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CHROMATOGRAPHIC STUDIES OF DRUG SUBSTANCES: A CASE STUDY IN UNIVERSITY SCIENTIFIC ACTIVITIES

Olena WELCHINSKA,
Doctor of Pharmacy, Professor;
Professor at the Medicinal Chemistry and Toxicology Department
Bogomolets National Medical University;
Kyiv, Ukraine;
ORCID ID: 0000-0001-7023-8493

Iryna NIZHENKOVSKA,
Doctor of Medicine, Professor;
Head at the Medicinal Chemistry and Toxicology Department
Bogomolets National Medical University;
Kyiv, Ukraine;
ORCID ID: 0000-0001-5065-3147

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ABSTRACT

Studying natural sciences at the O.O. Bogomolets National Medical University opens up for students the opportunity to become familiar with advanced scientific discoveries, the prospect of direct participation in conducting experimental research in drug quality control laboratories. The Case study method is used to investigate a problem in a specific context and discuss how the results relate to theory. Case study is actively used in chromatographic studies of medicinal substances, during which ways of solving pharmaceutical analysis problems. The main stages of scientific experimental work according to the requirements of the Case study are determining the purpose of the study with the motivation for the need to carry out this study, motivated selection of samples for the study, drawing up a research plan with a deadline, systematization of the obtained data. In chromatographic studies, an important role is played by the selection of a large number of objects and studies, which provides a high expected increase in information and results. In chemical experiments, it is advisable to use the design of single and multiple studies to compare the results obtained with standards and the design of establishing "anomalies" to register the formation of substances. During chromatographic studies of each specific pharmaceutical object, complex approaches are developed in the analysis of substances, since similar trends are often observed in chromatographic separation, the formation of chemical degradation products. The current task remains the implementation of the Case Study learning model in the performance of scientific work by students by HPLC method.

Key words

Case study, academic research, higher education, university, case study, HPLC, medicinal substances.

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INTRODUCTION

Among the natural sciences studied at the Faculty of Pharmacy of the O.O. Bogomolets National Medical University, the discipline "Pharmaceutical Chemistry" occupies an important place. This discipline provides students with the opportunity to become familiar with advanced scientific discoveries in the field of developing new medicines and the features of pharmaceutical analysis of medicines and their substances of various chemical origins. Students gain the prospect of direct participation in conducting experimental research in drug quality control laboratories and performing scientific experimental work. The case study method is used to investigate a problem in a specific context and discuss how the results relate to theory. Case study is actively used in performing chromatographic studies of medicinal substances, during which solutions to pharmaceutical analysis problems and recommendations for further research are developed - descriptive and problem cases. During chromatographic studies of each specific pharmaceutical object, complex approaches are developed in the analysis of biologically active substances of certain chemical classes, since similar trends are observed in the features of achieving the necessary chromatographic separation, the formation of chemical degradation products, and the detection of specified and unspecified impurities and accompanying substances. Therefore, the current task remains the implementation of the Case Study learning model in the performance of scientific experimental work by students using high-performance liquid chromatography, which gives us the opportunity to develop comprehensive approaches in the analysis of certain classes of drugs, taking into account the peculiarities of this analysis.

LITERATURE REVIEW

The Case study method helps develop critical thinking and is a type of problem-oriented learning. It allows you to implement the task of modeling an experiment, offering non-standard approaches to solving a problem, and finding ways to solve the task. Case studies are used in academia because they are not just a detailed analysis of a particular phenomenon or process, but a broader approach to the study of an object (Ridder, 2017; Rolls, 2013; Seawright & Gerring, 2008; Sikora, 1999). The study has a more standardized structure and uses more rigorous and systematic research methodologies - experiments and analysis. A case study can be used for either a single observation (N=1) or multiple observations (N>1). Due to the specificity of a particular study, the findings cannot be generalized and applied to a broader context. Exploratory research is intended to generalize, and the conclusions can be related to a larger set or scope. Among the types of analysis methods are: illustrative applied research, exploratory applied research, aggregate applied research, descriptive applied research, instrumental applied research (Fig. 1) (Joia, 2002; Koycheva & Yanovskaya, 2023; Pelo et al., 2020; Sheremeta & Kanishchenko, 1999).

Source: Authors.

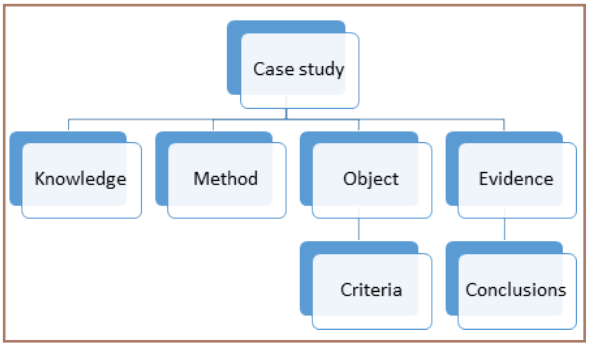

Figure 1. Main components of the Case study

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When using a case study, different research designs can be formed: a design based on methodological work; a research design that emphasizes the difference between single and multiple studies; a "realistic picture" design; a design to detect "anomalies". These designs have significant methodological differences, but are often used in combination. The choice of a research object is often related to a representative sample and different scales of theoretical interests. A representative sample is an average or typical case that does not carry much information. An effective method is to select such a number of studies and objects that will provide a high expected gain in information. The typology of Case study includes the definition of goals (assessment, research), approaches (theoretical justification), choice of processes (single or multiple studies), choice of study (retrospective, diachronic, parallel, sequential) (Hellström et al., 2005; Tsekhmister & Welchinska, 2016; Welchinska & Vilchynska, 2016).

Case studies, as a form of qualitative research, help inform professionals or make evidence-based decisions in a variety of fields. This approach is valuable for health research for developing theory, programs, and planning interventions because of its flexibility and precision.

Qualitative applied research of this method is an approach to research that facilitates the study of a particular phenomenon in its context using a variety of data sources. The question is not examined through a single lens, but rather through a variety of lenses. This approach allows for the discovery and understanding of multiple aspects of the phenomenon.

When planning a study, it is necessary to formulate a research question and understand the case design. It is necessary to understand what the unit of analysis (case) is. Answers to these questions can be effective strategies for further delineating the case.

After deciding whether a qualitative case study is best for the work being done, it is necessary to determine the type of case study. The choice of a specific type of case study design depends on the overall purpose of the study. Case studies are classified as explanatory, exploratory, or descriptive. There is also a distinction between individual, holistic case studies and multiple case studies. Case studies can be internal, instrumental or collective.

Explanatory Case study. Used in situations where it is necessary to explain the alleged cause-and-effect relationships in real-life processes. Such problems are too complex for survey, experimental strategies.

Case study exploratory. Used to investigate situations where the study being evaluated does not have a single set of results.

Case study descriptive. Used to describe a study in real time.

Multi-Case study. Multiple experiments allow the researcher to identify differences within and between experiments. The goal is to replicate findings across experiments. Experiments are compared, cases are carefully selected to predict similar results across experiments, and to predict opposite results based on theory.

Internal Case study. Using the term "internal" implies that the researcher has a strong interest in understanding the problem and aims to better understand the case. It is about a particular feature or problem that is of particular interest to the researcher.

Instrumental Case study. Used to achieve understanding not of a specific situation at the moment, but of those situations that may occur. This helps to understand the problem and improve the theory. The experiment is of

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secondary interest, playing a supporting role, but facilitating the understanding of another experiment. Such an experiment is considered in depth, described in detail. This helps the researcher pursue external interests.

Collective Case study. Collective case studies are similar to multiple case studies.

Single Case study. A specific type of case study and experiment are identified, and the feasibility of conducting a separate case study is considered. The question is whether understanding of the process can be gained by conducting multiple case studies.

Single Case study with Built-in Units. Solving a single experimental problem while conducting a holistic thematic study with built-in units makes it possible to study the experiment, taking into account the experience and capabilities of other laboratories and departments.

Data can be analyzed within the units separately - this is an analysis within the analysis, between different units - this is an analysis between different experiments, across all subunits - this is a cross-experiment analysis. The so-called "saturated analysis" is performed, which contributes to better coverage of the problem. The mistake is that sometimes researchers analyze at the level of an individual subunit, without returning to the global problem that needed to be solved.

Multi-Case study. If the study contains more than one experiment, then it is necessary to conduct a study of several experiments. A multi- or collective case study will allow for the analysis of each experiment and analysis between experiments. A holistic case study with embedded units allows for the understanding of only one unique/critical process. A multiple experiment study examines several procedures or reactions to understand their similarities or differences. Multiple case studies are performed to predict similar outcomes (replication), contrasting outcomes, or presumed causes. The evidence obtained from this study is considered reliable, but can be time-consuming to conduct.

When formulating specific objectives when planning a thematic study, the likelihood of the researcher setting limits on the scope of the study and the possibility of completing the study increase automatically. Conducting a study with a large number of proposals for its planning and stages of implementation always remains within acceptable limits. Proposals can come from laboratory management, research client, scientific supervisor, arise from new ideas and from personal/professional experience, based on theories and the need for their confirmation (Joia, 2002; Pelo et al., 2020).

OBJECTIVES

To introduce basic approaches of the Case study method into complex chromatographic studies using high-performance liquid chromatography (HPLC) of medicinal substances during experimental studies by students *in order* to investigate alternative conditions for HPLC chromatography of the studied samples, which could demonstrate higher identification ability when determining their purity and modifying research methods with optimal conditions for protecting molecules from chemical degradation.

METHODOLOGY

The main stages of scientific experimental work according to the requirements of the Case study are determining the purpose of the study with the motivation for the need to perform a specific study, motivated selection of samples for the study (purposeful, random, valuable for the study), consultation with the

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scientific supervisor and experts, drawing up a research plan with a deadline, systematizing the data obtained (primary, secondary, statistical), identifying 5-6 key strengths and weaknesses of the study using SWOT analysis to predict potential threats to the experiment and unplanned changes in the work strategy, taking into account the limitations of the method for a specific experiment, setting the limits of the planned study, outlining possible alternative solutions, replacing irrational approaches to performing the planned study. A serious drawback of pharmaceutical analysis of drugs and their substances is the lack of many parameters of their standardization, which must meet the requirements of GLP and GMP.

The State Pharmacopoeia of Ukraine (SPU) does not regulate the analysis of a certain number of substances and medicinal products. In addition, accompanying substances, specified and unspecified impurities, as well as related substances in the test samples, according to the recommendations of the SPU and the European Pharmacopoeia (Eur.Ph.), are analyzed only using the liquid chromatography (LC) method. The choice of the HPLC method for studying medicinal substances is justified by its modernity and high selectivity in studying the purity and integrity of medicinal substances, as it allows to increase the efficiency and effectiveness of their analysis. Experimental studies were performed on an Agilent 1260 Infinity II chromatograph with a UV detector, on INERTSIL ODS-3V, ZORBAX Eclipse Plus C18 columns. Pharmacopoeial standard samples (PSS) of SPU chlorhexidine, sodium formaldehyde sulfoxylate dihydrate (rongalite) and samples of the studied substances chlorhexidine, sodium metamizole monohydrate were used. Computer analysis was performed using the OpenLab CDS program.

RESULTS AND DISCUSSION

According to the typology of Case study, we used the design of single and multiple studies – chromatographic study by HPLC of the substances chlorhexidine and metamizole sodium, each of 5 samples from different batches and at 5 punctures and the design of detecting "anomalies" – identification and quantitative determination of accompanying impurities, unacceptable impurities, which can be represented by intermediates of synthesis of substances, products of chemical degradation of starting molecules and related substances. The selection of a large number of objects and their studies provided a high expected increase in information and results. The goal was set to adapt chromatography conditions and HPLC research methods for assessing the purity and identification and quantification of active pharmaceutical ingredients (API) of chlorhexidine and metamizole sodium as an alternative analysis method. Theoretical justification – introduction into pharmaceutical analysis of a modern highly selective HPLC method with higher identification ability as an alternative to the pharmacopoeial method of HPLC research, modification of chromatography conditions and research methods to create optimal conditions for protection against chemical degradation of the structure of substance molecules.

Process selection – multiple studies that allow accumulating results and analyzing them. Research selection – parallel studies with comparison of results and sequential studies were conducted.

The substances chlorhexidine and metamizole sodium were chosen as the objects of the study, which were to become the basis for the creation of dosage forms of medicinal products (Chlorhexidine (Oral Route) Precautions -

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Mayo Clinic, 2023; Muniz et al., 2023; Wade et al., 2021; Wade et al., 2021). Chlorhexidine is used in pharmacy in the form of salts - gluconate, digluconate, acetate or diacetate, as liquids or powders. Chlorhexidine molecules are based on a bis-condensed system consisting of biguanide, hexamethylene, 4-chlorophenyl fragments.

When ingested, chlorhexidine is poorly absorbed from the gastrointestinal tract, causing stomach irritation and nausea. Aspiration of chlorhexidine into the lungs can be fatal due to the high risk of acute respiratory distress syndrome. Chlorhexidine acetate is used as a general antiseptic in 0.05% and 0.1% solutions. It is used for cleaning and disinfecting wounds, for antiseptic treatment of burns (Picoli et al., 2022; Ribas et al., 2020; Soares et al., 2019). Chlorhexidine digluconate is a broad-spectrum antiseptic. It can be safely used in low concentrations in mouthwashes and contact lens solutions. Chlorhexidine gluconate is used as a mouthwash to treat gingivitis (swelling, redness, and bleeding of the gums). This drug is prescribed by a dentist. The bactericidal efficacy of guanide, biguanide, and bisbiguanide agents has been studied on intact microorganisms: *Streptococcus mutans, S. sanguis, Actinomyces viscosus*, and *A. naeslundii.* The pharmacological activity of the compounds was studied based on the features of their molecular configuration. Studies have shown that bis- and biguanide configurations are more effective. They have alkyl side chains of sufficient length in the molecule. At the same time, no single structural fragment has the effectiveness (Di Paolo et al., 2021; Lee et al., 2019; Villa et al., 2018).

Chlorhexidine is determined by a colorimetric method. The method is based on the formation of a yellow complex between chlorhexidine and bromocresol green, which is isolated by chloroform extraction. The absorption peak of this complex is at 410 nm. A linear response is achieved from 2.5 to 30 μg chlorhexidine/ml. The accuracy of this method makes it useful for the determination of chlorhexidine in pharmaceutical analysis of pharmaceutical mixtures.

The spectrophotometric determination of chlorhexidine is performed using a liquid-liquid extraction method using bromophenol blue. The chemical structure of chlorhexidine is determined using a combination of single crystal X-ray diffraction (SC-XRD), electrospray ionization mass spectrometry (ESI-MS), 1H nuclear magnetic resonance (NMR) spectroscopy, correlation spectroscopy (COSY) and attenuated total reflection Fourier transform infrared spectroscopy (ATR-FTIR). Also, an analytical technique based on the Box-Behnken design and using the HPLC method is used, which helps to quantitatively determine chlorhexidine and thymol simultaneously in a matrix with pharmaceutical excipients (Chandran et al., 2022; Sokolik et al., 2018; Vrachas et al., 2022).

SPU does not regulate the analysis of chlorhexidine substance. Pharmaceutical analysis is performed according to the European Pharmacopoeia (European Pharmacopoeia (11-th ed.), 2022) of medicinal products: Chlorhexidine diacetate, Chlorhexidine digluconate solution, Chlorhexidine dihydrochloride. Accompanying substances are examined by the LC method (2.2.29).

The substance is dissolved in a mixture of solvents: trifluoroacetic acid *P* - acetonitrile *P* - trifluoroacetic acid *P* in water for chromatography or alternatively: trifluoroacetic acid *P* - trifluoroacetic acid *P* in water for chromatography *P* - trifluoroacetic acid *P* in acetonitrile *P*.

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Among the specified and unspecified impurities of the substance regulated by the Pharmacopoeia, there are 16 substances: A, B, C, D, E, F, G, H, I, J, K, L, N, O, P, Q. Impurity P (chloroaniline) is a specified impurity. Impurity Q refers to unidentified impurities - substances with an unknown structure. Among the specified and unspecified impurities of the substance regulated by the Pharmacopoeia, there are 16 substances: A, B, C, D, E, F, G, H, I, J, K, L, N, O, P, Q. Impurity P (chloroaniline) is a specified impurity. Impurity Q refers to unidentified impurities - substances with an unknown structure.

We performed a chromatographic study of the chlorhexidine substance under the following chromatography conditions: column – INERTSIL ODS-3V with a temperature of 25˚C, UV detection at 254 nm, flow rate of 1.0 ml/min, injection volume of 10 µl, chromatography time of 60 min.

The following mobile phases were used: mobile phase A – a mixture of solvents for HPLC: trifluoroacetic acid *P* – acetonitrile *P* – trifluoroacetic acid *P* in water for chromatography, 0.1% *P* (20:20:80, V/V/V) and mobile phase B – a mixture of solvents for HPLC: trifluoroacetic acid *P* – trifluoroacetic acid *P* in water for chromatography *P* – trifluoroacetic acid *P* in acetonitrile *P* (10:10:90, V/V/V).

A gradient method was used to obtain separation and identification of a larger number of impurities (Table 1).

When studying the PSS and test samples after 5 stabs, the following results were obtained (Tables 2, 3, Fig. 2).

Table 1. Gradients

Source: Authors

Time (min)	Mobile phase A (%, V/V)	Mobile phase B (%, V/V)
0-2	100	0
2-32	80	20
32-47	80	20
37-47	70	30
47-54	70	30

Table 2. Results of chromatography of chlorhexidine PSS

Source: Authors

	PSS 1		PSS 2	
	Chlorhexidine			
1	2	3	4	5
	RT	Area	RT	Area
	2,901	59,837	2,897	62,047
	2,917	61,500	2,914	63,333
	2,917	61,440	2,911	62,680
	2,916	59,467	2,899	61,999
	2,902	60,900	2,897	61,985
Average	2,914	60,268	2.909	62,690

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Continuation of table 2

1	2	3	4	5
SD	0,093	1,083	0,070	0,909
RSD (≤2.0%)	0,38	1,80	0,30	1,45

Note: RT – retention time (min), Area – peak area, SD – standard deviation, used to determine RSD), RSD – relative standard deviation, according to the Pharmacopoeia, should be less than 2)

Table 3. Chromatography results of the tested chlorhexidine samples

Source: Authors

	Sample 1			Sample 2	
	Chlorhexidine RT	*Impurity P RT*	*Impurity 1 RT*	*Chlorhexidine RT*	*Impurity P RT*
	2,818	4,401	5,090	2,890	4,347
	2,919	4,300	5,260	2,914	4,333
	2,380	4,267	5,198	2,911	4,280
	2,916	4,465	5,199	2,899	4,099
	2,900	4,302	5,200	2,897	4,185
Average	2,786	4,347	5,189	2.902	4,248
SD	0,088	1,053	1,066	0,070	1,052
RSD (≤2.0%)	0,36	1,70	1,57	0,31	1,69

Note: RT – retention time (min), SD – standard deviation, used to determine RSD), RSD – relative standard deviation, according to the Pharmacopoeia, should be less than 2).

Source: Authors

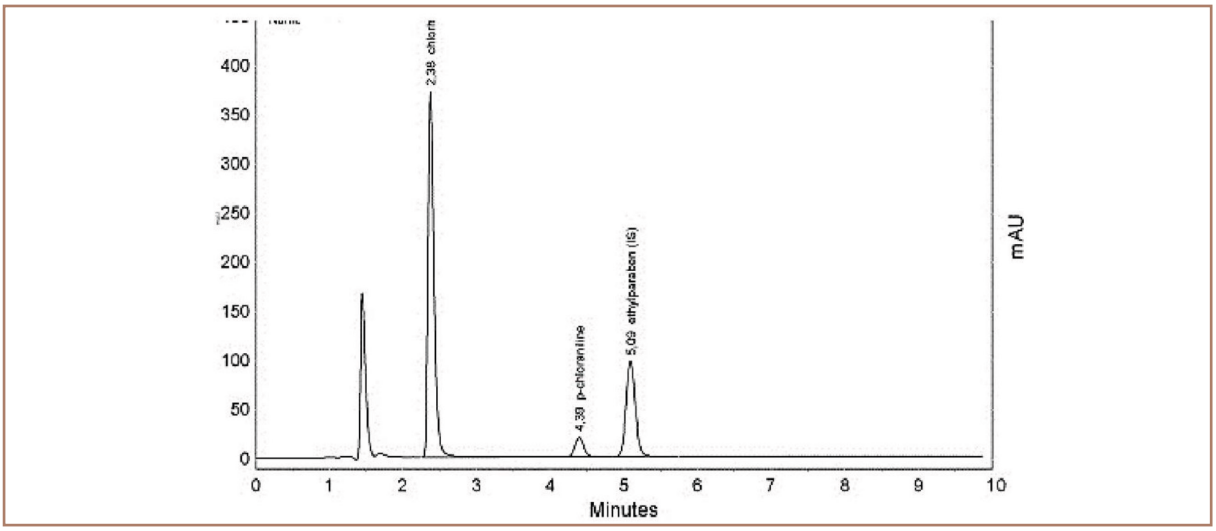

Figure 2. Chromatogram of test sample 1: chlorhexidine (Rt=2.380 min), specified impurity P (para-chloroaniline) (Rt=4.300 min), unacceptable impurity 1 (ethylparaben) (Rt=5.090 min)

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Metamizole sodium monohydrate is a well-known drug with analgesic, antipyretic and anti-inflammatory effects. Under certain conditions, this drug can cause undesirable effects, such as Quincke's edema, anaphylactic shock, Stevens-Johnson syndrome. It leads to the development of agranulocytosis, aplastic anemia, neutropenia and pancytopenia (European Medicines Agency (EMA), 2019; Rudin et al., 2020).

According to the SPU (Derzhavna Farmakopeya Ukrayiny, 2014) the identification of the substance metamizole sodium is performed by absorption spectrophotometry in the IR region, chemical methods, and tests for the transparency of the substance solution are performed (2.2.1).

Accompanying impurities are detected by the LC method (2.2.29) with UV detection at 254 nm: specified impurities C and E, unspecified impurities A, B, D. The test solution, reference solutions a, b, d, e are prepared in methanol, solution c – in methanol and menthol. The UV spectrum of metamizole sodium (in an acidic medium) contains an absorption maximum λmax = 258 nm.

According to the SPU, the purity of metamizole sodium is determined by the LC method. Accompanying substances are identified with UV detection at 254 nm: specified impurities include impurities C and E, unspecified impurities include A, B, D. We performed a chromatographic study of the substance metamizole sodium under the following chromatography conditions: column – ZORBAX Eclipse Plus C18 with a temperature of 25˚C, UV detection at 215 nm, flow rate 1.0 ml/min, injection volume 5 µl, chromatography time 13 min. The mobile phases used were: mobile phase A (3.2 g of triethylamine in 1000 ml of water, pH of the solution 3.0±0.05 using phosphoric acid), mobile phase B – methanol.

A gradient method was used to obtain separation and identification of impurities (Table 4).

Table 4. Gradients

Source: Authors

Time (min)	Mobile phase *A*, (%, V/V)	Mobile phase *B*, (%, V/V)
0,0	100	0
3,5	100	0
5,5	50	50
7,5	50	50
10,0	100	0
13,0	100	0

Sodium formaldehyde sulfoxylate dihydrate (rongalite) was used as the PSS of the SPU. Formaldehyde sulfoxylate dihydrate or sodium formaldehyde sulfoxylate (rongalite) is a chemical substance that is dangerous to the human body (Chen et al., 2020; Golla et al., 2020; He et al., 2021). It can be formed during the synthesis of the substance, so it is important to check its purity for the presence of rongalite.

When studying the PSS and test samples after 5 punctures, the following results were obtained (Tables 5, 6; Fig. 3).

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Table 5. Results of chromatography of the PSS of rongalite

Source: Authors

	PSS 1			PSS 2		
		Rongalite				
	RT	*Area*	*T (≤2.0)*	*RT*	*Area*	*T (≤2.0)*
	1,990	259,483	1,1	1,992	258,158	1,1
	1,993	258,894	1,1	1,993	260,702	1,1
	1,990	258,950	1,1	1,911	258,160	1,1
	1,994	258,473	1,1	1,899	259,333	1,1
	1,990	258,359	1,1	1,992	258,230	1,1
Average	1,991	258,832	1,1	1.993	259,430	1,1
SD	0,002	0,446		0,001	1,799	
RSD (≤2.0%)	0,10	0,17		0,04	0,69	

Note: RT – retention time (min), Area – peak area, SD – standard deviation, used to determine RSD), RSD – relative standard deviation, according to the Pharmacopoeia, should be less than 2), T-tailing (peak shape, often less than 2).

Table 6. Results of chromatography of tested samples of metamizole sodium for the presence of rongalite

Source: Authors

	Sample 1		Sample 2	
	Rongalite		*Rongalite*	
	RT	*Area*	*RT*	*Area*
	1,983	40,032	1,999	42,435
	2,009	40,692	1,997	44,148
	2,003	38,371	2,003	41,287
	1,918	39,008	2,001	41,300
	1,997	39,015	2,000	42,433
Average	1,998	39,698	2.000	42,623
SD	0,002	0,442	0,002	1,450
RSD (≤2.0%)	0,11	0,23	0,02	0,38

Note: RT – retention time (min), Area – peak area, SD – standard deviation, used to determine RSD), RSD – relative standard deviation, according to the Pharmacopoeia, should be less than 2).

Source: Authors

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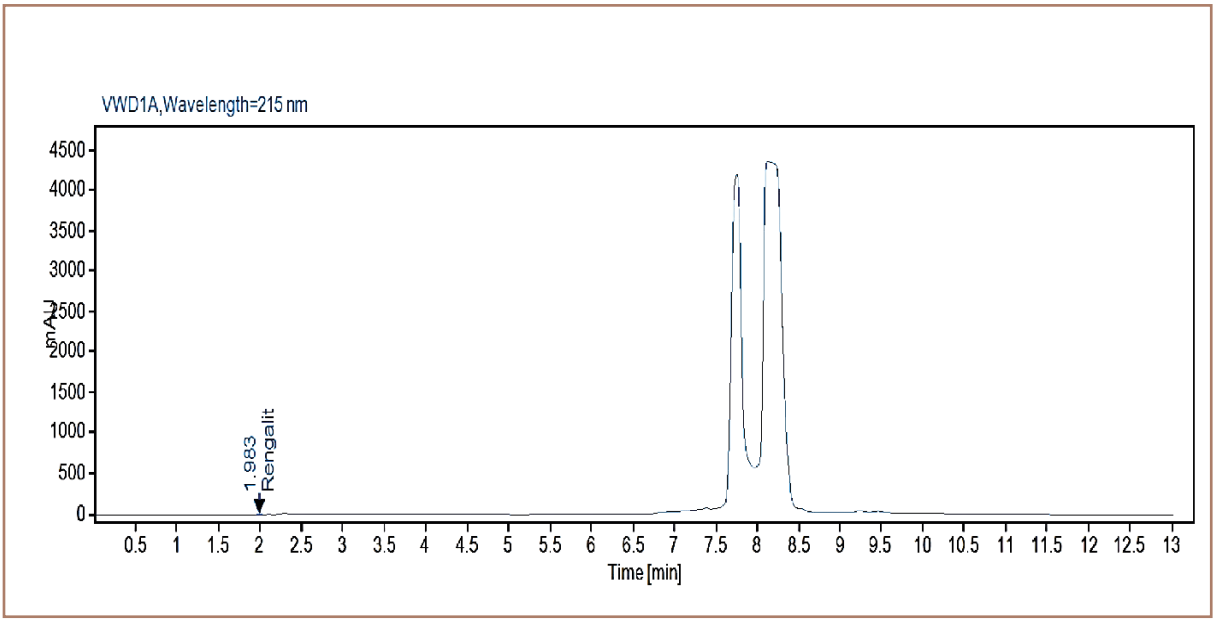

Figure 3. Chromatogram of the studied sample of metamizole sodium substance with an admixture of rongalite (HPLC method): Rt (rongalite) = 1.983 min

Thus, the presence of sodium formaldehyde sulfoxylate dihydrate (rongalite) – an unacceptable impurity – was chromatographically confirmed: Rt in the range of 1.918-2.009 min (at 215 nm).

A shift of the rongalite peak in the test substance is observed compared to standard rongalite samples (Rt 1.899-1.993 min, at 215 nm), which can be explained by the presence of metamizole sodium in the test substance.

A laboratory report is compiled based on the results of the research. It includes the following sections:

- introduction, formulation of the goal, hypothesis or task of the research;
- justification of the method (methods) used to perform the tasks set, methods of processing the obtained data;
- results, description of the data obtained, characteristics of products, characteristics of certain physicochemical parameters or properties of substances;
- discussion of the results obtained, which correspond or do not correspond to the purpose and hypothesis that were the reason for the start of the research;
- conclusion about the overall result of the practical work, how the conclusions correlate with the larger body of scientific knowledge.

Laboratory report of the performed chromatographic study according to the Case study typology.

Introduction: using the design of single and multiple studies and the design of detecting "anomalies", it is planned to conduct chromatographic studies by HPLC of the substances chlorhexidine and metamizole sodium (each of 5 samples from different batches and at 5 punctures) in order to adapt the chromatography conditions and the HPLC research methodology for the assessment of purity, identification and quantification of active pharmaceutical ingredients (API) of

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chlorhexidine and metamizole sodium as an alternative to the pharmacopoeial method of LC analysis.

Justification of the method. Introduction of a modern highly selective HPLC method with higher identification ability into pharmaceutical analysis as an alternative to the pharmacopoeial method of LC research, modification of chromatography conditions and research methods to create optimal conditions for protection against chemical degradation of the structure of substance molecules and a high degree of chromatographic separation of the components of the tested substances. The studies were conducted multiple times with the accumulation of results and analysis of the data obtained by comparison with the results obtained during the study of the PSS. and analyze them. Parallel and sequential studies were performed with the comparison of the results.

Results. HPLC chromatographic identification of API, quantitative determination of API and accompanying substances (specified and unspecified impurities, unacceptable impurities) was performed. The purity of the tested substances was determined. The selection of a large number of objects and their studies provided a high expected increase in information and results.

Discussion of the obtained results. During the chromatographic study of chlorhexidine substances by HPLC, in addition to the specified impurity P (para-chloroaniline) (Rt=4.300 min), an unacceptable impurity 1 (ethylparaben) (Rt=5.090 min) was identified.

Ethylparaben or methyl ester of para-hydroxybenzoic acid is used as a food additive E218 as a preservative and as an antiseptic.

When analyzing the chromatographic data and comparing the location of the peaks, their shifts were detected on the chromatograms of the tested chlorhexidine samples Rt from 2.380 min to 2.914 min (average Rt value from 2.786 min to 2.902 min) in comparison with the location of the chlorhexidine peaks on the chromatograms of the PSS Rt from 2.897 min to 2.917 min (average Rt value from 2.909 min to 2.914 min).

This can be explained by the presence of the impurity P (para-chloraniline) and the unacceptable impurity ethylparaben in the tested substances of chlorhexidine. The presence of sodium formaldehyde sulfoxylate dihydrate (rongalite) - an unacceptable impurity - was chromatographically confirmed in the composition of the tested substances of metamizole sodium: Rt from 1.918 min to 2.009 min. (at 215 nm).

There is a shift in the peak of rongalite in the composition of the test substance compared to the standard samples of rongalite (Rt from 1.899 min to 1.993 min, at 215 nm), which can be explained by the presence of metamizole sodium in the composition of the test substance. Rongalite is often formed as an intermediate product during the synthesis of the substance, is a toxic substance, therefore it is an unacceptable impurity.

Conclusion on the overall result of the research work. The design of single and multiple studies and the design of detecting “anomalies” by conducting parallel and sequential studies with a comparison of the results of an alternative pharmacopoeial method - a high-tech HPLC method for studying the test substances chlorhexidine and metamizole sodium - are proposed.

The HPLC method was tested in practice and found to provide higher identification capability compared to the liquid chromatography method, and also allows for in-depth pharmaceutical analysis of the studied objects in order to establish their quality.

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CONCLUSIONS

1. Using the Case study method, we have built an algorithm for performing chromatographic studies by HPLC of the tested medicinal substances chlorhexidine and metamizole sodium using the design of single and multiple studies and identifying "anomalies" and conducting parallel/sequential studies with a comparison of the results obtained.
2. The selection of a large number of objects – substances chlorhexidine and metamizole sodium (each from 5 samples from different batches and with 5 punctures, a total of 50 results) provided a high expected increase in information and results.
3. Chromatography conditions and research methods were adapted using HPLC, a method with high identification capacity for assessing the purity, identification and quantification of active pharmaceutical ingredients (API) of chlorhexidine and metamizole sodium substances and detecting accompanying substances in the composition of the substances.
4. During the chromatographic study of chlorhexidine substances by HPLC, an unacceptable impurity 1 (ethylparaben) (Rt=5.090 min) was identified, the presence of which likely affects the shifts of chlorhexidine peaks on the chromatograms of its tested samples in comparison with the location of chlorhexidine peaks in the composition of the PSS. In the composition of the tested substances of metamizole sodium, the presence of sodium formaldehyde sulfoxylate dihydrate (rongalite) - a toxic unacceptable impurity - was chromatographically confirmed, and a shift of the rongalite peak in the composition of the tested substance was also observed compared to the location of its peak in the composition of the PSS.

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ANALYSIS OF NUTRITION-RELATED DISEASES AMONG THE ADULT POPULATION OF WORKING AGE IN KYIV REGION (nutrition-related diseases, mortality)

Ignat MATASAR,
Doctor of Medicine, Professor,
Head of the Laboratory of Nutrition Hygiene and Food Safety of the State Institution 'National Research Center for Radiation Medicine, Hematology and Oncology of the National Academy of Sciences of Ukraine
Kyiv, Ukraine,
ORCID ID: 0000-0002-1404-283X

Ludmila PETRYSHCHENKO,
Candidate of Biological Sciences,
Senior Researcher of the Laboratory of Nutrition Hygiene and Food Safety of the State Institution 'National Research Center for Radiation Medicine, Hematology and Oncology of the National Academy of Sciences of Ukraine;
Kyiv, Ukraine,
ORCID ID: 0009-0009-4533-0816

Andrii CHERNYSHOV,
Candidate of Medical Sciences,
Senior Researcher, Researcher of the Cellular Radiobiology Laboratory of the State Institution 'National Research Center for Radiation Medicine, Hematology and Oncology of the National Academy of Sciences of Ukraine,
Kyiv, Ukraine,
ORCID ID: 0000-0002-9564-759X.

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ABSTRACT

Social unrest, martial law, man-made and radioactive environmental pollution (air, water, soil, food), noise, vibration, electromagnetic waves and other factors of physical, chemical and biological origin, as well as various psycho-emotional overloads with poor-quality, unbalanced nutrition form conditions that over time lead to permanent disruption of organ functioning, irre-versible pathological changes in the body's systems, to loss of working capacity, premature aging, and deaths.

The purpose of the study is to assess the prevalence of nutritionally dependent diseases among people of working age living in environmentally hazardous areas of Ivankiv and Obukhiv districts of Kyiv region in 2019–2021.

The work used bibliosemantic, epidemiological research methodologies and medical statistics methods. The level of nutritionally dependent morbidity was analyzed by disease classes, disease groups and individual nosological forms in accordance with the ICD-10, taking into account age, gender, and the nutritional status of the working age population. The priorities were diseases of the circulatory system, in-cluding diseases characterized by high blood pressure, ischemic heart disease, as well as diseases of the digestive system, in particular diseases of the esophagus, stomach and duodenum, gastric and duodenal ulcers, gastritis, duodenitis, diseases of the liver, gallbladder, biliary tract and pan-creas. The leading indicator of disorders in the body is the state of the cardiovascular system, which instantly reacts to the action of negative factors of various origins, including psycho-emotional ones.

Modern environmental conditions require constant monitoring of the dynamics of morbidity and require the development and implementation of effective large-scale programs aimed at preventing the occurrence of alimentary and alimentary-dependent diseases, restoring affected structures and eliminating the consequences of stress from living in an ecologically hazardous area.

Key words

Alimentary genesis, working age, Chernobyl accident, environmentally hazardous areas, thermal power plants.

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INTRODUCTION

A comprehensive indicator characterizing the impact of the environment on the human population is the state of health. According to the modern interpretation, health is a natural state characterized by complete balance with the biosphere and the absence of any pathological abnormalities in the body. The official definition of health by the World Health Organization (WHO) indicates that "health is a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity" (Towards a healthier..., 2020). The health of the population of a certain region depends on the ecological state of the environment and reflects the dynamic balance between the organism and the individual's habitat. In the human body, a dynamic stereotype is created with the preservation of homeostasis, which is formed in the process of evolutionary development in certain conditions and is maintained due to metabolic processes, neurohumoral and endocrine regulation.

LITERATURE REVIEW

Technogenic and radioactive pollution of the environment (air, water, soil, food), as well as noise, vibration, electromagnetic waves and other factors of physical, chemical and biological origin cause severe and irreversible pathological changes in the human body and a negative impact on the implementation of genetic information. Living in such conditions leads to loss of working capacity, a sharp increase in morbidity and premature aging, as well as an increase in the number of premature deaths (Mukhatska, 2016; Serdyuk et al., 2011; Ryngach, 2018; Shushpanov, 2017:132; Bazyka et al., 2021; Omelyanets et al., 2007).

After the Chernobyl disaster, as a result of natural processes and anti-radiation measures, the ecological state of the affected territories has changed significantly (Panov, 2021). However, due to the long half-lives, radioactive substances will still remain in the environment and will determine the health of several more generations of people.

Thermal power plants (TPPs) pose no less of a threat to the health and living conditions of the population. Today, emissions from TPPs in Ukraine exceed the European Union (EU) standards by 5–30 times and are the main pollutant of atmospheric air and the environment (Zhdanov, 2008 : 95; Serdyuk, 2018; Directive 2010/75/EU..., 2010). Ensuring acceptable living conditions for the population of such territories is an urgent problem that requires studying and analyzing the impact of harmful emissions from thermal power plants and nuclear power plants on the morbidity of the population, as well as developing ways to improve the current situation. Under these conditions, the relevance of preventive medicine has sharply increased (Mataus, 2024; Serdyuk et al., 2012; Zagorodniy, 2011; Boychuk, 2017).

In Ukraine, the situation with both nutrition and health is significantly complicated by environmental circumstances. The general result of the action of harmful exogenous and endogenous factors on the human body is the suppression of immune reactivity, the increase in non-communicable diseases, and the manifestation of carcinogenic and mutagenic effects (Biletska, et al., 2016; Nedelskaya & Taranova, 2013; Mokiya-Serbina, Sitalo, Yelchaninova, & Ponomareva, 2013). Scientific studies (Murashko & Rushchak, 2014; Korzun, 2012; Matasar et al., 2014; Derevyanko, 2009; Mikhneva, 2016) have shown that nutrition has a modifying effect on the action of toxicants entering the body. Diseases caused by the complex action of anthropo-

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gens include cardiovascular (hypertension, atherosclerosis, ischemic heart disease, etc.), oncological diseases, metabolic diseases, endocrine and digestive systems (Krekoten, 2008; Moskalenko, 2007; Gushchuk, 2006 : 101–102). The leading factor in the occurrence of these diseases is poor-quality, inadequate and unbalanced nutrition. In the prevention and treatment of such pathology, the nutritional factor plays a leading role. Diseases, the occurrence of which is due to a surplus or deficit in the body of nutrients and energy, as well as an imbalance of food ingredients, in particular essential substances in the diet, are called alimentary-related or alimentary (from the Latin alimentarius – food). Food-related diseases also include physiological conditions with impaired absorption of nutrients under the influence of exogenous and endogenous factors.

According to the WHO classification, there are 4 groups of causes that lead to alimentary diseases:

– insufficient and unbalanced nutrition;
– lack of minerals;
– lack of vitamins;
– surplus or deficit nutrition.

Thus, alimentary diseases are diseases whose etiology is associated with a lack or excess of food ingredients and calories in the body. They can develop both primarily and secondarily, and have a chronic course. The former include food poisoning and parasitic invasions (biohelminthiasis). Such diseases occur when consuming products contaminated with microorganisms or residues of their metabolism (toxins, etc.), as well as helminth eggs.

According to scientific publications, in recent years the overall incidence rate of the population of Ukraine has increased by almost 30%. The rate of increase in alimentary and alimentary-related diseases, as well as diabetes mellitus and bronchial asthma – 2.1 times, gastric and duodenal ulcer – 1.9 times, angina pectoris – 8.6 times, acute myocardial infarction – 2.6 times (Matasar & Petryshchenko, 2023; Matasar et al., 2022).

It has been established that the structure of the population's diet is a fairly stable indicator, the formation of which occurs over several generations. However, the structure of nutrition undergoes significant changes as a result of socio-economic upheavals or environmental disasters. Therefore, the issue of studying the possibilities of modifying the influence of the alimentary factor on the prevention of the action of negative factors of a chemical, biological nature emphasizes the relevance of such research, and solving the issues of health protection of the population living in technogenically polluted territories of Ukraine is extremely necessary.

The purpose of the study is to assess the prevalence of alimentary diseases among people aged 18 to 60 years who permanently live in environmentally hazardous territories of the Ivankiv and Obukhiv districts of the Kyiv region.

METHODOLOGY

To achieve the goal of the study, we divided working-age people into groups of 18-29; 30-39 and 40-60 years old, who permanently reside in the territory of Ivankiv and Obukhiv districts of Kyiv region. Then, an analysis of morbidity was conducted.

RESULTS AND DISCUSSION

In order to conduct an analysis of the incidence of alimentary and alimentary-dependent diseases, a general cohort of working-age people (men and women aged 18–29, 30–39, 40–60 years old) living in environmental-

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ly hazardous areas of Kyiv region, including Ivankiv and Obukhiv districts, was collected during 2019–2021.

The source of initial information for the epidemiological study and analysis was data provided by the State Institution "Ukrainian Center for Information Technologies and the National Register of the Ministry of Health of Ukraine" (SRU).

In total, the total cohort in the Kyiv region consisted of 306,835 people of both sexes registered with the State Health Service, including: men - 129,217 or 42.1%, women - 177,618 or 57.9%; in the Ivankivskyi district, the total cohort consisted of 21,029 people of both sexes, including: men - 8,255 or 39.3%, women - 12,774 or 60.7%; in the Obukhiv district, the total cohort consisted of 3,839 people of both sexes, including: men - 1,535 or 40.0%, women - 2,304 or 60.0%.

Data on morbidity, according to the State Health Service, among men aged 18 to 60 living in the Kyiv region for 2019–2021, are given in Table. 1.

Table 1. Morbidity among men in Kyiv region for 2019–2021

Source: Authors, based on data from the State Health Service

Nosological forms and classes of diseases	18-29 years old			30-39 years old			40-60 years old		
	2019	2020	2021	2019	2020	2021	2019	2020	2021
	n= 41066	n = 41066	n = 41066	n = 35686	n = 35686	n = 35686	n = 52465	n = 52465	n = 52465
1	2	3	4	5	6	7	8	9	10
Malignant neoplasm's of the digestive system	16	15	11	40	32	32	47	36	33
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (class II)	32	12	7	24	16	11	14	10	4
including nutritional anaemia	31	12	7	21	13	11	12	8	4
Diseases of the endocrine system, nutritional disorders and metabolic disorders (class IV)	411	266	203	460	295	233	393	272	221
thyroid diseases associated with iodine deficiency	63	30	30	39	17	15	29	21	20
hypothyroidism	10	8	8	9	6	6	9	7	7
thyrotoxicosis	0	0	0	0	0	0	0	0	0
(hyperthyroidism)	9	7	5	12	6	6	9	5	5
thyroiditis	212	135	108	284	186	148	280	183	152
diabetes	36	17	10	31	14	12	13	8	8
Diseases of the circulatory system (class IX)	9903	7354	3563	15542	10174	5332	17177	10772	6648

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Continuation of table 1.

1	2	3	4	5	6	7	8	9	10
diseases characterized by high blood pressure	3208	1981	996	4117	1744	822	4029	1505	668
ischemic heart disease	4732	4260	1988	8675	6928	3707	9893	7200	4608
Respiratory diseases (class X)	1722	1484	956	1372	1105	724	1103	864	629
chronic lower respiratory tract diseases	1008	813	427	988	755	426	902	690	482
Digestive diseases(class XI)	7467	6126	3849	6213	4879	3211	4422	3455	2331
diseases of the oesophagus, stomach and duodenum	3066	2331	1547	2506	1828	1238	1679	1261	858
gastric and duodenal ulcers	865	572	470	740	492	403	529	361	294
gastritis and duodenitis	1441	1257	871	1129	918	677	730	601	469
liver diseases	186	136	108	152	113	85	119	90	73
diseases of the gallbladder, biliary tract and pancreas	4099	3563	2141	3441	2849	1828	2524	2016	1330

The incidence of malignant neoplasms of the digestive organs according to ICD-10 in 2019 was highest among men aged 40–60 years.

Blood diseases in men were most common in the age category of 18–29 years. At the same time, their number in 2021 decreased by 4.5 times. As for the incidence of diseases of the blood and hematopoietic organs and certain disorders involving the immune mechanism, the decrease in their registration decreased in all age categories. However, men in the youngest category still suffered the most from anemia of alimentary genesis.

Diseases of the endocrine system, eating disorders and metabolic disorders occupy a significantly higher place when compared with the above-mentioned nosological forms and exceed the level of malignant neoplasms of the digestive organs by 25 times, and diseases of the blood and hematopoietic organs in 2019 by more than 12 times.

Thyroid disease is of particular concern, despite large-scale measures to prevent iodine deficiency among the population of Ukraine (Figure 1).

At the same time, hypothyroidism was more common in people aged 18-29. In middle-aged and older people (40-60 years old), there was a tendency to reduce the level of this incidence. No one suffered from thyrotoxicosis (hyperthyroidism) during the observation period. In 2019, men in the age category of 30-39 years old were more likely to suffer from thyroiditis. People aged 18-29 years old were more likely to suffer from diabetes. Diseases of the circulatory system occupy one of the first places among all the diseases analyzed by us. At the same time, people aged 40-60 years old were more likely to suffer from it. Ischemic heart disease (IHD) was recorded in all age categories, but more often in people 40 and older.

The incidence of respiratory diseases is significantly lower than that of the circulatory system, but significantly higher than that of malignant neoplasms, blood diseases and endocrine systems. At the same time, respiratory diseases were the most common in all surveyed individuals. However, for the period 2019–2021, there was a tendency to decrease the level of registration of this disease.

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Source: Authors, based on data from the State Health Service

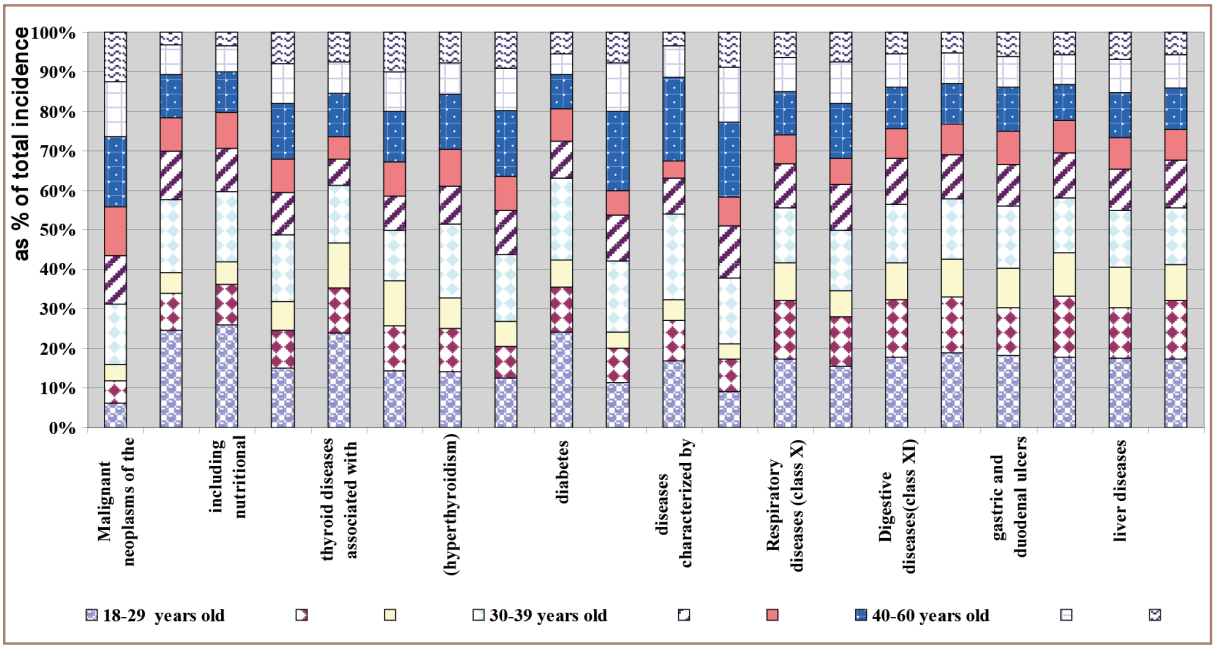

Figure 1. Incidence of men living in the Kyiv region in 2019–2021

Diseases of the digestive system take second place after diseases of the circulatory system.

At the same time, diseases of the gallbladder, biliary tract and pancreas account for almost 55% of all pathologies of the digestive system. This nosology is more pronounced in people aged 18-29. However, it is characteristic of all individuals. A somewhat lower level is occupied by diseases of the esophagus, stomach and duodenum, which make up 41% of all diseases of the digestive system. Gastritis and duodenitis take third place and account for 19%.

Gastric and duodenal ulcers were more frequently recorded in younger people, but were widely recorded in all categories of men. Liver diseases were significantly less common, when compared with the above forms and were more frequently recorded in 2019. The trend towards a decrease in incidence is more pronounced in men over 40 years of age.

Regarding the incidence of men living in the Ivankiv district of the Kyiv region in the period from 2019 to 2021, the data of dynamic observation (Table 2) indicate that malignant neoplasms of the digestive organs were recorded in one case in people aged 18-29, two cases in men aged 30-39, and 5 cases among people aged 40-60.

Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism were not recorded in people aged 40-60 throughout the entire observation period, and two and one case in 2019 among people aged 18-29 and 30-39, respectively. These were cases of alimentary anaemia.

According to the DRU data, diseases of the endocrine system, eating disorders and metabolic disorders were recorded only in 2019 and amounted to 17 in people aged 18-29 and 40-60. Men aged 30-39 were sick more often (22 cases in 2019). The data recorded by the DRU raise doubts. Apparently, there is unreliable reporting or its absence altogether, since thyroid diseases associated with iodine deficiency, hyperthyroidism, and only one case of

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hypothyroidism and thyroiditis were not recorded at all. Obesity and other types of excessive nutrition were recorded only in 2019 - 4; 3 and 2 cases, respectively, in people aged 18-29; 30-39 and 40-60. Diseases of the circulatory system are the most common. At the same time, people aged 40-60 were sick more often (Figure2).

Table 2. Morbidity among men in Ivankivskyi district, Kyiv region, 2019–2021

Source: Authors, based on data from the State Statistical Office

Nosological forms and classes of diseases	18-29 years old			30-39 years old			40-60 years old		
	2019	2020	2021	2019	2020	2021	2019	2020	2021
	n = 2584	n = 2584	n = 2584	n = 2176	n = 2176	n = 2176	n = 3495	n = 3495	n = 3495
1	2	3	4	5	6	7	8	9	10
Malignant neoplasms of the digestive system	1	0	0	2	0	0	5	0	0
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (class II)	2	0	0	1	0	0	0	0	0
ncluding nutritional anaemia	2	0	0	1	0	0	0	0	0
Diseases of the endocrine system, nutritional disorders and metabolic disorders (class IV)	17	0	0	22	0	0	17	0	0
thyroid diseases associated with iodine deficiency	0	0	0	0	0	0	0	0	0
hypothyroidism	0	0	0	1	0	0	0	0	0
thyrotoxicosis	0	0	0	0	0	0	0	0	0
(hyperthyroidism)	0	0	0	1	0	0	0	0	0
thyroiditis	10	0	0	16	0	0	15	0	0
diabetes	4	0	0	3	0	0	2	0	0
Diseases of the circulatory system (class IX)	572	497	267	812	624	398	1091	532	392
diseases characterized by high blood pressure	195	27	0	242	33	0	248	24	0
ischemic heart disease	341	469	267	532	590	398	779	507	391
Respiratory diseases (class X)	281	309	244	135	137	132	85	29	27
chronic lower respiratory tract diseases	43	9	5	44	8	3	63	1	0
Digestive diseases(class XI)	568	299	263	524	198	164	270	35	27
diseases of the esophagus, stomach and duodenum	285	88	15	262	53	6	104	5	0

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Continuation of table 2

1	2	3	4	5	6	7	8	9	10
gastric and duodenal ulcers	50	8	6	48	11	2	28	0	0
gastritis and duodenitis	195	80	9	186	42	4	69	5	0
liver diseases	21	0	1	15	0	0	11	0	0
diseases of the gallbladder, biliary tract and pancreas	260	211	244	244	144	156	153	30	26

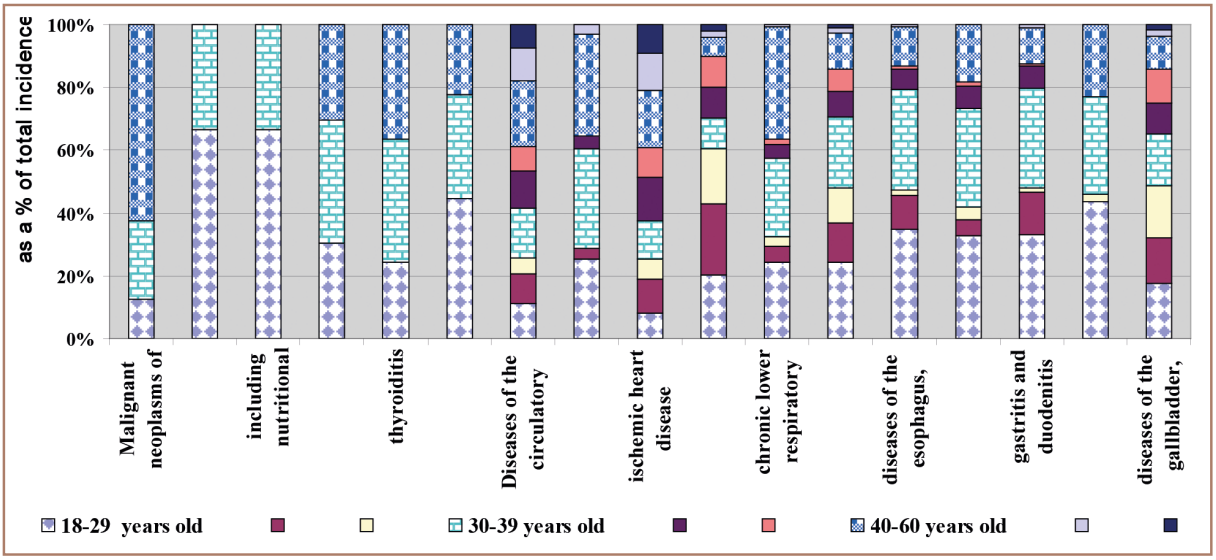

Figure 2. Morbidity of men living in Ivankivskyi district of Kyiv region in 2019-2021

The leading place among diseases of the circulatory system is occupied by coronary heart disease, which was more often recorded among the same category of people aged 40-60 in 2019. Coronary heart disease is less common among people aged 18-29. Diseases characterized by high blood pressure were not recorded at all in 2021 among all people (we believe that this is a shortcoming in the work of statistical bodies).

Diseases of the digestive system are widespread among the population of Ivankivskyi district and occupy second place after diseases of the circulatory system. It is worth noting that the leading place is occupied by ischemic heart disease. This nosological form was more often recorded among people aged 40-60.

Respiratory diseases are well expressed in people aged 18-29, especially in 2020, when the level increased by almost 10%. However, in 2021 it decreased by 26.6%, which may be due to the implementation of preventive measures caused by COVID-19. Chronic diseases of the lower respiratory tract were recorded more often in 2019. In 2020, their number decreased sharply, and in 2021 there were isolated cases, and among people aged 40-60 they were not recorded at all.

Digestive diseases require attention due to their significant level. Young people are more often ill. However, dynamic observations indicate a decrease in morbidity. People are less likely to suffer from gastric and duodenal ulcers (in 2021, not a single case was recorded among people aged 40-60). Liver diseases have

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the lowest level among all digestive disorders. However, diseases of the gallbladder, biliary tract, and pancreas are of particular concern among people aged 18-29, as their incidence is significantly higher than in older people (in 2020 and 2021, the incidence rate was 7 and 9 times higher than among people aged 40-60).

Statistical data on the incidence of men in the Obukhiv district of the Kyiv region are presented in Table 3.

Table 3. Morbidity among men in the Obukhiv district of the Kyiv region in 2019-2021

Source: Authors, based on data from the State Statistical Office

Nosological forms and classes of diseases	18-29 years old			30-39 years old			40-60 years old		
	2019	2020	2021	2019	2020	2021	2019	2020	2021
	n = 450	n = 450	n = 450	n = 367	n = 367	n = 367	n = 718	n = 718	n = 718
1	2	3	4	5	6	7	8	9	10
Malignant neoplasms of the digestive system	0	0	0	2	2	2	2	2	2
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (class II)	0	0	0	0	0	0	0	0	0
including nutritional anaemia	0	0	0	0	0	0	0	0	0
Diseases of the endocrine system, nutritional disorders and metabolic disorders (class IV)	5	5	5	13	13	13	7	7	7
thyroid diseases associated with iodine deficiency	1	1	1	1	1	1	0	0	0
hypothyroidism	0	0	0	1	1	1	0	0	0
thyrotoxicosis	0	0	0	0	0	0	0	0	0
(hyperthyroidism)	0	0	0	0	0	0	0	0	0
thyroiditis	4	4	4	4	4	4	5	5	5
diabetes	0	0	0	7	7	7	2	2	2
Diseases of the circulatory system (class IX)	120	120	120	186	186	186	246	246	246
diseases characterized by high blood pressure	64	64	64	29	29	29	17	17	17
ischemic heart disease	37	37	37	132	132	132	179	179	179
Respiratory diseases (class X)	23	23	23	11	11	11	23	23	23
chronic lower respiratory tract diseases	7	7	7	6	6	6	19	19	19
Digestive diseases(class XI)	133	133	133	151	151	151	180	180	180
diseases of the esophagus, stomach and duodenum	58	58	58	67	67	67	59	59	59
gastric and duodenal ulcers	20	20	20	24	24	24	20	20	20
gastritis and duodenitis	23	23	23	25	25	25	15	15	15

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Continuation of table 3.

1	2	3	4	5	6	7	8	9	10
liver diseases	4	4	4	5	5	5	5	5	5
diseases of the gallbladder, biliary tract and pancreas	70	70	70	77	77	77	112	112	112

As evidenced by the above data, malignant neoplasms of the digestive organs were not recorded in people aged 18-29 living in the Obukhiv district of the Kyiv region. Two cases were registered among men aged 30-39 and 40-60.

Blood and hematopoietic organ diseases and certain disorders involving the immune mechanism (class III), including alimentary anaemia, were also not detected.

Diseases of the endocrine system, nutritional disorders and metabolic disorders were most often recorded among people aged 30-39, which exceeded similar indicators in people aged 18-20 and 40-60 by two times. Thyroid diseases associated with iodine deficiency were not recorded at all among people aged 40-60 and one case each in men aged 18-20 and 30-39 during the entire observation period.

Hypothyroidism and hyperthyroidism, as well as thyroiditis - not a single case was recorded.

Four people aged 18-29 and 30-39 years and five people aged 40-60 years had diabetes.

Circulatory system diseases are the most common disease among men in Ivankivskyi district. Thus, people aged 18-29 years suffered from high blood pressure more often. Men aged 30-39 and 40-60 years suffered much less (2.2 and 3.7 times, respectively). Everyone complained of ischemic heart disease (IHD), but in people aged 30-39 years, IHD was recorded 3.6 times more often, and in people aged 40-60 years, 7.8 times, respectively (Figure 3).

Source: Authors, based on data from the State Statistical Office

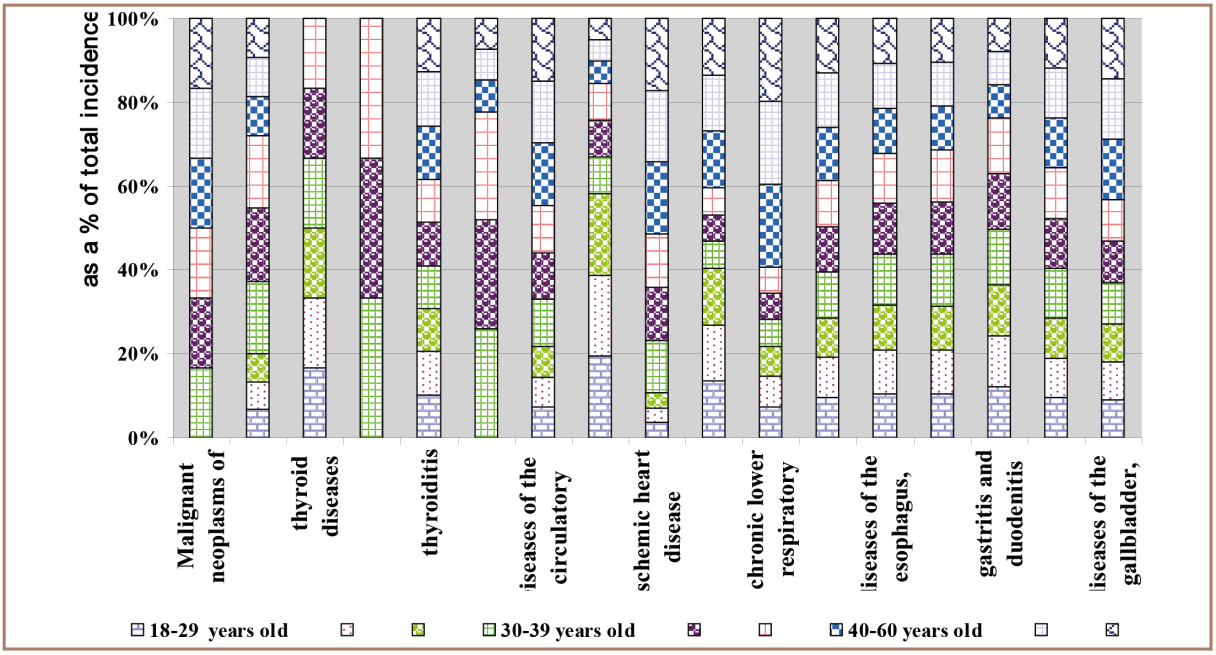

Figure 3. Morbidity of men living in Ivankivskyi district of Kyiv region for 2019-2021

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Seven people aged 30-39 and two people aged 40-60 suffered from obesity and other types of overeating.

Respiratory diseases were not significantly expressed and ranged from 11 to 23 cases, and lower respiratory tract diseases from 6 to 19 throughout the entire observation period. People aged 40-60 were more likely to suffer.

Digestive diseases are second only to diseases of the circulatory system. Diseases of the esophagus, stomach and duodenum took the leading place and were almost at the same level among all people throughout the entire observation period.

People aged 30-39 were more likely to suffer from stomach and duodenal ulcers. Gastritis and duodenitis were recorded in 23; 25 and 15 cases, respectively, among people aged 19-29; 30-39 and 40-60. Liver diseases were registered in 4 cases among people 18-29 and 5 cases among people from 30 to 60 years old.

Diseases of the gallbladder, biliary tract and pancreas are more typical for people 40-60 years old. Their number exceeds the incidence in younger men by an average of one and a half times (Figure 3).

Dynamics of morbidity among women of working age. Data on the morbidity of women of working age living in the Kyiv region for 2019-2021, according to the State Health Service, are given in Table 4.

Table 4. Morbidity of women aged 18 to 60 in Kyiv region in 2019-2021

Source: Authors, based on data from the State Statistical Office

Nosological forms and classes of diseases	18-29 years old			30-39 years old			40-60 years old		
	2019	2020	2021		2019	2020	2021		2019
	n = 51607	n = 51607	n = 51607	n = 45765	n = 45765	n = 45765	n = 80246	n = 80246	n = 80246
1	2	3	4	5	6	7	8	9	10
Malignant neoplasms of the digestive system	22	9	10	48	31	29	59	40	39
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (class III)	208	104	78	197	102	73	87	51	35
including nutritional anomies	202	99	75	183	89	68	80	47	35
Diseases of the endocrine system, nutritional disorders and metabolic disorders (class IV)	1321	800	666	1680	1026	873	1656	1119	949

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Continuation of table 4.

1	2	3	4	5	6	7	8	9	10
thyroid diseases associated with iodine deficiency	118	58	51	88	43	39	91	52	49
hypothyroidism	53	41	41	43	34	33	59	43	42
thyrotoxicosis (hyperthyroidism)	0	0	0	0	0	0	0	0	0
thyroiditis	127	70	70	174	101	97	80	55	54
diabetes	368	219	176	760	459	393	866	555	473
obesity and other types of overeating	117	60	41	90	51	35	63	38	30
Circulatory system diseases (class IX)	16214	10851	6101	26305	16281	9631	35091	21879	14623
diseases characterized by high blood pressure	5918	3199	1721	7825	3295	1702	8646	3290	1639
ischemic heart disease	4732	6200	3444	13876	10670	6420	19618	14363	10014
Respiratory diseases (class X)	2022	1728	1325	1771	1314	963	1743	1370	1063
chronic diseases of the lower respiratory tract	1014	790	529	1220	869	569	1359	1047	773
Digestive system diseases	11245	9127	6098	10619	8274	5684	9509	7316	5112
(class XI)	3528	2638	1763	3281	2312	1533	2919	2149	1488
diseases of the esophagus, stomach and duodenum	630	396	322	758	454	362	703	466	368
gastric and duodenal ulcers	1867	1564	1159	1625	1344	1009	1506	1196	926
gastritis and duodenitis	178	127	99	188	131	103	171	110	75
liver diseases	7361	6208	4133	6976	5672	3923	6155	4822	3357

Analysis of data on the incidence of malignant neoplasms of the digestive organs in women according to ICD-10 in 2019 was the highest, as in men aged 40-60 years and amounted to 59 cases out of the number of registered persons. It should be noted that neoplasms in dynamics decreased by 50% in persons aged 18-29 years, by 16.6% and by 15%, respectively, in persons aged 30-39 and 40-60 years.

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Blood and hematopoietic organ diseases and certain disorders involving the immune mechanism were the highest among persons aged 18-29 years and amounted to 208 out of all registered persons. The incidence of blood organs and disorders involving the immune mechanism was lower in persons aged 40-60 years (2.8 in 2019, 2 times in 2020 and 2.2 times in 2021). The incidence of people aged 30-39 was lower than among people aged 18-29, but significantly higher than among women aged 40-60. Similar differences are observed in relation to nutritional anaemia.

Diseases of the endocrine system, nutritional disorders and metabolic disorders are characterized by a high level in all age groups. At the same time, a higher level was observed in 2019 among people aged 40-60 (Table 4, Figure 4). Somewhat less endocrine diseases caused by nutritional disorders and metabolic disorders were registered in women aged 18-29. Over the analyzed period, there was a tendency to decrease the incidence by an average of 1.6-1.9 times in people aged 18-29 and 1.6-1.9 times and 1.5-1.4 times in people aged 30-39 and 40-60, respectively, when compared with 2019.

Source: Authors, based on data from the State Statistical Office

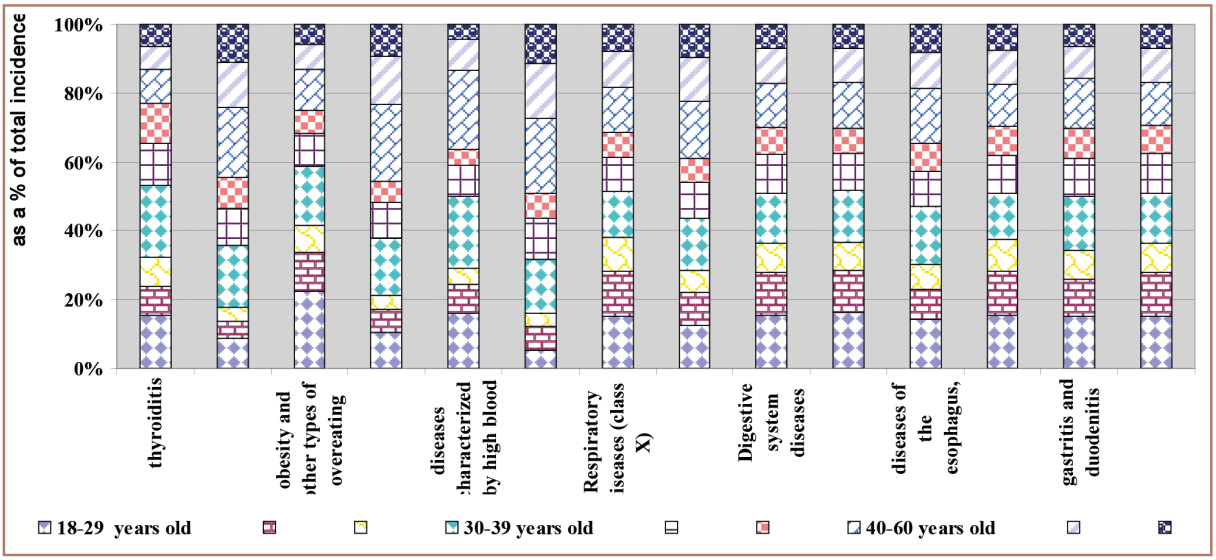

Figure 4. Morbidity of women living in the Kyiv region

Thyroid diseases associated with iodine deficiency were almost twice as common among people aged 18-29. The surveyed people suffered from hypothyroidism during the entire observation period at almost the same level. At the same time, there was a tendency to decrease the incidence rate. Hyperthyroidism was not recorded. Thyroiditis was more common in 2019. In later years, there was a tendency to decrease the incidence rate.

Diabetes mellitus was most common among people aged 40-60. Women aged 18-29 were significantly less likely to suffer from it than people aged 30-39. Women aged 18-29 suffered from obesity. Thus, in 2019, this indicator exceeded the similar one in the age group 40-60 by 1.8 times. Diseases of the circulatory system occupied a leading place throughout the entire observation period. People aged 40-60 were more likely to get sick. All women surveyed showed a tendency to a decrease in the incidence rate.

Diseases characterized by high blood pres-sure prevail over other nosologies of this

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class. All surveyed women suffer from coronary heart disease. However, the highest incidence was observed in people aged 40-60. In all women of this age, a tendency to decrease in the level of coronary heart disease was observed.

Respiratory diseases tend to decrease. However, their level is still high. Of particular concern are chronic diseases of the lower respiratory tract, which show a slight tendency to decrease in all age groups.

Digestive diseases are somewhat inferior to cardiovascular diseases, but are of concern. Thus, among women aged 19-29, they were the highest in 2019 among all surveyed. Diseases of the esophagus, stomach and duodenum occupied an average of 30% among all digestive diseases in people aged 18-29. This figure for people aged 30-39 was 30.9%; 28% and 27% respectively in 2019; 2020 and 2021. Regarding people aged 40-60, it should be noted that the share of diseases of the esophagus, stomach and duodenum was on average 29% of the total incidence of the gastrointestinal tract.

Gastric and duodenal ulcers were more frequently recorded among people aged 39-40. In dynamics, a tendency towards a decline in the incidence rate was observed. Gastritis and duodenitis are most common among women aged 18-29. The tendency towards a decrease in the incidence rate is found only in people aged 40-60 and then only in 2021.

Liver diseases are least pronounced in women aged 40-60, and gallbladder, biliary tract and pancreas diseases are more common in people aged 18-29.

CONCLUSIONS

The level of nutritionally dependent morbidity by classes and groups of diseases and individual nosological forms was analyzed, taking into account age, gender, and nutritional status of the working-age population living in ecologically hazardous regions of the Kyiv region, Ivankiv and Obukhiv districts. The priorities are diseases such as circulatory system diseases, including diseases characterized by high blood pressure, ischemic heart disease, as well as diseases of the digestive system, including diseases of the esophagus, stomach and duodenum, gastric and duodenal ulcers, gastritis, duodenitis, liver diseases, diseases of the gallbladder, biliary tract and pancreas.

The state of morbidity of alimentary genesis in the adult population of working age is of concern and requires nutritional correction, which should be aimed at improving the provision of the population with essential nutrients. Preventive measures should contribute to increasing the level of knowledge among the population regarding the balance of the diet, which will affect the nutritional status, which will contribute to improving the health index of the population, as well as extending creative longevity.

The study of the morbidity status of the adult population, which lives in conditions of constant exposure to exogenous factors of various nature, is promising for the scientific substantiation of measures to prevent diseases caused by poor-quality, unbalanced and insufficient nutrition.

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UNIVERSITY SCIENCE

SELECTION OF POWER LINE PARAMETERS

Pylyp HOVOROV,
Doctor of Technical Sciences, Professor,
Professor of the Department of Lighting Technology and Light Sources,
O. M. Beketov National University of Urban Economy in Kharkiv,
Kharkiv, Ukraine,
ORCID ID: 0000-0002-0379-1448

Roman TRISHCH,
Doctor of Technical Sciences, Professor,
Head of the Department of Mechatronics and Electrical Engineering,
M. E. Zhukovsky National Aerospace University "Kharkiv Aviation Institute",
Kharkiv, Ukraine,
ORCID ID: 0000-0002-9503-8428

Vladlen ZORIN,
Doctor of Technical Sciences, Professor,
Professor of National Technical University of Ukraine "Igor Sikorsky Kyiv Polytechnic Institute";
Kyiv, Ukraine,
ORCID ID:

Vladlen HOVOROV,
Candidate of Technical Sciences,
Docent of Ukrainian Engineering Pedagogical Academy,
Kharkiv, Ukraine,
ORCID ID:

Anastasiia KINDINOVA,
PhD student,
Assistant of the Department of Lighting Technology and Light Sources,
O.M. Beketov National University of Urban Economy in Kharkiv,
Kharkiv, Ukraine,
ORCID ID: 0000-0003-2575-0767

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ABSTRACT

In the current context of increasing loads on power grids and the urgent need for energy-saving solutions, the selection of conductor cross-sections for transmission lines is highly relevant. The article aims to investigate approaches to selecting the cross-section of power transmission lines, considering both technical and economic aspects; to assess the impact of this choice on energy losses, economic efficiency and reliability of the network, taking into account modern trends in the design and reconstruction of power transmission lines and the requirements of energy conservation and improving the quality of power supply. The study analyzes methods for determining the optimal cross-section, particularly the economic current density method and the method of economic intervals. Comparative calculations of energy losses for different cross-sections are performed, along with an evaluation of each method's efficiency both with and without discounting. The results confirm the appropriateness of applying the economic interval method during the design process, especially in the context of network reconstruction. Conclusions emphasize the influence of the selected method on operational costs and the overall energy efficiency of the system. This research provides a foundation for further development in the field of power transmission parameter optimization, considering modern requirements for reliability and sustainable energy development.

Key words

Conductor cross-section, economic current density, electricity losses, energy efficiency, power grids, reconstruction, power supply, cost optimization.

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INTRODUCTION

Since the invention of electric energy, the following issues have been regularly addressed: methods and means of transmission, parameters, and modes. The first power transmission of significant (at that time) power was carried out by the scientist Dolivo-Dobrovolsky in 1891. It was a three-phase alternating current line (Laufen-Frankfurt am Main) 175 km long at 35 kV. The works of Dolivo-Dobrovolsky are one of the foundations of the creation of electrical networks and alternating current systems on which modern electrification is built in all countries of the world. In developing power transmission lines, lines of increasingly higher nominal voltages were subsequently mastered. Currently, monitoring and cable power transmission lines with voltages from 0.38 to 1150 kV are being monitored. The total length of power transmission lines in Ukraine is about 1 million km, part of which has spent its useful life and requires serious reconstruction and replacement.

The unsatisfactory condition of electrical networks, especially distribution networks, is the cause of a noticeable increase in electrical energy losses and a decrease in its quality, a reduction in the reliability of power supply and safety of operation of power transmission lines. Market conditions in the electric power industry require a guaranteed high-quality power supply to consumers. In this regard, in the coming years, a sharp increase in the volume of work on the replacement and reconstruction of all voltage processes should be expected, as well as changes in trends in power transmission. An essential part is solving the problem of choosing wire sections and residential computers, considering modern conditions. As experience shows, selecting cross-sections is the most noticeable; therefore, insufficient justification and even a slight inaccuracy can lead to significant, unjustified external costs (Alazazmeh & Asif, 2021; Argyroudis, Mitoulis, Chatzi et al., 2021; Dagtekin, Kaya & Besli, 2022; Dasović & Klanšek, 2022; Fei, Opoku, Agyekum, Oppon, et al., 2021; Fonseca, Commenge, Camargo, Falk & Gil, 2020).

LITERATURE REVIEW

The selection of the cross-section of the wires of the power transmission line in the devices is carried out by the principle of the device of electrical installations (Pravyla vlashtuvannia elektroustanovok, 2017) ; they prescribe the selection of wire cross-sections and cross-sections operating in the network with a voltage of up to 220 kV, exclusively according to economic parameters by the norms of financial stability of the current. At the same time, in several publications and guidance documents (Costa, Silva, Faia, Gomes, Faria & Vale, 2024; Galychyn, Fath, Shah, Buonocore & Franzese, 2022; Haddad, Hammad, Castro, Vasco & Soares, 2021; Hovorov, Kindinova & Hovorov, 2021; Hovorov, Khvorost & Kindinova, 2023; Khoshnava, Rostami, Zin et al., 2019; Kupriyanov, Trishch, Dichev & Kupriianova, 2022; Picot & Guillaume, 2024; Pravyla vlashtuvannia elektroustanovok, 2017; Qiu, Wang & Zhang, 2021; Seyrfar, Ataei, Movahedi & Derrible, 2020; Sharifhosseini, Niknam, Taabodi et al., 2024; Trishch, Cherniak, Zdenek & Petraskevicius, 2024; Tripathi, Sindhwani, Anand & Dahiya, 2022; Um-E-Habiba, Ahmed, Alqahtani, Asif & Khalid, 2024; Utrilla & Górecki, 2023; Zech, Plörer, Pfluger & Breu, 2024; Zhu, Zhang, Gong & Li, 2023), wire cross-sections are selected according to the permissible currents that result from heating the wires in normal modes. Such recommendations cannot be recognized in reality because, in this case, the minimum possible, not the econom-

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ic cross-section, will be selected, and at the same time, there will be significant losses in productivity. In table. 1 (based on the author's research) lead to a multiplicity of increase in power losses δΔP (i.e., lines in addition to the economically justified power on the overhead line with aluminum wires at jek=1A/mm² and Tib=5000 h.

Table 1. Multiplicity of excess power losses

Source: Authors

Cross-sections, F, mm²	35	50	70	95	120
I_{dop}, A	175	210	265	330	390
δΔP, (o.s.)	25.0	17.6	14.4	12.3	10.9

As is evident from Table 1, selecting wire cross-sections according to heating conditions in normal mode compared to economy leads to increased losses (11+25) times, which contradicts modern energy-saving requirements. Normal mode is a long-term mode in which the criteria for reliability and quality of electricity are met at the highest economic rates. After the cross-section is selected according to economic conditions, it is necessary to check the technical heating conditions in normal mode and some post-war and repair modes.

The simplest method is the selection of cross-sections of economic current density.

$$F = \frac{I_p}{j_{ек}}, \quad (1)$$

Where F is the economic cross-section of the cable core, mm; Ip is the calculated current value, A; jek is the normalized value of the economic current density, A/mm².

The values of economic current density are normalized depending on the conductor material and design and the number of hours of use of the maximum load given in the (Pravyla vlashtuvannia elektroustanovok, 2017).

GOALS

The study analyzes approaches to choosing the cross-section of power transmission lines, considering both technical and economic aspects. The primary attention is paid to assessing the impact of this choice on energy losses, economic efficiency, and network operation reliability. An important aspect is to consider modern trends in the design and reconstruction of power transmission lines based on energy-saving requirements and improving the quality of power supply.

METHODOLOGY

The research methodology includes a theoretical analysis of scientific publications, regulatory documents, and modern standards that determine the optimal parameters of power transmission lines. Mathematical modeling allows you to estimate economic costs and energy losses depending on the selected cross-section and compare the effectiveness of different methods for its determination. Experimental research is based on analyzing actual operating indicators of existing networks, which allows you to check the correctness of the calculation models. In addition, comparative analysis helps to assess the advantages and disadvantages of different approaches, which, in the future, will allow you to formulate recommendations for optimizing the selection of parameters of power transmission lines.

RESULTS AND DISCUSSION

Despite its extreme simplicity, the method of selecting wire cross-sections and calculating the economic current density has several serious drawbacks:

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- The standards given in (Pravyla vlashtuvannia elektroustanovok, 2017) were established back in the 1950s and have not undergone any changes. By now, the cost ratios (electrical equipment, electricity costs) have changed;

The scale of standard cross-sections is responsible. When considering cross-sections, the costs were regarded as a continuous function of the wire cross-section, and this requires that the found cross-sections be rounded to standard cross-sections, i.e., the method does not give unambiguous solutions;

- A linear dependence of the cost of building a line of one kilometer on the cross-section is provided. It is inconvenient to do this, especially when using unified supports;

The essence of the economic interval method is to analyze the change in costs for a series cross-section Fi depending on the current I and is based on the following assumptions (Dagtekin, Kaya & Besli, 2022; Dasović & Klanšek, 2022; Fei, Opoku, Agyekum, Oppon, et al., 2021; Fonseca, Commenge, Camargo, Falk & Gil, 2020):

- The power transmission line is constructed in the first year of the settlement period (Tc = 1 year), and the one-time capital investment is Kot = Ko, after which its regular operation begins, for some time T until the end of the settlement period (Te = Tp - Tc);
- annual deductions from capital investments for maintenance of the AOBSL, repair, and renovation of arenas, as well as the price of electricity C0 during the calculation period remains constant AOBSL = const, arena = const, C0 = const;
- Part of the load schedule along the line during the calculation period remains the same (Tnb = const);
- losses from interruptions in the power supply of consumers and the quality of electricity are not considered in the cost functions.

When making assumptions, the expression leads to the total discounted costs for the construction and operation of 1 km of line will be as follows:

Specific construction costs:

$$З_{coop.oi} = К_{0баз.i} \bullet (1+E)^{-1} \quad (2)$$

Specific maintenance and repair costs for the period of operation until the end of the billing period:

$$З_{обсл.oi} = \sum_{t=2}^{T_p} К_{0i} \cdot a_{обсл} \cdot (1+E)^{-t} = \\ = К_{0баз.i} \cdot a_{обсл} \cdot Д_{р.е} \quad (3)$$

Specific costs for compensation of electricity losses at a constant design load for the period of operation Ipt =Ip

$$З_{пот.oi} = \sum_{t=2}^{T_p} C_0 \cdot \Delta W_{it} \cdot (1+E)^{-t} = \\ = C_0 \cdot I_p^2 \cdot r_{oi} \cdot 10^{-3} \cdot \tau \cdot Д_{р.е} \quad (4)$$

Specific costs, proportional liquidation costs

$$З_{ликв.oi} = К_{0баз.i} \cdot \left(1 - a_{рен} T_e\right) \cdot (1+E)^{-T_p} \quad (5)$$

where is the dimension of time; is the conditional discounted period of operation, is the availability

$$Д_{р.е} = \sum_{t=2}^{T_p} (1+E)^{-t}$$

E – discount rate during sensitivity analysis of optimal solutions at the level of changes can be taken as 0.05%1.5

K0base – the base cost of line construction.

Thus, the expression of individual discounted costs (per 1 km of single-circuit line) can be presented in the following video.

$$З_{0i} = З_{coop.oi} + З_{обсл.oi} - З_{ликв.oi} + З_{пот.oi} = \\ = К_{0баз.i} \cdot (1+E)^{-1} + К_{0баз.i} \cdot К_{деф} \cdot a_{обсл} \cdot Д_{р.е} - \\ - К_{0баз.i} \cdot \left(1 - a_{рен} T_e\right) \cdot (1+E)^{-T_p} + \\ + C_0 \cdot 3 \cdot I^2 \cdot r_0 \cdot 10^{-3} \cdot \tau \cdot Д_{р.е} \quad (6)$$

The last expression (6) can be written in the form of two examples, the first of which is proportional to the value of the line stability

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cost, and the second characterizes the specific expenses of electricity losses.

$$З_{oi} = З_{к.oi} + З_{пот.oi} = A \cdot К_{обаз.i} + B \cdot I_p^2 \cdot r_{oi} \quad (7)$$

Where

$$A = \left[(1+E)^{-1} + a_{обсл} \cdot Д_{р.е} - \left(1 - a_{рен} T_e\right) \cdot\right] \quad (8)$$

$$B = 3 \cdot C_0 \cdot \tau \cdot Д_{р.е} \cdot 10^{-6} \quad (9)$$

The expression in square brackets is some equivalent discount factor Dec.

$$Д_{екв} = (1+E)^{-1} + a_{обсл} \cdot Д_{р.е} - \\ - \left(1 - a_{рен} T_e\right) \cdot (1+E)^{-T_p} \quad (10)$$

IfandTo ensure this location, the value of the limiting current is determined under conditions of equal flows

$$З_{0i} = З_{0i+1} \quad (11)$$

When the expression is balanced, the costs per section are obtained as Fi and Fi+1.

$$A \cdot (К_{обаз.i+1} - К_{обаз.i}) = B \cdot (r_{oi} - r_{0i+1}) \cdot I_p^2 \quad (12)$$

Apply the limiting current for the sections Fi and Fi+1 will be equal to

$$I_{грн\ i,j+1} = \sqrt{\frac{A \cdot (К_{обаз.i+1} - К_{обаз.i})}{B \cdot (r_{oi} - r_{0i+1})}} = \\ = \sqrt{\frac{A}{B}} \cdot \sqrt{\frac{\delta К_{i+1,j}}{\delta r_{0i,i+1}}} \quad (13)$$

A graphical representation of economic intervals is shown in Fig. 1.

Source: Authors

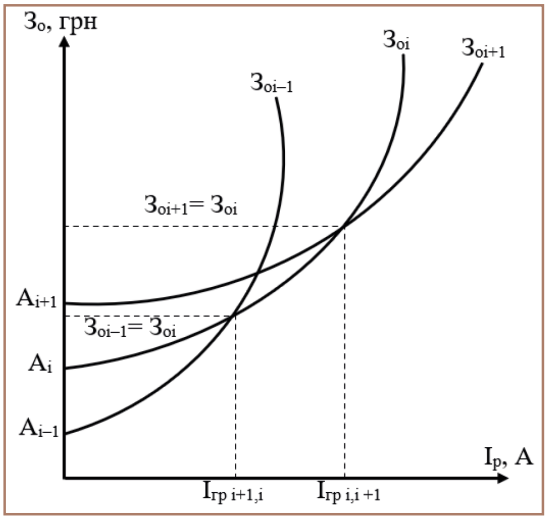

Figure 1. Dependence of costs on the design current Ir for three corresponding cross-sections Fi-1 <Fi <Fi+1

Applying the time factor accounting method using the compound interest formula (discounting) does not raise any fundamental objections. However, it is not a recovery in the most straightforward cases when annual operating costs remain unchanged throughout the entire service life of the facility, and additional capital investments in the facility are not made since they are made once during the first year. In these cases, methods for estimating savings using the payback method at average full costs Z=(En+Ra)≥K+I give the same result as calculations of discounted costs based on reducing the sum of capital investments and current costs to one year (Pravyla vlashtuvannia elektroustanovok, 2017) . It can be assumed that the payback or cost method sufficiently considers the timeliness of capital and current expenses (Kupriyanov, Trishch, Dichev & Kupriianova, 2022).

It should be remembered that with the parliament of options for total costs over the entire service life of the object (discounting), it is necessary to deduct the depreciation of instability from the composition of current expenses. At the same time, it must be considered when using the cost-based depreciation deduction method.

The standard payback period is Tn. In this case, three possible cases exist: T<Tn, T>Ti and T=Tn. If the actual payback period T is less than the standard Tn, the option with significant capital investments is more economical. If T is more critical than Tn, then it will be more economical to consider capital investments. If T = Tn, then the compared options are equally economical.

The payback period is 8 years. For new technical equipment (computers, microprocessor devices, etc.), the standard payback period is equal to 3 years. The reciprocal value

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Ен=1/Тн=1/8=0.12 is called the standard coefficient of comparative efficiency. In a modern market economy, the standard payback period and the corresponding standard coefficient of efficiency, depending on the existing conditions and requirements of the investor, the values Тн and Ен can prevent changes both in the more significant and in the lesser direction.

In addition to the above costs, other criteria for the economic efficiency of capital investments can be used in Ukraine. The final decision is made considering the analysis of the calculation results of one or more cases, depending on the nature of the problem being solved (Picot & Guillaume, 2024). The criteria include the integral discounted profit, which characterizes the excess of income over expenses. The profitability of investments is about revenue and costs. The payback period is the time during which investments are returned through income.

In this example, we will calculate the interval of economic cable lines of 10 kV with and without discounting. The fourth cable line l = 1 km of the AASHv type is laid in a trench in urban conditions with the following initial data: Tp = 10 years. Ts = 1 year. Tm = 3000 hours, E = 0.1, C0 = 0.65, aobsl = 0.008 e./hour.

Calculation considering discounting.

According to formula (5), the estimated discounted period of operation during the term is calculated.

$$T_e = 10 - 1 = 9 \text{ років}$$

$$Д_{ре} = \sum_2^{10}(1+0{,}1)^{-1} = \frac{1}{1{,}1^2} + \cdots + \frac{1}{1{,}1^{10}} = 5{,}235 \text{ років}$$

Then the equivalent discounting factor, according to formula (11) without considering the liquid value, will be equal to

$$Д_{екв} = A_л\,(1+0{,}1)^{-1} + 0{,}008 \cdot 5{,}235 = 0{,}952$$

We find the number of hours of maximum losses τ

$$\tau = \left(0{,}124 + \frac{T_м}{10^4}\right)^2 \cdot 8760 = \left(0{,}124 + \frac{3000}{10^4}\right)^2 \cdot 8760 = 1576 \text{ год}$$

And considering τ, the value of the coefficient Вл is determined by the formula (9)

$$B_л = 3 \cdot 0{,}65 \cdot 1575 \cdot 5{,}235 \cdot 10^{-6} = 0{,}0162 \text{ тис. грн./А}^2\text{Ом}$$

We find the boundary points Igr i,i+1 of the economic intervals using formula (13) and the values of the CL parameters (Table 2 - based on the author's research).

Table 2. CL parameters and intervals

Source: Authors.

Fi, mm2	35	50	70	95	120	150	185	240	Characteristic
C0, thousand UAH.	38	44	51	62	71	89	103	125	Association "Promkabel"
r0, Ohm/km	0.89	0.62	0.44	0.326	0.258	0.206	0.167	0.129	
Irp i,i+l, A	0-36.1	36.1-47.8	47.8-75.3	75.3-88.2	88.2-142.6	142.6-144.9	144.9-182.0	182.0 and above	Economic intervals
jek, A/mm2	1.03	1.03-0.96	0.96-1.08	1.08-0.93	0.93-1.19	1.19-0.96	0.96-0.98	0.98 and above	Estimated energy-saving lamp current

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Calculation based on the cost criterion without discounting

The expression for the cost of constructing 1 km of cable line, in this case, has the form

$$З = (E_н + P_a) \cdot К + \\ + 3 \cdot I^2 \cdot r \cdot C_0 \cdot \tau \cdot 10^{-6} \quad (14)$$

where En is the standard efficiency coefficient equal to En = 0.12 oe, Pa is the depreciation deduction Pa = 0.063 oe

Then, the formula for determining the value of the limiting current Irp,i,i+1 will be the same

$$I_{rp\ i,j+1} = \sqrt{\frac{E_н + P_a}{3 \cdot C_0 \cdot \tau \cdot 10^{-6}}} \cdot \sqrt{\frac{K_{i+1} - K_i}{r_{0i} - r_{0i+1}}} = \\ = Д \sqrt{\frac{\delta K_{i,i+1}}{\delta r_{i,i+1}}} \quad (15)$$

The calculation results are given in Table 3 (based on the author's research).

Table 3. Economic intervals and current density

Source: Authors.

Fi, mm2	35	50	70	95	120	150	185	240	Characteristic
Irp i,i+l, A	0-36.1	36.1-48.1	48.1-75.8	75.8-88.8	88.8-143.6	143.6-145.9	145.9-183.3	183.3 and above	Economic intervals
jek, A/mm2	1.04	1.04-0.96	0.96-1.08	1.08-0.93	0.93-1.2	1.2-0.97	0.97-0.99	0.99 and above	Estimated energy-saving lamp current

Analyzing the calculated values of economic current intervals with and without discounting (Table 2 and Table 3), they coincide. This is confirmed by the premise that in the case of one-time capital investments during the first year of construction of the power transmission line and fixed costs during the service life, calculations can be made using the cost criterion without discounting.

The obtained values of economic current density (Table 2 and Table 3) are 1.5+1.7 times lower than those of normalized economic current densities given in (Pravyla vlashtuvannia elektroustanovok, 2017) . The choice of wire cross-section and measurements at dynamic intervals allow the reduction of active power losses in lines by 2-3 times, contributing to the solution of energy-saving problems.

CONCLUSIONS

1. Due to their originality and mass, The economically justified choice of parameters of power transmission lines, primarily wire cross-sections and structures, can be changed to solve the most critical tasks. Insufficient scientific substantiation of the task's technical and economic model and the model's inadequacy of actual conditions can lead to significant calculation errors and damage.
2. The normalized values of current density in the (Pravyla vlashtuvannia elektroustanovok, 2017) do not have sufficient scientific and methodological justification. The recommended values of current density were established in the 50s of the last century, and the initial conditions adopted during the calculations have now changed. Therefore, using normalized current density results when choosing economic wire cross-sections and measurements cannot be better.
3. The method of economic intervals allows you to determine the accuracy of standard wire cross-sections and residential

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measurements and obtain unambiguous solutions manually. In this case, you can use the calculations not to average specific indicators but to essential values of basic costs (K, CT, E. R., etc.). The method makes it possible to analyze and obtain more reliable and economically justified solutions individually for each calculation, thereby solving the problems of resource and energy conservation in market conditions.

4. Calculations show that the values of current densities corresponding to the obtained economic intervals are 1.5+1.7 times lower than those normalized by the (Pravyla vlashtuvannia elektroustanovok, 2017) . Thus, the choice of wire cross-section and calculations based on economic intervals allow for reducing power losses in power transmission lines with a voltage of 10-220 kV by 2-3 times.
5. Power transmission lines in distribution networks are usually constructed with one-time capital investments during the year, and additional costs during the service life are assumed to be unchanged. Therefore, the choice of economic processing of wire cross-section data and measurement can be made according to the criterion of costs without considering their discounting. Lines with economic changes in operation provide maximum profit regardless of the forms of ownership in the industry.

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THE RELATIONSHIPS BETWEEN SOCIAL INTELLIGENCE AND INDIVIDUAL PERSONALITY TRAITS OF TEACHERS

Stanislav TABACHNIKOV,
Doctor in Medicine, Professor,
President of Public Organization "National Academy of Sciences of Higher Education of Ukraine",
Kyiv, Ukraine,
ORCID ID: 0000-0003-0492-9450
RESEARCHER ID: A-9440-2019
SCOPUS ID: 57214227898

Nataliia MYKHALCHUK,
Doctor in Psychology, Professor,
Head of the Expert Commission of the Educational and Methodological Council, Professor of the Department of Theory and Practice of Foreign Languages and Teaching Methodology, Rivne State University of the Humanities,
Rivne, Ukraine,
ORCID ID: 0000-0003-0492-9450
RESEARCHER ID: A-9440-2019
SCOPUS ID: 57214227898

Yevhen KHARCHENKO,
Doctor in Medicine, Professor,
Professor of the Department of Physical Rehabilitation and Ergo-Therapy, Communal institution of higher education "Rivne Medical Academy" of Rivne Regional Council,
Rivne, Ukraine,
ORCID ID: 0000-0002-4340-8503
RESEARCHER ID: AAU-7523-2020
SCOPUS ID: 57216872875

Eduard IVASHKEVYCH,
Doctor in Psychology, Professor,
Professor of the Department of General Psychology, Psychodiagnostics and Psychotherapy, Rivne State University of the Humanities,
Rivne, Ukraine,
ORCID ID: 0000-0003-0376-4615
RESEARCHER ID: V-8872-2018
SCOPUS AuthorID: 57216880484

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Ernest IVASHKEVYCH,
Ph.D. in Psychology, Associative Professor,
Doctoral Student, Translator Hryhorii Skovoroda
University in Pereiaslav,
Pereiaslav, Ukraine,
ORCID ID: 0000-0001-7219-1086
Researcher ID: F-3865-2019
SCOPUS D: 57216880485

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ABSTRACT

The purpose of the article is: to empirically investigate the relationships between social intelligence and individual personality traits of teachers; to show the connection between social intelligence of teachers and the process of the formation of individual personality's traits, his/her empathic abilities, Machiavellianism and meaningful life orientations. So, our purpose is to show what significant positive correlations social intelligence has with characterological qualities of the teacher.

Methods. Theoretical methods were categorical and structurally-functional analysis of lexical units, the methods of systematization, modeling, generalization; empirical ones – the experiment.

Results. Correlation analysis also allowed us to identify the connections between individual psychological characteristics of teachers' personalities and certain indicators of social intelligence. Thus, the subtest "Behavioral consequences" has positive correlations with the MMPI scales, such as: with the emotional lability scale ($r=0,59$, $p<0,01$) and the pessimism scale ($r=0,41$, $p<0,05$). The subtest "Nonverbal behavior" positively correlates with the rigidity scale ($r=0,58$, $p<0,01$) and negatively – with the Femininity – Masculinity Scale ($r=-0,40$, $p<0,05$). The subtest "Speech expression" also has two positive correlations – with the individuality scale ($r=0,41$, $p<0,05$) and the overcontrol scale ($r=0,61$, $p<0,01$).

Conclusions. The more teachers have such individual qualities as analytical thinking, individuality, self-confidence and a tendency to analyze interpersonal communication situations, the better specialists understand the nonverbal behavior of partners of communication. A high level of emotional stability and social extroversion are characteristics of teachers with a deep understanding of the patterns of the development of interpersonal relationships, which allows them to successfully predict the dynamics of these relationships.

Key words

Social intelligence, individual qualities, analytical thinking, individuality, emotional stability, social extroversion, social interaction.

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INTRODUCTION

The problem of social intelligence of specialists, in particular, teachers, is of great interest in view of the following points. First of all, its relevance is determined by the social situation of the transitional period, which is characterized by a fundamental collision between the understanding of the role of social intelligence in the structure of the individual's intelligence and the significance of social intelligence in the professional activity of a teacher. In a relatively stable situation of the not-so-distant past, a teacher did not have to actualize the main functions of social intelligence, because in fact every specialist used the acquired volume of knowledge, skills and abilities in his/her professional activity. If this resource was not enough, its replenishment could be postponed for the future, and social intelligence generally remained unclaimed.

But there are problems that have so far remained unnoticed by researchers. This is the problem of the relationships between social intelligence and individual characteristics of teachers, which is completely undisclosed in the scientific literature. It is this problem that became the subject of our research.

LITERATURE REVIEW

So, we'll show some main approaches to the problem of social intelligence of the person. Representatives of the Genetic Approach (Civitarese & Foresti, 2008), recognized the influence of the environment on the features of cognitive development of the individual (Dijkgraaf, Hartsuiker & Duyck, 2017). Intellectual abilities were assessed by scientists not only taking into account the formation of certain cognitive functions, but also the level of mastery of social experience (awareness (Tohidian, 2021), knowledge of the meaning of words (Rezaei & Mousanezhad Jeddi, 2020), possession of certain social skills (Aleksandrov, Memetova & Stankevich, 2020), the ability to moral judgments (Berkovitch & Dehaene, 2019), etc.) (Cilibrasi, Stojanovik, Riddell & Saddy, 2019). The content of the concept of "intelligence", thus, is quite voluminous both from the point of view of its manifestations and from the point of view of the factors of its formation (Batel, 2020). However, in the context of the genetic approach, intelligence was defined as an already achieved, stable level of mental development, and not as the ability to cognition (Drigas & Karyotaki, 2017).

The next approach to determining the nature of the intelligence of an individual is the Factor Approach (Guilford & O'Sulliven, 2021; Thorndike, 1986). The theories of the intelligence were based on the fact that there are positive correlations between the results of respondents performing various intellectual tests. The basis of the connection between the performance of various tests, according to the scientist, is the presence in each of them of the so-called "general factor" of intelligence ("general factor", abbreviated "g"). The "g" factor, scientists believed, is intelligence in its essence, and its essence is reduced to individual differences in the characteristics of "the mental energy" of the individual (Tillman & Louwerse, 2018). The level of mental energy manifests itself in the ability of an individual to identify connections and relationships both between individual elements of his/her own knowledge and between the content components of a certain test task (Murphy, Melandri & Bucci, 2021). Also, scientists identified the factor "s" as the consideration of which allows characterizing the specificity of each specific test task (Greco, Canal, Bambini & Moro, 2020). This theory was called "the two-factor theo-

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ry of intelligence" (Guilford, 1967; Guilford & O'Sulliven, 2021; Thorndike, 1986).

Another theory of intelligence, which refers to the Factor Approach, is the theory of intelligence of L. Thurstone (2002). The latter emphasizes the impossibility of the existence of general intelligence. As a result of the research conducted, L. Thurstone received more than 10 group factors, and 7 of them were identified by him and called "primary mental abilities" (2002: 32): S – spatial factor (the ability to operate mentally with spatial relations); P – perception factor (the ability of an individual to detail visual images); N – computational factor (the ability of an individual to perform basic arithmetic operations); V – verbal comprehension factor (the ability of a person to understand and analyze the meaning of words); F – speech speed (the ability to select quickly a right word according to a given criterion); M – information memorization factor (the ability to memorize and reproduce information); R – logical reasoning factor (the ability to detect patterns in the proposed list of letters, numbers and shapes).

Although, we'd like to note that in the results scientists (Razmi, Jabbari & Fazilatfar, 2020), in addition to general intelligence, some special factors, such as individual abilities, are clearly traced, and all the factors identified by L. Thurstone (2002) correlate with each other at a high level of reliability and have some common basis. Therefore, we conclude that we are talking about one and the same theory, within the paradigm of which the emphasis is either on general (according to C. Spearman (1904)) or on special (according to L. Thurstone (2002)) factors.

Studies of the "multiplicity" of factors of general intelligence are primarily related to the ideas of L. Thurstone (2002) about the multiplicity of intellectual abilities. Similar studies were also conducted by scientists (Hamedi & Pishghadam, 2021). The empirical results obtained, in particular, by scientists (Cui, Wang & Zhong, 2021) were used as the basis for the structural model created by the scientist, in which four types of intelligence are distinguished: "concrete" (Alahmadi, Shank & Foltz, 2018), "abstract" (Baranger & Baranger, 2008), "semantic" (Heidari, 2019) and "social" intelligence (Armstrong & Dienes, 2013). In factor model of intelligence of scientists (Alyami & Mohsen, 2019), social intelligence belongs to the conative, behavioral category, because the level of the development of social intelligence determines, first of all, the behavioral implementation of models of social interaction by a person (Brysbaert & Stevens, 2018).

Thus, the structure of general intelligence by J. Guilford & M. O'Sulliven (2021) contains 120 different intellectual abilities, which are distributed according to 15 factors. The principles of combining intellectual abilities are of great importance. In this model, 120 factors of intelligence should be understood by us as intellectual abilities, which J. Guilford & M. O'Sulliven (2021) classify according to three independent variables that characterize the information as some process. At the same time, each intellectual ability is described in terms of specific cognitive content, mental operations, and the result obtained, and it is denoted by a combination of three variables: 1) operations, which include: cognition (C); memory (M); divergent thinking (D); convergent thinking (N); evaluation (E); 2) content, which contains: images (F); symbols (S); semantics (M); behavior (B); 3) results of information processing, which include: units (elements) (U); classes (C); relations (R); systems (S); transformations (T); implications (I).

The conception of social intelligence also was proposed by scientists (Ferdowsi &

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Razmi, 2022). According to the scientists, social intelligence is an independent psychological phenomenon, and not a manifestation of general intelligence in social situations of interpersonal interaction. According to A.M. El-Zawawy (2021), social intelligence is a basic personal characteristic that arises on the basis of a complex of intellectual, personal and behavioural traits, including the level of energy activity of the individual and the processes of human self-regulation (Astle & Scerif, 2011); these traits, in turn, determine the prediction of the development of interpersonal situations, the peculiarities of the subject's interpretation of the received information and planning of his/her own behaviour (Bucci, 2021), readiness for social interaction and decision-making (Lu, Wang, Guo, Zeng, Zheng, Wang, Shao & Wang, 2019).

In the researches of scientists (Mytnyk, Matvienko, Guraliuk, Mykhalchuk & Ivashkevych Er. (2021), a positive correlation of social intelligence with different types of the activities of the person was diagnosed. Such type of correlation has the aim of achieving fairly high results in socially significant interpersonal interaction (Mytnyk, Ivashkevych Er., Chanchykov, Predko & Stakhova, 2023). It was proven that people with a high level of social intelligence had high indicators according to the criteria of "social success" (Mykhalchuk & Ivashkevych Ed., 2018), "cognitive activity" (Wong, 2017), "self-confidence" (Yatsenko, Halushko, Ivashkevych Er. & Kulakova, 2022), "high self-esteem" (Mykhalchuk & Bihunova, 2019).

Representatives of another, Socio-cultural Approach (Mykhalchuk, Bihunova, Fridrikh & Vietrova, 2021) stated that a person is formed according to the laws of cultural and historical development, mastering in the process of his/her life the material and spiritual values created by other people. And such socio-cultural factors as language, education, family, customs, traditions are determinants of the level and pace of mental (in particular, intellectual) development of all members of the society (Honcharuk, Onufriieva, Haletska, Kurytsia, Ivashkevych Er. & Nabochuk, 2023).

In the paradigm of the Socio-cultural Approach, cross-cultural studies were conducted that studied the features of intellectual activity of representatives of different cultures (Zuniga & Simard, 2019), as a rule, representatives of Western or technocratic culture, and representatives of primitive or traditional culture (Gilabert, 2007). As a result of the conducted empirical studies, it became clear that culture affects not only the level of intellectual development itself, but also the nature of the individual's intellectual preferences (Gilabert, 2007). In the studies of scientists (Dehaene, Changeux, Naccache, Sackur & Sergent, 2006), a difference in the level of the development of social intelligence was established depending on the country of residence (Dubovyk, Mytnyk, Mykhalchuk, Ivashkevych Er. & Hupavtseva, 2020). So, the trend of the development of social intelligence of children at the age of six depends on whether they live in Mexico or in the USA, although in the process of further age development, a Mexican child will be distinguished by an increasingly subtle perception of information, and a North American child has better developed abstract operations (Phani Krishna, Arulmozi, Shiva Ram & Mishra, 2020).

Another approach to defining social intelligence is the Learning Approach (Peel, Royals, Chouinard, 2022). Thus, scientists (McCandliss, Cohen & Dehaene, 2003) consider intelligence as a system of functional behavioral skills that are the result of learning, the result of the formation of intellectual skills. Intelligence is in-

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terpreted by scientists as a certain behavioral repertoire that is implemented in the process of learning activities (McCandliss, Cohen & Dehaene, 2003).

At the same time, scientists (Alahmadi & Foltz, 2020) note that social intelligence is formed as a result of a person mastering the basic cognitive skills: 1) skills of naming objects, their characteristics (color, size, etc.); 2) skills of performing oral transmission according to the type of "word-image"; 3) skills of working with word classes (such as with their genus-specific connections); 4) skills of verbal associations.

Similar in content is the theory of skills of A. Bazan (2018). The scientist notes that intellectual development is a system of educational operations that are specially organized by adults in order to form specific skills in the subject. Thus, scientists (Falé, Costa & Luegi, 2016) claims the existence of three interconnected "tiers" (types) of skills: sensorimotor, representative and abstract, which are the basis of the social intelligence of the individual. All these skills, the scientist (Chen, 2022) notes, are formed only in the process of clearly organized educational activity, which will be responsible for their interaction and transformation.

Thus, according to the Learning Approach (Mytnyk, Uninets, Ivashkevych Er., Rashkovska, Ivashkevych Ed. & Kuchai, 2024) Social intelligence is considered by us as the ability that ensures the success of social interaction between people in various fields of the activity (Tabachnikov, Mishyiev, Kharchenko, Osukhovskaya, Mykhalchuk, Zdoryk, Komplienko & Salden, 2021). We think, that social intelligence is one of the most important abilities that ensures effective interpersonal interaction and successful social adaptation of subjects of dialogical activity (Mykhalchuk, Levchuk, Ivashkevych Er. & Nabochuk, 2023). We consider social intelligence as a necessary ability to solve various problems that are arisen in situations of communication, management and social adaptation.

Interesting there are our researches (Tabachnikov, Mishyiev, Drevitskaya, Kharchenko, Osukhovskaya, Mykhalchuk, Salden & Aymedov, 2021), which study the relationships between the level of social intelligence and anxiety indicators in representatives of different professions. Having empirically investigated the characterological properties of individuals, we conclude that social intelligence is manifested, as a rule, in a complex or uncertain situations of communication and interpersonal interaction. At the same time, the level of the development of social intelligence is determined by the cognitive abilities of the individual.

In our researches (Maksymenko, Ivashkevych Er., Kharchenko, Tarnavska & Sinjavska, 2023) we actualize the point of view on the relationships between social intelligence and situational anxiety, as well as anxiety associated with the performance of cognitive activity and self-esteem are presented. The data obtained by us on the characteristics studied in different professional groups indicated that the highest indicators of social intelligence were most often found in people engaged in professional activities in the "person-sign" system, while representatives of the "person-person" profession (teachers and managers) were dominated by low data on social intelligence. In addition, teachers, for various reasons, are diagnosed with the highest indicators of all types of anxiety, and a low level of anxiety associated specifically with the performance of professional activity, with interpersonal relationships in the team and with self-esteem was not found in any teacher.

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In our researches we do not provide empirical results regarding the level of the development of social intelligence of teachers of different fields of professional activity, therefore this problem became the subject of our study. In our studies we diagnosed a positive significant correlation between the level of the development of social intelligence and anxiety in groups of successful and unsuccessful representatives of different professions. In the group of unsuccessful teachers in their activities, compared to successful ones, there was a greater number of respondents with social intelligence below average. Among successful teachers-innovators, an average or above average level of the development of social intelligence and low anxiety indicators were diagnosed.

Studying the problem of the correlation of cognitive and psychosocial characteristics of the individual of teachers, we proved that understanding emotional and social intelligence were determinants of the formation of the person's leadership position, leadership effectiveness, and effective use of leadership styles (Mykhalchuk & Ivashkevych Ed., 2018).

Difficulties in interpersonal communication of students with different levels of social intelligence were also studied by us. We concluded that the most relevant for students in terms of explication of difficulties, which were the communicative and perceptual aspects of communication, because the greatest complications arise during communication with teachers and other authoritative people for them, as well as with representatives of the opposite sex, parents, strangers (Mykhalchuk & Bihunova, 2019).

As the analysis of theoretical and experimental approaches to understanding a social intelligence has shown, this concept does not yet have a clear definition. Various scientific approaches to outlining the content of social intelligence reflect the ambiguity of its characteristics (Dehaene & Cohen, 2011). At the same time, a number of common points can be identified in the definitions of "social intelligence".

Firstly, in most definitions social intelligence is interpreted as a set of abilities (Abrams, 2005). Therefore, it is associated with a certain cognitive activity performed by a person (Bucci, Maskit & Murphy, 2016). Secondly, these abilities have the aim of organizing effective interpersonal interaction with other people (Ellis, 1987). Thirdly, the main criterion for the presence or absence of the ability to solve problems in order to establish effective interpersonal relationships is the adequacy of interpretation, accuracy of understanding, and prediction of the behavior of the interaction partner (Podobnik, Jerman & Selan, 2021). Fourthly, in whatever context, paradigmatic space, social intelligence is considered (Shiva Ram, Bhardwaj & Phani Krishna, 2017), it is described as a complex of personal formation consisting of a large number of abilities (Valis, Slaninova, Prazak, Poulova, Kacetl & Klimova, 2019).

In our opinion, social intelligence is a complex of the development of the person that includes various abilities that, in their aggregate, have the aim of understanding people's behavior in the process of interpersonal interaction. Based on the analysis of the conducted by us researches, we can state that in recent years scientists have held the opinion that social intelligence is a fairly clear, coherent set of mental abilities with the aim of analyzing social information; abilities that are fundamentally different from those ones which form the basis, in particular of more formal thinking, which there are the abilities that can be easily tested using tests to determine the level of the development of academic intelligence.

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In this regard, we believe that social intelligence is an independent neoplasm in the structure of the individual's intelligence. We define social intelligence as an integrative ability to adequately perceive, understand and predict the behavior and activities of other people. We will consider the wisdom of the individual as a kind of metacognition, which is presented at the level of the mnemonic component of the teacher's social intelligence.

Thus, a theoretical analysis of the literature on the problem of social intelligence indicates that social intelligence is relatively a new concept in Psychology, which is in the process of scientific substantiation, refinement and empirical verification. Defining the structure of social intelligence, researchers emphasize its connection with the cognition of social objects and situations, as well as its connection with the understanding of the processes of interpersonal interaction. In the first case, the concept of "intellectual abilities" is used to define social intelligence, which is associated with the cognition of an individual of purely conative (behavioral) information. In the second case, social intelligence is considered by us through a system of cognitive properties of the individual, on which the effectiveness of interpersonal interaction depends. The analysis of the structure of social intelligence and its functions described in psychological researches gives us grounds to assert that it is connected, first of all, with the understanding of the situation of interpersonal interaction. Thus, social intelligence is a relatively independent integral ability of a person, which is formed in the process of his/her activity in the social sphere, in the sphere of communication and social interactions, and allows the person to successfully solve tasks and problems of interpersonal interaction.

So, the purpose of our article is: to empirically investigate the relationships between social intelligence and individual personality traits of teachers; to show the connection between social intelligence of teachers and the process of the formation of individual personality's traits, his/her empathic abilities, Machiavellianism and meaningful life orientations. So, our purpose is to show what significant positive correlations social intelligence has with characterological qualities of the teacher.

METHODS

Theoretical methods were categorical and structurally-functional analysis of lexical units, the methods of systematization, modeling, generalization; empirical ones – the experiment.

In accordance with the purpose of our research, we selected a set of psychodiagnostic research Methodologies. In our research we used such Methodologies: Test "Research of Social Intelligence" by J. Guilford & M. O'Sullivan (adapted by E.S. Mihailova) (2021); Methodology "Study of personality orientation" by V. Smekalo & M. Kucher (2022); Minnesota Multidisciplinary Personality Inventory (MMPI) (2022); Psychological Test "Simple Symbol Personality Test" (DRBJ & SHERRY, 2022); SHL Occupational Personality Questionnaire (2022).

PARTICIPANTS

At the experimental stage of the empirical study teachers from all the groups participated (all educational institutions were in Ukraine, from different cities and towns in Ukraine, which are located in different parts of the country: in the western part of Ukraine – Rivne, Lviv, Kamianets-Podilskyi; in the central part of Ukraine – Kyiv, Vinnytsia, Chernihiv; in the eastern part of Ukraine – Kharkiv,

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Sumy). In total, 1177 teachers (356 men and 821 women) were involved in this stage of the experiment, such as:

- 114 teachers of preschool educational institutions (all women);
- 403 secondary school teachers (141 men and 262 women);
- 201 teachers of out-of-school educational institutions (all women);
- 459 university lecturers (215 men and 244 women).

RESULTS AND THEIR DISCUSSION

The research was conducted during 2023-2024 in several stages. The indicators of social intelligence of teachers obtained at the first stages of our research were compared using Test "Research of Social Intelligence" by J. Guilford & M. O'Sulliven (adapted by E.S. Mihailova) (2021). As a result, five groups were identified according to the level of development of social intelligence: 1) high; 2) above average; 3) average; 4) below average; 5) low. After that, individual personality traits, life-meaning orientations, empathy and Machiavellianism of the personality were studied, and differences in age, gender and activity experience of teachers with different levels of social intelligence were also taken into account. The choice of Methodology was not accidental, since in addition to the personal qualities themselves, we were interested in the relationships of the characteristics of social intelligence with such qualities as empathy and Machiavellianism that are significant for achieving social adaptability and establishing interpersonal relationships.

Thus, a comparison of the indicators of social intelligence of teachers of different professional qualifications revealed statistically significant differences according to the level of social intelligence. It turned out that teachers – Doctors and Candidates of Sciences, compared with teachers without a scientific degree, have a more developed ability to understand people and interact with them ($r=0,5261$, $p<0,05$). This is probably due to the specifics of the professional activity of teachers with scientific degrees and titles, which involves interaction with both managers and performers, which places higher demands on their role behavior, actualizes the ability to take into account the psychological characteristics, expectations, value and life orientations of colleagues, subordinates and management, especially if we take into account the fact that the majority of Doctors of Sciences (77%) and 24% of Candidates of Sciences who participated in the research hold managerial positions.

We also conducted a statistical analysis with the aim to identify gender differences in the level of the expression of social intelligence of managers. Women had higher scores than men according to communicative competence ($r=0,6311$, $p<0,05$) and indicators of understanding of speech expression ($r=0,4856$, $p<0,01$). Male managers had a more developed understanding of the consequences of people's behavior ($r=0,7148$, $p<0,01$), understanding of nonverbal behavior ($r=0,5397$, $p<0,05$) and understanding of interpersonal relationships in dynamics ($r=0,6831$, $p<0,01$).

A comparison of teachers with different levels of social intelligence and different activity experience shows that managers with low and below average social intelligence have the greatest professional experience in the pedagogical field (from 15 years). These respondents outperform teachers with an average level of social intelligence ($r=0,4056$, $p<0,05$) and teachers with high and above average social intelligence ($r=0,4751$, $p<0,05$).

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Managers with an average level of social intelligence have the least professional experience compared to other groups of managers (p<0,01).

The revealed patterns seem somewhat paradoxical, since it could be assumed that it is the greater personal (life and professional) experience that contributes to the better development of the ability to notice complex relationships in the social sphere. However, the obtained data indicate that the age factor is not a determining factor in the level of the development of social intelligence. Probably, other characteristics of individual personality development are more significant, in particular, gender characteristics, cognitive styles of performing professional activities and methods of resolving conflict situations, described by us at the previous stages of our research. It should also be noted that in general the obtained results show that age and gender are not determining characteristics of the effectiveness of professional activities of an individual who is under the direct influence of social factors.

Our empirical study showed that the social intelligence of teachers was closely related to such psychological formations as individual personality traits, empathic abilities, Machiavellianism, meaningful life orientations, etc. The research conducted by us using Methodology “Study of personality orientation” by V. Smekalo & E. Kucher (2022), Minnesota Multidisciplinary Personality Inventory (MMPI) (2022), Psychological Test "Simple Symbol Personality Test" (DRBJ & SHERRY, 2022), SHL Occupational Personality Questionnaire (2022) shows that the most pronounced was the average indicator on the hypomania scale (0,6897 points according to the results of factor analysis) of teachers with a high level of social intelligence. This indicates that developed social intelligence is inherent for individuals who are characterized by positive emotions, good mood, optimism, etc. Such teachers demonstrate ease in interpersonal contacts, a high level of the activity in interpersonal relationships and professional activities.

Statistical analysis revealed a fairly large number of significant differences in the individual characteristics of teachers with different levels of social intelligence. In particular, teachers with social intelligence levels above average and high have higher indicators than managers with average, below average and low levels of social intelligence. Thus, teachers with social intelligence of high and above average levels of assessment on validity scales (M = 59,1–56,7) are higher than teachers with lower indicators (M = 49,6–52,4). Teachers with high and above-average level of social intelligence outperform teachers with average social intelligence according to scales: No. 3 (emotional lability scale; r=0,54, p<0,01), No. 8 (scale of individuality; r=0,61, p<0,01), No. 9 (optimism scale; r=0,71, p<0,01). Similar results were diagnosed when comparing the individual psychological characteristics of teachers with average and low levels of social intelligence: on scale No. 3 (r=0,70, p<0,01), on scale No. 8 (r=0,65, p<0,01), on scale No. 9 (r=0,67, p<0,01).

On the other hand, teachers with above-average social intelligence had lower scores on the lying scale (r=0,48, p<0,05), scale No. 4 (impulsivity scale; r=0,47, p<0,05), scale No. 6 (rigidity scale; r=0,67, p<0,01) compared to teachers with the average level of social intelligence. At the same time, teachers with the average level of social intelligence outperform teachers with below average social intelligence on these scales: on the lying scale (r=0,51,

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p<0,05), scale No. 4 (r=0,49,p<0,05), scale No. 6 (r=0,57, p<0,01).

Teachers with a high level of social intelligence are characterized by expressiveness, active life position, lack of inclination to seriously delve into the essence of the problems, optimism, instability of emotions, high motivation for achievement, which is manifested, first of all, in self-expression and self-affirmation of the personality, and not in achieving specific goals. Teachers of this type of the personality are sociable, have a large number of interpersonal contacts and experience a sense of satisfaction from the process of interpersonal interaction.

Compared to other teachers, heads of structural units with a high level of social intelligence tend to control their emotions to a greater extent and to be guided by normative orders and rules. At the same time, they are sociable, self-confident, calm, more spontaneous in establishing and maintaining social contacts, demonstrative, can show openness and great interest according to other people, but in fact they occupy the individual-separating position in relation to others. They are largely characterized by a specific, clearly defined style of gender-role behavior, flexibility in interpersonal relationships, plasticity in the situations of role interaction.

At the same time, there are quite contradictory trends: a high level of self-esteem is combined with the need to participate in resolving conflict situations, to perform activities in the interests of the group, selfishness is combined with altruistic declarations, aggressiveness – with the desire to please others. The contradiction in this case may also consist, on the one hand, in the combination of teachers' orientation to compliance with accepted social norms, the ability to choose the optimal forms of behavioural activity for a particular situation, taking into account the logic of common sense, and, on the other hand, with the instability of emotions.

In general, it can be argued that a high level of social intelligence corresponds to such character traits of teachers as the activity, optimism, flexibility, the ability to establish and maintain interpersonal contacts. At the same time, such teachers are characterized by a clearly expressed individual position, which is compensated by a high level of self-control and orientation to social norms. Thus, if these teachers have well-developed manipulative abilities, they are well adapted to different social life, while using their creative abilities to organize interpersonal interaction with the aim of achieving, first of all, purely individual, not group goals.

Teachers with a high level of social intelligence have lower scores on the scale of test No. 2 – the pessimism scale (r=0,58, p<0,01 for teachers with an average level of social intelligence and r=0,47, p<0,05 for teachers with a low level of social intelligence). These results indicate the passivity of a real personal position at the moment of life, a more optimistic assessment of their life prospects, reflexivity and a lower degree of orientation to the values and norms of reference groups of teachers with a high level of social intelligence.

Teachers with low levels of social intelligence have higher scores on the lying scale (r=0,71, p<0,01 for respondents with high level of social intelligence and r=0,63, p<0,01 for teachers with average level). Lower scores were diagnosed on the first scale – the overcontrol scale (r=0,69, p<0,01 for teachers with a high level of social intelligence and r=0,65, p<0,01 for respondents with an average level), on scale No. 3 – the emotional lability scale (r=0,76, p<0,01 for teachers with a high level of social intelligence and r=0,45, p<0,05 for

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respondents with an average level), on scale No. 8 – the scale of individuality (r=0,69, p<0,01 for teachers with a high level of social intelligence and r=0,48, p<0,05 for respondents with an average level), as well as on scale No. 9 – the optimism scale (r=0,63, p<0,01 for teachers with a high level of social intelligence and r=0,41, p<0,05 for teachers with an average level). The differences revealed indicate a lower tendency of teachers with a low level of social intelligence to rigidly fixed gender-role behavior, greater sensitivity to the influences of the environment, anxiety, lack of confidence in themselves, their strengths and capabilities, orientation to the world of internal experiences, passivity of personal positions, dependence on the opinion of the vast majority of microgroup members, greater empathy and desire for real emotional involvement into interpersonal relationships with other people.

The qualitative analysis of the obtained research results allows us to characterize teachers with a high level of social intelligence as active, optimistic, self-confident people who are true masters of the art of communication, which they use to achieve their goals. In this case, there is an emotional alienation from active interpersonal relationships and, along with this, the presence of cognitive dissonance associated with the expectations of others, on the one hand, and the real attitude towards other subjects of interpersonal interaction, on the other. According to our observation, a high level of manipulativeness also led to cognitive dissonance (this conclusion applies to respondents with an average level of social intelligence who occupy management positions).

A separate direction of the empirical analysis was the study of correlations between social intelligence and other individual characteristics of teachers. As a result of statistical analysis, correlations were found, depicted in Fig. 1, in Appendix. In general, a high level of correlation of social intelligence with individual personal characteristics is noteworthy (out of 13 scales of the MMPI, 7 scales are directly related to social intelligence and its components). At the same time, the connections of individual characteristics of teachers with individual indicators of social intelligence (8 such connections) were diagnosed, and these individual connections are also connected with the general indicator of social intelligence.

Let us analyze the specifics of the relationships between individual characteristics of teachers with individual components and the general indicator of social intelligence. Thus, the general indicator of social intelligence has positive correlations with the social introversion scale (r=0,611, p<0,01), the optimism scale (r=0,41, p<0,05), the individuality scale (r=0,57, p<0,05), the femininity-masculinity scale (r=0,61, p<0,01), the overcontrol scale (r=0,61, p<0,01) and negative correlations with: the anxiety scale (r=-0,61, p<0,01) and the impulsivity scale (r=-0,42, p<0,05).

This allows us to conclude that the ability to accurately reflect social events and situations is such characteristic of teachers who are identified by emotional instability, vulnerability and the need for social encouragement. They are characterized by a high level of search activity, and the leading motivational orientation is the motivation for achievement, which is less focused on motor mobility and speech production, and more on the implementation of specific goals. Such specialists confidently and quickly make some important decisions (including complex and non-standard ones). A high level of social intelligence is associat-

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ed with the actualization of individuality, a well-considered, rational personal position, analytical thinking, etc. As for these teachers, the analytical structure of thinking, the tendency to reflection prevails over feelings. They are self-confident, have positive self-esteem. A higher level of social intelligence, the more actualized it is according to the teachers, such qualities as a tendency to demonstrativeness, flexibility, high self-control, a high level of interpersonal contacts, the desire to influence other people, egocentrism, independence. Teachers of this type are easily involved into solving of various non-standard situations, they like to compete, they attach a great importance to gain success and productive achievements.

Thus, social intelligence of teachers has significant positive correlations with many characterological qualities. These are self-confidence, optimism, orientation towards achievement motivation, high control of emotional manifestations, extroversion, individualism, and the desire to influence partners of communication.

Correlation analysis also allowed us to identify the connections between individual psychological characteristics of teachers' personalities and certain indicators of social intelligence. Thus, the subtest "Behavioral consequences" has positive correlations with the MMPI scales, such as: with the emotional lability scale ($r=0,59$, $p<0,01$) and the pessimism scale ($r=0,41$, $p<0,05$). The subtest "Nonverbal behavior" positively correlates with the rigidity scale ($r=0,58$, $p<0,01$) and negatively – with the Femininity – Masculinity Scale ($r=-0,40$, $p<0,05$). The subtest "Speech expression" also has two positive correlations – with the individuality scale ($r=0,41$, $p<0,05$) and the overcontrol scale ($r=0,61$, $p<0,01$). The subtest "Interpersonal relationships" is positively correlated with the overcontrol scale ($r=0,58$, $p<0,01$) and the impulsivity scale ($r=0,42$, $p<0,05$). In general, the results obtained indicate that the most significant for understanding social interaction and implementing optimal interpersonal communication strategies are such personal qualities as emotional lability, individuality and femininity.

So, the more teachers understand the consequences of their behavior, the more their desire to comply with normative criteria is manifested, the more conscientiously they control the manifestations of their aggressiveness; also, teachers with high level of social intelligence have been diagnosed with a contradictory combination of restraint and irritability, instability of emotions and feelings. In the activities of these teachers, there is a conflicting combination of multidirectional tendencies: a high level of demands is combined with the need to satisfy the interests of a socially significant group, selfishness has a positive correlation with altruistic declarations, aggressiveness – with the desire to please others.

CONCLUSIONS

The more teachers have such individual qualities as analytical thinking, individuality, self-confidence and a tendency to analyze interpersonal communication situations, the better specialists understand the nonverbal behavior of partners of communication. Low levels of emotional instability, high results in self-confidence and active life positions are associated with understanding the speech expression of interpersonal interaction partners.

A high level of emotional stability and social extroversion are characteristics of teachers with a deep understanding of the patterns

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of the development of interpersonal relationships, which allows them to successfully predict the dynamics of these relationships.

So, the results of our research show, social intelligence is a dynamic process of interaction between people and the world, so the basic criterion for the development of social intelligence is mobility (flexibility, plasticity) of the teacher's behavior. We propose to determine the nature of social intelligence through the mechanisms of implementation of "productive thinking", the essence of which lies in the individual's ability to acquire new knowledge (the ability to study, to learning activity). Accordingly, the basis of social intelligence is a person's ability to independently discover new knowledge and apply it in non-standard problem situations.

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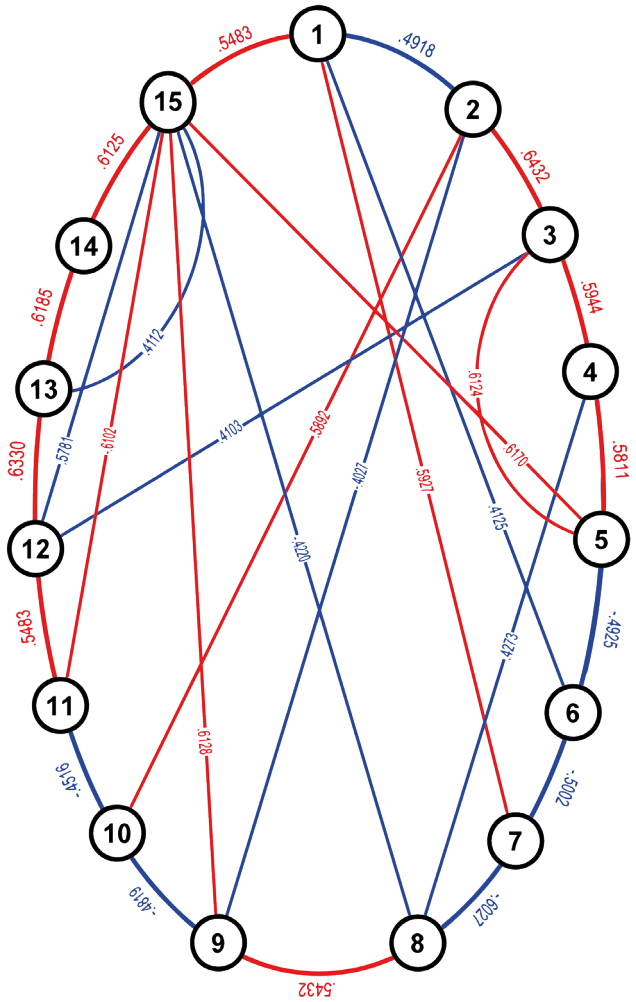
APPENDIX



LEGEND FOR FIGURE 1:

Red – Correlations are significant at the confidence level p<0,05

Blue – Correlations are significant at the confidence level p<0,01

1. consequences of the behavior
2. nonverbal behavior
3. speech expression
4. interpersonal relationships
5. manipulation scale
6. pessimism scale
7. emotional lability scale
8. impulsivity scale
9. femininity-masculinity scale
10. rigidity scale
11. anxiety scale
12. personality scale
13. optimism scale
14. social introversion scale
15. general indicator of social intelligence

Figure 1. Correlations between the scales of the MMPI test and the subtests of J. Guilford and M. O'Sulliven Test "Research of Social Intelligence" (adapted by E.S. Mikhailova)

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RETINAL AUTOPHAGY AND THE IMPACT OF PHARMACOLOGICAL BLOCKADE OF CELLULAR PROTEIN KINASES IN EXPERIMENTAL DIABETIC RETINOPATHY

Kateryna USENKO,
PhD in Medicine, Phthalmologist
Bogomolets National Medical University,
Kyiv, Ukraine
ORCID ID: 0000-0001-9907-6109

Viktoriia MIKHAJLOVSKA,
student,
Bogomolets National Medical University,
Kyiv, Ukraine
ORCID ID: 0009-0000-7218-4222

Serhii ZIABLITSEV,
Doctor of Medical Sciences, Professor,
Bogomolets National Medical University,
Kyiv, Ukraine
ORCID ID: 0000-0002-5309-3728
SCOPUS ID: 57210817217

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ABSTRACT

Background. Diabetic retinopathy (DR) remains the leading cause of irreversible vision loss among working-age patients, necessitating the search for new therapeutic targets in the early stages of the disease. Studying the effect of pharmacological blockade of cellular protein kinases on Beclin-1 expression in the retina will help uncover the molecular mechanisms of autophagy regulation and develop new treatment methods.

Aim: to determine the content of Beclin-1 protein in retinal tissue and the effect of the pharmacological cellular protein kinase blocker sorafenib on it in experimental DR.

Materials and methods. DR was modeled in male Wistar rats by single administration of streptozotocin (50 mg/kg; Sigma-Aldrich, Co, China). Rats were divided into 4 groups: control, with insulin administration (30 U; NovoNordisk A/S, Bagsvaerd, Denmark), protein kinase inhibitor sorafenib (Cipla, India) at a dose of 50 mg/kg, and with administration of insulin and sorafenib. Immunoblotting was performed using monoclonal antibodies against Beclin-1 (Invitrogen, USA).

Results. During the development of experimental DR, the level of Beclin-1 in the retina increased by 1.8-2.0 times ($p<0.05$) compared to intact animals, indicating activation of autophagy processes. Insulin administration normalized the Beclin-1 level to that of intact animals, while sorafenib monotherapy did not significantly affect its content. Combined use of insulin and sorafenib led to a significant decrease in Beclin-1 levels (1.5 times lower than the level of intact animals; $p<0.05$). The obtained results indicate potentiation of insulin effects with simultaneous blockade of cellular protein kinases, which may have therapeutic significance in DR.

Conclusion. Dysregulation of autophagy involving the Beclin-1 protein plays a key role in the pathogenesis of DR. Investigation of possibilities for pharmacological effects on cellular protein kinases to modulate Beclin-1 levels opens prospects for developing new approaches to retinal neuroprotection.

Key words

Diabetic retinopathy, autophagy, Beclin-1, sorafenib.

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BACKGROUND

Diabetic retinopathy (DR) is one of the most common and severe complications of diabetes mellitus (DM) and remains the leading cause of irreversible vision loss among working-age adults in developed countries (Simó & Hernández, 2014) . Epidemiological projections estimate that the number of patients with DR in the United States will reach 16 million by 2050, with approximately 3.4 million at risk of vision-threatening complications (Wong & Sabanayagam, 2020). Given the rapidly growing global prevalence of diabetes, the number of people affected is expected to rise to nearly 700 million by 2045, a substantial proportion of whom will be at risk of developing retinopathy (International Diabetes Federation, 2021).

Historically, DR has been considered a microvascular disease characterized by blood-retinal barrier disruption, thickening of the vascular basement membrane, leukocyte adhesion, acellular capillary formation, pericyte loss, and in advanced stages, pathological angiogenesis (Antonetti et al., 2012). According to the classical classification, DR is divided into non-proliferative and proliferative forms. The latter is marked by neovascularization, which may result in vitreous hemorrhage, tractional retinal detachment, and ultimately, complete vision loss (Solomon et al., 2017) .

However, over the past decade, the understanding of DR pathogenesis has significantly evolved. Accumulating experimental and clinical evidence indicates that DR is not solely a vascular disorder, but rather a complex neurovascular pathology of the retina (Simó, Stitt, & Gardner, 2018) Numerous studies have demonstrated that neurodegenerative changes occur early in the disease process, often preceding observable microvascular abnormalities. Functional impairment and apoptosis of retinal neurons, microglial activation, reactive gliosis, and disrupted neurovascular coupling are all evident before classical vascular lesions develop (Dehdashtian et al., 2018).

This paradigm shift is critical for the development of new preventive and therapeutic strategies. Current treatment approaches, primarily involving intravitreal injections of vascular endothelial growth factor (VEGF) inhibitors, target the late stages of DR when structural damage and vision loss are already substantial (Salminen & Kaarniranta, 2013). These therapies are limited by short duration of action, requiring frequent administration, which increases the risk of adverse events such as endophthalmitis, vitreous hemorrhage, retinal detachment, and cataract formation. Moreover, while VEGF blockade effectively suppresses pathological neovascularization, it may interfere with the physiological functions of VEGF, including its roles in neuroprotection and maintenance of normal vasculature (Salminen & Kaarniranta, 2013).

Accordingly, there is a growing interest in identifying new therapeutic targets and interventions aimed at the early stages of DR to prevent or slow disease progression. One promising direction involves the regulation of cellular autophagy–a tightly controlled process responsible for the degradation and recycling of damaged organelles, aggregated proteins, and other cellular components. Under physiological conditions, autophagy is essential for maintaining cellular homeostasis and survival during stress. However, in pathological conditions such as DM, dysregulated autophagy can contribute to cellular dysfunction and death (Dehdashtian et al., 2018).

Beclin-1 is a key regulator of autophagy. It forms part of the class III phosphoinositide 3-kinase (PI3KC3) complex, which initiates

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autophagosome formation. Beclin-1 interacts with a wide range of cellular proteins, including anti-apoptotic Bcl-2 family members, cell cycle regulators, protein kinases, and transcription factors–linking autophagy to various other cellular processes (Salminen & Kaarniranta, 2013)

Altered expression and activity of Beclin-1 have been implicated in a range of pathologies, including neurodegeneration, cancer, infection, and metabolic disorders. In the context of DR, the role of Beclin-1 and autophagy is not yet fully elucidated, although emerging evidence suggests their critical involvement in the disease's onset and progression.

Particular attention has been given to pharmacological modulation of autophagy via targeting intracellular signaling pathways, especially those involving protein kinases. These enzymes are central to signal transduction and regulate key cellular functions, including metabolism, proliferation, survival, and apoptosis. They are also instrumental in controlling autophagy by modulating Beclin-1 and other components of the autophagic machinery (Simó et al., 2018).

Among the diverse kinase pathways, RAF/MEK/ERK and PI3K/Akt/mTOR are particularly relevant in DR pathophysiology. These pathways influence retinal cell proliferation, survival, metabolism, inflammation, angiogenesis, and autophagy, and their dysregulation is associated with diabetic complications (Solomon, 2017).

Sorafenib, a multikinase inhibitor targeting RAF, VEGFR, and PDGFR, has demonstrated therapeutic potential in conditions involving overactivation of these signaling cascades. In DR, sorafenib may exert dual action: attenuating angiogenesis via VEGFR inhibition and modulating autophagy through intracellular signaling regulation (Antonetti et al., 2012).

Insulin, the cornerstone of DM treatment, exerts multiple effects beyond glycemic control by activating the insulin receptor and downstream signaling pathways. Notably, insulin is a potent activator of the PI3K/Akt/mTOR pathway, a known negative regulator of autophagy. Thus, insulin may also influence Beclin-1 expression and autophagic activity in retinal cells (Simó & Hernández, 2014).

The combined effects of insulin and sorafenib on autophagy in DR warrant particular attention, given their potential interaction at the level of intracellular signaling. However, studies addressing this question are virtually absent in the current literature, underscoring the novelty and importance of this research (International Diabetes Federation (IDF), 2021).

Aim: to determine the content of Beclin-1 protein in retinal tissue and evaluate the effect of the pharmacological cellular protein kinase inhibitor sorafenib in an experimental model of diabetic retinopathy.

MATERIALS AND METHODS

All procedures were conducted in accordance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986), Directive 86/609/EEC of the Council of Europe (1986), the Law of Ukraine No. 3447-IV "On the Protection of Animals from Cruel Treatment," the general ethical principles of animal experimentation approved by the First National Congress of Ukraine on Bioethics (2001), and the guidelines of the Bioethics and Scientific Ethics Committee at Bogomolets National Medical University.

The study involved 65 male Wistar rats aged 3 months and weighing 140–160 g. Experimental diabetes mellitus (DM) and diabetic retinopathy (DR) were induced in 60 rats via a

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single intraperitoneal injection of streptozotocin (STZ; 50 mg/kg; Sigma-Aldrich, Co., China) dissolved in freshly prepared cold 0.1 M citrate buffer (pH 4.5). Five animals served as the intact control group. Prior to STZ administration, the rats were fasted for 16 hours and provided with a 5% glucose solution for the subsequent 24 hours. Blood glucose levels were measured every three days using a glucometer (ACCU-Chek Instant, Roche Diagnostics, Germany) and test strips from tail vein blood samples collected after fasting. Rats with blood glucose levels ≥15 mmol/L three days post-STZ injection were considered diabetic and were monitored for 3 months.

After 7 days, animals with persistent hyperglycemia (n=60) were divided into 4 groups of 15 individuals by blind random method. In the 1st group (control), hyperglycemia was not treated. In the 2nd group, animals received intraperitoneal injections of short-acting insulin (Actrapid HM Penfill, Novo Nordisk A/S, Bagsvaerd, Denmark) at a dose of 30 U every other day. Animals in the 3rd group were administered per os daily a solution of the protein kinase inhibitor sorafenib (200 mg, Cipla, India) at a dose of 50 mg/kg in the form of sachets. Animals in the 4th group received insulin (according to the 2nd group protocol) as well as sorafenib solution (according to the 3rd group protocol).

Animals were removed from the experiment after 28 days, 2 and 3 months in quantities of 5 individuals in each group by a lethal injection of thiopental (75 mg/kg). Determination of Beclin-1 content in retinal tissue lysates was performed by immunoblotting. Tissue samples were kept in liquid nitrogen, crushed, and homogenized in 50 mmol Tris-HCl buffer (pH 7.4) with the addition of phosphatase and protease inhibitors (Pierce Protease and Phosphatase inhibitor, "ThermoScientific", USA, No. A32961). Electrophoresis was performed in 8% polyacrylamide gel with sodium dodecyl sulfate (SDS-PAGE) in a vertical gel electrophoresis chamber ("BioRad", USA). Proteins were transferred from the gel to a nitrocellulose membrane using electroblotting. Membranes were incubated with monoclonal antibodies against Beclin-1 (Invitrogen, USA). Antibodies to actin (β-actin (loading control), no. MA5-15739, mouse, 1:3,000, Invitrogen, USA) were used for its detection as a protein loading control.

After washing, membranes were incubated with species-specific horseradish peroxidase-conjugated secondary antibodies (goat anti-rabbit or anti-mouse IgG, Invitrogen, USA; cat. nos. G-21234 and 31430, 1:8000 dilution). Bands were visualized and analyzed densitometrically using TotalLab software (version TL120, Nonlinear Inc., USA). Protein levels were normalized to β-actin and expressed as arbitrary units relative to the control group.

Statistical analysis was conducted using Statistica 10.0 software (StatSoft Inc., USA). Data were expressed as mean ± standard error of the mean (SEM). Differences between groups were assessed using one-way ANOVA, with $p < 0.05$ considered statistically significant.

RESULTS

Immunoblotting analysis (Fig. 1) demonstrated a significant and sustained increase in Beclin-1 protein levels in the retinas of rats with experimental DR compared to intact animals. Specifically, Beclin-1 expression was elevated by 1.8-fold on day 28, by 2.0-fold after 2 months, and by 1.9-fold after 3 months ($p<0.05$ in all cases). This persistent elevation indicated continuous activation of early-stage autophagy in the diabetic retina, which, according to previous studies, is associated with reactive gliosis and apoptosis of Müller cells during this period (Usenko, 2025).

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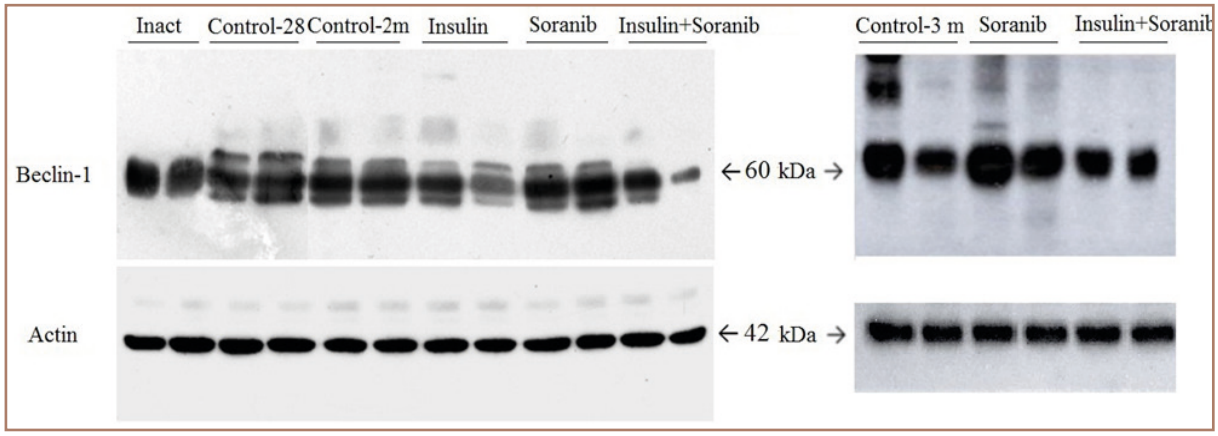
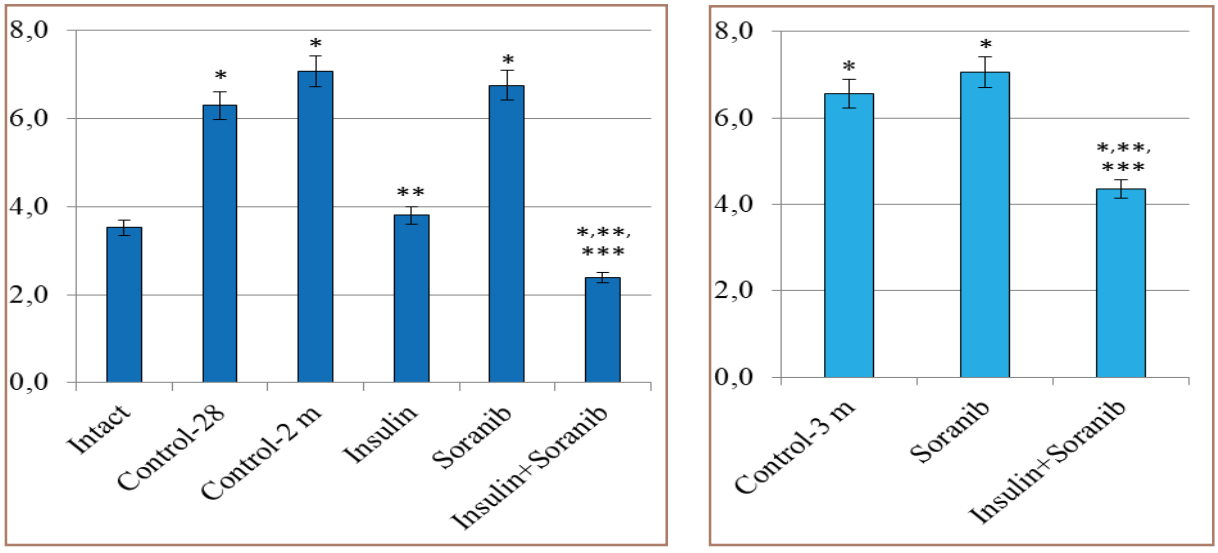


a b



c

Figure 1. Beclin-1 protein levels in retinal tissue of intact rats (Intact), and in the control group at 28 days (Control-28), 2 months (Control-2 m), and 3 months (Control-3 m); groups treated with insulin (Insulin), sorafenib (Sorafenib), and the combination (Insulin + Sorafenib).

a - representative blotograms of Beclin-1 protein and actin;
b - results of densitometric analysis of Beclin-1 protein blotograms (ratio to actin level);
* - p<0.05 compared to the level of intact rats;
** - p<0.05 compared to the control level (in a - with control after 2 months, in b - with control after 3 months);
*** - p<0.05 compared to the level with sorafenib administration.

Administration of insulin after 2 months of disease progression restored Beclin-1 expression to normal levels (Fig. 1a), suggesting an inhibitory effect of insulin on autophagic activity in DR. In contrast, monotherapy with sorafenib had no significant effect on diabetes-induced Beclin-1 upregulation. However, combined administration of insulin and

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sorafenib led to a further reduction in Beclin-1 levels, falling 1.5-fold below those observed in intact animals ($p<0.05$).

Comparable results were observed at the 3-month time point, where insulin + sorafenib co-treatment significantly reduced Beclin-1 levels compared to the control group (by 1.5-fold; $p<0.05$).

In summary, diabetic retinal tissue exhibited a consistent, nearly twofold increase in Beclin-1, indicating pronounced autophagy activation. Insulin treatment alone suppressed this response, while sorafenib alone had no effect. Their combined administration, however, led to a marked suppression of Beclin-1 expression.

DISCUSSION

Autophagy is an evolutionarily conserved membrane trafficking process responsible for the degradation of cytoplasmic proteins and dysfunctional organelles via lysosomal targeting. This intrinsic "self-cleaning" mechanism plays a fundamental role in maintaining intracellular homeostasis and facilitating cellular adaptation to stress conditions (Cao et al., 2014).

The Beclin-1 protein serves as a central regulator of autophagy initiation by promoting autophagosome formation through the activation of the class III phosphatidylinositol 3-kinase (PI3KC3) complex. Beclin-1 is considered a key driver of the early stages of the autophagic cascade. Experimental models have demonstrated that reduced expression of Beclin-1 is associated with impaired autophagic flux and the accumulation of damaged organelles, contributing to retinal cellular injury in DR (Di Rosa et al., 2016).

At the molecular level, autophagy is regulated by complex signaling pathways. Beclin-1 interacts with anti-apoptotic proteins of the Bcl-2 family, which inhibit autophagy by sequestering Beclin-1 and preventing autophagosome formation. Under stress conditions, disruption of the Beclin-1/Bcl-2 complex leads to the release of Beclin-1, thereby promoting autophagic vesicle formation.

In the retina, autophagy is activated at the early stages of DR, particularly in the dendrites of retinal ganglion cells (RGCs), where it serves a neuroprotective function. However, excessive or sustained autophagy activation may contribute to neuronal loss, particularly through autophagy-mediated cell death mechanisms (Kunchithapautham & Rohrer, 2007). Beclin-1 is essential for autophagosome formation within the ganglion cell layer, highlighting its role in retinal neurodegeneration and homeostasis.

One of the primary negative regulators of autophagy is the PI3K/Akt/mTOR signaling axis. The mammalian target of rapamycin (mTOR), a 289 kDa serine/threonine kinase, governs cell growth, metabolism, proliferation, and autophagy in response to a wide range of extracellular stimuli, including growth factors (IGF-I, VEGF), hormones (e.g., insulin), nutrients, and cytokines (Zoncu et al., 2011). Activation of mTORC1 inhibits autophagy by suppressing the activity of the Beclin-1-containing initiation complex (Di Rosa et al., 2016). Hence, chronic activation of mTOR in the diabetic retina may suppress autophagy, disrupt cellular equilibrium, and exacerbate DR progression.

In DR, hyperactivation of the mTORC1 complex is considered a pivotal pathophysiological event, leading not only to autophagy suppression but also to dysregulated lipogenesis and metabolic dysfunction in retinal cells (Laplante & Sabatini, 2013; Blommaart et al., 1995). Inhibition of autophagy via mTORC1 occurs through the phosphorylation and inactivation of autophagy-initiating proteins, in-

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cluding Beclin-1. In retinal cells, this leads to the accumulation of damaged organelles and proteins, increased oxidative stress, inflammation, and apoptosis (Di Rosa et al., 2016).

A reduction in Beclin-1 expression or functional activity observed in DR may serve as a molecular marker of impaired autophagy and diminished adaptive capacity. These findings highlight the therapeutic potential of targeting autophagy via modulation of protein kinase signaling. Pharmacological inhibition of kinases such as mTOR or MAPKs may help restore autophagic activity by reactivating Beclin-1-dependent pathways, thus promoting retinal cell survival and maintaining structural integrity in DR.

Changes in Beclin-1 Levels in Retinal Tissue in Experimental Diabetic Retinopathy and Their Pharmacological Modulation

Significant alterations in autophagic activity occur in retinal cells under conditions of diabetic retinopathy (DR), directly associated with dysregulation of Beclin-1 expression and its functional activity. Müller glial cells, which represent the principal glial elements of the retina and provide trophic and metabolic support to neurons and blood vessels, exhibit complex dynamics of autophagy under hyperglycemic conditions (Shen et al., 2012).

At the early stages of DR, increased levels of Beclin-1 and the autophagy marker LC3-II have been observed in Müller cells; however, due to lysosomal dysfunction, the degradation of autophagic cargo remains incomplete. This leads to the accumulation of p62, the release of VEGF, and the activation of apoptotic cascades (Lopes de Faria et al., 2016; Adornetto et al., 2021).

Experimental studies in rat Müller glial cell cultures have shown that chronic hyperglycemia progressively decreases the expression of Beclin-1 and LC3-II, while simultaneously increasing p62 accumulation. These findings reflect a deterioration of autophagic flux during the prolonged course of the disease. Pharmacological activation of autophagy with rapamycin—an mTOR inhibitor—promotes an increase in Beclin-1 levels, a decrease in p62, and reduced cell death, thereby supporting the therapeutic potential of autophagy modulation in DR (Adornetto et al., 2021).

Our experimental results revealed a significant and sustained elevation of Beclin-1 levels in retinal tissue under conditions of experimental DR. A progressive increase in the concentration of this protein was observed throughout the entire study period: by day 28, Beclin-1 levels had increased 1.8-fold; by 2 months, 2.0-fold; and by 3 months, they remained elevated at 1.9-fold compared to the control group ($p < 0.05$ in all cases). This dynamic reflects persistent activation of autophagic processes in response to hyperglycemia and oxidative stress, which may be considered a compensatory mechanism aimed at eliminating damaged cellular components (Lopes de Faria et al., 2016). At the molecular level, the regulation of Beclin-1 is largely dependent on its interaction with anti-apoptotic proteins of the Bcl-2 family. Under physiological conditions, Beclin-1 forms a complex with Bcl-2, preventing the initiation of autophagy. In response to cellular stress or external stimuli—such as phosphorylation activity by protein kinases including JNK1, DAPK, and ERK—either Bcl-2 or Beclin-1 becomes phosphorylated, resulting in the dissociation of the complex and activation of autophagy (Pattingre et al., 2005).

Transcription factors also play a crucial role in regulating Beclin-1 expression, particularly NF-κB and E2F. The p65 subunit of the classical NF-κB pathway binds to the Beclin-1 promoter, potentially enhancing its transcription. However, depending on the cellular context, NF-κB may act as either an activator or inhibitor of autophagy. In parallel, E2F direct-

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ly binds to the promoters of various autophagy-related genes, including Beclin-1, stimulating their expression.

Immunohistochemical studies have shown that the spatial distribution of Beclin-1 across retinal layers is altered in DR (Lopes de Faria et al., 2016). Normally, Beclin-1 is predominantly localized to the ganglion cell layer, inner nuclear layer, and photoreceptor segments (Chai et al., 2016). In DR, immunoreactivity for Beclin-1 is reduced in the ganglion and inner plexiform layers, correlating with neuronal injury in these regions (Xu & Chen, 2016).

Pharmacological blockade of cellular protein kinases, including JNK and ERK, can modulate Beclin-1 phosphorylation status and its interaction with Bcl-2, thereby influencing autophagic activity (Pattingre et al., 2005). Notably, inhibition of JNK1 prevents Bcl-2 phosphorylation, stabilizing the Bcl-2/Beclin-1 complex and reducing the pool of free Beclin-1 (Kim & Guan, 2015). This strategy may have therapeutic value in conditions of excessive autophagy associated with neuronal death. Conversely, in states of autophagy insufficiency, characterized by the accumulation of dysfunctional organelles and protein aggregates, activation of Beclin-1 via mTOR inhibition could restore cellular homeostasis.

Thus, pharmacological modulation of Beclin-1 expression and activity via targeted regulation of protein kinase pathways holds promise as a therapeutic strategy in DR, aimed at restoring autophagic balance and preserving retinal structural and functional integrity.

Caspases—cysteine-aspartyl proteases responsible for executing apoptosis—have been shown to cleave Beclin-1, thereby abolishing its pro-autophagic function (Shi, 2002; Wirawan et al., 2010). Caspases-3, -7, and -8 mediate specific proteolytic cleavage of Beclin-1, generating fragments incapable of initiating autophagy. The C-terminal cleavage products localize to mitochondria and enhance cellular susceptibility to apoptosis, establishing a positive feedback loop for cell death progression. Bax, a pro-apoptotic protein, also contributes to autophagy inhibition by promoting caspase-dependent Beclin-1 cleavage at residue D149 (Wang et al., 2006). Interestingly, expression of a cleavage-resistant mutant of Beclin-1 or co-expression with Bcl-XL may mitigate this effect (Pattingre et al., 2005). In certain models, including HeLa cells, TRAIL (TNF-related apoptosis-inducing ligand) has been shown to induce caspase-mediated Beclin-1 cleavage (Thorburn et al., 2014).

However, according to recent data, active caspase-8, an effector molecule in death receptor signaling pathways, can itself be degraded via autophagy, indicating a bidirectional relationship between these processes (Hou et al., 2010). Autophagy and apoptosis share multiple signaling components, and the final cellular fate often depends on the balance between these opposing programs. Notably, while proteolytic cleavage of Beclin-1 and Atg5 during apoptosis leads to autophagy inhibition, caspase-3-mediated cleavage of Atg4D, on the contrary, generates a fragment with enhanced autophagic activity (Betin & Lane, 2009). These findings highlight the complex and dynamic interplay between mechanisms of cellular adaptation and cell death.

The Effect of Insulin on Beclin-1 Levels and Autophagy in DR

Experimental data revealed that administration of insulin two months after the onset of DR led to a significant decrease in Beclin-1 levels to baseline values ($p < 0.05$), indicating an inhibitory effect of insulin on autophagic activity in the retina. The molecular mechanisms and physiological implications of this phenomenon warrant further discussion.

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Insulin is a potent regulator of metabolic processes, including autophagy. The Beclin-1 protein, encoded by the Becn1 gene, is known to facilitate adiponectin secretion through its interaction with the exocyst complex. While Beclin-1 is associated with improved insulin sensitivity, insulin can paradoxically suppress Beclin-1 expression by activating the PI3K/Akt/mTOR pathway—one of the key negative regulators of autophagy (Kuramoto et al., 2021). Therefore, insulin likely attenuates excessive autophagic activity in DR by downregulating Beclin-1 through PI3K/Akt/mTOR-dependent mechanisms, suggesting a compensatory role in restoring disrupted retinal homeostasis.

The Dual Effect of Insulin-Induced Autophagy Inhibition in the DR

One potential benefit of insulin therapy is the suppression of pathological autophagy overactivation. In DR, sustained hyperactivation of autophagy may result in the depletion of cellular resources and impaired function of photoreceptors and other retinal cells (Fu et al., 2016). Insulin-mediated normalization of Beclin-1 expression could mitigate this pathological overload and support cell survival.

Support for Retinal Neuron Survival

Excessive autophagy can progress to autophagy-dependent cell death. Studies have demonstrated that fine-tuned modulation of autophagy protects retinal neurons from degeneration (Rodriguez-Muela et al., 2012). Accordingly, insulin-induced suppression of Beclin-1 expression may help prevent overactivation of autophagy and protect retinal neurons from apoptosis.

Potential Adverse Effects of Insulin-Induced Autophagy Inhibition

However, a possible drawback of insulin therapy is the restriction of autophagy-dependent clearance of damaged organelles and protein aggregates. Autophagy serves as a protective mechanism during light-induced retinal degeneration, and its inhibition may compromise this defense, leading to accumulation of toxic components—especially under conditions of oxidative stress in DR (Chen et al., 2013).

Disruption of Cellular Homeostasis

Research shows that calpain-mediated cleavage of Beclin-1 following ischemic injury in the retina impairs autophagic regulation and increases cell death (Russo et al., 2011). These findings underscore the critical importance of maintaining optimal Beclin-1 levels for preserving retinal structure and function under diabetic conditions.

Impact on Retinal Cellular Homeostasis

The retina is a highly metabolically active tissue with significant energy demands. Disruption in autophagy homeostasis can have critical consequences for retinal function. In the context of diabetic retinopathy (DR), hyperglycemia leads to oxidative stress and inflammation, resulting in damage to cellular structures. Autophagy is a key protective mechanism that facilitates the clearance of such damaged components (Piano et al., 2016).

Insulin, by reducing Beclin-1 levels, may help restore autophagy to physiological levels and protect retinal cells from excessive self-digestion. However, this modulation may also limit the ability of cells to eliminate dysfunctional organelles and protein aggregates, particularly under chronic oxidative stress characteristic of DR.

Effect of Sorafenib on Beclin-1 Levels in Experimental DR

Our experimental data demonstrated that sorafenib monotherapy did not significantly alter the diabetes-induced elevation of Beclin-1 levels in retinal tissue ($p > 0.05$). According to previous studies, sorafenib can activate autophagy without affecting total Beclin-1 ex-

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pression (Tai et al., 2013). The proposed mechanism involves dissociation of the Beclin-1 complex from the anti-apoptotic protein Mcl-1 due to inhibition of the STAT3 signaling pathway. Under physiological conditions, Mcl-1 binds and sequesters Beclin-1, preventing its participation in autophagosome initiation. By inhibiting STAT3, sorafenib reduces Mcl-1 expression, which facilitates the release and activation of Beclin-1, even without increasing its total protein levels (Tai et al., 2013).

This mechanism may explain our finding that sorafenib treatment did not lead to changes in Beclin-1 content in experimental DR. It is likely that sorafenib enhanced Beclin-1 activity indirectly by modulating its interaction with Mcl-1, rather than by altering its expression level.

Effect of Sorafenib on the mTOR Signaling Pathway

An additional important mechanism by which sorafenib induces autophagy is via inhibition of the mTOR signaling pathway. Shimizu et al. (2012) demonstrated that sorafenib promotes autophagy in hepatocellular carcinoma cells by suppressing mTOR signaling (Shimizu et al., 2012). Notably, this induction was not associated with significant changes in Beclin-1 expression, but rather with increased LC3-I to LC3-II conversion—a hallmark of autophagosome membrane formation.

Since mTOR is a well-established negative regulator of autophagy, its inhibition triggers autophagic flux independent of Beclin-1 protein levels. Normally, mTOR phosphorylates and inhibits the ULK1/Atg13/FIP200 complex, thereby blocking autophagy initiation. Sorafenib-mediated inhibition of mTOR results in dephosphorylation and activation of ULK1, which initiates autophagosome biogenesis (Zhu et al., 2011).

Anti-Angiogenic Effects of Sorafenib in DR

Pathological angiogenesis is a central feature of DR progression, particularly in the proliferative stage. Sorafenib, as a multikinase inhibitor that targets vascular endothelial growth factor receptors (VEGFRs), has demonstrated efficacy in suppressing retinal neovascularization and vascular permeability independently of its autophagy-modulating effects.

In a murine model of oxygen-induced retinopathy, sorafenib significantly reduced VEGF expression and inhibited neovascularization (Yang et al., 2018). This was accompanied by improvement in blood-retinal barrier integrity and a reduction in retinal edema. Importantly, these anti-angiogenic effects occurred without concomitant changes in Beclin-1 or other autophagy markers, suggesting that the vascular and autophagic mechanisms of sorafenib are distinct and independently regulated.

Anti-inflammatory and Antioxidant Effects

Chronic inflammation and oxidative stress are key pathogenic factors in the development of DR (Li et al., 2009). Sorafenib has demonstrated anti-inflammatory and antioxidant properties through the inhibition of various kinases and signaling pathways. For instance, it reduces the levels of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and chemokines (MCP-1) in the retina of diabetic rats by suppressing NF-κB activation (Li et al., 2009). This effect is accompanied by reduced activation of microglia and macrophages, key mediators of retinal inflammation in diabetes.

Our experimental findings showed that sorafenib does not alter Beclin-1 levels in the retina in experimental DR. However, literature analysis indicates that sorafenib may activate autophagy through mechanisms independent of Beclin-1 expression. These include: disruption of the Beclin-1/Mcl-1 complex via STAT3 inhibi-

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tion, allowing Beclin-1 to participate in autophagy initiation; inhibition of the mTOR signaling pathway, leading to ULK1 activation and autophagy induction; and modulation of other autophagy-related proteins such as LC3, p62, ATG5, and ATG12 (Tai et al., 2013; Shimizu et al., 2012).

Furthermore, sorafenib may exert therapeutic effects in DR through autophagy-independent mechanisms, particularly its anti-angiogenic activity via inhibition of VEGFR and PDGFR, as well as its anti-inflammatory and antioxidant effects (Adornetto et al., 2021).

Taken together, these findings highlight the pleiotropic effects of sorafenib, which may offer therapeutic benefits in the integrated management of DR. The lack of effect on Beclin-1 levels does not rule out modulation of autophagy via other mechanisms, nor does it diminish the therapeutic potential of sorafenib through alternative signaling pathways.

Synergistic Effect of Insulin and Sorafenib on Beclin-1 Levels in Experimental DR

Our results revealed a marked increase in Beclin-1 levels in the retina during experimental DR, indicating activation of autophagic processes. Insulin monotherapy restored Beclin-1 to physiological levels, while the combined administration of insulin and sorafenib led to a further reduction in Beclin-1 expression—falling even below that of intact animals (by 1.5-fold; $p<0.05$). Notably, sorafenib alone did not produce a similar effect.

Comparable results were observed after three months of follow-up: combined treatment with insulin and sorafenib significantly reduced Beclin-1 levels in comparison to the control group (by 1.5-fold; $p<0.05$).

Molecular Mechanisms of the Synergistic Effect

The mechanisms underlying the synergistic effect of insulin and sorafenib are complex and require thorough molecular elucidation. Autophagy is regulated by several intracellular signaling pathways, with the PI3K/Akt/mTOR axis playing a central role. Insulin activates this pathway, resulting in suppression of autophagy (Fu et al., 2016). Specifically, activated mTOR phosphorylates and inactivates the ULK1/2–ATG13–FIP200 complex, which is essential for autophagy initiation. It also phosphorylates AMBRA1, leading to dissociation of the Beclin-1–AMBRA1–VPS34 complex and subsequent inhibition of autophagosome formation.

Sorafenib, a multi-target protein kinase inhibitor, exerts more complex and context-dependent effects. Previous studies have demonstrated that sorafenib can exhibit a biphasic influence on autophagy, depending on tissue type, dosage, and exposure duration (Zhang et al., 2019). It inhibits RAF kinase and consequently downregulates the RAF/MEK/ERK pathway, potentially suppressing Beclin-1 expression. Concurrently, sorafenib may induce autophagy under certain conditions through inhibition of the mTOR pathway, either by activating AMPK or suppressing PI3K/Akt signaling.

The seemingly paradoxical finding in our study, that sorafenib, in combination with insulin, enhances autophagy inhibition, can be explained by several mechanisms.

Firstly, interaction at the level of the PI3K/Akt/mTOR cascade: although sorafenib has the capacity to inhibit mTOR, the concurrent presence of insulin may redirect its signaling influence toward alternative pathways such as ERK. This may result in additional suppression of Beclin-1 expression via ERK-dependent transcriptional regulators (Chen et al., 2018).

Secondly, effects on Beclin-1 interactions with anti-apoptotic Bcl-2 family proteins: insulin-induced Akt activation promotes Bcl-2

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phosphorylation, which enhances its binding affinity to Beclin-1, thereby further suppressing autophagy. Meanwhile, sorafenib may downregulate Mcl-1, another Bcl-2 family member, thereby indirectly influencing Beclin-1 availability. In the context of insulin-activated Akt signaling, this could potentiate the sequestration of Beclin-1 by Bcl-2 proteins, leading to enhanced autophagy inhibition.

Clinical Significance of the Synergistic Effect

The observed reduction in Beclin-1 levels below those seen in intact controls following combined insulin and sorafenib treatment is of particular interest for its clinical implications.

Excessive autophagy activation in DR has been linked to pericyte loss, a key event in the breakdown of the blood-retinal barrier (Fu et al., 2016). Hyperglycemic conditions upregulate Beclin-1 expression and autophagic markers, resulting in autophagic cell death of pericytes. Inhibition of autophagy in this context improves cell survival and stabilizes vascular permeability.

Overactivated autophagy also exacerbates inflammatory responses and oxidative stress in the diabetic retina (Zhang et al., 2019). Moderate suppression of this process leads to decreased production of pro-inflammatory cytokines and reactive oxygen species (ROS), and attenuates activation of the NLRP3 inflammasome – one of the primary components of the inflammatory cascade in DR.

Furthermore, Beclin-1 contains a BH3 domain, enabling it to interact with Bcl-2 family proteins. Reduced Beclin-1 levels may increase the availability of anti-apoptotic proteins such as Bcl-2 and Bcl-xL, which can inhibit pro-apoptotic factors like Bax and Bak, thus contributing to neuronal survival in the retina.

However, profound suppression of Beclin-1 and autophagic activity could have adverse consequences. Basal autophagy is critical for maintaining mitochondrial quality control and homeostasis in retinal cells (Kaarniranta et al., 2013). Complete inhibition of this pathway can result in the accumulation of dysfunctional mitochondria, excessive ROS production, and activation of mitochondrial apoptosis.

Moreover, autophagy is essential for the clearance of protein aggregates and adaptation to cellular stressors such as hypoxia and oxidative stress. In the chronic progression of DR, impaired autophagic flux may aggravate tissue damage and worsen visual prognosis.

CONCLUSION:

1. In experimental diabetic retinopathy, the content of Beclin-1 protein in retinal tissue was significantly elevated throughout 3 months (by 1.8-2.0 times compared to the intact group; $p<0.05$), indicating persistent activation of autophagic processes in response to hyperglycemia. Insulin monotherapy contributed to the normalization of Beclin-1 levels by the 2nd month of observation, indicating its inhibitory effect on autophagy under DR conditions.
2. The use of sorafenib as monotherapy did not affect Beclin-1 levels; however, its combination with insulin reduced the protein content below the indices of the intact group (by 1.5 times; $p<0.05$), suggesting a potential synergistic effect in inhibiting autophagy.
3. The obtained data demonstrate the promising nature of combined use of insulin with cellular protein kinase inhibitors (specifically, sorafenib) for modulation of autophagy and prevention of structural and functional retinal damage in diabetic retinopathy.

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