction [2,16,17].

Determining the causes of homelessness is often difficult due to personality traits of the homeless and how they perceive their destinies. From a psychological point of view, it is better for a homeless person to see the situation from a non-personal point of view. It reduces the feeling of guilt and helps to overcome life's hardships because homeless people do not feel responsible for creating a problem, but instead, they feel responsible for solving it [15].

Many of us thinking about a homeless person have a picture of alcoholism and other mental disorders in front of their eyes, but is this the right thing to think? Due to insufficient of the research, alcohol as a cause for homelessness, cannot be positively determined. Alcohol is there and virtually ever-present, but we cannot say for sure whether it does cause homelessness or is instead an effect of it. Note that homeless people themselves point out, alcoholism is one of the leading causes of their homelessness problems, but it seems the problem of addiction becomes a significant risk factor when it overlaps with other problems of the individual. The concept of "homeless by choice" can legitimately be applied in a narrow scope and its overuse could obscure the essence of the problem of homelessness [5, 18,19].

Due to their complicated life situation or addictions, health issues of homeless people are often being put on the backburner. Due to the low socio-economic status, the incidence of diseases is much higher than in the general population. [20,21,22].

People staying in shelters are usually in better health than people after a long period of life on

the street. It is associated with a low level of hygiene, malnutrition, long-term stress, lack of sufficient protection against low temperatures or alcohol abuse. According to a survey conducted in Silesia, 1/3 of homeless people admitted to the hospital were dressed in filthy clothes, and 41% of these admitted showed evidence of malnutrition. Due to low temperatures and inclement weather, the health of the homeless is getting worse, as evidenced by the most significant number of hospitalizations from October to April [23,24].

The most common health problems of homeless people include parasitic and infectious diseases of the skin such as scabies, lice, and fungal infections. Homeless people are the reservoir of these pathogens, which is promoted by a low level of personal hygiene. In young people, injuries resulting from beatings such as fractures of the limbs and head traumas are also frequently caused by alcoholism or epileptic seizures. An equally important problem is lower extremity sores caused by nicotinism, poor diet, and consequently atherosclerosis and ischemia of the lower limbs. Their treatment requires a long time, constant and comprehensive care, and sometimes requirement for a person to change dressings by themselves, which for the homeless is a significant, often impossible challenge. The diseases more prevalent than in the non-homeless population include mental disorders, schizophrenia, depression, cognitive limitations, nicotinism, alcoholism, spine disorders, gastrointestinal tract, disorders, tuberculosis, HIV infection, syphilis, and periodontal disease [2,20,25,26].

A significant therapeutic challenge in homeless people is being presented by diseases such as hypertension and diabetes, which are very hard to control in a stable and long-term manner due to low compliance and insufficient access to medicines. This is a significant problem because, as US research shows, 40% of homeless people are chronically ill. Point to note; despite the above data, it cannot be concluded that homelessness is a defined risk factor for hypertension [20,24].

Research carried out in hostel of Brother St. Albert's, Szczodro in 2009-2011 showed an increased incidence of diabetes, atherosclerosis and critical ischemia of the lower limbs, with relation to the duration in homelessness and age. Also, lower limb ulcers, trauma, and abdominal hernia are more common in homeless abusing alcohol [27].

Addiction to alcohol is a general population problem. As the data presented by the World Health Organization (WHO) in Poland shows, the problem of alcohol abuse concerns 4.4% of the population older than 15 years [28]. Among the homeless, the percentage of addicts is far greater. Depending on the population considered, it hovers between 12.9% - 50.8% [29]. However, attention should be paid to the fact that alcohol consumption can be a way to fight

the stressful situation of homelessness. It carries many problems: no permanent place of residence, social rejection, a sense of being a disappointment for relatives, or even the exclusion of homeless people from the circle of relatives, problems with the purchase of food. In such situations, people are looking for ways to alleviate their worries, and alcohol is one of the simplest and at the same time the most treacherous ways. Intoxication gives short-term relief and also increases one's mood.

However, in the long run,, it causes further problems - people become disengaged, inclined to take irrational and risky behaviors. Alcohol consumed by homeless people is often of poor quality, has an uncertain origin, so it can also be methanol, which can cause serious health complications. Excessive alcohol consumption can lead to premature death due to poisoning or injury. Patients abusing alcohol are more likely to be injured as a result of, for example, a fall, drop or brawl, and therefore often return to the emergency departments. Treatment of such patients can be problematic, also due to aggression. The aggression of patients towards medical personnel is fortunately rare, but the frequency of its occurrence increases. Many people are performing medical professions - doctors, nurses, paramedics - are dealing with the aggression of patients, presented in various forms. Aggression does not only take on a physical dimension, but it can also take the form of verbal aggression and auto-aggression. However, this problem does not only affect homeless patients and should not be equated with homelessness. However, some states predispose to aggressive behavior. This is, for example, alcoholic intoxication. As mentioned above, a large percentage of homeless people are affected by alcoholism. Patients under the influence of alcohol do not control their behavior, often disrupt the work of emergency departments, are aggressive not only towards doctors and nurses, but also other patients. In such situations, the medical staff faces a difficult task. A drunken patient requires the involvement of many people, and it is difficult to delegate most of the duty team to care for one patient.

The extra challenge of homeless patient care may also stem from the state of their mental health. Homeless people are characterized by low self-esteem [29]. The reason is the lack of permanent residence, malnutrition, problems that led to homelessness, as well as resulting from it, such as hygienic neglect. In most cases, the condition of homeless people is bad or very bad. Homelessness is associated with inadequate protection against adverse weather conditions, which in turn favors frequent infections and frostbites in the autumn and winter. Malnutrition itself can generate not only physical problems, such as wound healing disorders, decreased immunity and, consequently, a tendency to develop an infection in such

patients, but also psychological nature, such as depression. A homeless patient in a hospital ward may feel being stereotyped by other patients because of their poverty. This can cause shyness, which will be expressed, for example, by not reporting to the doctors that the treatment that is proposed is too expensive or that they do not understand the instructions of the medical staff. This requires an individual approach to such a patient, trying to understand his situation and adopting recommendations accordingly to his capabilities. Sometimes it is worth talking with such a patient in private, create an atmosphere of trust so that the patient can open up to the doctor, tell him about all his worries and doubts. Often such attempts may turn out to be unsuccessful due to the patient's deep conviction of rejection or a general lack of understanding of his or her situation. During contact with a homeless patient, it is necessary to assess his/her understanding of the words being addressed. Problems concerning the lack of self-confidence and a sense of stigmatization also have a bearing on the use of medical services. Homeless people significantly less often than the rest of the population benefit from accessible healthcare, but more often from emergency care (hospital emergency departments, ambulance) [30]. As the authors of the cited article point out, one of the reasons for this is the lack of trust in medical staff. However, a study conducted in Poland shows that about 80% of homeless people have a positive attitude towards the health care system [31].

A doctor caring for homeless people may come across several problems. Research shows that a large percentage of homeless people suffer from conditions that may make it difficult to assess their situation, prevent understanding or follow the instructions of medical personnel. Such states are alcoholism, which, as mentioned above, affects a large percentage of this group, and mental illness, which are also more common among homeless people than in the general population [29,32]. People who care for the homeless should keep all this in in mind. Sometimes such patients cannot afford medicines that are necessary for treatment, or they prefer to allocate funds they have for food, or alcohol for those addicted to it. A possible solution to this problem is the selection of an equally effective but cheaper method of treatment, referring the patient to places where he can get help (shelter for homeless people, addiction treatment center).

A large percentage of homeless people are disabled. 40% of this group are certified disable [31]. Disability is another problem in the treatment of patients. Often, they do not have access to care or help required, so even common situation, such as seeing a doctor or going to another medical facility may be quite problematic if not outright impossible. Another aspect of care for homeless patients is the issue of medical costs coverage.

According to the data provided by the authors of "Compendium of Homelessness and Health," 80.5% of homeless people do have health insurance. Persons who are unable to pay health insurance contributions may be covered by insurance if they meet quite simple conditions: they live in Poland, have Polish citizenship, and their income does not exceed PLN 400 a month. Then such a person may apply for free medical insurance, which will be provided by the City Mayor or any head of local governing body [32]. However, such a person should have a permanent address; some of the homeless do not.

According to article 15 of the Medical Care Act, the institution providing health services is obliged to provide care only in life-threatening conditions [33,34]. Otherwise, if the patient does not have insurance, the hospital may demand full reimbursement for care given.

As shown above, homeless people face many problems. They are starting from existential, financial to healthy ones. Their particularly unfavorable situation affects their mental condition. This is the reason for the frequent occurrence in this group of mental illnesses, addictions and other somatic diseases resulting from poor living conditions. All these factors may make it difficult to treat such a patient at various stages - collecting the interview, making a diagnosis, setting up therapy and implementation of the patient's recommendations.

A doctor who accepts a homeless person in the office, in the emergency room or the ambulance should have in mind some specific aspects of the patient's psyche. Homeless people feel devalued by others; they have reduced self-esteem. Often, when conducting an interview, they do not talk about their ailments either because of shame or because they treat them as a healthy state of affairs in their community. An example is a chronic cough. Talking to the homeless one must take care of the atmosphere of mutual trust; such a person cannot possibly be judged.

Regardless of the sources, people who research the problem of alcoholism among the homeless and the homeless themselves often indicate alcohol as the cause of their condition. Addiction to alcohol is, and the firm will alone is not sufficient for it to be cured; moreover, homeless people often stay in an environment where almost everyone is abusing alcohol. It is worth to talk with the patient about his problem, offer him ways to fight this addiction, help in getting to the addiction treatment center.

One of the most challenging aspects of homeless care is to fight poverty. Patients may not have the money to buy medicines or dressings. This can lead to a deterioration of their health condition, the development of post-operative wound infections. It should, therefore, be established each time, whether the patient has the means for further treatment, and if not,

refer him to the facility, where he can receive, for example, dressing for free.

Homelessness is an underestimated general social problem. Programs are helping to get out of homelessness. When treating a homeless patient, pay attention to his poverty and try to direct to a place or institution where he or she will get help.

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Difficulties concerning the treatment of Jehovah's witnesses: a current medicine’s view

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Jehovah's Witnesses are a religious group that considers Yahweh to be the only God. They belong to the mainstream of the Bible Students, which is based on the literal interpretation of the Bible and evangelization activity aimed at spreading their ideology. The founder is considered to be Charles Taze Russell, who, having rejected Presbyterianism, in 1868 took up the independent study of the Word of God. The organization of Jehovah's Witnesses was officially established in 1914 and functions today, bringing together over 8 million people around the world. In Poland, the number of Jehovah's Witnesses in 2011 was 137.3 thousand (0.36% of the population), the largest in the Śląskie Voivodeship. They are the third largest denominational group [1,2]. The principles of faith, based on a direct analysis of the Bible, are implemented not only on the spiritual level but also in everyday life, which in some aspects distinguishes them from the typical representative of Polish society. They do not care about established holidays; they strictly observe the principles of modest life; they are not allowed to possess weapons. They also oppose any use of human blood - which is often the reason for a dispute between them and the medical professionals.

The consent of a man to perform any activity related to his person is one of the definitions of a highly developed civilization. This principle applies in every aspect of life - including in medicine. In order for a given medical activity to be done - the patient must first approve it. It is not always necessary to confirm in a written form, in some cases nonverbal consent is enough, for example when the doctor wants to measure the patient's pressure - as the consent of the law treats that the subject pulls up the sleeve and gives the elbow to the

medic. There is also a second situation in which written authorization is not required, namely a threat to life in which the victim is unable to give informed consent because of a severe mental or physical condition. In Poland, freedom and personal inviolability is guaranteed by the Constitution Articles 41 and 47) but also other laws directly affecting the medical community:

(Ustawy o Zawodzie Lekarza i Lekarza Dentysty z 05.12.1996 roku (Dz.U. 1997, Nr 28, poz.1520 z późn. zm.),

- Ustawa o Zakładach Opieki Zdrowotnej z dnia 30.08.1991 roku (Dz.U. 1991, Nr 91, poz. 408)- artykuł 19,
- Kodeks Etyki Lekarskiej [3].

Doctors, nurses and midwives act in accordance with the principles of modern Evidence Based Medicine, although they must respect the will of the subject. Because of the common interest (both doctor and patient) that is the wellbeing of the patient, there is rarely a discord in this area. Difficulties arise when the patient's view differs or does not allow for practices based on previous scientific achievements - and this is the case for Jehovah's Witnesses.

They do not contradict the generally accepted treatment standards, but question the blood transfusion [4,5]. They are based on verses from the Holy Bible [4,5]:

> *3" Every moving thing that lives will be food for you. As the green herb, I have given everything to you+. 4 But flesh with the life of it, the blood of it, you shall not eat."*

> ***10*** *"Whatever man there be of the house of Israel, or of the strangers who sojourn among them, who eats any manner of blood, I will set my face against that soul who eats blood, and will cut him off from among his people."*

> ***23*** *"Only be sure that you don't eat the blood: for the blood is the life; and you shall not eat the life with the flesh."*

> ***29*** *"that you abstain from things sacrificed to idols, from blood, from things strangled, and from sexual immorality, from which if you keep yourselves, it will be well with you. Farewell"*

According to the teachings of Jehovah's Witnesses, blood is the nucleus of life. Accepting it in any form testifies to the opposition of the will of God, provokes the wrath of the Creator and is compared to immoral sexual contacts. Lack of consent also applies to all blood products - i.e. the concentrate of red blood cells, thrombocytes, plasma, clotting factors.

Partial elimination of this problem could be autotransfusion - transfusion of the blood previously collected from the patient. However, this case is also a forbidden practice, because if liquids lost direct contact with the donor they are already foreign. The alternative is extracorporeal circulation - in which the patient is hooked to special tubes and the blood cells passing through the duct systems do not lose their communication with the injured or liquid therapy with the blood substitutes. However, according to sources of evidence-based medicine, these formulations show less efficacy [6] and their use is only recommended in cases where access to high-value blood is limited.

Comparison of the composition of selected crystalloid solutions compared to plasma.

	Plasma	**0,9% NaCl**	**5% glucose with electrolytes**	**Ringer’s solution**
Na^+(mmol/l)	135–145	154	49.1	147.2
Cl^- (mmol/l)	95–105	154	49.1	155.6
K^+ (mmol/l)	3.5–5.3	0	24.9	0
HCO_3^- (mmol/l)	3.5–5.3	0	20	0
glucose (mmol/l)	3.5–5.5	0	278	0
pH	7.35–7.45	4.5–7.0	4.5–5.5	5.0–7.5
Chart based on: Interna Szczeklika, 2017				

Transfusion of blood or blood derivatives is treated as a life-saving procedure in many situations - in serious traffic accidents, multi-organ injuries, intravascular coagulation syndrome, shock. These are moments that require an immediate reaction from the doctor, often leaving little time for reflection. However, for this eventuality, representatives of the JW have developed a solution - each Jehovah's Witness carries with him/her (usually in a wallet) a statement of will, in which the opposed to any blood

transfusion is clearly stated, it also does and relieve the physician of his responsibility for said procedures.

Jehovah's Witnesses statement / disclaimer

"I, the undersigned, make this statement following firm decision. I declare that regardless of the circumstances, I do not agree to any form of blood transfusion (transfusions of whole blood, red blood cells, white blood cells, platelets), even if in the opinion of the doctor such procedure was necessary to save my health or life. I do hereby agree to administration of non-plasma substances that increase its volume (such as dextran, saline, Ringer's solution or hydroxy ethylated starch) and agree to other alternative treatments without blood being transferred. I am issuing this document in accordance with my right to express or refuse my treatment, as appropriate to my beliefs and recognized principles. I am a Jehovah's Witness and I want to be obedient to the commands of the Bible, and one of them is, "Prevent yourselves from [...] blood." (Acts 15:28, 29, Millennia Bible). I am ..... years old and I have been following this commandment for ..... years. I am also aware of the various risks associated with the transfusion and I decide not to put myself at risk, and instead bear all the risks that can arise from alternative treatment without using blood or its derivates. I hereby release doctors, anesthesiologists and hospitals together with their staff from liability for any damage that could result from my refusal - despite their proper care, completed in all other respects. I also authorize people whose names are listed on the reverse side of this disclaimer to ensure that my will expressed in this document is respected and to answer any questions related to my categorical refusal to accept blood. "

source: Consent of Jehovah's Witnesses for treatment with blood preparates - legal and ethical aspects

Considering an adult patient - the case is quite simple. Everyone has the right to decide for himself and although the paramedic may not agree with the patient's opinion - he must fulfill his wish – otherwise he is facing legal consequences. The situation becomes more complicated when the patient is a minor. In the light of law, it is parents who make decisions about their child, although in a life-threatening situation, the doctor has the right to undermine the opinions of legal guardians and refer the case to the Guardianship Court. However, the process may take a few days and in those moments minutes or even seconds count [3]. It raises ethical and legal problems, generates frustration, sometimes a sense of helplessness - both on the side of the follower of

Yahweh, who wants to remain faithful to his ideology and the doctor who wants to act in accordance with the acquired knowledge conscience sand Hippocrates Oath. Interestingly, the position of Jehovah's Witnesses changed over the years. The pioneer of faith, Charles Taze Russel and his successor, were in favor of transfusions [7], and in 1940 [8] one could find approval of transfusions in one of the articles (The Consolation). Then suddenly, in 1945 after the end of World War II, Nathan Knorr in the pages of The Watchtower announced a ban [7,8].

Another controversial aspect is transplantation of organs and bone marrow [9]. According to Jehovah's Witnesses, mankind was created as a picture of God, therefore using another person's organ is a crime against the Creator. Additionally, in their opinion, transplantation is compared to „eating a part of human body' so it is considered cannibalism [7] (this does not concern animals, because God gave man a right to reign over them: -*„And God gave them his blessing and said to them, Be fertile and reproduce, and make the earth full and be masters of it; be rulers over the fish in the sea and over the birds of the air and over every living thing moving on the earth* [8].

Organ transplantation in today's medicine has two meanings. The first one is used to improve comfort of life- and so it is in case of kidneys failure. It is possible to exist without them, but that means everyday dialysis which last from 3 to 6 hours. That deteriorates standards of living – makes working virtually impossible. Another important argument standing for transplantation are life threatening cases in which patient receive heart, liver or bone marrow transplant. Although, two first situations are extremely rare, the acute leucoblastic leukaemia are diagnosed in 1.100 children per year in Poland. Across the ages the statement of Jehovah's Witnesses Governing Body has been changing as well. The first successful transplantation, in which kidney was exchanged, occurred in 1954 in the USA and considered monozygotic twins. Since then the procedure become much more widespread and accessible. In 1960 paper was published in the journal „Awake" and in 1962 in „Watchtower" describing the operation in positive light. Report stated that transplanted organ regained the function in short period of time with a benefit for patient's health. In 1968 the Governing Body changed their view by 180 degrees; telling that transplantation is a sin and committing it will result in disfellowship. The congregation put forward the argument that such kind of operation is the form of consuming human tissues. However, since the 1986 until now individual approach is allowed. There was no official ban of the procedure and it can be performed under 2 conditions:

- The transplanted organ must be cleansed from blood and no other form of blood preparations can be transfused during operation
- Chairman of the congregation has issued an individual consent

The current statement is based on the lack of an appropriate sentence in the Bible on the matter [7,9,10].

Jehovah's Witnesses belongs to a peculiar enclave, which ensures followers to strictly adhere to the rules. These principles are based on the literal interpretation of the Bible and are modified by Governing Body in the USA. As an officially registered religion group, they have a right to cultivate their own beliefs. Undoubtedly, a part of their rites does not agree with current medicine view and the content has changed over the years. The most criticized situations are those which describe the threat to human life. In these cases, two aspects should be taken into consideration- what is right? Evidence-based medicine, with empirical data behind it or decision based on teachings of religion based on the thousand-year-old source of information.

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Problems of the old age

Amiodarone – application safety in the geriatric population – a systemic review

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List of abbreviations

ADRAC - Adverse Drug Reaction Advisory Committee,
AF - atrial fibrillation
AIH - amiodarone-induced hipothyroidism,
AIPT - amiodarone-induced pulmonary toxicity,
AIT - amiodarone-induced thyreotoxicosis
ALI - amiodarone lung injury,
ALS - Advanced Life Support,
BVP - bilateral vestibulopathy
CDER - Center for Drug Evaluation and Research
DALI - drug associated liver injury,
HF - heart failure,
TdP - Torsade de Pointes,
VF - ventricular fibrillation

Introduction

Amiodarone is one of the most widely spread and potent antiarrhythmic agents. It is a benzofuranic, iodine-rich drug, applicated in oral as well as intravenous form. Nowadays it is widely used in a number of indications including ventricular arrhythmias or atrial fibrillation and is a first line medicament in patients with preexisting heart failure (HF) and structural heart disease [1,2]. It is also used in the Advanced Life Support (ALS) procedures.

Drug chemistry and pharmacology: Classified as a group III antiarrhythmic according to the Vaughan-Williams classification, amiodarone not only inhibits sodium-, potassium- and calcium channels in the myocardium but also is alfa- and beta-adrenergic receptor blocker. Thus it has a negative inotropic, dromotropic and chronotropic effect. The drug undergoes hepatic metabolism, which is cytochrome P450 – dependent and the main and active metabolite undergoes enterohepatic circulation. Due to intrapopulational cytochrome polymorphism, the drug blood halftime may be heterogeneous, posing a danger of its cumulation, especially in the geriatric population where the metabolic processes, pharmacokinetics, and pharmacodynamics are altered.

Adverse effects: The most important side effects of amiodarone are thyrotoxicosis, pulmonary- and hepatic- toxicosis, corneal deposits, dermatopathy, peripheral neuropathies, secondary arrhythmias. The induced prolonged QT-interval may be a source of potentially life-threatening tachyarrhythmias as Torsade-de-Pointes or even ventricular fibrillation (VF). Most of these adverse effects are dose- and time-dependent, but it has also been reported that they may be more prevalent in the geriatric population. The underlying causes are **:**drug impaired gastrointestinal absorption

- decline of liver metabolism and glomerular filtration
- changes in drug distribution
- remodelling of the myocardium
- multipharmacotherapy
- comorbidities

The most common adverse effects observed during amiodarone therapy are corneal microdeposits, unspecific gastrointestinal symptoms, photosensitivity and a temporary rise of aminotransferases, which appear in almost 1-2 in 10 patients and do not require any medical intervention [3]. About 1-5 pro 100 cases come up with pulmonary and thyroid disorders, bradycardia, jaundice with liver insufficiency, tremor or other extrapyramidal signs, sleep disturbances and skin hyperpigmentation.

As described, some of these abnormalities may lead to unreversible health deterioration if not diagnosed on time. That is why patients on amiodarone should undergo regular specialistic controls, including periodical chest X-rays, aminotransferases serum levels, thyroid function check. What is more the number of amiodarone adverse effects rises with age and the number of other medicaments taken by the patients, especially in the

geriatric population. The list of potential interactions is long and should be abided by the clinicians to avoid possible interaction.

Studies show that elderly patients are at increased risk of pulmonary toxicity, ataxia, polyneuropathy and myxoedema in connection with amiodarone treatment. What is more, some of the amiodarone adverse effects may be the cause of increased mortality in the geriatric population. Meanwhile, other complications as drug-associated liver injury (DILI), photosensitivity, ocular symptoms, and others are not age-dependent [4,5,6].

Literature review

Amiodarone-induced-pulmonary-toxicity (AIPT)

The most common pulmonary adverse effects of the amiodarone therapy are interstitial lung disease, pulmonary fibrosis and pleural effusion [7]. The symptoms include dyspnea at exertion, non-productive cough at night, fatigue or rarely finger-clubbing. However, acute lung injury (ALI) with respiratory failure is the most feared AIPT form, where the hospital mortality reaches 50%. In a study conducted by D. K. Ernawati et al, all reported adverse effects from two different register databases concerning amiodarone treatment: ADRAC (Adverse Drug Reaction Advisory Committee) and CDER (Center for Drug Evaluation and Research) were analysed [8]. AITP was the third most common event, following thyroid disorders and skin reactions, being about half of the reported cases. In the multivariate analysis, age appeared to be an independent risk factor predicting the onset of the AIPT. Some studies suggest that AIPT is also connected with duration of treatment and the cumulative amiodarone dose, which was not supported by the CDER registry data. Other studies revealed that chronic obstructive pulmonary disease and other pulmonary diseases are predisposing factors to AIPT occurrence [7]. That is why amiodarone treatment in such patients should be intensively supervised.

Torsade de Pointes and secondary arrhythmias

Despite its antiarrhythmic properties, amiodarone is a QT-lengthening agent and thus a proarrhythmic. The long-QT syndrome is well known to be the underlying cause of Torsade de Pointes tachycardia and may the cause of cardiac arrest. One of the risk factors is age, female gender as well as parallel treatment with other QT-lengthening agents [9]. For instance, patients treated with amiodarone and levofloxacin were at higher risk of such events [10]. The prognosis after TdP event is favorably provided it is recognised early, and

adequate treatment is applied. Withdrawal of amiodarone treatment and its replacement with other agent is also indicated in such cases.

Thyroid disorders

There are two main types of thyroid dysfunctions connected with amiodarone: Amiodarone-Induced-Thyrotoxicosis (AIT) and Amiodarone-Induced-Hypothyroidism (AIH), which occur in up to 12% and 22% of patients [11]. The symptoms usually arise in 2-3 years after treatment initiation a may appear up to 2 years after the treatment modification. Both AIH and AIT may occur in healthy individuals as well as in patients with underlying thyroid disease [12]. Extensive clinical trials failed to identify any risk factors predicting both forms of thyroid gland dysfunction. It has been shown that AIT is connected with higher mortality in elderly patients with left ventricular systolic dysfunction [13].

Physicians must be aware that the management of patients on amiodarone with AIT, regarding the thyroid function, may be different. For instance, patients on amiodarone may tolerate high levels of thyroid hormones due to the inhibition of beta-adrenergic receptors and T4 to T3 conversion. That is why AIT symptoms occur inadequately late or may be attenuated. On the other hand, AIH does not require any other interventions but for L-thyroxin supplementation [14]. Some articles suggest that in AIH the elderly are at increased risk of developing myxoedema and hypothyroidism crisis, which can naturally be prevented by appropriate treatment [15]. Because amiodarone has a long elimination time, none of the discussed disorders is an absolute indication to treatment discontinuation, except for patients with thyrotoxic crisis and heavy AIT 1 forms, where radical treatment should be considered, especially by underlying heart failure [12,13].

Neurological adverse effects

The neurological adverse effects are a group of rare amiodarone related complications. Several studies have reported cases of ataxia, tremor, dyskinesia, polyneuropathy or encephalopathy being induced by this medicament. Although the literature does not confirm age being a risk factor, the symptoms may be especially burdening for the elderly population, leading to the treatment discontinuation.

In most studies, the neurologic manifestation of amiodarone was fully reversible after its withdrawal [16,17,18]. The population of patients affected by such disorders is rather small; thus we lack precise data which would help clarify this matter.

Interestingly, in recent years, a new form of amiodarone neurotoxicity was reported - a bilateral vestibulopathy (BVP). It was first published in 2017 by Ruehl et al. [19]. In another study, it has also been suggested that amiodarone use may be a risk factor for acute vestibulopathy in the future [20,21].

Discussion

Amiodarone is a medicament with a high pharmacological profile and is widely used in different fields of medicine. The range of adverse effects it may cause is diverse. Although substantial complications are rare, physicians must be aware of them to act quickly if any of them shall occur. Numerous potential pharmacological interactions may also be a cause of potentially life-threatening events. That is why, a thorough patient control must be conducted in every patient taking amiodarone, including chest X-ray every 6-12 months, aminotransferase activity in serum, thyroid panel every six months.

What is more, ECG should be registered before and after therapy initiation, with QT-time assessment. All patients should also be informed to contact ophthalmologist or neurologist by any ocular or neurological symptoms. Before every sun exposure, UV-filters should be administered on the skin. The minimal effective dose should be used to avoid some interactions and adverse effects associated with amiodarone,

The geriatric population, due to its different metabolic state, may be at risk of amiodarone-associated-complications development. However, the literature states that amiodarone should still be the first line medicament in the same indication as it is in the overall population. Although some complications may be more frequent in the elderly, the treatment profits still outweigh possible complication that may occur.

In recent years we have also witnessed significant progress in arrhythmology. Numerous transcatheter ablation technics for arrhythmia treatment have been developed and are nowadays available in most of the high volume centers. New medicaments like vernacular, as well as old ones, for example, antazoline, have also found their application in the treatment of arrhythmias as atrial fibrillation (AF) [22,23].

Lately, supradural anesthesia has also been proven to be a promising treatment method of an electrical storm, resistant to previous therapy [24]. All physicians should be aware of these alternatives and ought to use them wisely, especially if the amiodarone treatment is unsuccessful, contraindicated or intolerable by the patient.

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Ecological aspects of aging

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Introduction

Aging is an irreversible process that occurs at all structural levels of life. Therefore, since it disrupts the body's balance, it reduces the ability to respond to the environmental stress [1].

In the consequence functioning of the body is impaired and the progressive accumulation of harmful cell changes leads to their death. This subject, however, is not completely obvious. Despite the fact, bacteria also age, their death does not appear as a natural end to their existence.

Interestingly, simple animals such as jellyfish, sponges, and corals, as well as more complex ones, like hydrozoa representative – *Turritopsis nutricula*, often show longevity and potential immortality [2].

In plants, this phenomenon is also widespread as the oldest plant genet of *Lomatia tasmanica* is 43,600 years old [3]. Although aging is inevitable, its effects can be successfully delayed and reduced. An excellent example of this is the 30-year extension of the average age of people in the 20th century in developed countries.

Theories of aging

Over the years, scientists have come to many theories explaining the aging process. These include [4]:

- poisoning theory,
- wear-and-tear theory,
- cross-linking theory
- Hayflick’s limited cell divisions theory

- Orgel's error catastrophes theory
- shortening of telomeres
- somatic mutations theory
- mitochondrial theory
- free radical theory.

The most popular one is the shortening telomeres theory; however, it is burdened with many problematic issues. Telomeres are repetitive nucleotide sequences found at the end of the chromosomes, which are not fully copied during the replication. Studies show that yeast cells of S. Cerevisiae have DNA telomerase - nuclear enzymes which add the telomere sequences, hence the telomeres are not shortened in subsequent divisions. Nevertheless, these organisms have a limited number of cell divisions. Therefore, it is assumed that more indicators are informing the cell when it should stop dividing. The primary determinant of the body's resistance to external stress is its ability to repair DNA. Unfixed mutations not only lead to accelerated aging but also underlie many inherited diseases and cancerous transformations [5]. Although there are various studies conducted to prove different theories, many of them have been already confirmed, as the whole process is caused by many factors internally related to each other.

In the mid-twentieth century, two theories were proposed to explain the aging process. One of them was the model of two-hit, developed by a physicist Leo Szilard, which is still popular today. It shows that somatic mutations accumulate in the genome, disrupting the proper expression of the genes, but both the genetic and cellular redundancies of the organism prevent impaired gene expression leading to aging until they are completely spent. About the same time, Leslie Orgel proposed a different theory of aging. In contrast to Szilard's suggestion of a constant rate of DNA mutations occurrence, Orgel attributed aging to the exponential increase in proteins' structure errors. Since proteins are responsible for the translation, decreasing their architectural fidelity can result in the positive feedback loop of the incorrect synthesis. Thus, the exponential escalation of this process leads to increased aging. However, this theory has not been proved yet, but it may be caused by technical limitations [6].

It may be worth combining some elements of both Szilard and Orgel's models since the catastrophic error theory explains why the number of somatic mutations increases exponentially with age and what role they play in the aging promotion (Fig. 1).

To fully understand the mechanisms of aging, physiological, molecular, as well as the evolutionary approach should be applied. In this part of the work, we will present general

patterns of the evolution of aging and consider the influence of the reproductive strategy on the survival of the Y chromosome and men's viability.

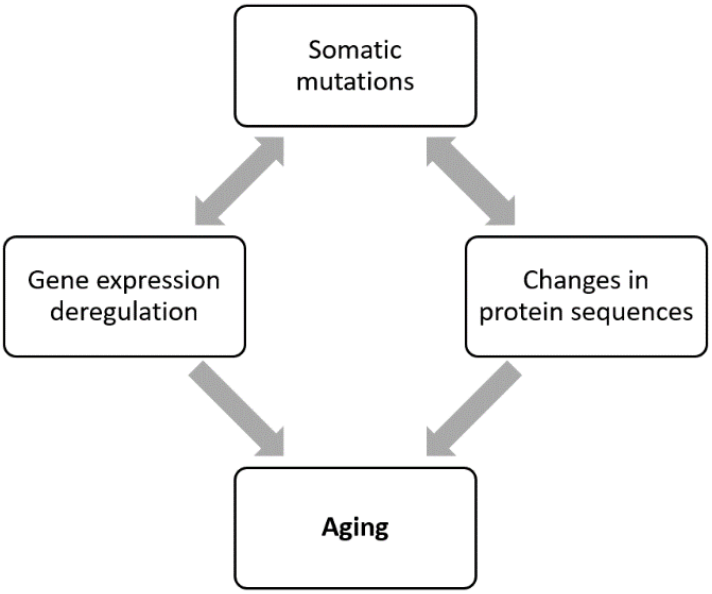

Figure 1. Model of the catastrophic error theory

How does the evolution shape the lifetime?

Recent findings show that basic assumptions about the functional basis of aging, such as the molecular damage caused by reactive oxygen species generated in metabolic and immune processes, must be reconsidered. New hypotheses, such as the hyperfunction hypothesis i.e. carry-over of activity of early life programs for growth and reproduction into later life, are gaining in importance [7].

Since the beginning, the evolution of aging has been attributed to compromises in response to the patterns of external mortality in adults. It emerges as a by-product of selection and leads to maximizing reproduction. This compromise occurs because mortality originating from the external sources, such as predation or random causes (i.e., external mortality), weakens natural selection in later life. With high external mortality, few individuals survive to reproduce at a later age, therefore, significantly reducing the role of selection which promotes longevity. This allows the accumulation of harmful mutations, whose effect manifests at a later age of individuals. It also enables favoring the fertility at an early age at the sacrifice of the longevity, which is called antagonistic pleiotropy [7]. Comparison of the infant mortality rate in the US in

the early twentieth century to today's shows that there is a relevant decrease in external mortality in human populations when good access to medical care is provided [8]. This creates new conditions for natural selection, which can nowadays favor "longevity genes", not in the context of increasing the number of offspring, but care for grandchildren and even great-grandchildren, especially in the case of women's inheritance in the feminine line [9].

More recent publications draw attention to linking the condition of individuals with their survival. This may apply not only to factors with little impact on the human, such as the ability to escape from the predator, but also the significant ones faced by people, such as the resistance to diseases and stress. Studies on *Caenorhabditis elegans* have shown that when increased mortality was induced by heat shock (i.e. condition-dependent), life expectancy increased in subsequent generations, while shorter life span evolved when mortality was random. In addition, Shokhirev and Johnson's research suggests that high external mortality promotes longevity when the cost of reproduction is high and the access to resources is unlimited. Contrarily, high external mortality would relevantly shorten the life span when resources were limited and reproduction was inexpensive. Moreover, the epigenetic factor is also greatly important, because such changes may affect the features of several generations [7]. It is also worth paying special attention to the recently discovered impact of the Y chromosome on longevity.

Why is it beneficial for men to be faithful?

The human X and Y chromosomes were formed about 200-300 million years ago in eutherian mammals. Sex chromosomes transferring sex-determining genes are subject to unique evolutionary forces and play a significant role in many evolutionary processes, such as speciation, adaptation and genomic conflict [10].

There have been many evolutionary models proposed to explain Y degeneration. Their common feature is that the net effectiveness of natural selection is strongly reduced on the non-recombinant chromosome. Oppositely, in a recombinant chromosome, selection can work independently of each mutation. However, in case of recombination absence, selection works on whole chromosomes. The whole chromosome will be fixed in the population if a favorable mutation appears on it, or the whole chromosome will be deleted if it carries a harmful mutation. There are several following factors, which relate to this issue.

Muller's ratchet mechanism refers to the irreversible accumulation of harmful mutations

in a finite non-recombinant population. In finite populations, chromosomes can accumulate mutations due to random effects. Recombination at X chromosome allows the reconstruction of mutation-free chromosomes, whereas this genome loss is irreversible to the non-recombinant Y chromosome and preserves a specific harmful mutation on Y.

In genetic hitchhiking the newly created beneficial mutations can occur on the chromosome which also contains harmful mutations. By recombination, preferred alleles can be fixed on the X chromosome without dragging along the associated deleterious mutations. However, on the non-recombinant Y chromosome, the preservation of the preferred mutation simultaneously preserves the linked deleterious mutation. In genetic hitchhiking it is required for the selective advantage of the preferred mutation to outweigh the effect of the combined harmful allele so that the Y chromosome containing the preferred mutation has a net selection advantage. If it is not, ruby in the rubbish occurs.

In ruby in the rubbish, Y chromosomes may undergo a smaller adaptive evolution in relation to the X chromosome, due to the connection of beneficial alleles with harmful mutations. Preferred low-performance mutations can be detached from linked, highly deleterious mutations by recombination on the X-chromosome and consolidation in the population. However, in the case of non-recombinant Y chromosomes, they will be eliminated by purifying selection. Genes linked to the X chromosome will continue to adapt and introduce beneficial mutations, while the Y chromosome will lag behind. Ultimately, it may be beneficial for a male not to express already incompatible Y-conjugated genes and silence or deactivate them [10].

Transmission limited to males implies that Y is an ideal part of the genome to transfer genes increasing the efficiency of males, because mutations beneficial to males are always transmitted by the sex in which they are beneficial and protected against counter-selection in females if they are sexually antagonistic (i.e. good for males but harmful to females). Thus, predictions about the content of the Y chromosome gene are clear – gene degradation predominates, and the surviving genes associated with Y are enriched with features beneficial to men.

However, while the general properties of these models are well understood theoretically, their relative contribution to the observed degeneracy of Y chromosomes in natural populations is less pronounced. Significant mechanisms are described below. The process of Y chromosome depletion may suggest that further gene loss will lead to the final disappearance of the human Y chromosome. These predictions are based on the model of the rate of gene loss from the Y chromosome. However, recent theoretical and experimental studies have clearly showed that Y

degeneration does not occur in this simple, linear way and disproves sensational claims about the complete disappearance of the human Y chromosome [10].

Lobo and Onody showed in computer modeling that the Y chromosome degenerates, even if both XX and XY pairs do not recombine. They tried to explain these phenomena by specific differences in the inheritance of the sex chromosomes – the Y chromosome never experiences selective pressure in the female body, whereas the X chromosomes spend one third of the time of evolution in the male body and two thirds in the female body. Exclusion of recombination between sex chromosomes is insufficient to induce degeneration of the Y chromosome. It is rather a specific reproduction strategy that is responsible for this process [11].

Biecek and Cebrat, using a computer simulation, showed that in panmictic populations, when females (XX) are free to choose a male partner (XY) for reproduction from the entire population, the Y chromosome accumulates defects and ultimately the only information it carries is the male's determination. As a result of the shrinking of the Y chromosome, male genomes lose one copy of the X chromosome information, resulting in males burdened with higher mortality, also observed in human populations.

If the model assumes that the presence of a man is indispensable at least during the pregnancy of his partner and he cannot be seduced by another woman at least during one reproduction cycle – the Y chromosome retains its content, does not shrink, and the life expectancy of women and men is equal. Thus, the Y chromosome shrinks not because of being in one copy, without the possibility of recombination, but because it is under weaker selection pressure. In panmictic populations without the need to be faithful, a significant proportion of males are unnecessary and can be eliminated from the population without reducing its reproductive potential [11].

Sirtuins – a key to aging inhibition?

Recently there are more and more studies conducted focusing on the sirtuins functions, especially their influence on cell aging inhibition and, due to this fact, their possible usage in therapy of age-related diseases. The family of SIR2 proteins (Sirtuins), described as Silent Information Regulator 2, are enzymes classified as NAD+-dependent deacetylases. Initially discovered in *Saccharomyces cerevisiae* yeast, are currently found to be present in nearly every organism [12].

Research has proved that decreased sirtuin level in *Saccharomyces cerevisiae* can lead to many metabolic disorders, related with DNA repair, recombinational silencing and cell senescence [13]. It has been shown that prolonged caloric restriction stunts aging processes by inducing the sirtuins genes expression. However, this effect was not observed in case of SIR2 genes damage, whereas it was increased in overexpression [14].

Sirtuins have been divided into 5 classes: I-IV and U (undifferentiated). Homologues present in prokaryotes were assigned to class II and III, the eukaryotic ones to class I-IV, while the U class includes enzymes produced by gram-positive bacteria and some archaea. In *Saccharomyces cerevisiae* beside Sir2p there can be distinguished 4 more sirtuin genes sequences: Hst1-4. Whereas in mammals there were 7 homologues found so far named SIRT1-7. SIRT1-3 form class 1, SIRT4 compose class 2, SIRT5 – class III, as SIRT6 and 7 constitute class IV. Yet, no clear correlation has been observed between sirtuins function and this classification. All SIRTs comprise similar catalytic domain though and require NAD+ as a cosubstrate to their deacetylating enzymatic activity [15].

Sirtuins stunt aging in various ways

SIRT1 is the best known of sirtuins and the most similar to the yeast Sir2p as well. Localized in the nucleus, it is responsible for DNA damage repair, gene silencing and genome stability. SIRT2 present in cytoplasm is functionally associated with tubulin and therefore with chromatin condensation during mitosis [16]. SIRT3-5 are located mostly in mitochondria, where they affect the mitochondrial enzymes regulating apoptosis, oxidative stress and cell energy metabolism [17]. SIRT3 and 4 improve the efficacy of the electron transport chain, whereas SIRT5 is able to activate mitochondrial superoxide dismutase. SIRT6 and 7 are mainly responsible for genome repair and maintaining its stability [18].

The most studied and known function of sirtuins is epigenetic modifications, the majority of which have a positive impact on aging stunting. As the NAD+-dependent deacetylases, SIRTs are responsible for the deacetylation of lysine residues of N-terminal tails of mainly H3 and H4 histones, leading to the more compact structure of chromatin and hence expending the lifespan of the cell as a result of transcriptional repression. This functionality is related to SIRT1, 2 and 6 activity [19]. Furthermore, scientists observed that inhibition of SIRT1 in mammalian cells through hyperacetylation of H3K56 histone increases genome instability. It is inferred that elevated level of H3K56Ac (an acetylated form of H3K56) induces

SIRT1 genes, what is also related to DNA damage repair due to its vital role in binding newly synthesized DNA to chromatin [20,21].

The influence of SIRT1 on the cell lifespan can be a result of histone methylation as well as DNA itself. Not only is it responsible for direct deacetylation of histones, essential for further methylation, but it also induces and activates histone methyltransferases. Moreover, by enhancing methylation of damaged DNA regions, it leads to epigenetic silencing, which can be a potential target for tumor research and the future therapy [22].

Through the regulation of transcription factors SIRT1 is affecting metabolism control, in particular, promotion of hepatic gluconeogenesis and β-oxidation of fatty acids. It is possible because of enzymatic modification of transcription factors by deacetylation. It results in decreased inhibiting activity of CRTC2, which through ubiquitination leads to its degradation, and STAT3, which turns less active without acetyl group, as well as FOXO1 and its cofactor PGC-1α, responsible for increased stimulation after deacetylation. Therefore, the maximalization of gluconeogenesis effectivity is achieved during fasting [23]. Activation of SIRT1 also enhances lipolysis and free fatty acids mobilization. By downregulating expression of nuclear receptor PPAR-γ, which stimulates adipogenesis and is present mainly in fatty tissue, the fat loss is favored. SIRT1 likewise impacts the carbohydrate metabolism, increasing insulin secretion by beta cells in pancreatic islets, as a result of reduction in UCP2 level due to direct suppression of genes encoding them. UCP2 are mitochondrial inner membrane proteins allowing proton leakage from the cytoplasm to mitochondria. Lowered UCP2 level affects intracellular ATP level in islets, elevating it, therefore increasing the insulin release [24,25].

According to the studies, sirtuins influence the inflammation. NF-κB - a nuclear factor kappa-light-chain-enhancer, related to B-cells is a protein complex, essential in initiating immunological response to infection. It is also able to induce proliferation and angiogenesis, as well as inhibition of apoptosis, which may promote tumorigenesis. SIRT1 stunting the signalization of NF-κB by deacetylation of its subunits leads to the decrease in tissue inflammation. However, NF-κB downregulates SIRT1 by expression of factors such as miR-34a (a regulatory microRNA) or interferon gamma, thus enhancing inflammation [26].

In nuclear SIRT6 beside the deacetylation there has also been discovered ADP-ribosyltransferase activity. Researches show that in many tumor cells overexpression of SIRT6 generates massive apoptosis, requiring this enzymatic functionality. Nevertheless, such phenomenon has not been observed in nontumorous cells, which may turn to be crucial in studies on carcinogenesis [27].

SIRT1 impacts the cell aging also by regulating the activity of p53 – the guardian of the genome. The p53 is induced by many stress factors the cell undergoes and damage cumulating through the lifespan. It regulates DNA repair and, if it cannot be avoided, leads to apoptosis in order to protect the organism from tumorigenesis. It has been proved that SIRT1 through deacetylation of p53 inhibits its ability to promote apoptosis and, due to it, precocious cell death. Hence, it is suggested that SIRT1 acts as a balance regulator between death and repair of cells [28]. Although SIRT1 was initially classified because of those findings as a potential carcinogenesis promotor, it can stunt it as well. Antineoplastic activity is achieved through favoring maintaining the genome integrity and DNA repair by Ku70 protein, responsible for erasing DNA strand breaks produced by radiation. It has been shown, that Ku70 is not active enough in case of deficit of SIRT1 activation. Furthermore, restriction of tumorigenesis can be conducted by SIRT1 through inhibition of inflammation, as described above, as well as by influencing the localization of some regulators inside the cell, for example by deacetylation of β-catenin and thus promotion of cytoplasmic localization of the nuclear-localized oncogenic form of β-catenin [29,30].

Pharmacological regulation of sirtuins activity

Sirtuins activity can be regulated through various endogenic and exogenic factors, which can be used to beneficially and selectively influence the cells. Since NAD+ is a necessary cosubstrate for SIRTs to fulfill their deacetylation, studies have been conducted to find, whether its level relevantly impacts sirtuins activity. It has been shown that the NAD+/NADH ratio is crucial, because of an excess of NAD+ increases SIRT activity, whereas NADH is its competitive inhibitor. One of the main factors impacting the NAD+/NADH ratio is energy supply status of the organism. Caloric restriction leads to displacement of this balance towards NAD+ and therefore allosteric activation of the majority of SIRTs, except SIRT4, which is inhibited by low energy supply [31]. Exogenic elevation of NAD+ level by its supplementation can result in beneficial influence on the organism functioning. It pertains to the therapy of cardiovascular diseases in particular, as SIRTs can protectively enhance the endothelial condition. SIRTs influence is also noticeable in neurodegenerative disorders, especially in Alzheimer's disease – an age-dependent disease as well, where SIRT1 acts neuroprotective, decreasing β-amyloid production. However, in SIRT2 such an observation has not been made. On the contrary, it increases the risk of neurodegenerative diseases in the case of overexpression. Having in mind the information introduced above about SIRT1 activity on

energy metabolism, studies indicate a beneficial impact of caloric restriction in preventing aging, in the context of sirtuins functions [18,32].According to the studies, low energy effect can be elicited pharmacologically as well. Hence, such compounds act as indirect SIRTs activators. One of them is resveratrol, present in grapes peel and therefore in red wine. Resveratrol does not directly activate SIRTs, however directly inhibits some phosphodiesterases (PDE). Through enhancing the level of intracellular second messenger cAMP, and thus by Ca2+-dependent signaling pathway, it leads to the activation of AMPK, an AMP-activated protein kinase. This results in increased NAD+ level and elevated SIRTs activity. Furthermore, SIRTs can be activated concurrently through their phosphorylation by cAMP-dependent PKA (protein kinase A), due to the increased cAMP level, as mentioned above [33].

Beside activators, there have also been found exogenic SIRTs inhibitors. One of the products of NAD+-dependent deacetylation conducted by SIRTs is nicotinamide, a form of vitamin B3, found to be a potent uncompetitive SIRT inhibitor. Therefore, to proper activity, SIRTs require the expression of PNC1 genes, responsible for nicotinamidase synthesis, which hydrolases nicotinamide to nicotinate acid, preventing from its excessive accumulation, and thus SIRTs inhibition [34,35]. Other SIRTs inhibitors are β-naphtols, with representatives such as sirtinol, splitomicin, and much more stable and effective cambinol. These compounds are unselective inhibitors of SIRT1 and 2, although their impact on other SIRTs has not been observed. Their binding site is different from NAD+'s, which is suggested to decrease their potential toxicity. There have also been found inhibitors sharing their binding site with NAD+, such as EX-527, useful in the low nanomolar range. This indole derivative, competitively prevents NAD+ binding to SIRTs, disallowing their activity, since they require NAD+ as a cosubstrate. SIRTs inhibitors, similar to activators, can find a use in the therapy of age-related diseases. Through blocking SIRTs, resulting in increased antitumor-acting p53 activity, they enhance cells apoptosis. Therefore, by promoting cell death leading to stunting tumor growth, they find potential use in the treatment of neoplastic diseases, such as lymphoma or melanoma [36].

Conclusions

Aging is not only a physiological phenomenon but also has significant ecological fundaments. Therefore, the evolutionary approach should be applied in medicine. Natural selection does not always promote longevity; hence knowledge about the evolutionary factors

these processes are dependent on is a key to control them competently. It is possible that evolutionary paths of Y chromosome present lower lifespan of men and prolonging men's life may be reached by modification of this chromosome. The future of aging counteracting lies in recognition of epigenetic mechanisms and epigenome editing. Proteins like sirtuins, regulating many metabolic paths can turn out crucial in achieving increased longevity. Thus, further studies over substances inducing or inhibiting their particular activity are desirable.

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Pharmacological and non-pharmacological treatment of depression and anxiety induced by inflammatory bowel disease

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List of abbreviations

ACT – Acceptance and Commitment Therapy

CBT – Cognitive Behavioral Therapy

CD – Crohn"s disease

HPA axis – hypothalamic-pituitary-adrenal axis

IBD – inflammatory bowel diseases

IL – interleukin

SSRi – selective serotonin reuptake inhibitors

UC – ulcerative colitis

Introduction

Inflammatory bowel disease (IBD) is a group of chronic, relapsing inflammatory disorders of the gut. The two main IBDs, Crohn's disease (CD) and ulcerative colitis (UC), consist of chronic relapsing and remitting conditions and account for high levels of individual and social impairment. UC is restricted to the large intestine whereas CD can affect any part of the gastrointestinal tract.

The immune system produces an inflammatory reaction, leading to symptoms such as bloody diarrhoea, fatigue, abdominal pain, loss of appetite, weight loss and fever.

The etiology of these diseases is multifactorial and depends on both genetic and environmental factors. Recently, a psycho-neuro-immunological view of IBD has developed due to intriguing observations, that psychological status directly influences inflammatory lesions in the gut.

There is increasing evidence that brain-gut interactions are altered during the development of IBDs. Understanding the relationship between the neurobiology, psychological symptoms, and social ramifications of IBD can guide comprehensive care for the whole patient. The most common psychological conditions in patients with IBD are depression, anxiety, and chronic abdominal pain.

Depression and anxiety should be considered as extraintestinal manifestations of IBD. Both diagnoses are significantly increased in patients with UC and Crohn's disease, compared with the general population, even when individuals are in remission, and they occur even more frequently during flares of the bowel disease [1].

Compared with the general population, patients with IBD seem to be twice as likely to experience depressive disorders. The rate of depression and/or anxiety in IBD is estimated at 15%–35% during remission and ≤80% for anxiety and 60% for depression during IBD relapse [1].

According to these studies, the physical symptoms of UC or CD, anxiety, depression, and stress are integral to the morbidity with which many patients content. Interventions directed at these modifiable factors might yield profound benefit [2].

It is crucial to highlight the importance physicians must place on ensuring the mental health of patients with IBD is both assessed and treated appropriately as suicide is the most severe manifestation of depression [2].

In some studies, it was sought to identify if patients with IBD have a higher incidence of suicide and it turned out that patients with Crohn's disease and ulcerative colitis may have an increased risk of suicide [2].

The goal of this literature review is to summarize the evidence on the utilization and effectiveness of pharmacological treatment with particular reference to antidepressants and non-pharmacological treatment focusing on encouraging studies in ACT (Acceptance Commitment Therapy) and CBT (Cognitive Behavioral Therapy) psychotherapy for depression and anxiety in people with IBD.

Methods

The systematic literature review was conducted by using three different electronic databases: PubMed, Researchgate and Clinical Key. Electronic databases were searched, without any language restriction. All relevant papers issued after 2001 were examined.

Results

Depression and anxiety in IBD - pathopsychology

The etiology of mood disorders in patients with IBD seems multifactorial. Recently, there has been considerable interest in the combined role of inflammatory and stress biomarkers to cause changes in brain structure and function, with resultant mood disorders. Most of the evidence that links inflammation to depression comes from 3 observations:

- One-third of patients with major depression show elevated peripheral concentrations of inflammatory biomarkers, even in the absence of medical illness:
  - C-reactive protein,
  - tumor necrosis factor-α
  - interleukin (IL)-6.
- Patients with IBD with higher levels of acute phase reactants have a higher incidence of depression compared with those with normal inflammatory marker levels. A recent meta-analysis found treatment with selective serotonin reuptake inhibitors produced a decrease in IL-1b and IL-6 levels that paralleled improvement in depressive symptoms.
- Patients treated with cytokines (small proteins, that are important in cell signaling) at greater risk of developing major depressive illness

Proposed mechanisms include the direct effects of proinflammatory cytokines on dysregulation of:

- the hypothalamic–pituitary–adrenal axis,
- pathologic microglial cell activation,
- impaired neuroplasticity,
- structural and functional brain changes.

A holistic approach would potentially target underlying inflammation, and in turn, this would decrease the excitability of sensitized afferent pathways and alter

emotional and/or cognitive functions, ultimately enabling more effective management of both inflammation and depression in patients with IBD.

Both anxiety disorders and depression are criterion-based diagnoses:

Depression	Anxiety
Persistently depressed mood	Excessive anxiety or worry, difficult controlling worry
Insomnia or hypersomnia	Sleep disturbance
Psychomotor agitation or retardation	Muscle tension, irritability
Fatigue or loss of energy	Fatigue or loss of energy
Feelings of worthlessness or inappropriate guilt	Feelings of restlessness or keyed up or on edge
Diminished ability to think or concentrate	Diminished ability to think or concentrate
Recurrent suicidal ideation	
Diminished interest or pleasure	
Significant weight loss or change in appetite	

The role of brain-gut axis in IBD

There are research suggesting a bidirectional relationship between IBD activity and psychological disorders, that is, the “brain–gut axis,” wherein relief of depression and anxiety symptoms by the use of antidepressants potentially affects gut health [3.] The brain regulates the gut and its microbiota via neuroanatomic, immunological, and neuroendocrine-hypothalamic-pituitary-adrenal axis (HPA axis) pathways, communicating via neurotransmitters, neuropeptides or microbial-derived products affecting gut microbiota [4]. There is evidence that the course of IBD is worse in depressed patients and in an animal model of colitis, induction of a depressive episode in mice reactivated the colitic inflammation [5]. Moreover, there is strong evidence for an association between perceived stress levels and IBD flares [5]. Preclinical data from animal models reveal that stress is involved in the initiation and relapse of experimental colitis. It has been suggested that stress-induced alterations of brain–gut axis may exert a deleterious effect on IBD via:

- increasing intestinal permeability and bacterial translocation
- changing gut microbiota growth, structure, colonization pattern and infectious susceptibility to intestinal pathogens
- altering both the mucosal immunity and HPA axis response [6].

Visceral hyperalgesia also seems to play a role in IBD associated mood disorders. Pain is the presenting symptom in up to 70% of patients with IBD. The relationship between chronic pain and depression, like the brain–gut axis, is bidirectional. Depression can present itself as chronic abdominal pain, and patients with pain are at increased risk for depression independent of disease activity [7]. Chronic inflammation, as seen in IBD, induces persistent sensitizing effects in the sensory afferent pathways and leads to altered processing of pain by the central nervous system, with downstream alterations in the emotional and cognitive processing of this increased visceral input [7].

Pharmacological treatment

According to clinical guidelines, patients with IBD should be treated with antidepressants for symptoms of anxiety and depression when required, since psychiatric comorbidity might modify the disease course adversely [8]. Patients with IBD have increased the use of antidepressants compared to the general population (19% vs. 28%) [8]. However, no antidepressants are currently approved by regulatory agencies for individually treating anxiety and depression comorbid with IBD, to manage physical symptoms of IBD or to reduce bowel inflammation [9]. It is assumed that antidepressants can reduce symptoms of anxiety and depression and improve quality of life in IBD. In clinical practice, antidepressant treatment of concomitant mood disorders in IBD seem to reduce relapse rates, use of steroids, and endoscopies in the year after their introduction [6,8,10]. Gastroenterologists reported that antidepressants were successful in reducing pain, gut irritability, and urgency of defecation. [11]. Further, treatments which improve inflammation in IBD are known also to improve quality of life [12]. The most favourable influence of antidepressant treatment was observed among patients with CD compared with UC patients. This favorable influence of antidepressant treatment on the IBD course was found regardless of being exposed to monotherapy or mixed-use [8].

It is hypothesized that antidepressants may help treat depression in IBD due to immunoregulatory effects [13]. Some studies have shown that antidepressants have anti-

inflammatory properties and thus improve not only mood but also bowel symptoms, by extending or inducing remission [9,14]. The anti-inflammatory effects of antidepressants have different mechanisms. In humans, a significant drop in serum C-reactive protein concentrations - inflammatory biomarker (independent of depressive symptoms being resolved) has been observed following four weeks of treatment with SSRIs (selective serotonin reuptake inhibitors) [15]. Even in healthy volunteers, antidepressants have been shown to improve immunoregulatory activity [16] and in sufferers of chronic inflammatory conditions, antidepressants are reported to reduce the need for steroids [17] and improve overall immune function [18].

An antidepressant drug which is widely used for the treatment of IBD and gastrointestinal disorders is amitriptyline. It is useful for treating psychological and somatic symptoms in patients suffering from IBD [14]. Amitriptyline appears to have direct effects on pro-inflammatory cytokines that may arise via actions on the nuclear factor-kB. It is a protein complex playing a key role in regulating the immune response to inflammation and is implicated in the pathogenesis of IBD [3]. Furthermore, amitriptyline acts on α1-adrenoceptors to produce anti-inflammatory effects [14].

Paroxetine, bupropion, and phenelzine also were found effective for treating both psychological and somatic symptoms in patients with IBD [19,20]; moreover, bupropion was particularly useful for fatigue and concentration difficulties [5]. Mirtazapine was not recommended for use in IBD patients [5].

A group of medications known as selective serotonin reuptake inhibitors, such as citalopram, fluoxetine, and sertraline, and another group - serotonin-norepinephrine reuptake inhibitors, such as venlafaxine, are both safe and effective in the treatment of anxiety and depressive disorders, with a significant percentage of IBD patients with anxiety or depression reporting a favorable response. In addition to controlling symptoms of anxiety and depression, both selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors have been reported to decrease pain, gut irritability, and urgency of defecation. Patients in better psychological health report fewer functional gastrointestinal symptoms. A recent survey found that almost 80% of gastrointestinal specialists had prescribed antidepressants as adjunctive therapy, especially for pain and sleep difficulties [7].

Anti-inflammatory effect leading to improvement of IBD promotes psychological amelioration, which was associated with a better gut and general health, increased activity engagement and symptom tolerance, less pain and perceived stress, and declined medical

visits [6]. Studies with healthy volunteers have demonstrated that antidepressants can improve immunoregulatory activity [21] and thus there is a potential for antidepressants to not only help with psychological difficulties but also positively impact the disease course [11].

Complementary treatment

There is a growing interest in the use of complementary treatments for IBD. Recently, medical marijuana has received considerable attention for the potential management of CD and is one of the most popular treatment requests by patients. Cannabinoid receptors and their endogenous ligands are known to be involved in the regulation of gastrointestinal motility and secretion. In a small, randomized controlled trial of medical marijuana, CD patients randomized to 115 mg tetrahydrocannabinol cigarettes had a subjective improvement in clinical response but did not meet the primary endpoint of clinical remission. Patient satisfaction with tetrahydrocannabinol was significant, and there was an improvement in self-reported appetite and sleep. However, the lack of improvement of measurable outcomes, including C reactive protein or endoscopic healing, brings into question the benefit of tetrahydrocannabinol for IBD. Additional studies are planned in IBD, but until those results are available, the potential cognitive effects (e.g.: response time, verbal memory, and executive functioning), mood (anxiety and depression) and psychotic effects of cannabis, particularly with long-term usage, and poorer outcomes of patients with CD, the regular use of cannabis is currently not recommended. For patients who have failed established medical therapies for IBD, cannabis should only be considered after a careful risk-benefit assessment [7].

Medications used in the treatment of IBD, such as glucocorticosteroids, have also been linked to mood disorders. Results from analyses have suggested that more than one-quarter of patients on corticosteroids may experience adverse psychiatric effects. It was found that 10% of patients on greater than 20 mg of daily prednisone for three months required hospitalization for either mania or severe depression. In 1 survey, psychiatric symptoms were second only to “moon facies” as the most distressing side effect of corticosteroids. The incidence of psychiatric disorders seems to be related directly to medication dosage. Patients with a prior history of steroid-induced psychiatric symptoms are also at higher risk [7].

There is renewed interest in exploring vagal nerve abnormalities in IBD and IBS—particularly as treatment targets in IBD for inflammation and treatment-refractory depression.

The vagal nerve plays a role in the neuroendocrine-immune−autonomic nervous system axis in maintaining homeostasis between the autonomic afferents (via the hypothalamic−pituitary−adrenal axis) and the cholinergic efferent branches that have been shown to have anti-inflammatory properties. Vagal nerve stimulation reduced inflammation in an animal model of colitis and may be a feasible option for humans with IBD [7].

Non-pharmacological treatment

Over the past several decades, research into factors that influence patient outcomes in IBD has been steadily expanding beyond immunology to include genetics, microbiome and the environment, and, more recently, psychological elements. Psychosocial aspects, seen not long ago as mostly irrelevant, are increasingly recognized as important in shaping the disease course.

Despite significant mental comorbidities with IBD and impact on disease course, mental disorders are not routinely treated in this population. In fact, less than 40% of those with IBD reporting mental symptoms receive psychotherapy [9].

According to the resources and recent studies, Acceptance and Commitment Therapy (ACT) and Cognitive Behavioral Therapy (CBT) seem to be promising methods of treating depression and anxiety in patients with IBD.

Acceptance and Commitment Therapy - ACT

ACT is a psychological intervention that comprises acceptance and mindfulness commitment and behavior change strategies, to increase psychological flexibility and reduce stress, as stress is associated with IBD activity. This hypothesis is supported by a recent study indicating a significant bidirectional brain-gut axis interaction in IBD patients [22]. In terms of ACT for IBS specifically, its use is in guiding patients to develop a willingness to come in contact with their unpleasant experiences of physical symptoms and with the feeling of embarrassment, anticipatory anxiety and distressing thoughts associated with IBS.

In publication *Acceptance and Commitment Therapy Reduces Psychological Stress in Patients With Inflammatory Bowel Disease* [22] a randomized controlled trial to investigate the effect of ACT on stress in patients with IBD was performed. Total of 122 patients with quiescent or stable, mildly active IBD were randomly assigned to an 8-week ACT program or

treatment as usual (control group). Clinical, demographic, disease activity, and psychological data and blood and feces were collected at baseline and at 8 weeks and 3 months after the intervention (week 20). Scalp hair was collected at baseline and week 20 for measurement of steroid concentrations. Hair cortisol serves as a prolonged stress diary and smooths out diurnal steroid fluctuations and variations caused by transient stressors. The primary endpoint was change in stress symptoms, assessed with the Depression Anxiety Stress Scale. Secondary endpoints included changes in perceived stress, anxiety, depression, quality-of-life domains, disease activity, and cortisol concentration in hair.

Overall, 79 participants were included in the complete case intention-to-treat analysis. There were 39% and 45% reductions in stress in the treatment group from baseline to 8 and 20 weeks, respectively, compared with 8% and 11% in the control group. ACT was associated with reduced perceived stress and depression, but not anxiety, compared with control individuals.

In an 8-week ACT therapy course improved stress and other indices of psychological health. In addition, positive effects were found on perceived stress and depression, and therapy also appeared to have some impact on the general well-being quality-of-life domain, at least in those adherent to the protocol. In contrast, no significant treatment effect was found on anxiety levels over the study, although it should be noted that participants were not selected based on preexisting anxiety and that the relatively low baseline levels may have made it less likely that a posttreatment difference in groups could be detected.

According to another study included in the same publication titled *ACT and Stress Reduction: Potential Mechanism of Action* to determine if ACT therapy improves emotional well-being by increasing psychological flexibility, changes in psychological flexibility was assessed over the 8 ACT sessions. There was an increase in psychological flexibility beginning after the third ACT session and that this continued to increase steadily over the later sessions. There was as well a significant inverse correlation between psychological flexibility and stress over the 20-week study, with positive changes in psychological flexibility associated with a reduction in stress.

Many studies reported patient satisfaction with psychotherapy. These patients reported that the psychotherapeutic interventions offered them the chance to meet and exchange experiences with other patients and health professionals, to improve stress management and to receive information about diet, nutrition, and surgery [22] Nevertheless, further research should evaluate the longer-term efficacy of ACT in IBD populations and compare this intervention to allied therapies.

Cognitive Behavioral Therapy - CBT

Cognitive Behavioral Therapy (CBT) has extensive support for treatment of depression and anxiety. It is a well-established form of psychotherapy based on identification and modification of maladaptive behaviors using therapist-mediated cognitive restructuring techniques and has approach based on the theory that psychiatric symptoms and distress are caused and maintained by maladaptive cognitions and behaviors. A CBT framework posits that beliefs that one holds about oneself, the world, and the future are formed by previous experiences and shape an individual's perceptions and reactions to future experiences [12]. The aim of CBT is to modify negative thoughts, feelings, and behaviors and replace them with more positive views, thereby decreasing emotional distress, improving some quality-of-life domains, and increasing treatment adherence [22].

Most studies have found that beginning with empirically supported behavior interventions is the best approach for treatment of depression, anxiety and pain. Given their modest positive effects and the fact that most patients with IBD patients take multiple medications, psychotropic agents should be reserved for those who do not respond to behavior interventions or who have more severe psychopathology [22].

Taking into account combination between pharmacologic treatment and psychotherapy such as CBT, there is a question whether medications, added to CBT, could improve outcomes over CBT alone. Across studies, antidepressants show superiority over compared to pill placebo for depression, although the overall effect is small, and may be clinically meaningful only in more severe cases. Among the anxiety disorders, the antidepressant medications also show a superiority to compared to pill placebo across studies, with medium effects overall. When medications and CBT have been compared directly, across studies the effects are roughly equivalent, at least in the short term [5].

In patients with IBD, a randomized controlled trial reported significantly decreased depression and improved global functioning after cognitive–behavioral therapy. For those who also had a comorbid anxiety disorder, there was a significant decrease in anxiety as well. Similar findings were reported in adults in a Spanish randomized controlled trial after a structured cognitive–behavioral therapy program that included relaxation training, distraction, and cognitive restructuring. The benefits in both studies were maintained at 12-month follow-up [7].

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ACT and CBT have differing analytical approaches, but the 2 treatments are also similar in many ways, so some comparison can be attempted. Based on a review of 5 small studies conducted with a total of 170 participants, Knowles et al. [23] concluded that CBT had little effect in reducing IBD symptoms or improving overall quality of life but that there was promising evidence for improving mental health in the short and medium term; Keefer et al. [24] also acknowledge the benefits of CBT in various gastroenterological conditions. A more recent randomized controlled trial of 118 IBD patients found that anxiety, depression, and quality of life improved in those allocated to receive CBT when compared with waiting-list control individuals, although stress was not specifically assessed in that study [25]. The present results suggest that an 8-week ACT program has similar effects on comparable mental health indices to that of an 8-week CBT course [22].

Discussion

In the most of analysed studies IBDs are associated with mood disorders, such as anxiety or depression, but it is still not clear whether one contributes to the development of the other, or if the interaction is bi-directional [3]. It is not possible to differentiate between whether the beneficial influence of antidepressants on IBD course derives from mood improvements or the effect of the anti-inflammatory properties of the drug [8]. Most studies have found that beginning with empirically supported behavioral interventions is the best approach for the treatment of depression, anxiety, and pain. Given their modest positive effects and the fact that most patients with IBD patients take multiple medications, psychotropic agents should be reserved for those who do not respond to behavior interventions or who have more severe psychopathology [7]. The significant advantage of psychological treatments over pharmacological agents is their ability to sustain improved depression and anxiety symptoms in patients post-treatment [26].

Additionally, acute psychological stress induces the production of proinflammatory cytokines in both the serum and mucosa of patients with IBD. Small retrospective studies of the effect of psychological counseling or antidepressants in IBD have demonstrated fewer relapses of disease activity, and reduced use of glucocorticosteroids. The recent results show that even an 8-week ACT intervention improves stress and other mental health indices, emphasizing the need for researchers and clinicians to further develop and optimize the content and delivery of psychological programs for IBD patients [27]. Although some meta-analysis showed no clear benefit of psychological therapies on disease activity in IBD,

individual trials of hypnotherapy, cognitive behavioral therapy, and meditation have all shown some promise [3].

Most psychotropic medications are said to have the potential for serious side effects (e.g., increased suicidal ideation), may have drug-drug interactions with IBD-related medications, and require careful monitoring [5]. For example, amitriptyline has side effects due to its anticholinergic activity, including weight gain, changes in appetite and muscle stiffness. Other side effects include seizures, mania, and psychosis [3]. Thus, the first-line approach to psychological problems is psychosocial intervention [5]. These side effects, however, are infrequent and the two main side effects of antidepressants are drowsiness and dry mouth [10]. However, given the fact that a much lower dose will possibly be used to exert an anti-inflammatory action on IBD, these side effects may be very minimal. Therefore, by adjusting the dose to suit the anti-inflammatory effects of antidepressants on IBD, they can be used as an effective anti-inflammatory drug for the treatment of IBD [14]. The dose of these medications should be adjusted or altered to ensure maximum therapeutic benefit while minimizing side effects [7].

Additionally, patients should be made aware that clinical benefit is generally not seen for at least 2 to 4 weeks after start of treatment. Up to 50% of patients discontinue treatment within the first weeks or months, often because of side effects, limiting the effectiveness of the treatment. Relapse is common after discontinuation of treatment; maintenance of treatment gains requires long-term treatment in patients who demonstrate a good response to therapy [7].

Importantly, health care providers must be aware of compliance issues in patients with depression [7]. Approaches such as improving the physician–patient relationship, individualized therapy, providing patient information and support, self-management programs and practical memory aids can increase the likelihood of adherence and prolonged remission rates [7].

Concerning psychological treatment, it is not indicated for all patients with IBD. In patients with no evidence of depression or anxiety, evidence that psychological interventions help patients to cope with the disease is lacking. In a large pooled analysis of unselected adult patients with IBD, psychotherapy was ineffective in improving the quality of life, emotional problems, and disease activity [7]. Also, cognitive–behavioral therapy is less readily available, costlier, and more labor/time intensive than pharmacologic treatment. Some research show weak evidence for psychotherapy to be useful for mental disorders and any physical complaints in this population [9]. There are reports that cognitive-behavioral therapy

may provide some benefit in patients with IBD [23]. However, only a few studies are available, and recent trials demonstrate only short-term improvements in quality of life [28].

A significant limitation of our research is the fact that methodological limitations hamper the majority of existing clinical studies in terms of small and selected IBD populations (< 100 patients) and short observation periods (< 2 years). Moreover, existing studies have mainly used symptom-based scoring systems and not objective markers when assessing IBD activity with the limitation of subjective interpretations [8].

Another limitation of the clinical studies is the fact that both central effects of some of the drugs used to treat IBD and differences in the microbiome between individuals were not taken into account. As an example, glucocorticosteroids may have central effects and can induce mood disorders, and thus they can disturb the results of treatment [3]. Furthermore, some studies were limited by a lack of information on medication adherence, as nonadherence to IBD treatment is found to be a significant trigger for disease flare.

Conclusions

IBD is chronic, debilitating disease whose effects spread far beyond the gut. This kind of illness does not generally result in excess mortality; however, patients spend many years coping with their condition and its associated morbidity. A holistic approach should be applied while examining IBD patients [8]. Psychological co-morbidities in patients with inflammatory bowel disease are often unrecognized and ignored mainly in standard treatment paradigms [20]. Screening for the early signs of depression or anxiety and the initiation of pharmacologic or psychological treatment can lead to improved functioning and positively impact the course of disease [7]. Despite the high prevalence of these highly treatable conditions, it is found that IBD patients often do not receive appropriate treatment [26]. Co-existent anxiety or depression, if unrecognized or untreated, may have deleterious effects on the natural history and prognosis of IBD, while ongoing disease activity may have implications for psychological health [3]. Physicians treating IBD patients should be vigilant about expressions of suicidal ideation or signs and symptoms of self-harm. Studies have demonstrated an increased rate of suicide among patients with CD and UC, even after adjusting for confounders [7].

These are important issues because patients with quiescent IBD may be at a lower risk of relapse if co-existing mood disorders are identified and treated. This, in turn, may lead to a

more benign disease course, with a reduced need for subsequent escalation of therapy to drugs with more serious side effects, hospitalization, or surgery [3].

Antidepressants have the potential to be an adjuvant treatment to the conventional therapy for IBD, however future trials examining the efficacy of antidepressants on the IBD course are warranted. Psychotherapeutic and psychopharmacological treatments are also helpful for psychological wellbeing and quality of life and for reducing IBD activity and gastrointestinal symptom severity.

Our systematic literature review showed that at present only a limited number of studies had been conducted on the prevalence and effectiveness of psychopharmacological and psychotherapeutic treatments in people with IBD, so further studies with larger sample sizes and more comparable measurements are needed.

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Selected therapeutic and diagnostic problems

Treatment process and preventive medicine in Poland: obstacles and facilitations for the retirees

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Introduction

The social group of pensioners plays a significant role in the life of each of us; something not everyone is aware of. They are a living source of the history of our country; they serve young people with their experience and wisdom; they acquire through the years. Many of them are an example to follow, ones we can all learn quite a lot from.

Retirement as a concept of leaving work for rest and tranquillity after reaching a certain age is a relatively new phenomenon. The first legal regulations can be seen in various countries dating at the turn of the 19th and 20th centuries [1]. The development and consolidation of the pension system in the legal system were forced by the progress in medicine, which completely changed the structure of society – also leading to a demographic explosion. The average life expectancy increased, which revealed the problems humans would start to face while working into old age.

Currently, in Poland, the pension system generally is being governed by the Social Insurance Institution. There are also additional forms of social insurance, which are entirely optional and constitute additional security. In Poland, the retirement age is differentiated by gender; it is 60 and 65 for women and men respectively. Importantly, retirement is not obligatory at this age; it is a voluntary decision of every citizen.

The population of Poland is an aging society, which was caused, among other things, by the extension of life expectancy. People aged 60 and more at the end of 2014 constituted 22% of the population, which corresponds to around 8.5 million people [2]. These statistics show how

significant part of the patients requiring medical care are pensioners and how much of the problems that doctors face in their daily practice, are associated with retirees.

To improve the health care system in Poland, it is necessary to draw attention to the geriatrics, which is problems of older patients, often pensioners, because it creates challenges that are not encountered in other social groups, therefore requiring a holistic approach to geriatric care. Without much empathy, it is impossible to provide help to pensioners, carry out complete diagnosis and correct pharmacotherapy. It is necessary to focus on the general and individual difficulties that each of them experiences. Some of them stem from the deepening psychical restrictions placed on them by age; others are the result of government policy. Both of these categories often lead to unpleasant situations that are potentially avoidable. Limiting the number of obstacles that pensioners encounter in the process of treating chronic diseases is what modern society should focus on, in the context of improving the quality of healthcare.

Problems in treatment

The inconsistent adherence to treatment is a significant problem in present-day society, which increasingly consists of older people, who often present with chronic illnesses. The World Health Organization classified this as one of the most significant healthcare issues facing humanity in a special report and stated that it is one of the most significant barriers preventing patients from benefiting from therapies based on current medical knowledge [3]. Correct adherence to prescribed therapies consists of four steps:

- the patient's understanding and acceptance of medical advice
- filling the prescription in a pharmacy
- starting treatment
- continuing treatment — either on an ongoing basis or until the proscribed end.

Each of these steps can create problems and in effect lead to non-adherence. The most common forms of non-adherence are not filling the prescription (primary non-adherence); or if the patient filled the prescription, not starting the treatment, delaying it, or incorrectly following it, such as skipping doses, changing the frequency of doses, taking long breaks between doses, and prematurely stopping treatment [4].

Older people tend to seek treatment more often than other age groups. As a medical professional, approaching older patients incorrectly can intensify not only physical pain but also social pain — and erode trust in the doctor-patient relationship. Half of all patients over

55 feels that their doctor does not spend enough time on their care [5]. A patient who feels that their problems are misunderstood might avoid taking their medication or even not start treatment, uncertain if the doctor prescribed the right treatment. It is recommended that the patient have their questions answered, know why they need treatment, what the treatment consists of, and what the side effects are. Both long-term and short-term treatment can be affected by inadequate patient-doctor communication.

The healthcare needs of patients increase with age. In Poland, the average lifespan is increasing, and the number of births is decreasing, which results in older people becoming an ever-larger portion of the population. In 2009, healthcare costs increased in three distinct age groups, one of which was people over 65 [6].

In 2014, people over 65 amounted to 14.7% of Poland's population, which is well over the 7% threshold for aging populations according to the UN. In 2009, older people amounted to 26.3% of all hospitalized patients (1,350,128 people), and 8,083,842,408 PLN was spent on their hospitalization, which is 33.6% of total expenses. The number of people aged over 65 is predicted to grow by 3 million by 2030 [7]. Nursing, palliative care, and hospice costs will rise accordingly.

In Poland, the primary source of income for older people is social security and welfare. After food and housing costs, healthcare expenditures (including medication and doctor's visits) are the most significant expense in retiree households. The average healthcare cost per capita in retiree households was 84,92 PLN in 2010, 2-3 times higher than other kinds of households [8]. Over 18% of people surveyed said they lacked funds to cover medical costs during the preceding 12 months, and 4.1% said they had this problem frequently. 13.5% could not afford diets prescribed by their doctor, and 6.6% could not afford to visit a doctor.

People in those situations tended to purchase only part of their prescription, fulfill it in installments, or even purchase cheaper substitutes to the prescribed medication. The largest group (27.4%) decided to forgo buying medication altogether [8]. It is a significant indicator that a large part of the population refrains from treatment in the face of poverty. Those are the people that most often consider their health to be very poor and are the most likely to require extended subsequent hospitalization.

Single-person households are the worst off, as they have a large number of fixed costs and low disposable income. Older people, used to the fast-acting medication, very often do not feel like their medication is beneficial to them [5]. It is essential to include them in the

diagnostic and therapeutic process, e.g., by allowing them to control essential parameters in their illness, such as blood pressure in hypertension, glucose levels in diabetes, weight in circulatory insufficiency or peak expiratory flow in asthma. The patient can then personally witness the benefits of their treatment. A relationship between self-efficacy and functional status and satisfaction with life in older people has been observed. Patients with feelings of high self-efficacy have better mobility, are more active in daily life, and exercise more, which results in more independence. Higher physical activity helps to satisfy biopsychosocial needs and gives personal satisfaction. It has been shown that patients with locomotory disorders were keener to exercise regularly. Therapy that increases self-efficacy after heart attacks or pulmonary disease increased patients' physical activity and as a result increased their quality of life and independence [9].

Problems with medications

A huge problem among older people is dysphagia, which is difficulty in swallowing. According to research, it occurs in 7-10% of people aged over 50, 25% of all hospitalized patients and in 40% of extended care facilities and nursing homes [10]. There are insufficient medications in liquid form on the market and patients must often split or crush pills, which is especially difficult for people with bad eyesight or if a pill is not intended to be cut and is not scored. This often leads people to forget their doses or to refrain from taking their pills altogether if the pill is too large to swallow.

Multi-morbidity and polypharmacy increase with age. According to research in Europe, the majority of older people takes at least one daily medication. Around 80.1-93.3% of people over 59 take medication regularly in Sweden. 99.8% of people over 70 in Germany take at least one prescription medication. In Poland, 95-97% of people surveyed over 69 said they take medicine regularly [8]. Older people with multiple illnesses take prescription medication as well as an over-the-counter medicine. Drug interactions, as well as lower metabolism in older people, resulting in more occurrences of side effects, which cause more visits to the doctor, which in turn result in a more prescribed medication, resulting in a prescription cascade. Very often people with severe and chronic illnesses, cared for by their family, do not understand the mechanisms of action of their medication.

One problem with polypharmacy (taking five or more medications concurrently) is that older people are often under the care of multiple specialists, who do not communicate

with each other. Additionally, older people tend to prefer to take more, rather than fewer, medications. This undoubtedly increases the cost of medical care, both in the case of subsidized and unsubsidized medications.

Free of charge medications for people over 75 years old

The lowest guaranteed pension benefit in Poland is PLN 1,100 gross and PLN 934.5 net [11]. For the correct assessment of the value of this amount, it is necessary to compare it to others that describe the wealth of the society. With the beginning of 2019, the minimum wage has changed, which is now PLN 2,250 gross [12], while the value of the average remuneration in the fourth quarter of 2018 amounted to PLN 4,863.74 gross [13]. Only the comparison of these three amounts reveals the background of problems related to the health care of pensioners in Poland.

One of the conditions for the success of the treatment process and maintaining a satisfactory health condition is proper pharmacotherapy. The share of average monthly expenditure on health in total expenditure per person in pensioners' households in 2017 amounted to 8.7% of the total budget, of which almost 95% were costs related to the purchase of medicines [14]. In response to public debates and social pressure, a government program was created to provide free access to medicines for people over 75 years of age. All regulations related to it entered into force in 2016. In 2017, the first full year of the regulation's validity, PLN 564 million was allocated for financing the project. This reduced the expenses for reimbursed drugs of patients under the program by about 65%, including PLN 860 million in 2015 to PLN 296 million [15].

The main goal of the project was to reduce the expenses related to the treatment of old-age diseases. Initially, access to free medicines was available to people taking preparations with a 30% level of payment used in the treatment of hypertension, ischemic heart disease, thromboembolism, asthma, chronic obstructive pulmonary disease, diabetes, depression, and dementia. Over time, the range of refunded preparations has been enriched with human insulin and insulin analogs, preparations used to treat patients with symptoms of Parkinson's disease, glaucoma, hypercholesterolemia. The latest list of reimbursed drugs, special-purpose foods, and medical devices become valid from January 1, 2019. The list of free medicines for seniors included in it contains 2017 items including 147 active substances [15]. From year to year, the amount of funds earmarked for the implementation of the program is to be higher, which involves the reimbursement of subsequent funds.

The total abolition of the fee for selected pharmacological agents is not unique on a global scale. In Estonia, children up to 10 years of age, pensioners and people over 63 receive some medicines at a 90% discount. In Spain, pensioners are fully exempted from fees in the pharmacy. In Germany, fees for reimbursed drugs do not apply to children and adolescents up to 18 years of age and pregnant women, as in the United Kingdom, but there, also, are relevant programs for people over 60 years of age. In Belgium, the Czech Republic, the Netherlands, Liechtenstein, Portugal, Slovenia and Iceland, Lithuania, Latvia and Hungary, some of the medicines are covered by a full refund [16].

The idea of financial support for older people is common in European medicine. Economically developed countries expand their activities towards children and pregnant women. In Poland, this is just the beginning of the development of a program for the total refund of certain medicines, but it is a good start for geriatric care. Undoubtedly, the actions taken are a drop in the sea of pensioners' needs in our country, but this is a step towards better healthcare for seniors. What remains is the observation of the evolution of the "Leki 75+" program and the way it is implemented, as well as the work on successive solutions facilitating the functioning of older people in our society.

Preventive medicine in retirees

Thanks to the early detection of the disease we can slow down its progress, prevent complications, reduce the costs of treatment and enable patients to function normally in everyday life. Prevention of health is particularly important in older people due to the greater number of diseases that appear with age, hence the development of geriatric care.

In 2009, the then minister of health recognized geriatrics as a key field of medicine and drew attention to the need to increase its funding, availability and quality improvement. The effect of the undertaken activities was the development of a medical procedure called “Complete Geriatric Assessment” (COG), which has been in use at hospital geriatric wards since beginning of 2012. It allows for an orderly and comprehensive assessment of the health condition of an elderly patient. It includes tests in various fields of medicine, thanks to which the patient's independence is also checked. The use of COG, due to the accurate categorization of patients and understanding their needs, increases the accuracy of diagnosis, which indirectly reduces the mortality rate among geriatric patients. Thanks to this procedure, you can also reduce the amount of medicines taken by older people and reduce the number of

unnecessary medical services, especially admission to the hospital. Seniors' quality of life was easily improved without raising the cost of caring for them. From 30 June 2016, COG is carried out in every hospital, even if it does not have a geriatric ward. Obviously, maternity wards and care for newborns and children do not complete this assessment [17].

An important aspect of health care for retirees is oncological prophylaxis. In its foundation is patient education. One of the ways used to implement it, addressed to all age groups, is the European Code of Fight against Cancer [18]. Publication "12 ways to health" answers basic cancer questions and presents ways to reduce the risk of developing cancer.

It can be stated that pensioners as a social group are excluded from screening programs for cancer. Only women aged 50-69 can apply for a free mammography screening organized by the Population Program for Early Breast Cancer Detection [19]. There are local initiatives in the form of so-called "White Sunday". These are actions organized by local authorities, in various places and at different times. They aim is in enabling the elderly to take advantage of free medical examinations and consultations without specialist referrals and queues. For example, the long-standing tradition of the Wrocław Grand Finale of the Great Orchestra of Christmas Charity is the organization of a similar event in which local hospitals and clinics take part. Health and pro-health education is also provided by foundations operating for pensioners.

Undoubtedly, the screening program in Poland should focus its activities also on people at an older age. It is necessary to take legal action to structure social actions similar to the "White Sunday" described earlier. Advertisement of similar activities among pensioners is necessary. The procedure of a comprehensive geriatric assessment has brought excellent benefits, it is worth working on the next ones that will help in caring for the oldest patients.

The most common reasons for hospitalization of seniors and their consequences

Despite the occurrence of a large variety of diseases affecting the elderly people, it is possible to distinguish diseases that are most common among this age group. Making an unambiguous diagnosis is often difficult due to the coexistence of several diseases at the same time, moreover many of them may be chronic.

The most common causes of hospitalization of the seniors are cardiovascular diseases. They are the first cause of death among patients over 65 years [20].

One of the main risk factors for stroke, heart failure or coronary heart disease is

hypertension. This problem affects 61% of patients above 65 years of age. One of the factors that causes this disease is decrease in elasticity of the arteries, and it is an important fact since this process is physiological for the progressive age. The consequences of hypertension can not only lead to death, but also significantly affect the way and comfort of a senior's life. The effect may be a significant limitation of independence, impairment of vital functions which may lead to a total dependence on the family or caregivers. Therefore, proper diagnostics, rapid implementation of therapy and, if possible, prevention are the main goals of treatment. In addition to pharmacotherapy, adapted to the advanced age of the patient, an important element of treatment should be a change in lifestyle. It is recommended to include aspects such as: maintaining a proper body weight, using a specific diet, with adequate sodium content, maintaining physical activity and avoiding smoking [21].

A serious consequence of hypertension is ischemic stroke. Other risk factors are alcohol consumption, dyslipidaemia, atrial fibrillation, obesity, and smoking. The risk of stroke increases with age, in patients between 75 and 84 years of age it is 10 times higher than in those aged 55-64. This is the third leading cause of death, above the age of 65 and one of the main reasons for the loss of mobility and independence [22]. One of the most important elements of treatment is the rehabilitation, it requires commitment and education of the patient as well as the family, because the treatment does not always bring the expected results. Drastic limitation of the patient's independence, as well as difficult contact, often requires major changes in the home environment, such as adapting it to the new limits of an elderly person, or providing equipment for rehabilitation. Very often when long-term professional care is necessary, apart from investments in equipping the environment in which the patient is staying, it entails high costs. In addition, even those patients who do not have such drastic mobility restrictions after stroke, prefer to rely on the opinion of others, what causes limiting their own independence [22].

Besides of cardiovascular diseases, a major cause of hospitalization for seniors are injuries, most often occurring as a result of falls. Their cause may be external, depending on the environment or internal, resulting from deteriorating health. The internal factors include osteoporosis, amblyopia, disturbances of balance, dizziness, and the external one is mainly the non-adaptation of the environment to the seniors' movement limitations [23]. A very serious consequence of the falls of the elderly people is a fracture in the proximal femur. It affects a woman more often, it accounts for 75% of all fractures, due to the occurrence of osteoporosis. In addition to prolonged immobility and loss of independence it carries a high risk of death.

Research shows that within 12 months of injury, 37.1% of men and 26.4% of women die [24]. Loss of independence, like in the case of previous illnesses, eliminates a senior from many spheres of social life. This may be the reason for isolation, loneliness and as a result, feeling of helplessness and depression.

The basis of therapy is properly selected surgical treatment, but an important element is also rehabilitation. The support of family and friends is extremely important in the process of treatment, group exercises show a positive influence on the psyche of the elderly person, and thus on the whole process [24]. On this basis, it can be concluded that belonging to a group that is struggling with a similar problem eliminates the feeling of loneliness and helplessness, gives motivation for action, which can be additionally increased by contact with the family.

Discrimination and its manifestations in various wards

Aging of society causes changes in the age structure of patients, both in the primary care clinic and hospital departments [22]. It creates the need to develop the geriatric part of health care programme but also to adjust the way of communication and care of such patients by medical personnel. The main factors determining the occurrence of problems in caring for seniors is their multi-morbidity, as well as functional impairment, which often causes reluctance, neglect or in extreme cases, discrimination of older people by medical personnel.

By the concept of discrimination, we mean the often occurring form of social exclusion, manifested by treating a person less favorably than another in a comparable situation, due to some feature [23]. If the feature is a late age, this phenomenon is called ageism. It can have various forms, based on the division contained in the sources we can distinguish [23]:

- imperceptibly, concerns seniors both as individuals, when they need help in public places, but also as a consumer group whose needs are not noticed by service providers,
- disrespect, behavior that expresses the lower value of the opinions and needs of older people compared to younger ones,
- ridiculing, conscious misrepresentation and mocking the problems of seniors and ways of dealing with them,
- overprotection, imposing help, treating an older adult as unable to deal with problems

in situations where they could cope alone, without any difficulty

- condescending, treating the senior as a person unable to function independently,
- neglecting, overlooking the essential psychosomatic, social and material needs of older people, often in the area of their rights, including health,
- segregation, isolation of seniors as a group from the rest of the community, which can lead to social isolation and rejection,
- financial abuse, unjustified, unlawful use of material resources, often associated with neglect,
- physical abuse, physical aggression towards seniors which can take various forms, from mild to violent behavior.

Discrimination of seniors on the health market can be analysed in many respects. One of them is the state of geriatric care in Poland. The number of specialists in the field of geriatrics for 2014 is 321; however, due to the lack of geriatric units, it is estimated that in fact, a much smaller number of these doctors work with the elderly. Additionally, in Poland, there are only 0.8 geriatricians per 100,000 inhabitants, which is a very low result compared to other European countries, even those with a similar history and degree of economic development as the Czech Republic or Slovakia, where the value is 2.1 and 3.1 per 100,000 inhabitants [23]. Lack of specialized units means that the older adults are placed under the care of the personnel and on the wards unsuitable for their needs. According to the presented division, this phenomenon can be classified as negligence, because despite the number of seniors as a social group, their needs are ignored.

To assess the remaining forms of discrimination, a study was carried out on a group of nurses, paramedics, and doctors, in two medical facilities in Szczecin and Bydgoszcz. The results show differences in the care of the younger patient and the elderly one [24]. Taking care of a senior is a problem for 11.4% of respondents; however, geriatric patients do not cause negative emotions in 96.7% of respondents. This data suggest that the medical staff does not have adequate training to care for an older adult, which may be the source of the problem. Also, the lack of negative attitude may indicate an excellent base to develop better contact with the senior citizen. Analysis of the results showed a significant difference in the approach to patient care depending on the ward where it is located. Less favourable treatment of patients was confirmed by 11.1% of ER employees and 12.2% of EMT employees.

Furthermore, research has shown that the reluctance to seniors was more frequent in the group of employees with the shortest seniority [24]. Except for the opinion about their

feelings and approach to the geriatric patients, the observations of the subjects were examined too. The results showed that the reluctance to provide medical services was observed to the greatest extent in the orthopedic ward (35%) and ER (31.3%). In addition to unpleasantness, unethical behaviour and unsuccessful or delayed medical services were also observed in relation to older patients in these wards [24].

These results should lead to a more in-depth analysis of the problem, especially that the large percentage of the patients who stays on these branches, are seniors [24]. Lack of appropriate geriatric units means that older patients usually first go to the Hospital Emergency Department [25]. The most common reasons for taking seniors to the hospital are cardiovascular diseases, which often force a more extended stay in the hospital. Another reason for the prolonged hospital treatment are injuries, especially woman fractures of long bones. Because of them, patients after admission to SOR goes to the orthopedic ward, where, due to the long treatment process, they often stay on for many weeks [26]. Because of the multi mentioned above - morbidity of geriatric patients, their time spent in the hospital often prolongs after staying in one of the departments. This is caused by exacerbation of further diseases, by unfavourable conditions prevailing in the hospital, decreased the condition of the immune system of seniors, and as a consequence of one-way treatment only when the health problem is complex. It causes the situation when the patient is transferred from one ward to another, where attempts are made to treat each disease separately, while maintaining previous therapies, without updating them during the implementation of new procedures about subsequent diseases [27].

The result of such proceedings is not only the long time spent in the hospital for a senior but also the perception of a geriatric patient, as a permanent element of many departments, requiring special care. Such a picture of the situation is conducive to the occurrence of the phenomenon of ageism because the process of treatment and care for the older adult requires greater involvement of medical personnel, both at the level of multi-directional therapy and often difficult contact with senior patients. Lack of proper training of the staff, limited time to care for one patient and lack of adaptation of the departments only exacerbates the situation.

The arguments quoted above confirm that discrimination against older people in the Polish healthcare system exists and is a severe problem. Its solution requires multidirectional, effective and quick action, due to the continually progressing process of the aging population. It seems necessary to train employees in the area of communication and the specificity of care

for a geriatric patient, which will improve the quality and comfort of seniors' treatment.

Geriatric care homes in Poland

Health problems of an aging population, multi-morbidity, and poverty cause social problems. Unfortunately, the healthcare and social welfare system in Poland is not well suited to demographic changes and the increasing needs of older people. This, in addition to declining public healthcare funding, leads to older and disabled people having the most inferior access to healthcare [21]. In-home care is especially pertinent, as it has a lower overall cost and is more beneficial to patients, who prefer to stay at home. The lack of in-home care leads to deteriorating health of single people and the necessity of standalone nursing care, which has long waiting times that cause even further health deterioration.

There is a significant deficit in geriatric care homes in Poland [24], and patients have a low opinion of it. It results from patients perceiving them as "old people's homes," which historically had no standards of care and were not regulated. It leads to an image of places where their families completely abandon people. Even now, many of the facilities are grim and unappealing places to live. In Poland, in 2000, only 0.9% of people over 65 used long-term care homes or similar facilities, even though research showed that around 1.6% of people over 65 are not able to bathe by themselves and 12.9% require significant help in doing so. A similar portion of seniors had difficulty with dressing up [9]. Most of the responsibility of caring for older people fall on their families, which means family members have to sacrifice their work time to care for them.

In Poland, in 2017 there were 1723 nursing homes with around 109,000 patients, of which 303 provided around the clock care for older people. Older people in those numbered 24,044, which is a grossly insufficient number compared to the overall need [24]. Privately run nursing homes exist which have a much better reputation, although they are inaccessible to most people due to high cost, which is often much higher than the average monthly pension.

Conclusions

Analysis of the presented issues shows not only the state of geriatric care in Poland but also the difficulties in self - health care and independent treatment of seniors. The multitude

of diseases that older people experience and their simultaneous co-existence is a problem not only for the doctor in the selection of treatment and, if necessary, referral to the appropriate facility. It is also a problem for patients because it requires significant expenses, as well as a good understanding of medical recommendations and often complicated treatment procedures.

The scale of the difficulties faced by older people shows that care and information programs are not sufficiently developed and that there are not enough personnel and specialized geriatric units. Despite almost doubling the number of geriatricians over seven years, it is still an insufficient number to ensure a high level of health care for older people [24,27]. This is confirmed not only by the long period of hospital treatment, which involves multiple branch changes but also by many difficulties with observance to medical recommendations when the patient is at home.

Failure to follow recommendations, caused by difficulties both in understanding the information provided by the doctor, as well as resulting from other disease entities, such as dysphagia, causes re-contact with the doctor and often another hospital stay. This causes a vicious cycle of treatment and hospitalization in which a senior is imprisoned and without specialist help is unable to get out.

Solutions that are intended to help seniors in treatment and self - care, in fact, give diverse effects. Reimbursement of drugs for seniors has an excellent chance to have a positive impact on the regularity of drug use, through the financial relief that will allow them to purchase of medicines. The effect of this program covers a large group of patients because it includes the treatment of diseases occurring with the highest frequency. The development of the reimbursed drug base will help a bigger group of older people in the future, whose financial resources often do not allow the purchase of essential medicines.

Another necessary action to improve the state of geriatric care in Poland is not only increasing of several geriatricians, but also the education of medical personnel in non-geriatric wards, in the area of care and contact with older adults. The development of social care homes is also necessary to ensure the comfort of living for seniors who live alone.

In the process of treatment, seniors have to fight many difficulties and problems. On the one hand, there are noticeable development trends regarding geriatric medicine and care. However, on the other hand, the rapidly progressing process of population aging is a huge challenge, the resolution of which requires thoughtful, but quick and effective decisions.

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A review of smartphone applications and wearable medical devices as tools in the management of chronic diseases

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List of shortcuts

CVD – cardiovascular diseases,
ECG – electrocardiogram,
WMD - Wearable Medical Device,
GPS - Global Positioning System,
HR - Heart Rate
T1D - type 1 diabetes
T2D - type 2 diabetes

Introduction

In the world of rapidly developing technology, there is no surprise that technological novelties enter the healthcare sector [1].

More and more participants in the field (doctors, patients, insurance companies, pharmacies, government) use new technologies for medical purposes. Smartphone applications and wearable devices described in the article are gaining more interest and can become an important element of control of diseases [1].

What is a medical application?

A medical application is a software developed for medical purposes which are very broadly defined. The software may include medical databases, diagnostic tools for specialists based on simple algorithms or artificial intelligence, as well as home monitoring systems for patients.

What is a wearable device?

Electronic devices that can be incorporated into human clothing or worn as accessories such as ring, watch or bracelet are called "wearable device", "wearable technology" or just "wearable" [2]. They are able to perform a broad spectrum of operations and in this are similar to modern smartphones or even computers. Moreover, there are some fields where surpass standard laptop, for instance the feature of being an activity tracker, navigation system or basic life parameters monitor are tasks that goes far beyond just an electronic device. The wearable device can play a role of a companion that has a vast knowledge about his user's physical condition.

These devices are often equipped with sensors such as GPS, pedometer, speed sensor, sleep and movement detector, accelerometer, pulse rate monitor, and even ECG sensor. It enables to track physical activity in terms of number of taken steps, walking distance, speed, altitude and heart rate.

How many people use wearable technology?

The sector of wearable devices is growing astoundingly, and the trend has been noticed worldwide. The most common type of device in 2017 were wristbands, hybrid watches, and smartwatches [3].

In 2019 the technology continues to popularize itself with the prediction of 350,4 million global users bringing 14,528 million US dollars in revenue [4].

In Poland 1,95 million people use wearables, in which most (38.4%) are aged 25-34 years, 26.2% are aged 35-44 years, 22.0% have 18-24 years, then 9.1% of people within 45-54 years and the rest (4.3%) that are 55 years old or more [5].

The market of wearable devices is expected to grow due to rapid product adaptation, low-cost product and device development [6].

What is clinicians' view on smartphone health applications?

Karduck et al. asked 719 clinicians about their attitude towards mobile health applications through a questionnaire [7]. Although only 55% confessed to using them professionally, most of the physicians (77%) admitted to using them for personal purposes [7]. Majority of them (62%) agreed that smartphone health apps are superior to traditional methods for patients to track their dietary intake, monitoring physical activity, making better food choices, losing weight and tracking blood glucose level [7]. Among all the advantages listed the most important were:

- Better accountability/compliance: for some people, it is easier to monitor their health behaviors on the smartphone, and they would not do it on the paper
- Accessible for low-literacy patients: most calorie-counting apps have built-in barcode scanner which facilitates product listing - it enables to make a photo of the product
- According to clinicians specialized in dietetics or diabetes, it is easier to count calories and carbohydrates through smartphone applications
- Most of the applications are free and only their very advanced features demands subscription

Therefore these type of self-monitoring applications for patients with obesity and diabetes can improve their treatment outcomes.

Apps in management of cardiovascular diseases (CVD apps)

Epidemiology and management of cardiovascular diseases

Cardiovascular diseases (CVD) are the most common reason for death worldwide, accounting for 17.3 million deaths annually in 2013. The absolute number of CVD is on the rise, accompanying the growing number of world populations [8]. Even in the majority of developed countries, with a growing rate of cancer deaths, the CVD deaths have not been outnumbered by the other diseases. In Europe, these two were responsible for 37% and 26% of all deaths respectively [9]. As for morbidity, CVD is one of the most common diseases in the general population and affects the majority of adults aged 60 or more [10].

Leading manifestations of CVD are ischemic heart disease, heart failure, hypertension,

arrhythmias or vein thrombosis which can lead to possibly life-threatening emergencies as heart block, myocardial infarction, pulmonary embolism or stroke. Despite the overwhelming numbers, mortality ratios of CVD have been reported to decline significantly [11], although the phenomenon is confined primarily to developed countries. This can be greatly attributed to the development of new treatment schemes of CVD in controlling both chronic states (which decrease the number of life-threatening cardiac events) as well as management of acute states. Treatment scheme in many CVD includes more than one medication.

Moreover, among cardiovascular drugs,, there are particularly many groups of medications with similar effects, e.g. on heart tropisms, although with different pharmacokinetics or pleiotropic events. The doses are often adjusted to the course of the disease (which can be assessed with many parameters, although one of the most important as well as simple diagnostic tests includes: heart rate, pulse, systolic and diastolic pressure, and ECG). Somewhat complicated treatment schedule, the great importance of quick identification and management of acute cardiac events and high prevalence of CVD disease indicate that patients suffering from CVD are a excellent target group for medical applications developers.

Characteristics of CVD apps: price, popularity, developers

In general, the applications with basic functions described below are often available for free, although users can purchase extended versions which offer a recording of the measurements, graphical presentations or even dietary recommendations for cardiological patients. Despite that, one of the most popular apps (Instant Heart Rate) costs 10 euro/month (or less with a yearly subscription). Although the differences inaccuracies of measures can explain the discrepancy, prices also depend on advertising policy of a company – some perform many advertisements, which might be unpleasant for the user, but are for free instead.

The applications are mostly in English, although some can be installed with different language version. This is important concerning the fact that people who are more prone to CVD and therefore who more often monitor cardiac parameters are older, and if an app would be available only in a foreign language, it would deter them from using it.

In Poland, there are few popular domestic developers of apps which, e.g., measure HR. Among applications for recording blood pressure measures (measured independently from the app), the

polish app Blood pressure (by Klimaszewski Szymon) has gained great acknowledgment with more than 5 million downloads.

The most successful apps are developed by start-ups rather than "big players" like Google, although they create medical applications as well (e.g., Cardio journal - Blood pressure diary by Google) Majority of applications are available for both iOS and Android although there exist apps for iOS which don't have a counterpart for Android. Example of that is Cardiio Version, an app which clinical usefulness has been confirmed in studies [5].

As far as the number of users is concerned, it is relatively hard to compare the popularity of an app in the country since the data presented in online stores often do not differentiate customers by country and the number of customers includes worldwide users. It is also worth remembering that the number of downloads is far lower than the number of actual users.

However, the scale of apps usage can be illustrated by the fact that apps: Instant heart rate by Azumio Inc. and above mentioned Blood pressure by Klimaszewski Szymon have more than 10 and 5 million users respectively as far as the safety of sensitive data is concerned, among apps for the recording of blood pressure, less than a half-tracked personal background data [12].

Apps for heart rate measures

The most popular facility provided in the CVD apps is determining the user's heart rate. The apps use plethysmography in which smartphone camera capture tiny changes in reflected light, mostly from the user's finger which should be put closely in front of the camera. E.g. *Cardiio Version by Cardiio Inc.* is based on technology licensed from renowned research center MIT. A study assessed the accuracy of the measures of 4 apps: *Instant Heart Rate and, Heart Fitness, Cardioo Version* and *Whats My Heart Rate*) with the well-renowned method i.e. electrocardiogram (ECG) and pulse oximetry (to obtain pulse oximetry-derived heart rate. All apps use plethysmography technique, although in case of *Instant Heart Rate* and *Heart Fitness* it is contact and in *Cardioo Version* and *Whats My Heart Rateit* non-contact plethysmography. Summing up, the mean absolute error of the pulse oximetry and the tested apps, comparing to ECG was lowest in pulse oximetry (2 ± 0.35). However, in one app which also used contact plethysmography it wasn't much higher (2 ± 0.5). Although there are substantial performance differences between ECG and apps which use non-contact plethysmography (8.1 ± 1.4) for *Cardio Version* [13]. The mentioned study was conducted on iPhones 4 and 5 and it is to

consider, that the measures can differ depending on smartphone producer, but primarily on resolution and quality of the built-in camera.,

Apps for blood pressure control

Another important parameter in the control of CVD is blood pressure. There are many apps (along with the most popular is Blood pressure) which are aimed primarily at gathering blood pressure measurements, which are introduced to the app by the patient (after being measured by sphygmomanometer). By default, they register time and date of the result, and some allow to introduce include additional information, e.g. about the position of a body. Additionally, some have a reminder function. In a study which assessed 'recording apps,' it was confirmed that parameters as aesthetics, functionality, information quality, and engagement which are crucial for the usefulness of any smartphone app, apply to the medical app as well and that patients are more involved in their treatment through the use of high-quality app [12]. What can be the initial problem while choosing a proper app for monitoring of blood pressure is the abundance of poor quality apps which do not supply services which they suggest in the name and description of the product. There is a possibility of discouraging the patient and therefore lower accuracy of his monitoring.

Another area of CVD management is blood pressure measurement. This standard medical test is usually performed using attested sphygmomanometer. However, there are apps which evaluate blood pressure, and these are the most controversial. Names of the apps (e.g., Instant blood pressure) misleadingly suggest that they can measure blood pressure. The developers do not describe the technique used for measurement, although the procedure of measuring involves placing the index finger on the bright flashlight and camera while holding the phone's microphone against the chest. The company does write in the description that the app provides estimations and that the patient "should not rely on Instant Blood Pressure for medical advice or diagnosis."

However, to be true many renowned medical tests are estimation up to a point and the fact that the patient performs some procedure and becomes a result inclines him to treat the results as reliable parameters.

Moreover, the description is often skipped by patients and interface of apps often make it

hard to realize that the given results should not be considered valid. Mainly, the app mentioned above Instant blood pressure which gained much popularity in 2015 (was among 50 best-selling apps that year) drew the attention of scientists on dangers associated with unreliable medical apps. Validation of the considering blood pressure Measurement [14] reported much higher discrepancies in actual and measured blood pressure (mean absolute error was 12.4 and 8.1 mmHg for systolic and diastolic pressure respectively).

Moreover, it underestimated much-elevated blood pressure and overestimated lower blood pressure. There is no doubt that high accuracy should be primary feature of a blood pressure measuring device and providing app which doesn't match this criterion can be life-threatening for patients, who can overlook alarming results of blood pressure and instead of taking action and consulting the doctor, they will remain falsely reassured of their seemingly good condition [15].

Apps in management of diabetes

Diabetes is a chronic disease which holds its position as one of the biggest health concerns worldwide. With the number of people diagnosed with said condition reaching up to half a billion and 1.6 million of deaths caused directly by it (7th most common cause of death globally), it is but a necessity for major health organizations to pursue even better ways of improving its treatment [16]

Although pharmacotherapy and regular check-ups remain irreplaceable factors in managing diabetes and preventing its consequences such as kidney failure or retinopathy, patient's self-care still plays a key role in medical care in diabetics [16].

Controlling one's disease is no easy task. It requires a strong will and number of sacrifices. However new technologies can prove incredibly useful in simplifying and refining this procedure. Variety of applications, available for both iOS and Android, is a perfect example [17].

For most researchers, the presence of tracing glycemic levels function is required for the app to be considered in the analysis of their effectiveness in managing diabetes. The exact approach was chosen for the following text. As of 2017 85 applications which met this criterion were noted [17]. This number will surely rise in the nearest future.

Glucose levels measurement

They can be implemented in number of ways. The most important function that helps differentiate apps that have some actual therapeutic value from others (apps focused on diets, exercises, just providing information and etc.) is availability of glucose levels tracking. This simple feature enables patients to store crucial data on their phones instead of using old-fashioned paper journals. Research proves that capturing data on handheld devices is faster and preferred by most users with exception of patients not familiar with that technology [18].

Recording glucose levels is without a doubt main tool for self-care in diabetes. Not only does it provide useful information to the doctor, which helps controlling effectiveness of treatment and developing new strategies for combating the disease, but it also tells the patient what doses of insulin should he administer as well. For example patients whose treatment regimen includes either several insulin injections throughout the day or usage of insulin pump ought to check their glucose levels at least thrice a day (American Diabetes Association recommendations). This means a large number of values that have to be written down and kept. Apps simplify the process and dispatch the burden of paper journal. Although in majority of apps input has to be read from glucometer and added into the phone manually, in a few cases app can connect to glucometer and harvest data directly from it, further facilitating described action. Moreover records can be effortlessly moved between different electronic devices or even sent directly to healthcare provider or GP. This approach rises patient's level of compliance which is key factor in successful management of diabetes.

Dosing medicaments

Another advantage of apps usage is their ability to support pharmacotherapy through both alerts and calculating insulin doses. First aspect comprises of assortment of reminders which act through different means. They vary from plain sound signals or vibrations to SMS and their purpose is to inform diabetics that it is time for medication intake or glucose levels measurement. It is immensely beneficial since patients, especially older, tend to forget about fulfilling their duties regularly and as a consequence omit them. Such behavior damages treatment and decreases its gains. Therefore apps which help diseased keep track of their drugs and tests have potential for improving results of therapy.

Another issue regarding pharmacotherapy in certain cases of diabetes is dosing of insulin. Although basic insulin dosage regimen is prescribed by healthcare provider some doses have to be calculated by patients themselves. Since human body is a dynamic system its insulin requirements are not exact at all times. For that reason apart from permanent daily application additional bolus insulin replacement is obligatory. This value depends on many factors such as quantity and quality of food intake, physical activity, stress and so on. Generally the amount of insulin needed for blood sugar levels correction is based on how much one unit of rapid-acting insulin drops the blood sugar [19]. On average one unit is capable of dispatching 12-15 gram of carbohydrates. However this range can vary depending on individual sensitivity to insulin. After acquiring the knowledge of their sensitivity to insulin, patients are able to calculate insulin dosage depending on their amount of sugar they consumed or difference between their current blood sugar levels and correct blood sugar levels.

It is All but complex system nevertheless it demands abundance of input from diseased thus being at risk of failure which leads to dire consequences. Sheer possibility of contracting this hardship through apps can make a huge change. Not only does it take part of responsibility from patients but can also enable them to complete this task much quicker and with better precision. Furthermore an app can take into account more variables for example physical activity. In conclusion apps can strengthen effectiveness of treating diabetes by administration insulin.

HbA1c estimation

Certainly, blood sugar levels inform us about the patient's current state, yet its usefulness in case of average glycemic control leaves much to desire. In response in 1976 HbA1c tests were proposed and are now established as standard clinical measurement. This test shows what percentage of patient's hemoglobin has been glycated (the norm being 6%) which correlates with average blood sugar levels. Since maintaining adequate glycemic control may decrease the risk of macrovascular and microvascular complications its importance should not be underestimated. However, taking blood and testing it in a laboratory with high frequency is not only inconvenient but often impossible as well. To solve this issue between laboratory measurements HbA1c can be estimated based on blood sugar levels taken throughout a minimum

one week. There is a large variety of algorithms used for that purpose some of which have relatively similar accuracy to tests carried out in laboratories [20].

The number of apps has incorporated this solution into their systems. It can be noted in same of the ones highest rated users such as Glucosio, mySugr and Glucose Buddy. In some cases this feature may not be included in the free version but exist as a purchasable add-on. Upon taking the number of measurements the user's HbA1c is calculated. Results are clearly just an estimation but they can give the patient a general idea on how good his or her glycemic control is. Should the results worsen, the app could additionally point out possible cause using other information given by the user such as daily diet or amount of physical activities.

Physical and mental condition

Other functions are not main focus however they are worth mentioning. Some apps include elements which are more associated with diet, exercises and overall body weight loss. Although apps designed strictly for that aim are available on the market, sometimes encapsulating everything in just one app can prove more beneficial since it is easier to manage.

As motivation is crucial in self-care it can not be dismissed as well. Apps' creators address this issue in a number of ways. Adding colorful visuals, namely charts and tables is viewed positively by many users. Making app more game-like by keeping patient's results in the form of score can improve experience as well shape a more tangible improvement. For competitive users there exists an option of comparing their scores via build in scoreboard. Moreover better engagement can be stimulated by encouraging messages on the screen each time patient's results improve or remain on satisfying levels. Noteworthy creators of mySugr app have prepared another version aimed for children. Furthermore couple of developers hire experts in the field of diabetes who can be accessed through app by user seeking advice.

Performance

In practice there is no general conclusion regarding effectiveness of applications used in managing diabetes. Research [22] based on just one app, namely "bant", which had 92 participants with type 1 diabetes (T1D) (46 using bant and 46 in the control group) showed no changes in primary and secondary clinical outcomes. However it did show statistically

significant improvement regarding Hba1c levels of 0.58% (P=.02) compared to decrease of 0,06% (P=.86) in control group. This test had difficulties such as relatively small sample size and necessity of deploying secondary research phones instead of patient's personal devices. Nevertheless it's results show much promise.

Different studies [22] have randomly selected 211 users of SocialDiabetes app and monitored their glucose levels at starting point, after 3 and 6 months. In patients with type 1 diabetes after baseline glucose decreased from 213.61 (SD 31.57) mg/Dl to 175.15 (SD 37.88) mg/Dl in one group and from 206.43 (SD 18.65) mg/Dl to 180.6 (SD 40.47) mg/Dl in the other. In patients with type 2 diabetes(T2D baseline glucose decreased from 218.77 (SD 40.18) mg/dL and 232.55 (SD 46.78) mg/Dl to 160.51 (SD 39.32) mg/dL and 173.14 (SD 52.81) mg/Dl respectively. Furthermore eHbA1c levels were reduced by 1.3% (P<.001) In T1D and 2% (P<.001) In T2D. This tendencies seem more optimistic especially when it comes to T2D.

Wearable technology and its medical uses

It goes without saying that permanent monitoring of patients' vital signs will significantly improve a treatment process through objective measurement that enables an assessment of compliance with medical recommendations. The major therapeutic use of wearable technology is physical activity tracking, a crucial parameter in many chronic diseases, for example in hypertension, diabetes or dyslipidemia. Therefore a new term - wearable medical device (WMD) - has been established [6].

Are wrist-worn heart rate monitors accurate?

Apple Watch, Fitbit Blaze, Garmin Forerunner 235, TomTom Spark Cardio, Polar H7 Chest Strap and Scosche Rythm+ have been tested in their accuracy during different types of exercise [23]. Heart rate was tested at rest and light, moderate and vigorous exercise. Participants of the experiment have also been monitored with standard ECG. It occurred that accuracy significantly depended on the type of exercise: on the treadmill, all devices except the Fitbit Blaze had acceptable accuracy compared to the ECG [23]. Apple Watch, Garmin and Scosche Rythm+ were trustworthy during biking. Only Apple Watch could cope with monitoring heart rate using elliptical trainer without arm levers, although while using the arm levers its accuracy was insufficient [23]. Therefore the accuracy of wearable medical devices in terms of heart rate

monitoring is highly variable and depends on the type of exercise and generally is higher in moderate physical activity.

Patients with coronary heart disease and the exercise-based rehabilitation

Wearable devices are intervention that improves the outcomes of rehabilitation for patients after an myocardial infarction. They are an alternative for a traditional cardiac rehabilitation which tends to be neglected in terms of attendance and completion. Combination of wearable medical device and telerehabilitation performed at home is an effective behavioral strategy that includes individualized and goal-directed treatment [24].

Bites counting

There are also types of wearable medical devices that are able to count bites. How does it affect dietary habits? It turns out that an electronic device providing bite count feedback alters behaviour and can shift the way of eating: a reduced overall consumption in a single meal has been noticed [25]. Therefore it can help to reduce total calories intake which helps to control many chronic diseases, for instance diabetes [26].

Smartwatches detecting atrial fibrillation

The episodes of atrial fibrillation have no symptoms and are the leading cause of stroke [27,28]. A perfect screening device should be non-invasive, provide real-time data and accurate in detecting the abnormal heart rhythm. Smartwatches are able to fulfill these criteria, together with proper software based on deep neural networks to passively screen for atrial fibrillation [29]. Although not every patients' results can be interpreted by the modern algorithms one study discovered that there are remote devices that when paired with a smartwatch are able to detect atrial fibrillation with 93% sensitivity and 84% specificity [30]. On the other hand, physicians' interpretation showed 99% sensitivity and 83% specificity [30].

Bariatric surgery

Mobile health applications are a great complement to the traditional treatment recommendation. One prospective randomized control trial performed on 56 patients who underwent a bariatric operation - laparoscopic sleeve gastrectomy - showed that health app

intervention significantly enhances therapy results [31]. In a study group each patient obtained iPad mini with installed the MyFitnessPal application and the control group were provided with standard post-operative monitoring. After 12 months patients in the control group lost 74,41% of excess body weight versus 81,41% of excess body weight lost in the study group [31]. After 24 months of trial results were 59,10% loss of excess body weight in the control group and 71,47% loss among the patients who used mobile health application [31]. These results are very promising and thus implementing new technology as an adjuvant therapy can significantly improve treatment outcomes [31].

Summary

Combating chronic diseases makes for an arduous challenge in which patients' life and wellbeing are continuously at stake. Modern medicine strives to find better means of facilitating this struggle. Upon reviewing the data regarding usage of applications for medical purposes we come to the conclusion that they can be considered an addition to its arsenal.

Through helping their users with organising self-care, motivating them, simplifying their tasks, mobile apps already show much promise in supporting traditional treatment. With mobile devices becoming more frequent and sophisticated by the day it is very likely that the number of possibilities will only grow. Nevertheless estimating range of this phenomenon requires further investigation.

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Life with diabetes mellitus – modern trends in insulin therapy

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Introduction

From a few decades, a steady increase in the prevalence of diabetes was noted throughout the world. More and more people hear a diagnosis that completely changes their life. To avoid health-related severe consequences induced by this illness, it is crucial to begin treatment which requires much involvement from a patient, diligence, and attention. Modification of lifestyle, diet and physical activity are part of this change too. People with diabetes have to learn how to notice symptoms alarming them about hypoglycemia, remember about blood sugar measurements during the day and, finally, know how to react in case of high or low blood glucose level. People with type 1 diabetes have to adjust insulin doses to each meal. Quite often, diabetic treatment is a financial burden for many people [1,2].

Studies of therapeutic techniques and methods of insulin therapy for people with diabetes are still moving forward. Every few years pharmaceutical companies release newer types of insulins. Moreover, in the last decades, the technology (such as continuous blood glucose monitoring) that improves diabetes control and gives patients more freedom and flexibility is becoming more popular and accessible. Furthermore, the process of insulin delivery becomes partly automated by the use of insulin pumps. This paper presents already existing techniques of insulin therapy and those that can replace them in the future.

"Sweet" chronic condition

Diabetes mellitus is a group of metabolic disorders resulting in increased blood glucose level, called hyperglycemia, and decreased or declined glucose tolerance. This condition is caused by many dysfunctions including insufficient (or lacking) production of insulin by Langerhans'

islets in the pancreas and inappropriate tissue response to peptide. Insulin resistance may result from: receptor dysfunction or a decreased number of the receptors on cells' surfaces, postreceptoral proteins damage and disorders related to the secretion of substances, which can potentiate the effect of tissue unresponsiveness like adipokines, substances secreted by fatty tissue [3,4].

Insulin physiology

Pancreatic islets are a miniature factory, producing, among others, a peptide hormone called insulin. In physiological conditions, when the glucose level in the blood rises, insulin is being released to the bloodstream. This process is controlled by glucokinase, an enzyme involved in glucose biochemical pathway. Intensified metabolism of glucose in pancreatic cells increases the level of ATP (adenosine triphosphate), causing the closure of the ATP-dependent potassium ion channels. Retention of potassium ions in cells results in a change of cell membrane potential and accordingly leads to the opening of voltage-gated calcium ion channels. As calcium level in cell increase, synthesis of insulin in beta cells and it is secretion from secretory vesicles mounts [3,5].

The central role of insulin is its hypoglycemic activity. It causes a drop of plasmatic glucose level by increasing transport of glucose from the blood to the tissues sensitive to this hormone. This happens due to activation of GLUT-4, one of the glucose transporters, present mainly in muscle and fatty tissue. As the insulin receptor is stimulated, GLUT-4 is being built in a cell membrane, enabling the glucose flow into the cell. Insulin also inhibits gluconeogenesis and secretion of glucose by the liver [6].

Depending on the type of meal consumed, glycemia usually begins to raise 5-10 minutes after the beginning of the meal and reaches the maximal level approximately 1 hour later. Right after the meal is started, increasing glucose level in the blood stimulates the secretion of already produced insulin from the secretory vesicles. This phase is called the rapid one and last until 10 minutes. Then, when the resources of the insulin are spent, the second phase begins, and last till 2 hours. The time of the second phase can reflect beta cells' ability to produce insulin de novo. In a healthy organism, the glucose level goes back to the premeal concentration in 2-3 hours [7,8].

Hypoglycemic action of insulin is one of its rapid activities, whose lasting time is counted in seconds. Another rapid metabolic impact is increased transport of potassium ions and amino

acids to the sensitive cells. Moreover, after a few minutes, this hormone also influences the synthesis of proteins and suppression of their lysis, activates glycogenesis and increases the number of glycolytic enzymes. As a late effect of insulin, occurring after a few hours, more enzymes engaged in lipogenesis are being synthesized [6].

Considering all metabolic pathways, insulin deficiency and disorders connected with its synthesis, secretion or tissues' response to the hormone leads to many serious consequences, associated not only with carbohydrates, but also lipids and proteins metabolism. In the case of untreated or too late diagnosed diabetes, complications can occur. They are divided into two groups. Acute ones: diabetic ketoacidosis can result in diabetic or hyperosmolar nonketotic coma, and severe hypoglycemia can lead to unconsciousness and brain damage. Chronic ones, associated with long-term diabetes, include: microangiopathy - damage to small blood vessels (retinopathy, nephropathy), macroangiopathy - relating to bigger blood vessels, such as coronary arteries, brain vessels and peripheral blood vessels; neuropathy - damage of cranial, peripheral or autonomic nerves, and skin diseases - bacterial and fungal infections, xanthelasma or diabetic dermopathy [9].

One illness, many types

Different etiopathogenesis and the clinical course became the basis for the division of diabetes into four main types. These are type I diabetes, type II diabetes, gestational diabetes and other specific types [10].

Type I diabetes is an autoimmune condition, and it accounts for about 5 to 10% of all diabetes cases [11]. It can affect people of any age, but the incidence is the most common in childhood. Symptoms usually manifest when almost all pancreatic islets responsible for insulin synthesis are destroyed. As a consequence, the organism is not able to produce insulin and the only way of treatment is its replacement - insulin therapy. In the presence of a trigger factor like viral infections or congenital rubella syndrome, affecting pancreatic cells, autoantibodies are produced, and the destruction of the islets begins. Genetic factors also have a significant role in the pathogenesis of type I diabetes [3,12].

LADA (latent autoimmune diabetes in adults) is a specific kind of type I diabetes. Development of this disease is slow, and the occurrence of symptoms is not as severe as in children with type I diabetes. Manifestations usually appear in the 30-70 age group [13].

Type II diabetes affects people typically over 40 years old, but the incidence of it is significantly rising in the pediatric population as well. Initially, its course can be asymptomatic. The reasons for this condition are insulin resistance and a relative deficit of insulin. Genetic and environmental factors take part in its development as well. Moreover, type II diabetes very often co-exists with obesity [10]. Studies show that substances secreted by fatty tissue like leptin, tumor necrosis factor alfa (TNF alfa), resistin and adiponectin escalate the effect of insulin resistance [9]. The ability of insulin production by beta cells usually is not entirely lost. Therefore, it is possible to treat this disorder by modification of a diet and lifestyle. Usually, type 2 diabetes is treated by oral hypoglycemic agents (i.e., metformin, etc.) but in some cases, insulin therapy is necessary too [14].

Every condition of glucose intolerance, manifesting itself in hyperglycemia that has been noticed for the first time during pregnancy is called gestational diabetes mellitus (GDM). It is estimated that about 7% of the population of pregnant women suffers from GDM. Depending on the level of the symptoms' exacerbation, diet modification or insulin therapy is administered. The group of patients who are more susceptible to GDM involves women with a family history of diabetes, obese ones and with GDM history during previous pregnancies [15].

Treatment of diabetes

Treatment methods are adjusted to the type of diabetes and individualized to a person needs. The aim is to maintain blood glucose levels "in range" to be as similar, as to healthy people, as possible, and thus, to decrease the risk of complications. Nowadays there are many ways to treat diabetes: pharmacotherapy includes oral hypoglycemic agents, GLP-1 and -2 agonists, insulins, lifestyle changes include the healthy diet and less sedentary behaviors, and less popular methods, including pancreas or Langerhans islets transplant [3].

Insulin therapy and insulin analogs

One of the treatment methods is insulin therapy, in which human insulin or its analogs are administered subcutaneously or intravenously to the patient's body. Indications of therapy are type I diabetes (also LADA), type II diabetes with no effect after treatment including diet modification and antidiabetic drugs or contraindications of taking antidiabetic drugs in type II diabetes. Also in temporary treatment in case of newly diagnosed diabetes, it is used to quickly eliminate significant hyperglycemia in order to avoid complications due to the high blood glucose level [16].

Other indications involve cases of type II diabetes concerning pregnant women when a change of diet is not enough to maintain proper glycemia, as well as the postoperative period. Patients with the acute coronary syndrome, during treatment with diabetogenic medications or with other diseases that can decompensate diabetes are also eligible for insulin therapy [17].

Currently, insulins used in insulin therapy are the solution of human peptide and its analogs obtained by methods of genetic engineering. Animal insulin is practically out of use leading to a decrease of prevalence rate of allergic reaction in patients treated with it.

Analogs differ with a time of their onset and duration. Insulins with a shorter time of duration are used before each meal as boluses, while the long- and intermediate-acting ones provide the basal dose of insulin.

The group of short-acting analogs consists of regular insulin and rapid-acting analogs (lispro, aspart, glulisine).

Regular insulin reaches the bloodstream slower than rapid-acting insulins, acts longer and has a more extended and latter peak, which may cause hypoglycemia after the meal.

Ultra-rapid-acting insulin-like faster as part, approved by the drug monitoring institutions in 2017 in the treatment of adults, have a faster onset and offset than aspart, lispro or glulisine, hence it can decrease elevated blood glucose level quicker.

Moreover, there is a smaller risk of hypoglycemia after a few hours in comparison to rapid-acting analogs.

„Basal insulins" differ based on the peak-time – intermediate-acting insulins (e.g., isophane insulin) lasts up to 18 hours and have a peak after 4-8 hours. Long-acting analogs (detemir, glargine, degludec) have no peak at all and are active up to 24 or even 48 hours [14,18,19].

Insulin therapy is administered in various ways and patterns

There are a few methods of insulin therapy, differing in the number of essential insulin doses during one day, and the number of new administrations, taken before the meals. The simplest one, helpful especially in case of the older adults, unable to apply the drug by themselves, is conventional insulin therapy. It consists of two injections of the basal dose of premixed insulin preparation - one in the morning and one in the evening in the proportion 2:1 or 1:1. Depending on the glycemia measurements during the day, a correctional amount can be introduced by increasing the dose with 1-2 units every few days, until proper glycemia measurements are not achieved. During the treatment in a model of conventional insulin therapy, there is a necessity to respect a solid daily plan of the meals, their nutritional value and maintaining the physical activity on a constant level [20].

Intensive insulin therapy (basal-bolus model) is a method that mimics the daily physiological changes of insulin. Patients get at minimum four or more doses per day. One or very rarely two, with intermediate or long-acting analogs, provide a primary insulin demand. The rest are additional doses of rapid-acting insulins (boluses) administered immediately before every consumed meal (some people make even 10-15 injections a day). Multiple Daily Injections (MDI) is the recommended way of adult type 1 diabetes treatment – the basis for it is carb-counting, as every insulin dose (bolus) has to be calculated accordingly to the amount of carbohydrate intake [21].

In all methods of insulin therapy described above, insulin is administered subcutaneously in the abdomen, lateral aspect of arm, thigh or lateral upper quadrant of the buttocks. The absorption of insulin is the fastest after injection into the abdomen (15 minutes) and the slowest in case of an injection into the area of thigh or buttocks (30 minutes) [18]. Insulin can be applied by using insulin syringes with a needle not longer than 6mm, insulin pens - the automatic device with needle and cartridge containing insulin, or with an insulin pump that provides continuous subcutaneous insulin infusion (CSII). There is also a way of insulin administration that does not require needle - a jet injector. This device squeezes the insulin under appropriate pressure through the skin to the subcutaneous layer. It is a good alternative for those, who are afraid of needles; however, it can be

even more painful than traditional methods and is not very popular [22].

Insulin doses

In conventional insulin therapy, doses are fixed and prescribed by health-care professionals. In intensive insulin therapy, basal rates are fixed, and boluses are calculated based on the carbohydrate and, in particular in Poland, fat and protein intake. In some parts of the world (i.e., UK), insulin-carb ratios are being calculated based on the equation below:

$$Number\ of\ carbohydrates\ [g]\ for\ 1\ insulin\ unit\ = \frac{500}{Total\ Daily\ Dose}$$

Thus, the insulin-carb ratio is how much grams of carbs can be covered by one insulin unit. In Poland, "exchanges" or "portions" are used that simplify the estimation of the amount of the insulin per 1 carbohydrate exchange/portion. One carbohydrate exchange/portion (CP) corresponds to 10 grams of metabolized carbohydrates, excluding fiber. Therefore, the insulin-carb ratio is an amount of insulin needed to metabolize 10 grams of carbs.

Enhanced level of proteins and fats leads to a slower passage of food from the stomach to the small intestine and is caused by hormones produced there. Around 150 minutes after a high protein meal, level of glucose in the blood significantly rises due to a surge of glucagon. In patients with type 1 diabetes, this natural process is abnormal since glucagon intensifies the delivery of glucose from the tissues causing hyperglycemia. The idea of insulin adjustments for fat-protein and mixed meals comes and is popular mainly in Poland. Fat-protein portions provide effective insulin therapy when consuming mixed meals. One fat-protein exchange represents 100 calories from these nutrients. It is estimated that in children the amount of units of insulin per 1 protein-fat portion is equal to several units of insulin per 1 CP. In adults, this proportion is lower and in the range of 0.3-0.5 units per 1 CP.

Patients based on readily available charts, online calculators or smartphone applications can count grams of carbohydrates supplied with the meal on their own and therefore count the CP after successful education people with diabetes can specify the quantity of prandial insulin on their own [23,24].

Monitoring is crucial for treatment success

The choice of the insulin therapy and ratios should be individualized, depending on the patient's age, frequency and nutritional value of meals, routine physical activity, type of work and overall health status. Diabetes education starting from the onset of diabetes, and education before starting of every new type of treatment, as well as glucose monitoring, play the leading role in successful diabetes management [25].

In the glycemic control, occasional measurements, as well as abbreviated (twelve-hour profile) and full diurnal glucose profiles are used. The twelve-hour profile includes the fasting glycemia and 2-hour post-prandial blood sugar level, whereas the full diurnal profile also includes measurements before each of the main meals, before bedtime and additional individual tests.

The basic parameters used in the monitoring of the treatment of diabetes mellitus are blood sugar level, glycated hemoglobin level (HbA1c), total cholesterol, including LDL and HDL, and blood pressure measurements, used as criteria for leveling off diabetes mellitus. Also, it is recommended to perform once a year: general urine tests with sediment, eGFR, measurement of urine albumin and retinal screen to control the organs that are usually affected by diabetes-related long-term complications. Also, in patients with type 1, diabetes thyroid function and transglutaminase test should be performed yearly, as the incidence of other autoimmune conditions, such as coeliac disease and hypothyroidism (Hashimoto) is much higher than in healthy population.

One of the criteria for leveling off diabetes mellitus relates to carbohydrate metabolism. To control the effectiveness of the diabetes management and therapy, glycated hemoglobin A1c test are being performed (every three months in the pediatric population, every six months in adults with type 1 diabetes, or less in people with type 2 diabetes). Generally, according to the Polish guidelines, the A1c targets are below 53 mmol/mol (<7.0%), which applies to all patients with some exceptions such as pregnant women and those planning pregnancy, older adults and advanced long-term diabetes with complications or severe comorbidities. For them, the HbA1c specific criteria are used [3]. However, a minority of patients are meeting the recommended values.

Another criterion involves lipid metabolism. Depending on the cardiovascular risk in SCORE scale, patients should aim for LDL level <70 mg/dl (1,8mmol/l) at very high cardiovascular risk. At high risk, the targeted LDL level is <100 mg/dl (2.6 mmol/l) and in low and moderate risk LDL <115 mg/dl (3.0 mmol/l [26,27].

The blood pressure equalization criterion is the same for all adult patients, reaching <140/90 mmHg, except for pregnant women with diabetic kidney disease and children above 12 years – in their case the level is <130/80 mmHg) [3,27,28].

To control diabetes, patients use diabetes glucometers, and they should note every blood test in their diabetes diary to allow to adjust insulin doses/treatment. In modern glucometers, the data can be downloaded onto a computer and analyzed by dedicated software – therefore written diaries are not a very popular way of diabetes monitoring, in particular in the pediatric population and people with type 1 diabetes.

A well-recognized method involves carrying out a self-control log (diabetes diary) by a patient, in which he independently makes glycemic tests for appropriate glycemia profile depending on the treatment used and individual indications, such as body weight and blood pressure measurements, as well as observed symptoms of hypo and hyperglycemia. That allows the independent assessment of the multifactorial impact of lifestyle, diet, and medications on the course of the disease. What is more, it also facilitates the achievement of therapeutic goals and cooperation between the patient and the doctor [2].

Technology to control diabetes

In last years the dawn of technology has been observed, aiming to improve the quality and frequency of blood sugar monitoring. Flash Glucose System (Libre) allows patients to control their blood-sugar levels by only connecting a device (meter or mobile phone) to a sensor – without finger-pricking. More advanced technology - continuous glucose monitoring system (CGMS) allows for 24/7 hours monitoring of glycemia, with alarms informing about the rise or fall of glycemic levels. CGM use is associated with a 1.2% decrease in HbA1c [29]. This system uses a subcutaneous placed sensor that measures the glucose concentration in the interstitial fluid in few-minutes intervals. The glycemia readout is possible retrospectively or in a real-time, depending on the insulin pump model (concerning hybrid pumps) or a separate device [3,30,31]. There are specific indications for the use of this system, which lie within the indications for the use of insulin pumps, including: nocturnal hypoglycemia and morning hyperglycemia (Somogyi phenomenon), dawn phenomenon, hyperglycemia at dusk, hypo unawareness, difficulty in achieving the goal in diabetes with unsteady course, pregestational diabetes, and fear of hypoglycemia.

Hyperglycemia at dawn and hyperglycemia at dusk have both alleged and correct forms. The reason for the true hyperglycemia at dawn is a physiological increase in the growth hormone and prolactin secretion between 5 and 8 AM, resulting in insulin resistance and hyperglycemia. However, the most common is the alleged form of this phenomenon. The fading of the insulin doses causes it, injected only in the morning or both in the morning and early evening. A premature fading of insulin also causes an alleged form of hyperglycemia at dusk with a long-lasting component. Somogyi phenomenon takes place after a phase of hypoglycemia. Neuroglycopenia stimulates the pituitary-adrenal gland and the adrenergic nervous system with all its consequences. It also has a strong influence on the secretion of catabolic hormones, such as catecholamines, cortisol, glucagon and growth hormone. Therefore, it releases glucose from glycogen and causes subsequent reactive hyperglycemia. Excessive amounts of morning insulin with a prolonged action or evening long-acting analogs can cause nocturnal neuroglycopenia with anti-regulating hyperglycemia, especially at dawn hours [2].

Sequelae of insulin therapy

Hypoglycemia is the main complication of insulin therapy, associated with a considerable health risk. Clinically significant hypoglycemia is regarded as the blood sugar level <3 mmol/l. It may be mild when the patient can manage it himself, or severe – when he is experiencing cognitive impairment and requires assistance or even hospitalization. Statistically, it is more common among people with type 1 diabetes (10%) who are unaware of hypoglycemia, have strict glycemic control and seek to achieve HbA1c <6.1% by intensive insulin therapy [3].

Furthermore, in long-lasting diabetes, there is an additional risk of hypoglycemia, resulting from damage to the vegetative system, to which contributed the previously experienced events of decrease in blood sugar. In this case, the patient does not see any alarming symptoms and hypoglycemia manifests immediately with the features of neuroglycopenia – this disorder is called hypo-unawareness and is a primary recommendation for a CGM use. The role of adequately selected therapy and glucose control are crucial, and proper education of the patients should be emphasized in the prevention of low blood glucose levels [3,32,33].

Insulin therapy, apart from being the only treatment to type 1 diabetes, is not free from many side effects, which vary depending on the chosen method. Hypoglycemia is the main side

effect, but some of them include allergy or skin problems. Therapy involving syringes (conventional therapy) requires less knowledge and training from the patient, although the risk of hypoglycemia is much higher, as there is lots of insulin on board – this type of treatment requires form patient to be very persistent and regular in terms of mealtimes and food content (6 meals a day, at the same time). If the time of the meal is being missed or delayed, or if the amount of food is smaller than expected, or if there is any spontaneous activity, then the hypoglycemia may occur. In basal-bolus therapies, the leading causes of hypoglycemia are the insulin dose miscalculation, exercise, alcohol intake and too frequent and too many boluses in one period.

Furthermore, low blood glucose levels can occur while switching between different analog types with variant pharmacodynamics. In case of frequent injections, the patient may develop resistant areas of the body where the drug will not absorb correctly, along with thickening of subcutaneous fatty tissue [34].

The beginning of conventional insulin therapy

Since 1921, when Banting and Best discovered the insulin extract, methods of its administration and insulin therapy strategies have improved a lot through the years of studies. Initially, the only possible way of supply were vials and syringes. However, it carried many inconveniences, as well as elevated the risk of incorrect dosage. Patients manifested fear of the treatment due to needle usage. This method was poorly accepted, not only psychologically, but also socially, forcing its users to change their daily routines significantly. The training took a long time and was rarely completely capable, whereas syringes were cumbersome in use and transport.

Moreover, by the time of the disposable needle era, they had to be sterilized and sharpened before every injection. Therefore, the patients had undergone the therapy reluctantly, because it was substantially constraining their work and social life. It has been shown that 80% of patients took incorrect dosages, resulting in decreased treatment effectivity. Due to the displacing of vial and syringe by newer methods of insulin supply, today it is used mainly in hospitals, where insulin is administered intravenously to quickly stabilize glycemia, in patients who lost the metabolic control of diabetes mellitus of their own [35-37].

Insulin pens enhance patients convenience

In order to increase the dosage precision and the patients' comfort, systems of insulin administration are constantly improved. Therefore, in 1985, as a result of a combination of an insulin container and a syringe, single units were developed, called insulin pens. They reduced the inconveniences of vial and syringe use. A significant improvement has been noticed in dosage accuracy, especially in patients experiencing usage difficulties, such as people over 60 years old.

Furthermore, patients no longer had to carry cumbersome sets, whereas application was more discreet, hence decreasing the potential reluctance due to the social unacceptance. Thanks to increased flexibility, the treatment had less affected patients life and their daily routines. Moreover, the injection pain had been reduced and the whole procedure became more user-friendly. Patients were not obliged to manually aspirate the insulin by needle from the vial since the manufacturer has already prepared the drug. Studies show decreased fear of needles and treatment self-management in patients due to the administration with their own hands.

Further, thanks to premade insulin cartridges, the dosage accuracy and application confidence relevantly increased, as 74% of patients declare and therefore treatment compliance improved. It resulted in a positive influence on therapy, satisfaction, and standard of living with diabetes mellitus in comparison to the vial and syringe method. Despite many advantages, insulin pens are problematical for patients taking insulin mixes. While using a syringe, they could apply several insulins in one injection, whereas with pens insulins cannot be mixed, so they are forced to make two or more injections for every use [35, 37-39].

There are distinguished two types of insulin pens: prefilled disposable pens and refillable pens, which allow the subcutaneous supply of insulin. Both of them contain 3ml of insulin, which is an equivalent of 300 units. Pens also require complementary needles, sold in numerous variants, chosen by the doctor. Usage of pens is quicker and more comfortable in comparison to vial and syringe. Firstly, an appropriate needle has to be attached to the pen. Then, an air-shot or safety test needs to be done. An injection up to 2 units into the air, in order to discard the gases present in the needle, resulting in achieving a consistent flow of insulin and assuring dosage accuracy. It needs to be performed each time a pen or a cartridge is replaced. Following, a demanded dose needs be chosen on the dosage knob. The pen should be inserted subcutaneously, perpendicularly to a place

rich in fatty tissue, such as abdomen or thigh, releasing the insulin through pressing the injection button. The device has to be kept in this position for several seconds, according to the manual, in order to receive the complete dose. This extends the procedure time since pens expel the liquid longer than the syringes. After usage, a needle has to be detached and disposed of. Insulin cartridges require proper storage. They should be kept in the refrigerator in congruent temperature and need to be warmed to the room temperature before the application. Once in pen, the temperature should not go beyond 30°C, to maintain insulin quality. Pens can be used solely by an individual. Disobedience can lead to the transmission of communicable diseases, induced mostly by hepatitis or HIV viruses [40].

Prefilled pens contain a built-in insulin cartridge. Once used, the whole device is discarded. They are characterized by high dosage accuracy, durability, and portability. No interaction despite the dose selection and injection itself is needed, resulting in high user-friendliness. Therefore, they are used in particular by the patients who find reusable pens unacceptably complicated due to the difficulties with the cartridge replacement. However, they are more expensive in long-standing therapy.

Reusable pen requires the patient to insert the insulin cartridge into the proper compartment. This allows the change of insulin used into a different type, thereby increasing the patient's freedom in therapy management. It results in lower costs of the treatment since the purchase of a new pen to every insulin type taken is not needed. Nevertheless, reusable pens require more attention and involvement in comparison to prefilled ones. Also, due to the long-standing usage, impairment and loss of sterility over time is possible [41,42].

Jet injectors - a non-needle solution

For patients experiencing severe needle phobia, methods above were a serious discomfort though, discouraging them from the therapy. To resolve this problem of psychological needle aversion, insulin jet injector was developed. This device enables insulin administration using a high-pressure air mechanism, where the employed gas is usually nitrogen or carbon dioxide. Accelerated to even 100 meters per second gas particles, gaining high kinetic energy, produce a micropuncture in the skin, allowing insulin to reach the epidermis, where it is distributed. Most

favorable places are rich in fatty tissue, such as the abdomen, thighs, and buttocks. Jet injectors efficiency reaches over 90%.

Moreover, studies show that insulin administered this way works quicker in comparison to conventional pen injection and has more similar action to the endogenous peptide. However, due to their complex structure, these devices are more challenging to use, less user-friendly and more expensive in a long-standing therapy. They are more problematic in cleanness maintenance as well. Therefore, proper caring and sterilization regularly is required [43,44].

Insulin pumps - a breakthrough in diabetes treatment

Researches over continuous control of blood glucose level have led to the prototype of the insulin pump in the 70s of the XX century. During the first years, hormone was delivered by intravenous cannula in the ambulatory environment. However, the main disadvantage of this method was a recurrent obstruction of the cannula by the blood clots and the size of the pump itself. The renaissance of insulin pump therapy came in the late 90s when fast-acting analogs and much smaller and modern devices have been released.

Nowadays insulin pumps are small, safe, user-friendly and durable devices weighing around 100 grams. They supply the hormone nearest to the physiological rhythm of its secretion. The natural product consists of an engine, microprocessor, place for disposable insulin container and infusion set. The drug is delivered by tubing with subcutaneous cannula [45,46].

For continuous subcutaneous insulin infusion (CSII) only fast-acting insulin analog is used. The basal-bolus method depends on the functions that are used in the pump. The basal rate is programmed in consultation with the diabetes team and always delivers insulin automatically. It is tailored to individual needs, lifestyle and patterns. The basal rate should represent 30-40% of the total daily dose of the hormone. Accurate programming of basal insulin infusion and individually adjusted dosage prevents from hypoglycemia due to the excess of insulin. Initial estimates are based on factors like age, weight, level of insulin resistance, physical activity or daily schedule. A user can modify basal rates through the pump options: basal patterns and temporary basal rate. Basal patterns allow keeping in the pump memory different basal rates, prepared for significant changes in lifestyle, i.e., sports camp, long-term infection, etc. Temporary basal rate allows to

reduce or increase the basal rate for a period of time. This option is beneficial to avoid exercise-induced hypoglycemia or hyperglycemia caused by a preplanned stressful event. In comparison to pens, it allows for much more possibilities to adjust insulin – that is why diabetes education is essential to use the pump adequately [47].

The pump gives the option of three different boluses types: standard – that works precisely the same as a fast-acting analog injection, extended bolus that allows programming insulin delivery for an extended period, or dual-wave or multi-wave bolus that combines standard and extended insulin delivery. Extended boluses are ideal for meals containing only fats and proteins. Dual-wave boluses are an option for mixed meals [23,48,49].

Pump therapy is a first choice treatment for the infants and toddlers with type 1 diabetes due to their uncontrollable lifestyle, low insulin requirements and fear of needles. It is also recommended in type 1 diabetes, especially for patients with uncontrolled glycemia, with more than four episodes of hypoglycemia during the day, as well as playing sports regularly or working shifts on changing and irregular basis [48].

The main contraindication is proliferative retinopathy. Moreover, incorporating the treatment may be impossible in patients diagnosed with mental diseases as despite the education they are not able to control the device.

Numerous benefits establish pump therapy as the most commonly chosen method of treatment in children. The device is characterized as compact and easy to operate. After education user independently programs adequate doses of the drug, changes infusion sets, knows how and when to set up additional functions. Proper use of insulin pump and its options helps to stabilize the glycemia, reduces hypoglycemic episodes, reduces total daily doses and improves the precision of treatment. In comparison to pens, the need for necessary injections is decreased from at least 5-6 per day to 1 infusion set per 3 days.

However, pumps also have some disadvantages. Adverse events such as pump malfunction or infusion set crushes are not rare. It is estimated, that 40-68% of users experienced such problems during the therapy. Occlusion of canula constitutes to a risk of dangerous diabetes ketoacidosis or ketosis due to the physiology of fast-acting insulin, because the deposited amount of subcutaneous insulin is small and insufficient in the case of sudden, significantly increased demand for it. Furthermore, subjects showed infections and local irritation at the site of the injection associated

with higher insulin intake. Therefore, proper diabetes education is essential to avoid and reduce this risk and to know what steps to take when the problem occurs.

Complications of insulin therapy with pumps result from technical failures and human errors. The use of insulin pumps requires training and engagement from patients. They have to will to cooperate with the diabetes team, maintain effective diabetes control and use the options that the pump gives. Patients also should know how to carb and fat-protein count. Meeting these criteria will improve the effectiveness of the treatment and help avoid many side effects. Despite many conveniences of the therapy with insulin pumps, for some people, "being attached" to a device can be a significant disadvantage [48,50,51].

Insulin pump and CGM

Connecting the pump with a continuous glucose monitoring system (CGMS) presents a promising advantage. The measurement is taken from the interstitial fluid by an electrode inserted subcutaneously. The sensor is covered by layers of membranes, which contain an enzyme - glucose oxidase, reacting with glucose. Oxidation of substrate induces an electric signal. Its strength changes in direct proportion to the concentration of glucose. Mediator runs the electric impulse to the transmitter; however, proper calibration is essential for the correct functioning of the device.

Calibration is carried out, when blood glucose level remains stabilized in referential values. This process is based on comparing data from glucometer with data from CGMS. Patient injects sensor on his own using automatic device added to the set. CGM sensor lasts from 3 to 7 days, depending on manufacturer recommendations. Measurements are taken from the electrode in 5 minutes intervals, sent to the insulin pump or separate monitor by radio signals and presented on a monitor in a graph. The device also has a function of sending the notification about the level of glycemia. Monitoring trends of glycemia evolution assure continuous control of treatment. Although, the decision about changes in the doses cannot be made solely based on CGMS. Completing the data by measurements from glucometer is required [52-54].

Studies show many advantages of this system, as a decrease in the glycated hemoglobin level after insulin therapy with CGMS was observed, in comparison to pumps without it. Furthermore, more patients from the group using CGMS had the level of HbA1c less than 7%

without incident of hypoglycemia as opposed to the control group [53]. Research also showed a reduction of the need for glucose control using a glucometer, increased detection of extreme glycemia deviations and improvement in its regulation [48].

Sensor-augmented insulin therapy - low glucose suspend (LGS) system

Subsequent innovation is a pump with incorporated CGM, that allows the system to automatically suspend the insulin delivery when blood-glucose values are falling too quickly or if they reach the low level. This option allows to avoid blood sugars from further falling and may increase the glycemia. This function is beneficial for parents of small children with diabetes, especially at night-times, people with hypo-unawareness, and all those who experience frequent hypoglycemic episodes. When the CGMS informs about glucose level falling under the programmed limit, the supply of insulin is stopped for some time. Delivery can be suspended during the hypoglycemia or before its occurrence, depending on the device type and its calibration. However, this system also allows resuming insulin delivery manually. Some of the pumps can proceed it automatically based on the CGMS when the glucose level is above critical value and is estimated to be stable for at least 30 minutes. Therefore, patients reported severe enhancement in the quality of life after using this system. They observed a drop in the frequency of headaches, tiredness or drowsiness. Stress and fear of the event of hypoglycemia decreased. Continuous control performed by the device helps patients to incorporate an adjusted schedule of the measurements of glycemia to their daily plan. Additionally, the occurrence of hypoglycemia and the percentage of glycated hemoglobin lowered [54-57].

Insulin pumps with hybrid closed-loop algorithm

One of the newest solutions is an insulin pump with a hybrid closed-loop (HCL) algorithm, also known as “artificial pancreas.” The first project of this invention appeared in 2006 and was presented by the Juvenile Diabetes Research Foundation International (JDRF). Ten years later Food and Drug Administration (FDA) approved the design. It works like beta cells in the pancreas. The pump includes CGMS, LGS and a specific algorithm that commands insulin delivery. Although the secretion of basal insulin is automatized, the insulin bolus must be delivered

manually. During a more significant part of the day, the device sustains the glucose level in a reference value and indicates the lowering level of glycated hemoglobin or reduction of nocturnal hypoglycemia in comparison to traditional pump therapy. The appearance of those new products with HCL on the market is challenging for clinicians. To ensure that this innovative solution is widely available, they are obliged to learn how to adopt the device to the patient. Only proper calculations and adjustment of insulin doses, knowledge when the system stops the automatic insulin intake and successful education of the patient guarantees an effective treatment [46,58-60].

HCL technology opened a way to new opportunities in the battle with diabetes. Next step is designing a device, that will automatically apply the insulin and glucagon according to the needs of the organism. This idea is a great challenge for the future [46].

Future methods of insulin therapy

In order to increase the effectiveness and satisfaction from therapy, studies are being conducted continuously to improve insulin therapies. Some of them may in the future turn out to be a revolutionary treatment form of different diabetes mellitus types. Since the discovery of insulin, scientists have been searching for a useful oral method of its administration. While being one of the most promising ways of dosage, it is currently studied. However, insulin as a protein is not resistant to the acidic environment and digestive enzymes of the stomach and small intestine, generating many barriers that need to be overcome.

Furthermore, the insulin absorption by the intestinal epithelium is restricted by permeability, reducing the bioavailability. There are many advantages of oral administration though. Psychological, as oral drugs are better tolerated and more willingly taken by patients, increasing therapy compliance. Physiological, since after absorption insulin directly affects liver through the portal venous system, suppressing the rise of hepatic glucose level. Studies show promising outcomes of nanotechnology, which made possible the creation of potential carriers for insulin through the digestive system. Biodegradable polymers, such as chitosan, newer compounds like vitamin B12 derivatives, lipid nanoparticles, and calcium phosphate are the most popular in this type of hydrophilic drugs administration. They are applied as a coating, thereby protecting insulin from acidic pH, present in the stomach. In a mildly alkaline environment, the carrier dissolves, releasing the drug held in its structure. Deployment of a proper carrier increase drug

retention enhances adhesion to intestinal epithelium and permeation through it; thus, usage of a correct one is crucial in order to obtain the best results in therapy [42,61].

Another studied method of insulin administration is transdermal systems. Due to their noninvasive character, they could present an alternative for subcutaneous bolus injections, especially for the patients finding the use of the needles unpleasant. Initially, this idea was taken into account with studies over inhaled insulin, using devices similar to the asthma inhalers with the drug in a solution or a powder formula. Since lungs are characterized by high accessibility and bioavailability for drugs as well as the large surface of absorption, they are a pharmacologically pleasant and user-friendly way of application. However, using insulin inhalers is contraindicated for patients with respiratory diseases.

Moreover, there are few types of research concerning the pulmonary toxicity of the inhalers and their influence on pulmonary carcinoma development. Therefore the only currently available drug of this type is Afrezza. It consists of rapid-acting monomeric insulin, inhaled as a dry powder. It showed fewer side-effects, such as hypoglycemia or body weight gain, than previously used inhalers and the most observed one was a mild dry cough, decreasing over time [62,63].

Buccal delivery of insulin is another example of a transdermal system, applied in two ways: aerosol sprays with permeation enhancers for oral cavity or embedded gold nanoparticles on a dissolvable film. The drug is absorbed through mucosa present on the internal surfaces of the cheeks and the back of the mouth. Due to the deployment of relatively large spheres of aerosol, insulin administered this way cannot reach the lower respiratory tract, thereby differing from the inhaled route. In comparison to subcutaneous injections, buccal insulin acted quicker but over a shorter time and was well tolerated by the patients. However, it required many puffs in order to achieve the demanded dose, which is time-consuming. Despite promising results at the beginning, buccal delivery has not gained drug monitoring institutions acceptance due to the poor efficiency, low user-friendliness and high variability in pharmacokinetics and pharmacodynamics; therefore the idea has been abandoned [64,65].

Searching for alternatives to pens and subcutaneous systems of insulin administration, the transdermal application has also been taken into account. This route is suitable for long-acting insulin rather than bolus injected rapid-acting ones. It has relatively mild adverse reactions – mainly skin irritation, as well as local infections. Many benefits of the transdermal system have been noticed, mostly psychological, since it does not require large, tangible needles, it enables a long-

standing, user-friendly therapy, resulting in enhanced compliance. Also, physiological advantages are observed, as the first pass effect is reduced. Although the major limitation is the outermost layer of the skin, creating a barrier which restricts especially lipophobic compounds permeation and hence their absorption. In order to improve penetration, various methods are employed. The most prominent ones are microneedle patches inserted into the skin, which distribute the insulin into the epidermis, without damage to the nerve's endings. By puncturing, aqueous pores in stratum corneum are created, forming hydrophilic channels, which allow various molecules to be transported through the skin, such as insulin. There are different types of microneedles: they can be drug-coated, drug-encapsulated – releasing in self-dissolving, and hollow – infusing liquid formulation. There are also solid microneedles, which disrupt stratum corneum only, a drug-loaded patch is applied afterward, which liberate the medication. This microinvasive method is painless to the patient as well as cost-effective and easy to use. Overcoming skin barriers can also be achieved in different ways: microdermabrasion - a skin planning, revealing the deeper layers of the skin; or thermal ablation – were using electric pulse thermal energy is generated, achieved high temperature impairs stratum corneum by forming micropores, though causing no damage to the deep skin [66,67].

Conclusion

Research and technological development have significantly contributed to improvements in patients life from the perspective of the reduced risk of diabetes-related complications, as well as increased quality of life, flexibility, and freedom.

New insulin analogs fulfilling an organism's needs more and more effective and advanced methods of their administration become standard in modern therapies.

Although a universal insulin therapy does not exist, using various patterns and routes makes it possible to get near to the physiological metabolism.

Firstly, the complexity of diabetes and patient-dependent factors decide on the individual treatment choice.

Secondly, abiding insulin therapy rules and awareness of the disease mechanisms are crucial not only for the treated ones but also for diabetes teams.

Without nonredundant patients compliance, even the best method might not be valid. Thirdly, despite a low chance of finding an ideal treatment method, studies over new patterns and improving the existing ones are continually going forward.

This gives patients hope for even better management of their disease in the future.

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Interactions of anti-vaccine movements, vaccination coverage and communicable diseases on the example of measles

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List of abbreviations

AB2109 - Assembly Bill 2109
CDC - Centers for Disease Control and Prevention
DTP - Diphtheria-Pertussis-Tetanus
ECDC - European Centre for Disease Prevention and Control
MBs - Medical Exemptions
MMR - Measles-Mumps-Rubella
PBEs - Personal Belief Exemptions
SB277 - Senate Bill No. 277
SIDS - Sudden Infant Death Syndrome

The topic which can be described using the title of this paper is an immense one. We aimed to describe some more interesting, and vivid aspects of anti-vaccine movements and of the way they impact the effectiveness of the vaccination programs.

By doing, so we wanted to draw attention to the problem of vaccination and the fact that it has an impact on public health.

We have focused on both historical and contemporary situations to show the ubiquity of the problems caused by anti-vaccine movements.

The data from different countries have been used but we did not compare them as it was not the exact purpose of our work.

Introduction

Vaccines are considered to be one of the greatest achievements of modern medicine. According to the World Health Organization, they prevented at least 10 million deaths between 2010-2015 and protected many more people from illnesses and their complications [1]. Their impact on the morbidity of communicable diseases and public health, in general, is undeniable and should not be questioned. There are diseases, which have been completely eradicated due to vaccines - such as smallpox and rinderpest [2]. Moreover, the incidence of certain infectious diseases has decreased in the global range. For example poliomyelitis – a fatal contagious disease is nearly eradicated. According to the CDC in 2016 wild poliovirus cases were observed in only two countries - Afghanistan and Pakistan and 4 out of 6 WHO regions have been certified polio-free [3].

However, more and more individuals tend to underestimate and even stigmatize the value of this form of immunisation. WHO defines vaccine hesitancy as a "delay in acceptance or refusal of vaccines despite the availability of vaccination services". It is recognized as a complex and context-specific problem, which varies depending on time, place and vaccine. In the 3Cs model developed by WHO vaccine hesitancy is influenced by three major factors:

- complacency (the risk of disease is perceived as low and thus vaccination is perceived as unnecessary),
- convenience (how easily can the vaccine be accessed)
- confidence (level of trust in the vaccine or its provider).

"*Vaccine-hesitant individuals are a heterogeneous group that is indecisive in varying degrees about specific vaccines or vaccination in general. Vaccine-hesitant individuals may accept all vaccines but remain concerned about vaccines, some may refuse or delay some vaccines, but accept others, and some individuals may refuse all vaccines*" [4,5].

Vaccine hesitancy has been qualified by the World Health Organisation as one of the top ten global threats in 2019. That puts it on equal footing with problems such as air pollution and climate change, global influenza pandemic or weak primary health care [6].

Numerous groups of vaccine-hesitant individuals are parents, who are unwilling to vaccinate their children. They are lead by the fear of possible complications and diseases, which may occur as a side effect after vaccination. There are neither medical basis nor evidence to justify this anxiety. Parents are misled and intimidated by the knowledge from the Internet, which makes them perceive a potentially deadly disease as a lower threat than it is [7].

The beginnings of the modern anti-vaccination movements in the USA can be traced back to the events of the 19th of April 1982. At that time, WRC-TV in Washington, D.C. aired a program, in which the pertussis component of the DPT vaccine was accused of causing severe brain damage, seizures and delayed mental and motor development. As a result of having watched "DPT: Vaccine Roulette" many parents decided not to vaccinate their children, which caused a decrease in vaccination coverage. Furthermore, parents who considered vaccines as a cause of damage to their children started suing vaccine manufacturers [7].

Just eight years earlier in the United Kingdom in 1974 successful vaccination programme was interrupted by a report, which ascribed 36 neurological reactions to the whole cell pertussis vaccine. At a similar time Dr. Gordon Stewart claimed, that vaccination causes more dangers than benefits. These events resulted in a lack of confidence, which decreased the vaccination coverage and entailed pertussis epidemic [8].

Another event which had a significant impact on anti-vaccine movements formation was Andrew Wakefield's publication in The Lancet. In his work British doctor claimed, that MMR vaccine is associated with gastrointestinal disease and developmental regression including autism [9]. However later studies refuted this theory [10], Wakefield's impact on the case of vaccines can be seen to this day.

Herd immunity

High vaccination coverage and the high percentage of immunized people in a community, which is threatened by anti-vaccine movements, is particularly essential on the grounds of "Herd Immunity." It is defined as a form of indirect resistance of a group of people against infectious diseases, which occurs when a large percentage of the population has become immune to infection, and so ensures the protection of those not vaccinated [11,12].

Reports on the possibility of eradication of diseases and reduction of severe complications in ill people who have been vaccinated, and cost-benefit analysis from the vaccination program, contributed to the spread of this term [11].

When WHO developed the Expanded Program of Immunization in 1974 and Smith in 1970 [13] and Dietz in 1975 [14] uncovered a simple threshold theorem, this term becomes widely used. This theorem assumes that members of a society mix at random. On average,

every person who contacts with R_0 number of individuals in a way adequate to transmit the infection and given that immunity (vaccinations) is supplied at random, then the incidence of the infection will decline, if the proportion of immune one's excesses $(R_0 - 1)/ R_0$ [11]. This is illustrated in Figure 1.

The diagram illustrates the transmission of infection over three generations with a primary reproduction number $R_0 = 4$. A – Totally vulnerable population; 1 case is leading to 4 cases in the second generation, and then to 16 cases in the third generation. B- Population has the level of immunity by about 75%.

In this situation only one individual is susceptible, so each case is leading to only one prosperous transmission of the infection. If a big part of the community is immune, then incidence will decline.[11] On this basis, we can set a "herd immunity threshold" at $(R_0 - 1)/ R_0$ [11].

Term. 1 R_0 - Basic reproduction number. (Number of secondary cases caused by an ordinary infectious person when the rest of the population is not immune) [11].

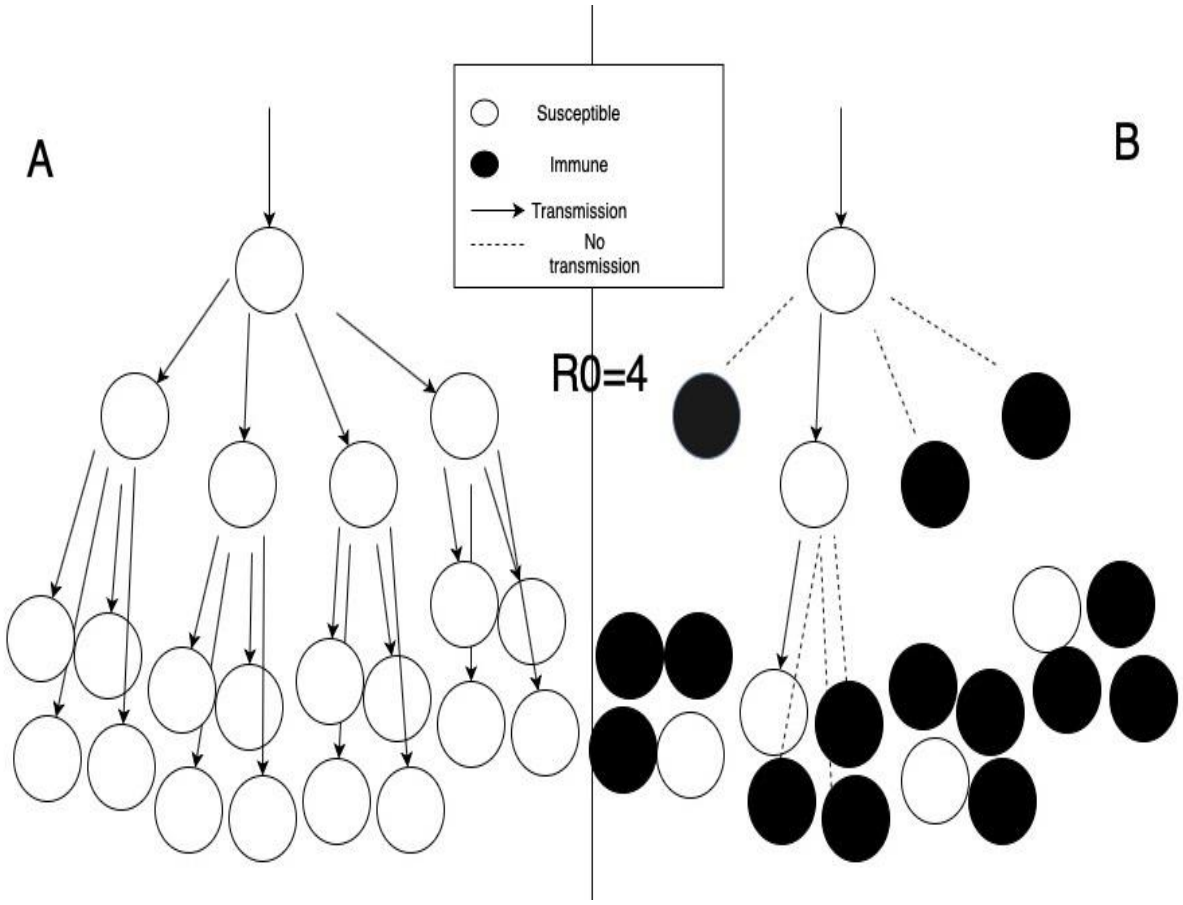

Fig. 1. Transmission of an infection over 3 generations

The human population is very heterogeneous, therefore the concept of simple thresholds, which assumes simple mixing and dissemination, is not appropriate for the assumptions of public health and it must be treated with reserve [11].

Numerous authors mention the possibility of eliminating infections at a certain level of immunization. The $(R_0 - 1)/R_0$ threshold as the assumed target of excretion is often suggested, after deriving and determining *R0* for each infection [11,15].

The real herd immunity threshold calculated for some diseases usually requires 90-95% resistance in the population and is defined as the percentage of people immunized against this disease in the population, after which the number of newly infected begins to decrease [16].

However, the percentage of people immunized by vaccination has different values depending on the disease.

Herd immunity thresholds [16]	
Measles	95%
Whooping cough	92-94%
Diphtheria	83-86%
Rubella	83-86%
Mumps	75-86%

It means, that given percentage of the population must be immune to the disease in order to prevent infections on a larger scale.

It is important to remember that herd immunity is not equal to biologic immunity; people protected only by indirect herd effects in case of exposition remain fully susceptible to infection [11].

Herd immunity allows protecting individuals with contraindications to vaccination or those, who for other reasons, miss vaccination. Nevertheless, the examples of consequences of the profusion of susceptible individuals who are not protected by vaccination, and eluded an infection because of herd immunity can be observed. In this group, an increased incidence was revealed during measles and mumps outbreaks among university students and pertussis outbreaks in adults [11,17].

Vaccination coverage levels and what influences them

It is needless to say that vaccination ratio and incidence are strictly correlated. However, people tend to neglect the importance of vaccines when the danger of the disease and epidemy is neither experienced personally nor publicly discussed. Such a situation occurred in the ’70s in the UK. Immunization against pertussis began in 1942, reaching its highest point in 1970. Due to fears over the safety of pertussis vaccines and pertussis vaccine reactions, immunization levels dropped from 77% or 80% in 1974 to 30% in 1978 [18,19]. This had led to massive pertussis outbreaks, reaching their peak between 1976 and 1981. The incidence rose up to 4.4-fold for children aged 1-4 years at the time.

More recent comparison of whooping cough incidence in countries with and without anti-vaccine movements has shown that the disease incidence was 10 to 100 times lower in countries where vaccine coverage had been maintained [20]. The comparison does not only refer to the UK. Other studies seem to confirm these data, without giving exact numbers. Therefore, the risk of an outbreak of a suppressed disease, something rather apparent for healthcare professionals, had been publicly noticed for the first time. There were several concerns about the vaccine at the time, among them economic profitability, effectiveness, and question whether vaccines cause a fall in incidence. There were also movements or not organized groups of people [20] who raised arguments about dangers connected with the vaccine, SIDS, acute encephalopathy and attack of convulsions among them. Some of the arguments had been quite reasonable. As it has been mentioned before, in 36 children with neurological problems, who had been given a whole cell vaccine, those problems were credited with the complications. Authors of then published papers had emphasized the role of TV in spreading of those concerns [21]. If only they had seen modern mass media…. Autism had not been correlated with vaccines at the time.

Great Britain has very good vaccination coverage surveillance system, which also presents interesting data about measles. The measles vaccine introduced in 1968. In 1992 the level of vaccine coverage reached 90%. In the 1998 year, the infamous Andrew Wakefield’s paper saw the day of light, and the trouble began. In 2003 the level of coverage was slightly below 80% [22] - the lowest one since the beginning of immunization (this number applies to England only). There were some large outbreaks of measles in the group of teenagers, those who had not been vaccinated. On the chart, it can be seen that, unlike in the case of pertussis, there is no quick correlation between vaccination coverage and measles incidence. However,

those single outbreaks make the disease-endemic again and thus endanger everybody who had not been immunized, especially the weak ones [23].

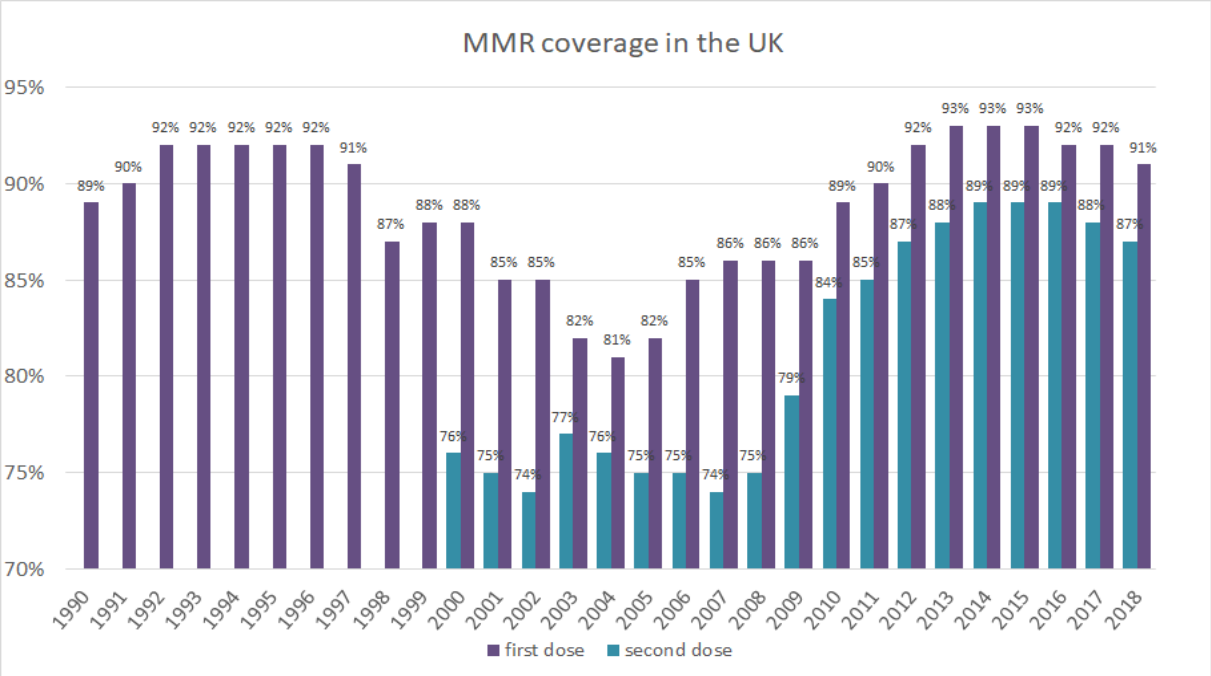

Fig. 2 Vaccination coverage for MMR vaccine in the UK according to WHO data for years 1990-2017, data for 2018 according to Public Health England [24,25]

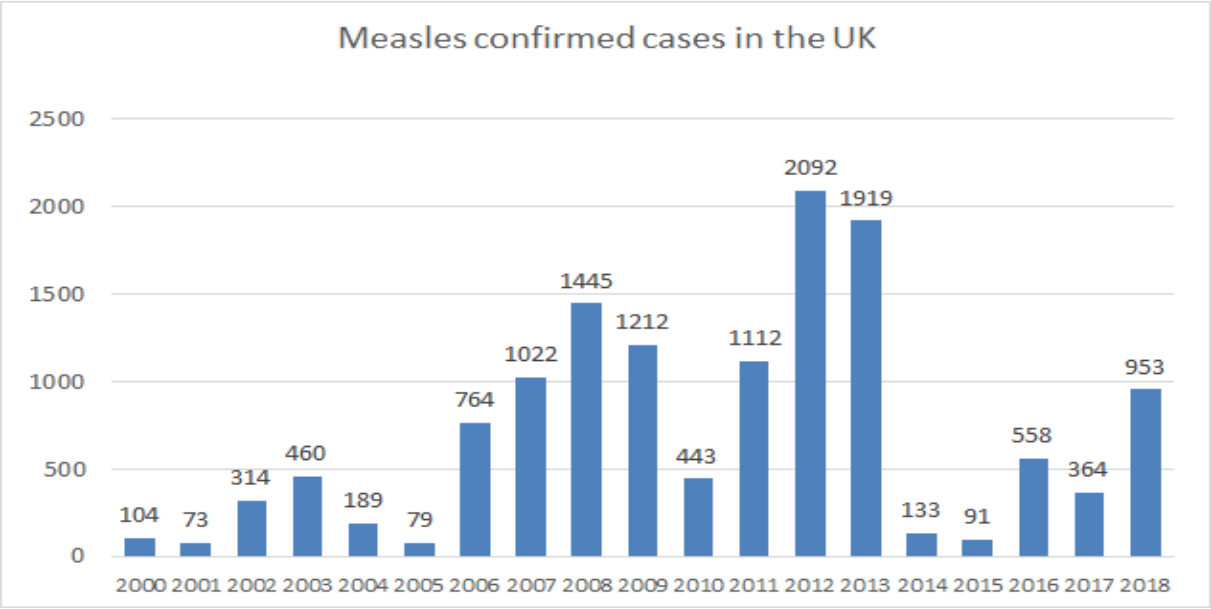

Fig. 3 Measles confirmed cases in the UK in the 2000-2018 according to the WHO. Data for 2018 are provisional based on monthly data reported to WHO (Geneva) as of March 2019 [26,27]

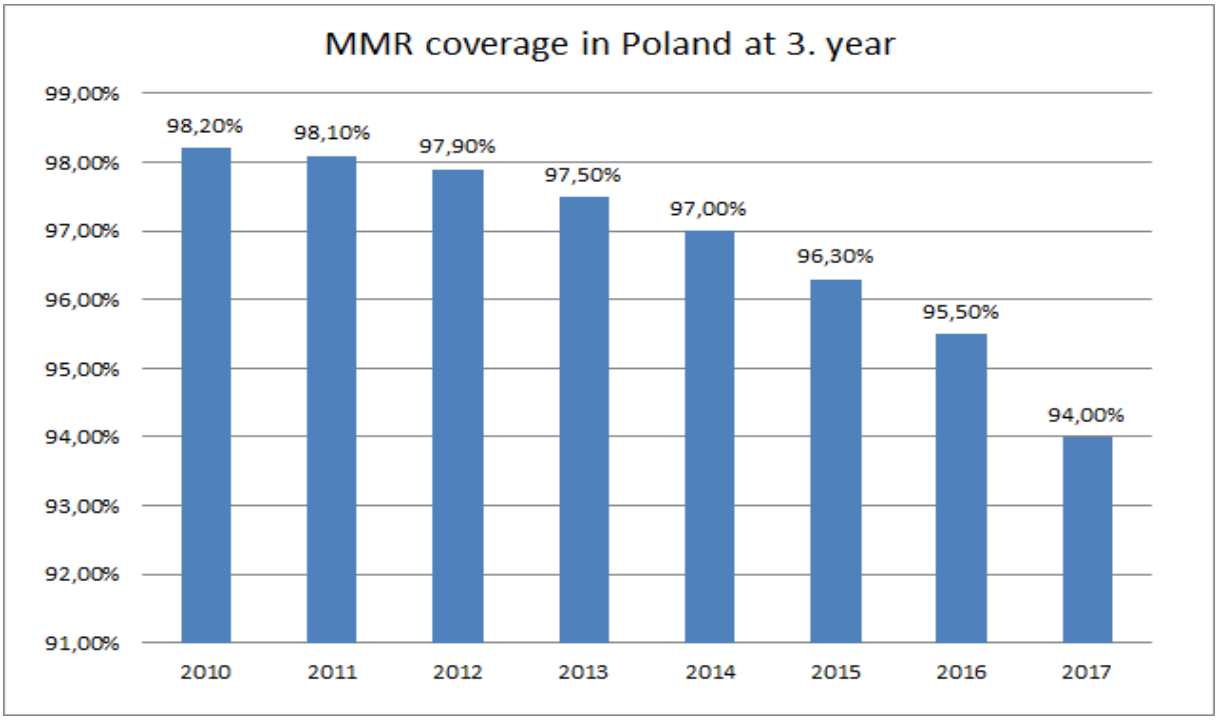

Fig. 4 MMR vaccination coverage in Poland in years 2010-2017 according to National Institute of Public Health [28]

Nowadays, after a brief period of increased immunization, MMR vaccine coverage level measured at the age of 2 had been dropping again, since 2014. Although some increases (in particular age groups) in the level has been noticed, the general tendency is declining.
The situation in Poland is quite different. Before 1989 Polish anti-vaccine movements had been rather inactive [20]. However, change can be seen. The most recent available data come from 2017. 94% of children at the age of 3 had been immunized in 2017 vs. 98,2% in 2010 [28]. The tendency, which can be seen on the chart is declining. The data for 2 years old children have even the biggest gap; however, at that age, many vaccinations are being postponed due to medical conditions.

However, the incidence does not seem to increase [29]. In none of the diseases suppressed by the MMR vaccine, a regular upward trend can be found, though one should not underestimate the state of affairs. The weakest members of society, who for multiple reasons cannot be immunized, may be endangered [30]. The vaccination coverage can also drop below the level of community resistance, which leads to renewed endemicity of the disease.

Another situation can be described in the case of Italy. The immunization coverage can be only estimated by WHO - there is no representative national databank on the topic - but still, the estimations are low, 85% in the worst year - 2015. The incidence - also according

to data from WHO - is quite high. Italy has been described as a country with a strong anti-vaccine movement in the past [8]. There is no reliable source to assess its nowadays condition, but according to multiple presses reports the movement is still active and popular. Cut on health care funding also had a negative effect. Authors of a complicated paper describing the case has discovered that for every 1% of decline of funding, there had been a 0.5% decline in vaccination rate [31]. They connect it with more mediocre health protection among minorities and the poorest [31]. In the case of minorities, some voices have been raised that the control of compliance with epidemiological requirements among them can be generally weaker in Italy [31]. No trace of such statements can be found in papers covering the topic in the case of the UK.

The case of California is certainly worth mentioning. Thanks to the high level of vaccination coverage the endemic measles has been announced eliminated from the United States by the CDC [32]. Despite that, there were several measles outbreaks since then including 2017 one in Minnesota and 2014 one in California [32,33]. Most of the incidences were found to be internationally imported [32]. 2014 California outbreak, one of the biggest ones, is also a good example of vaccination importance. It probably began in two nearby Disney theme parks in the Orange County. California Department of Public Health reports that at least 131 California residents were infected [34,35]. The outbreak happened despite the high and long-lasting MMR vaccination coverage in California [36]. According to the theory of Herd Immunity, Californian citizens should be safe from such a big outbreak. The key factor in this problem is vaccination coverage in the individual counties. According to the report published on the CDC site on 13th February 2015 among 110 infected patients reported till then, 49 (45%) were unvaccinated, and 47 (43%) had unknown vaccination status. Only 13 (12%) of them were known to be vaccinated with at least one dose of MMR vaccine [34]. After that outbreak, California introduced the Senate Bill No. 277 (SB277). It removed the Personal Belief Exemptions (PBEs), which allowed children unvaccinated due to personal beliefs of their parents to get to the schools and kindergarten. The new law was introduced in 2016 [37]. Back in the 2014 general MMR vaccination coverage in kids admitted to the kindergartens was 92,6%. 209546 children (39,15%) were attending to kindergartens placed in counties with coverage ratio below 90% and 11900 (2,22%) in these with coverage below 87,5%. In some counties, like Humboldt, the coverage dropped even below 80%, which was way less than safe levels [38]. However, thanks to the new law the numbers have changed. In 2017 no more than 3136 (0,56%) kids attended to kindergartens in counties with coverage below 90% and 3065 (0,54%) in those below 87,5%. None of the counties has dropped below

the 80% level. The general vaccination coverage was also improved to the level of 96,9% [39]. SB277, however, was not the first law introduced by the state of California in order to restrain the influence of the anti-vaccination movements. Back in 2012 an Assembly Bill 2109 (AB2109) was passed. It required a signature from certified health care provider stating, that the parent was informed about benefits and potential risk of vaccination in order to obtain PBEs [40]. It was introduced in 2014 and resulted in a drop in the percentage of PBEs from 3,1% in 2013 to respectively 2,5% in 2014 and 2,35 in 2013 [40]. Alongside with elimination of PBE priorly in 2016 to 0,6% and then to 0 in 2017 an increase in Medical Exemptions (MEs) could be observed. From the 0,2 % level in 2015, it reached the level of 0,7% in 2017. Despite that, the percentage of total exemptions dropped from 2,6 in 2015 to 0,7% in 2017 [39]. The biggest growth in MEs number was observed in counties with high levels of PBE before the SB277 was introduced. It suggests that some vaccine-hesitant parents have "switched" from PBE to false MEs [41].

Conclusions

What can we learn from the situation in the countries described above? For the UK, the conclusions seem to be precise. Strong anti-vaccine movements can influence both vaccine coverage level and, therefore, the incidence will grow - quite obvious. However, there had already been a pertussis outbreak connected with vaccine hesitancy in the UK [8]. The public opinion had not concluded it, or they were quickly forgotten. One can say that a small outbreak of a disease can be a "lesson" for those who oppose the immunization. Apparently, it is a fast forgotten truth. As happens in Italy, there are many people who need to be either informed about the benefits of vaccines or somehow (for example by their family doctor) encouraged. Of course, money is required here, and their lack makes the immunization level worse [31]. It is also probable that special emphasis needs to be put on minorities and immigrants, who may be in worse condition (unfamiliarity of the language, lack of insurance). Poland is an example of a country, where the anti-vaccine movement has started rising quite recently [8]. The vaccination coverage of measles is falling. While the incidence remains low [29], huge outbreaks among teenagers in the UK show that we can expect the same in the future. In our opinion, the "postponed" effects of lack of immunization make it harder to fight with anti-vaccine movements. It must also be admitted that Poland, just like the UK, has a good system of surveillance and fine databanks.

As it is shown on the example of California legal conditions should not be undermined. By introducing appropriate laws vaccination coverage can be changed and diseases outbreaks prevented, even to some individuals may resist vaccination despite their obligatoriness [40,41]. Herd immunity allows to avoid an epidemic among a susceptible percentage of the population, but as mentioned earlier, it is not equal with natural immunity and implies a sustained programmatic responsibility to the society [11]. Vaccination should be obligatory, and kids should be checked whether they are up to date on their immunization schedules. All of these steps can stop or at least limit the consequences of the observed rise of the anti-vaccination movements and their influence on the herd immunity of our societies.

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The state of knowledge of blood donors of the Regional Center for Blood Donation and Blood Treatment in Gdańsk (Poland) on HIV viral infections

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Introduction

In Poland, since 2016, there were about 22,000 people infected with HIV (*Human Immunodeficiency Virus*) and aware of their infection. However, it is estimated that the unconscious is over 10,000 people. Currently, the etiology of HIV, as well as the ways of transmission of the virus are very well known, although infection is one of the most important epidemiological problems in the modern world.

High safety of blood transfusions and its components has been achieved thanks to the introduction of research on markers of viral infections. The duty of the Blood Donation Center is to examine donors and donor candidates for the diagnosis of infectious agents, including hepatitis B (HBV) and C (HCV) viruses and HIV. The review studies are carried out with serological and molecular biology techniques [1].

The very rapid pace of spread of HIV infection in the eighties forced to extend the scope of blood donor screening. Immediately after the discovery of the virus, the risk of transfusion infection was very high, in some areas of America, e.g. San Francisco, was estimated approximately 1:100. A test for the detection of anti-HIV antibodies was developed by American researchers in 1985, one year later it was introduced to the list of mandatory tests for blood donors. In Poland, it was widely used at the end of 1987, it detected only anti-HIV1 antibodies, currently tests for the detection of antibodies HIV1 and HIV2 (detecting

antigen p-24) are used. Detection of HIV RNA was introduced in 2003 and since 2005 it has been performed with every donation. For that reason, the risk of HIV infection by transfusion is minimal. Between 1995 and 2007 there was any HIV infection detected in Poland after blood transfusion or after administration of blood products [2].

Infectious agents that can potentially be transmitted by transfusion are now very well known. The risk of HIV infection after blood and its components transfusion is currently unlikely. This was achieved by the introduction and use of sensitive tests and screening of blood donors. Moreover, there were introduced additional procedures limiting the transferability of infectious agents:

- Donors qualifications on the basis of physical examination, medical interviews and epidemiological questionnaire;
- Screening of viral markers prior to each donation of blood for HBV, HCV and HIV infection using serological tests with the highest sensitivity and specificity; molecular and screening tests for syphilis;
- Minimization of mistakes caused by laboratory analysts and introduction automation, computerization and internal control processes during testing;
- Filtration of blood preparations - reducing the risk of transmission of infectious diseases by microbes contained in leukocytes;
- Introducing a grace period for the production of blood products;
- Inactivation of viruses in blood products if it is possible [3].

Organizational units of the public blood service maintain a system of watching over the safety of blood and collected, examined, processed, stored, brought out or distributed its components on the territory of the Republic of Poland, hereinafter referred to as the "watching system". It allows tracing the blood and its components from the blood donor to the recipient blood and vice versa. The watching system comprises medical subjects where transfusions are carried out to blood recipients. This mentioned process is extremely important because the increasing globalization and migration of people increases the risk of transfusion uncommon contagious agent in given country. Potential donors and blood donors travel around the world and are exposed to infectious agents that are endemic. Infectious agents in the blood with very long latency period are the most important in transfusiology. There is the higher risk of transmission when the period of asymptomatic infection is longer.

The World Health Organization, the European Union and the European Council oblige to detect the markers of infections in every blood donation. At present, in the Regional Blood

Donation and Treatment Center in Gdańsk, tests are carried out to detect HCV, HBV, HIV and bacteria that causes syphilis (*Treponema pallidum*) in each collected donation. Directives 2005/61/WE and 2002/98/WE oblige the blood service to fully monitor the way of blood and its components from the donor to the recipient and vice versa. Furthermore the Blood Donation Centers have the obligation to have a system to identify each blood donation and its component [3,4,5].

Epidemiology HIV and AIDS

The first reports on AIDS appeared in the journal "Moriditity and MorlityWeekly Report" which describes the pneumonia caused by *Pneumocystis carinni* in young healthy men. Subsequent illnesses were observed in various hospitals in Los Angeles in which, in addition to *Pneumocistis carinni* infection, ulceration of the skin around the anus, cytomegalovirus infection, enlargement of lymph nodes and reduction of T4 blood lymphocytes were detected. The new unknown disease in 1982 was called the Acquired Immunodeficiency Syndrome - AIDS, which caused the HIV retrovirus, resulting in the failure of the immune system in the infected person. Analyzes of medical cases showed that in the USA, Europe and Africa cases of this disease occurred already in the 1950s. A preserved blood sample infected with HIV comes from 1959. from Zaire. Most likely, HIV infection appeared between the 20's and 30's of the 20th century, then SIV (Simon Immunodeficiency Virus) switched to a chimpanzee in West Africa [6].

Human Immunodeficiency Virus (HIV) belongs to the Retroviridae family, a genus of Lentivirus. Like other retroviruses, this virus contains two identical single-stranded RNA molecules, about 9,500 nucleotides in length.

There are two types of virus: HIV-1, which occurs worldwide and HIV-2, occurring in limited areas of West and Central Africa. HIV1 is responsible for the global pandemic and the research conducted so far concerns this type of virus. There are 3 main groups within HIV 1 [7,8]:

- M (main),
- O (outlier)
- N (new).

HIV in the human body limits the immune response, quickly leading to the complete destruction of the immune system. The body is not able to destroy or eliminate the infection,

because the virus, after entering the cell, prescribes its genetic material from viral RNA to the cell's DNA. It enables this allows HIV interference in the host's DNA and use of cells to create new viruses, which are then transferred to the testicle cellular [7,8].

The transmission routes of the infection are well-known, and the most modern treatment is introduced, however, HIV is still spreading and is one of the major epidemiological problems in the modern world. Data from 2015 estimate that there are approximately 40 million HIV infected people in the world, including 19 million women and 2 million children. The most serious epidemiological situation occurs in Africa (the sub-Saharan part), where 25% of the adult population is infected with HIV. In Poland, by 2016, over 21,000 registered cases of HIV infection, actual cases can be around 30-40 thousand. The long-term asymptomatic period of the disease causes that people are unaware that they are seropositive and are the cause of most new diseases. In Third World countries, due to starvation, there is a lot of vertical infections. Because it is allowed situations in which an infected mother feeds her child naturally [9].

In recent years, an increase in HIV infection has been observed, with concurrent fall of cases and deaths on AIDS. This is due to the introduction of the latest anti-retroviral therapies.

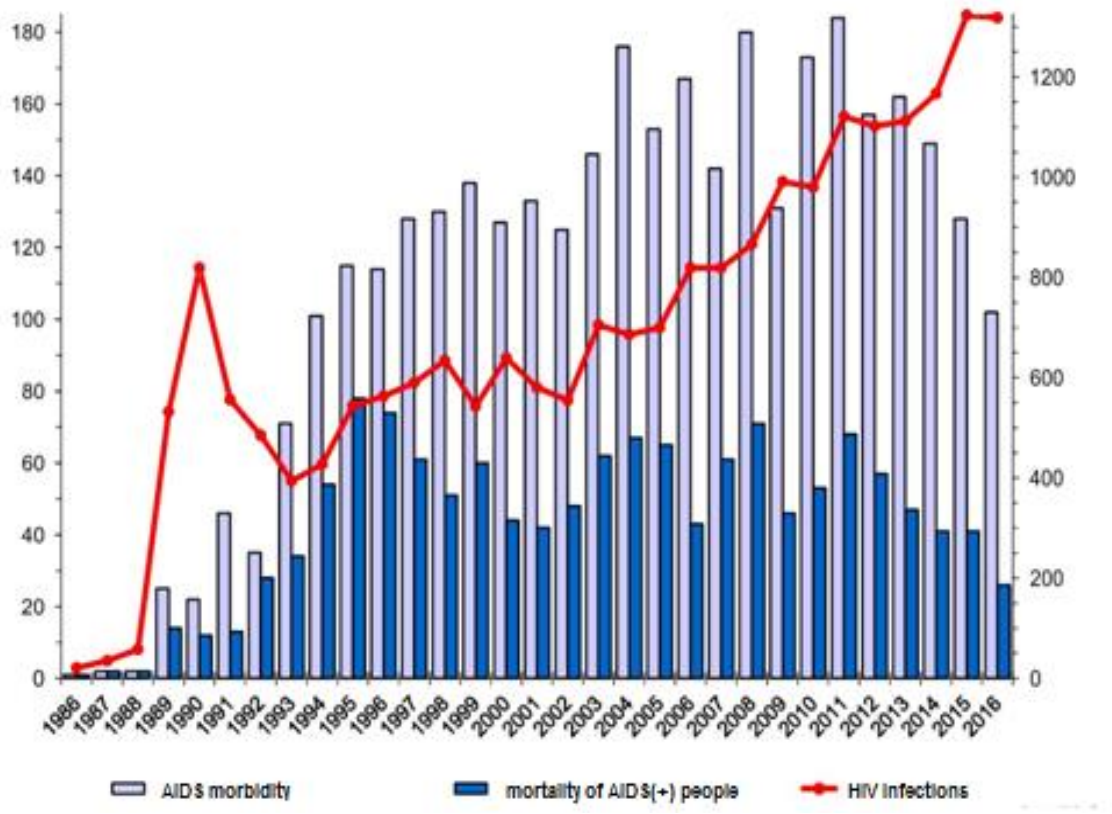

Figure 1. Infections of HIV, AIDS and deaths of AIDS patients in 1986-2016 [10].

Objectives

The objectives of the work is to know the state of blood donor's knowledge about HIV infection. They wanted to know the basic information about infections, knowledge of the routes of infection and situations conducive to HIV infection among this category of respondents. The research was carried out among blood donors of the Regional Center for Blood Donation and Blood Treatment in Gdańsk, from January to March 2018.

Methods; selection and characteristics of the respondent

The quantitative method was used for research, while the sociological questionnaire was used as a research tool.

The questionnaire contained 26 basic questions and 6 additional socio-demographic questions. Most of them were single-choice but in a few questions the respondents could give more than one answer.

The respondents' answers were developed using a spreadsheet of the Microsoft Excel computer program and presented in a descriptive, statistical and figure form.

The basic issue was to verify the knowledge of blood donors on the epidemiological risks of HIV.

The research was carried out among blood donors of the Regional Center for Blood Donation and Blood Treatment in Gdańsk, Poland and in a mobile blood donation point. During the pilot study, 10 questionnaires were carried out.

This research allowed us to confirm the usefulness of the research tool and continue the study. The studies were held from January to March 2018.

The respondents were characterized according to the following data: age, sex, residence and education.

Analyzing the age of the respondents, the greatest number were people between 18 - 29 years (51%), 30 - 45 years (35%), 46 - 60 years (14%), any responder was over 60 years old. A total number of blood donors who participated in the study was 100: 49 men and 51 women.

There were more residents of the village (53%), while the city residents were 47%. The highest number of respondents had a higher education (33%), secondary education - 28%, vocational - 18% and basic education - 21%.

Results

The analysis of the distribution of responses in the questionnaire concerned the level of knowledge about HIV infection among the blood donors. More than half of the respondents

67%) indicated the correct meaning of acronym HIV as "Human immunodeficiency virus", the answer "I do not know." in 18% of cases, the next answers were incorrect and concerned "Human papilloma virus" (10%) and "Influenza virus" (5 %).

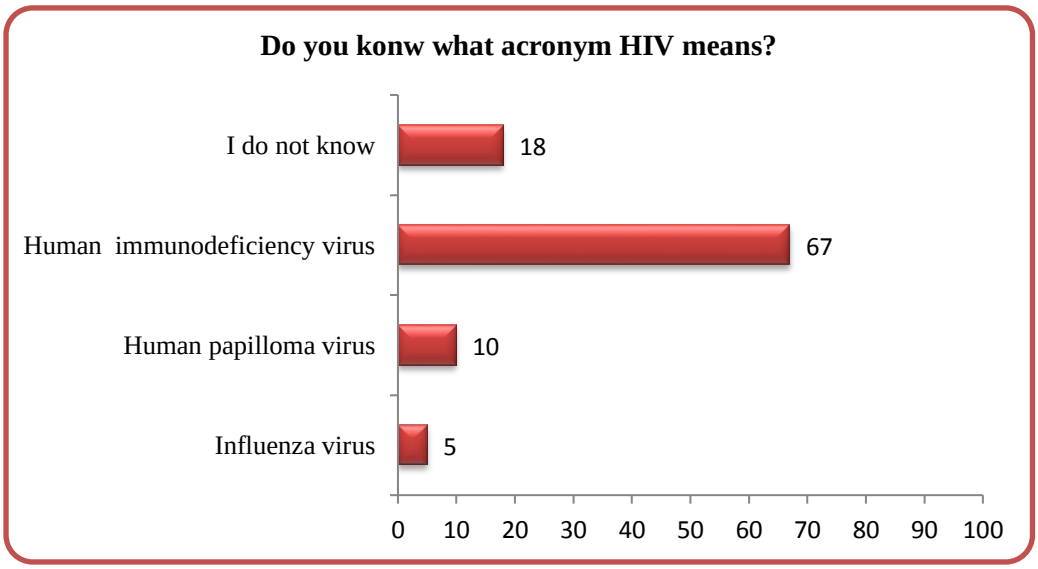

Figure 2. Responses to question about meaning acronym HIV [own study]

Respondents as the direct risk of HIV infection subsequently mentioned: risky sexual behavior (84%), use of common needles (75%). Further responses of blood donors indicating the risk of infection in situations, i.e.: using a shared toilet (17%), sharing cutlery and cups (13%), hospital stay (10%), handshake (3%), show deficits in knowledge about HIV. The results are shown in the fig. 3.

Most of the respondents mentioned that AIDS is not a curable disease (74%), 13% of them do not have the knowledge in this area, and also 13% think that AIDS is a curable disease. The results are presented in fig. 4.

The next question concerned the responders' knowledge about the routes of HIV transmissions. Participants listed the following routes of infection: blood (92%), sexual contact (86%), saliva (37%), oral (7%), airborne (5%), sweat (2%), and touch, while 1% of the respondents ignored the routes of infection. The results are presented in fig. 5.

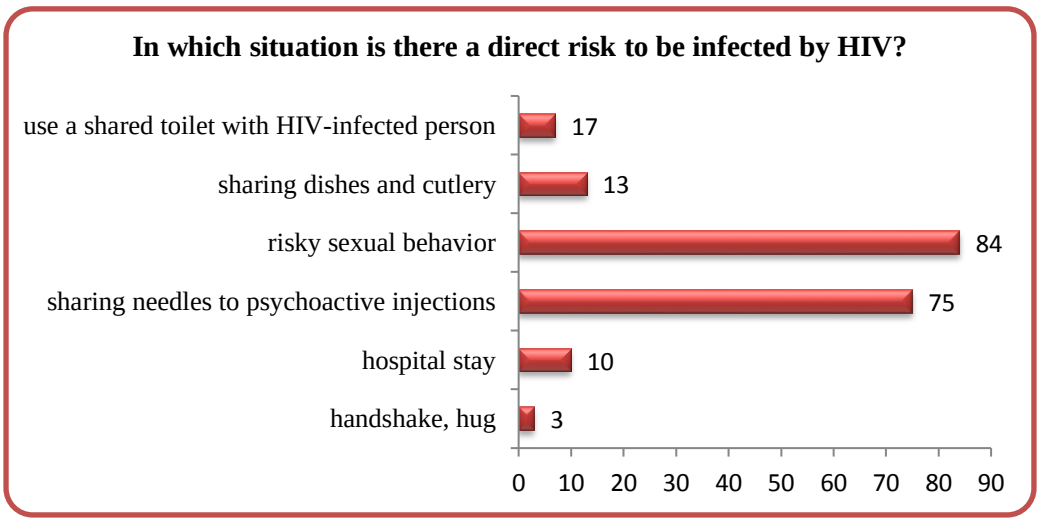

Figure 3. Responses to question about risky situations connected with HIV infection [own study]

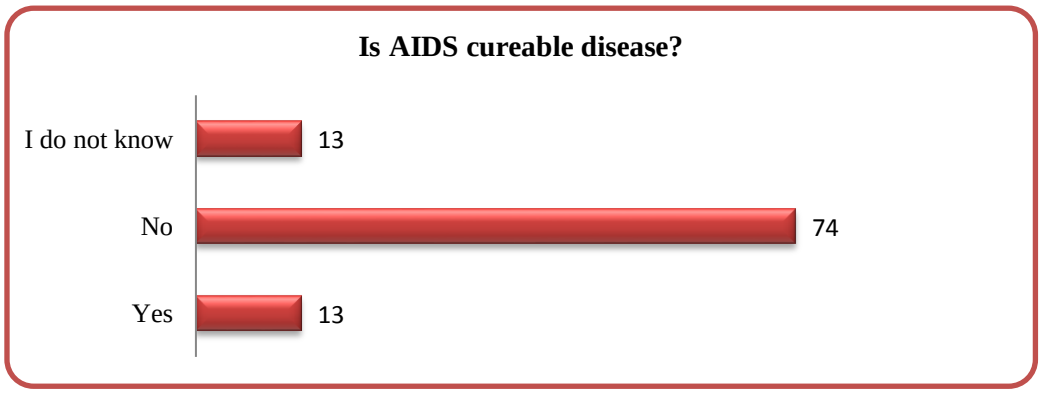

Figure 4. Responses to question about AIDS curability [own study]

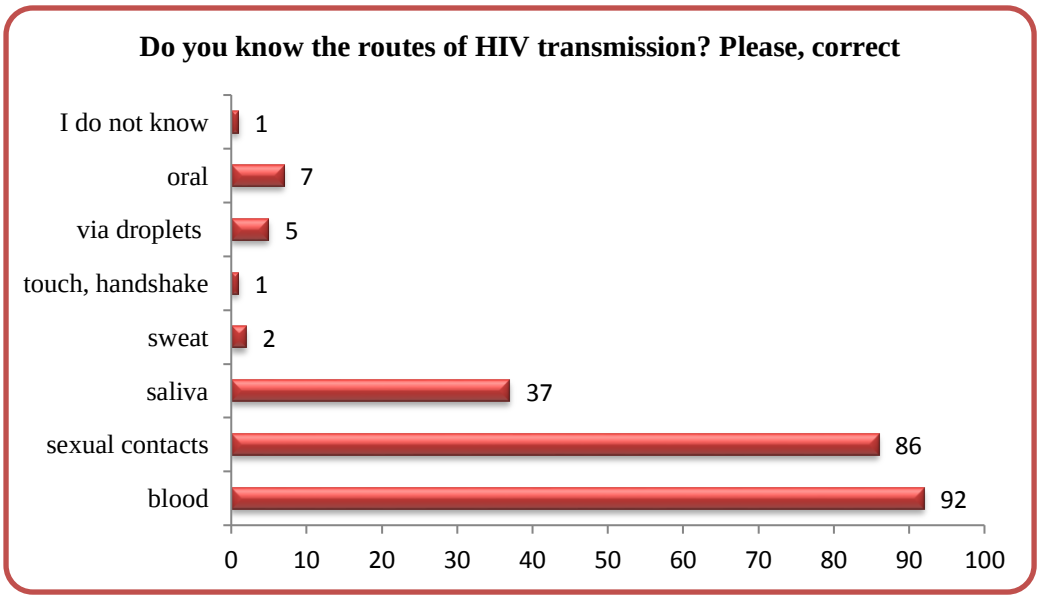

Figure 5. Responses to the question about router of HIV transmission [own study]

Knowledge about the number of people infected with HIV in Poland among the surveyed blood donors is as follows: 41% responders reported that there is infected 10,000 to 20,000 people, 34% of them think that there are more than 21,000 infected people, and 25% that there are infected less than 10,000 people. The results are presented below in fig. 6.

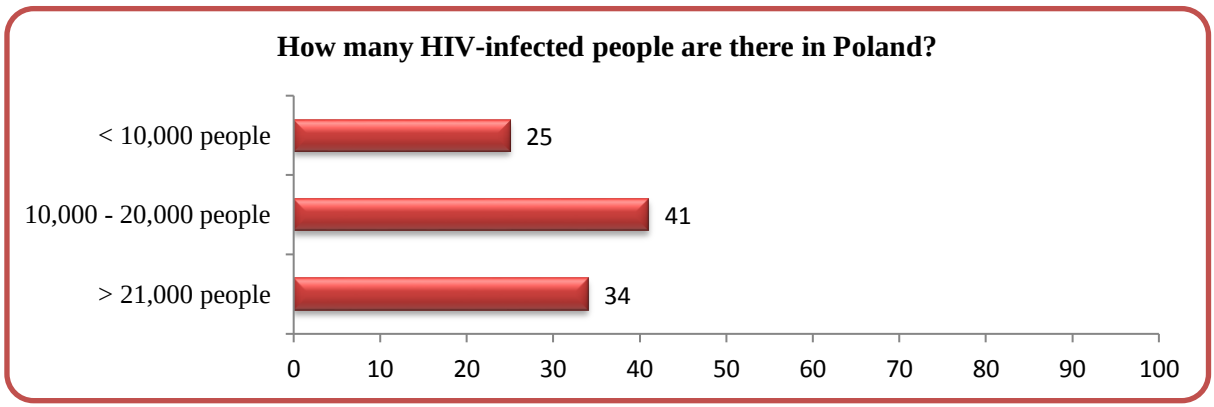

Figure 6. Responses to question about number of HIV-infected people in Poland [own study]

The most significant methods of preventing HIV infection were correctly mentioned by the respondents: avoidance of intravenous drug use and risky sexual behaviors (53%) and public awareness campaigns (22%). Further respondents' answers showed deficits in knowledge about the possibilities of preventing HIV infection, as 19 % of participants mentioned avoiding contacts with an infected person and 6% has no knowledge on this topic. The results are presented in Fig. 7.

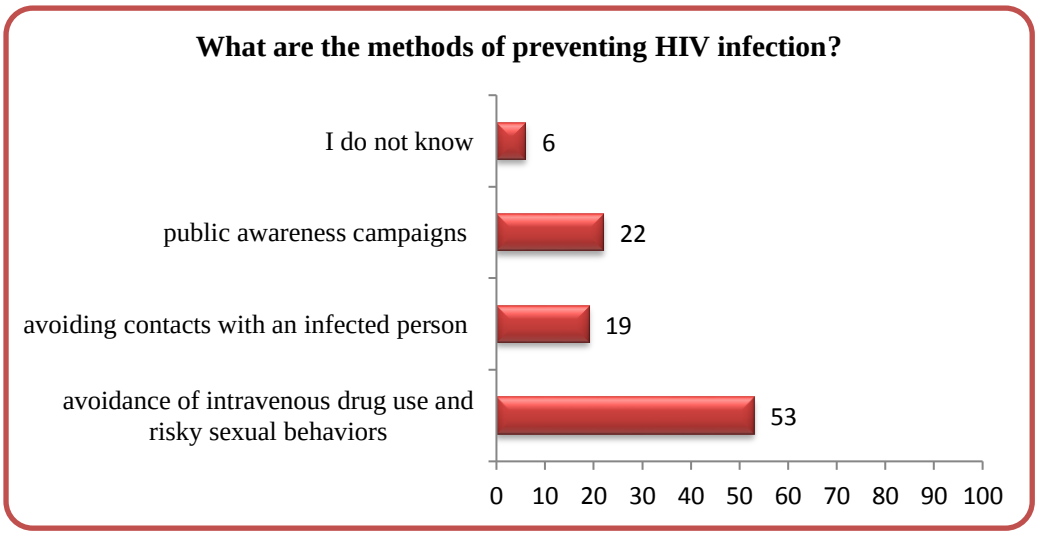

Figure 7. Responses to question about methods of preventing HIV infection [own study]

More than half of the respondents (63%) donated blood again, only 37% of them were single donors. The figure 8 presents the results.

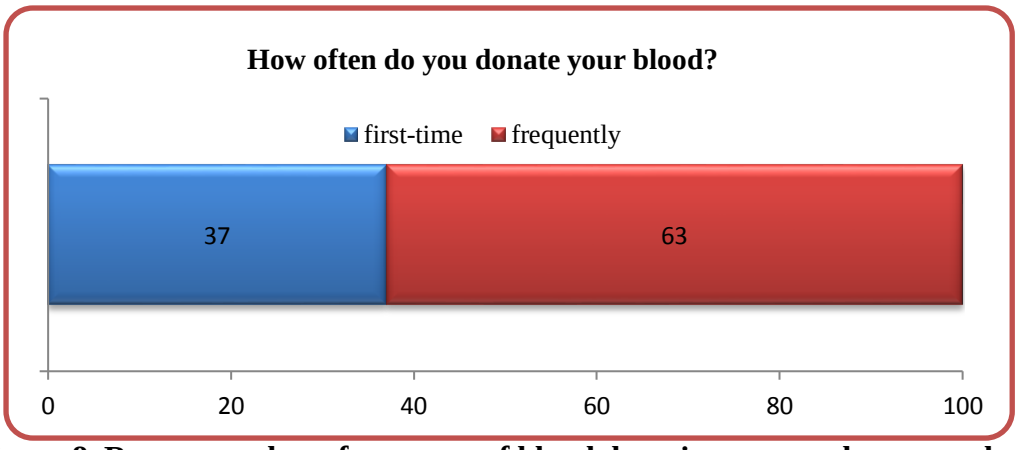

Figure 8. Responses about frequency of blood donation among the responders [own study]

Discussion

There are no scientific publications in the literature that would address the state of knowledge of honorary blood donors about HIV infections, which is why adults were referred to their state of knowledge on the above topic.

Analyzing the literature, we see that HIV infection is one of the biggest health problems on a global scale. In Poland, about one thousand infections are reported annually. It worries that every fifth infected person cannot explain and give a potential source of infection. Until 1985, the main sources of infection were sexual contact, blood transfusion and blood products, organ transplants, and addicts using addicts. After the introduction of anti-HIV and HIV RNA tests, transfusion infection has become almost impossible. Health care workers are exposed to infection by stabbing an infected needle, according to the literature, the risk is 0.3%. Frequent change of sexual partners also carries an increased risk of HIV transmission, statistically easier to pass from male to female than vice versa. Infection in children is the transmission of the virus from mother to child during pregnancy, delivery and breastfeeding [9].

A study by Szymusiak et al. [11] indicates that respondents as the route of HIV infection most often give - sexual contacts over 90% and intravenous drug intake over 80% of respondents. These results correspond to our own research results, in which blood donors indicated blood 92% and sexual contact 86% as a way and a situation that could carry the risk

of infection. Analyzing own research in the question about the importance of HIV abbreviation, less than 70% of respondents correctly indicated that it is a human immunodeficiency virus. Also, studies by Szymusiak et al. [11] showed a very good knowledge of HIV abbreviation, because over 80% of respondents indicated a correct answer. Noteworthy is the abstraction of knowledge of blood donors, both repeated and single on the topic of potential routes of infection, where 19% of respondents indicate that they can be infected by contacting the HIV carrier. Such a scale of ignorance in this area should be the reason for implementing numerous educational campaigns on the etiology of HIV.

Conclusions

1. The surveyed blood donor is a person between the ages of 18-45, having higher or secondary education and being professionally active.
2. In the group of respondents with multiple donors' dominance (63%) understanding of the acronym HIV is 67%.
3. The respondents have knowledge about basic behaviors that generate a direct risk of HIV infection.
4. The responders do not have adequate knowledge about methods of preventing potential HIV infection.
5. The respondents do not have sufficient knowledge about the scale of HIV/AIDS incidence in Poland.

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