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Content

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Letter from the Editor-in-Chief

Dear Colleagues,

For 4 years, Journal of Biomedical and Medical Sciences has been a vehicle for the delivery of timely and thoughtful information and opinion on the many issues that involve the fundament and apply multidiscipli-nary medical and biomedical area. Firstly, I would like to join all the members of board in thanking the authors, readers for their service and research. I also would like to thank those who served on the journal staff and its editorial board, and particularly the reviewers for providing the support and feedback necessary to find, develop and publish high-quality material. Finally, I really want to thank our readers. Journal of Biomedical and Medical Sciences has evolved to become a frequently-cited journal. Starting with this volume, we've made some significant changes. For this reason, we've decided to meet the standards set out by the "Uniform Requirements for Manuscripts Submitted to Biomedical Jour-nals" developed by the International Committee of Medical Journal Editors (http://www.icmje.org), and have refined our Author Guidelines accordingly. For more information on submitting a paper, please visit the journal's guide for authors https://bmms.ge/index.php/bmms/about/submissions. For readers of our journal, these changes should have a positive impact. We hope you enjoy and learn from our journal, as in the past, and find it a source of up-to-date and high-quality information in the medical and biomedical field. For authors, both current and future, we expect that these changes will improve our citation rankings, and we hope that your publication in this journal will benefit you as well. For us, it is important what our authors have to communicate. Papers are welcomed in multiple areas, and those in which the novelty of the study has been accurately portrayed. The Journal will traditionally publish original articles (clinical trials, cohort studies, case-control studies, cross-sectional surveys, and diagnostic test assessments) as well as case reports (unique,

highly relevant and educationally valuable cases), case series, clinical techniques and methodologies (a short report of unique or original methods for surgical techniques, medical management, or new devices or technologies), editorials (including editorial guests – special contributions) and letters to the editors. Finally, the journal will host invited reviews and commissioned commentaries from opinion leaders. Now that we've begun to change, we will also hope to continue to evolve and have good idea on how to proceed. In guiding the editorial team in the choices, we have to make, we ask our readers to help us to explore new ways to make the journal useful: please share your ideas and thoughts with us. We can be reached at editor-in-chief@eu.edu.ge. We look forward to hearing from you soon. I strongly encourage you to submit your work for consideration for publication in Journal of Biomedical and Medical Sciences. An enthusiastic submission requires an energetic and dedicated editorial board to ensure that your article will be reviewed and published rapidly. To reach this goal, we have tested many solutions and have adopted a simple Online Submission System for Authors and Reviewers. Starting immediately, all manuscripts and editorial communications should be sent via our Online Submission System by log-ging on to https://bmms.ge/index.php/bmms. The quality and pace of publication along with the anti-plagiarism campaign is our credo. We would not be able to provide a scientific product of such a format as the Journal of Biomedical and Medical Sciences if not for the constant moral and financial support from Lasha Kandelakashvili and Tamar Zarinava. On my behalf, on behalf of the co-editors and editors as well as on behalf of the authors of publications, and readers, we thank them. Best regards, yours truly,

Sincerely,

Prof. Maka Mantskava

Focus and Scope

We refer, peer-review and publish science articles about original study and clinical trial, theoretical reviews, preview and report of researcher project, preliminary data and the description of new and the newest hypothesis, essay in next directions.

- Epidemiology methods. Infection Diseases and Non-infection Diseases. Vaccinations
- Prevention of Epidemic. Prevention of Pandemic
- Multidisciplinary Approaches of Modern Science
- Polyprofile Medicine
- Biomedicine, Biorheology and Biotechnology
- Biochemistry and Biophysics in Fundamental and Applied Medicine. Micro – and Nanobiomechanics
- Innovative Methods. Bioinformatics. Biological Models. Mathematical Models
- Economic and Strategic Aspects of Biomedicine
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- The Role of Biomaterials in Biomedicine
- Theoretical, Clinical and Environmental Toxicology
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- Nutritionology. Food, Biologically Active Substances, Medicines and Health. Enzyme
- Balneology, Wellness and SPA. Physical Education
- Beauty Industry
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- Alternative medicine
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- Medical Linguistics
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  - ◊ Adaptation of Medical Literature
  - ◊ Translation Problems of Medical Literature
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- New Approaches and Challenges for the Medical Education System
- Authorization, Certification, Licensing Issues in Health Care Institutions, University
- History of medicine
- Philosophy and medicine
- Medical Tourism
- Medical Low
- All about COVID-19
- etc.

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Association of hepatitis C with liver cirrhosis and hepatocellular carcinoma – a case study

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Abstract

Hepatitis C virus infection (HCV) is endemic in many countries of the world including Georgia. Georgia has a high burden of HCV infection with an estimated 5.4% of adult population (1,50,000) people have identified with HCV. According to NCDC (National Centre for Disease Control and Public Health from May 2015 national HCV programme have been launched, supported by the American company "Gilead" and the government of Georgia. Our main goal is to investigate and manage the hepatocellular carcinoma. According to the study done from the patient at Infectious Disease AIIDS and clinical immunology scientific research centre it has been found that in 57-year-old male patient who was chronically infected with HCV, cirrhosis, the virus has been directly associated with the development of hepatocellular carcinoma. He was diagnosed as chronic hepatitis-c and liver cirrhosis (genotype 3a). Treatment with pegylated interferon and DAA (direct acting antivirals) for 6 months was continued. Treatment finished without side effects but after 6 months HCV RNA was detectable or patient relapsed. In 2015, the patient was switched in elimination

programme and antiviral treatment combined with interferon for 12 weeks. Sustained viral response developed 6 months after termination of therapy. The alpha-fetoprotein is important tumor marker and was elevated around 583 μ/l. Ultrasound didn't reveal any lesion but after MRI scan 3rd grade hepatocellular carcinoma was confirmed. Following 2015 every month patient has been assessed for liver function tests, total bilirubin, complete blood count, alpha-fetoprotein and ultrasound investigation and as a result liver enzyme found to be elevated. It's crucial for every patient (end stage of liver disease) to undergo ultrasound investigations, liver function test for follow up.

KEYWORDS: DAA (direct acting antiviral); HCV RNA; INF (Interferon); Hepatitis C; Hepatocellular carcinoma

Introduction

A principal element named chronic hepatitis C virus (HCV) infection is representative for the occurrence of liver cirrhosis and hepatocellular carcinoma. The majority of cases have identified with chronic infection after transmission of virus. Due to lack of symptoms and progression of disease towards chronic stage large number of cases have been investigated in later stage of disease. In the beginning stage of screening in chronic Hepatitis C-infection HCV antibodies is considered satisfactory and for differentiating continuing infection or past infection sensitive assay is important in positive HCV antibodies [1]. An estimated yearly incidence of 2,59,000 of Hepatocellular carcinoma has been estimated worldwide. Carcinoma has not been detected from hepatitis-C whereas hepatitis-B without cirrhosis was linked to hepatocellular carcinoma with higher frequency according to previous studies. Exact mechanism behind causing carcinoma is unknown since reverse transcriptase activity is seen to be associated with hepatitis-B rather than HCV virus. Some studies disclosed the information regarding prevention by directly suppressing the IFN of cell division and leading to the activation of proto-oncogenes and inhibition of tumor suppressor gene [2]. Research performed in many centers of French have proved that there is higher association of hepatocellular carcinoma in HCV patients with cirrhosis who had received DAA (direct acting antivirals) rather than patients with sustained viral response who acquired this after interferon therapy and the most cases of carcinoma had certain characteristics like older age,

severely impaired function of liver and increase blood pressure in the portal veins [3]. Decision about prognosis and management of hepatitis is based on degree of fibrosis or liver cirrhosis. For identification of liver cirrhosis or related complications transient elastography or fibro scan can be performed which is non-invasive and most appropriate according to studies since liver biopsy is invasive and painful rather worsen the condition of severe patients [4]. Japanese hospitals and clinics have treated near about 8000 patients of hepatitis-C with interferon and investigated them for 1 year between July and august after withdrawing interferon treatment. 33% of patients had confirmed with sustained viral response after 6 months of abolition of treatment and 0.4 % had developed hepatocellular carcinoma [5]. If the patient fulfils the criteria of having tumor size of less than 2 cm then liver resection is possible in 90% of cases which is created by BCLS Staging System as it is the primary treatment option for hepatocellular carcinoma but still not the best choice or suitable for all the patients although other options like liver transplantation can also be chosen according to patient comfort [6]. Tumor marker alpha-fetoprotein in detection of hepatocellular carcinoma or with liver cirrhosis ensures maximum sensitivity and specificity but still using alpha-fetoprotein forlorn may not give accurate results [7]. Research performed during 4 consecutive years have revealed measurement of liver stiffness together with transient elastography was successful to investigate recurrence after resection of hepatocellular carcinoma [8]. Study done in Japanese patients has revealed the development of hepatocellular carcinoma after termination of treatment with Peg IFN α-2b+ribavirin. Although cirrhosis is a self-reliant risk factor in the development of hepatocellular carcinoma, even after elimination of hepatitis requires further careful monitoring in HCV related cirrhosis whether it is compensated or decompensated [9]. Liver resection, radiofrequency ablation, arterial chemoembolization and liver transplantation are the best options if hepatocellular carcinoma is diagnosed at early stages but in later stages tyrosinase kinase inhibitors have showed a promising result since tumor was unresectable [10].

Methods

In this case study male patient (57 years old) various tests including echocardiography, Respiratory function test, ultrasound and MRI Scan, biopsy studies or histological; investigations have been performed. This article includes information from various databases such as PubMed, google scholar, science direct etc. it’s a case study review.

Results

After performing echocardiography, Respiratory function test, ultrasound and MRI Scan, biopsy study of this patient showed following results**:**

1. Alpha-fetoprotein was elevated to 583 μ/l.
2. On assessment of respiratory function ventilation disorders were not detected and post FVC (Functional vital capacity)-94%, FEV1(forced expiratory volume)-100%, FEV1/FVC-0.81.
3. On assessment of echocardiography light tricuspid valve defect, high pulmonary artery pressure PASP of 30 mmHg, IVC-1.4cm, collapsed more than 50%, longitudinal aorta-3.75cm, abdominal aorta-2.2cm (normal) was observed.
4. On ultrasound hepatocellular carcinoma was not suspected.
5. MRI of 57-year-old-patient revealed localized operable hepatocellular carcinoma in the 8th segment of size 3.5/2.6 cm.
6. Biopsy: – Histological investigations: –

   a) Microscopy: – Samples taken from 8th segment of examined liver reveal tumor tissue represented by atypical, polymorphic, hepatocytes which was pronounced, consisting of trabeculae and solid structures. In the part of cells, a sharp polymorphism of nuclei is expressed. Lymph angioinvasion and invasion of normal liver is expressed. There was no damage noticed on the edges of resection. No tumor tissue was detected in 4th and 6th segments of the liver.

   b) Macroscopy: – Material was placed in 3 containers:

1. Tissue measuring 4*3*2 cm was revealed in 8th segment of the liver which was white in color and dense in consistency.
2. One fragment measuring 0.4*0.1*0.1 cm was revealed 4th segment of the liver.
3. One fragment measuring 0.5*0.2*0.2 was found in 6th segment.
4. On the basis of histologic investigations 3rd grade hepatocellular carcinoma was identified with lymphangion-invasion and there was no spread to other structures or organs and tumor was localized in 8th segment of the liver.

Below given is the chart showing laboratory values of 57-year-old male patient according to test evaluated during December 2019. In this chart varied levels of liver enzymes (alanine transaminase-ALT, aspartate transaminase-AST, Gamma glutamyl transferase-GGT) are mentioned in IU/L (international units per liter) and total bilirubin levels which are given in μ mol/l. Initially increased levels of enzymes have been observed and then it got normalized at the end of December.

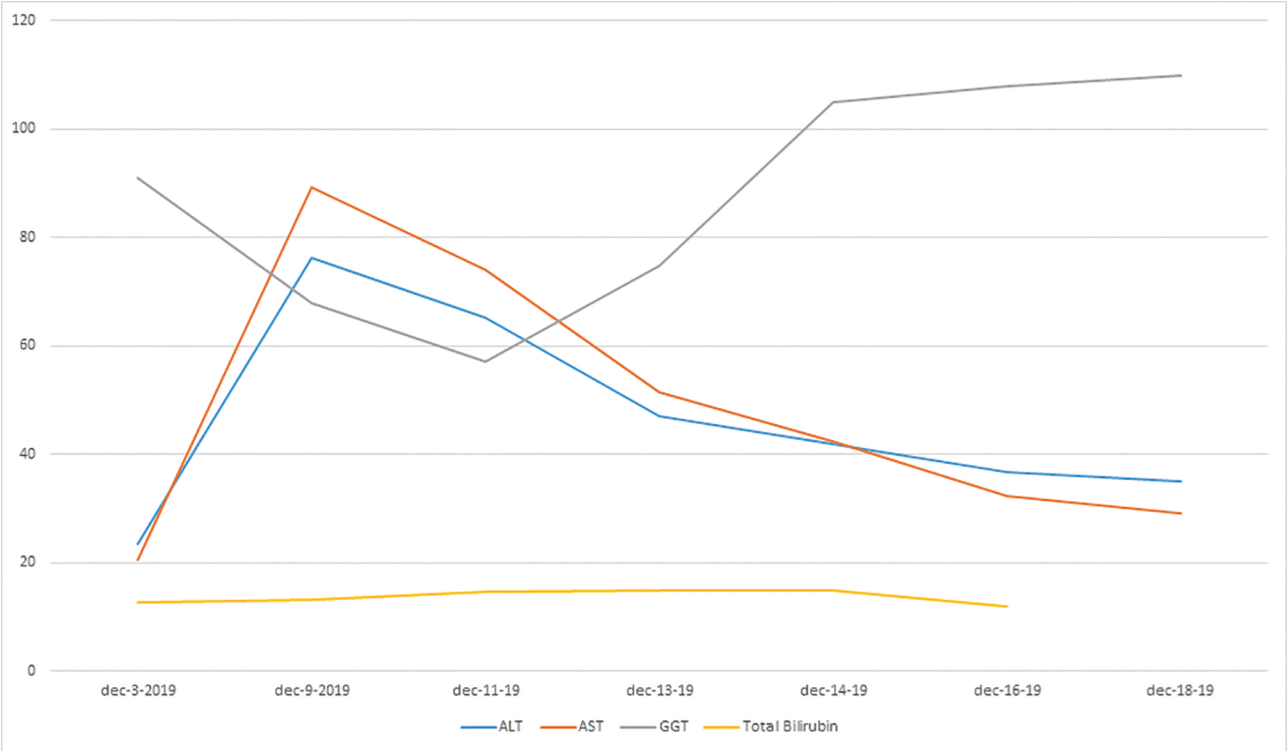

Fig.1. Clinical results (ALT, AST, GGT, total bilirubin) of male patient during December 2019.

Following 2015 every month patient have been assessed for liver function tests, ALT, AST, GGT, total bilirubin direct and indirect, complete blood count, alpha-fetoprotein and ultrasound investigation that's why this case is really interesting because more than 80% patient don't visit clinic for follow up and as a result suffers from complications later. According to study of this male patient lobectomy has been performed at GEORGIAN-ISRAEL CLINIC HELISCOR in Tbilisi, Georgia since other costly treatments like liver transplant was not suitable for this patient.

Discussion

According to the recent studies done from the patient at Infectious Disease AIIDS and clinical immunology scientific research center showed chronic infection with HCV and cirrhosis in 57-year-old male patient, the virus is directly linked to the development of hepatocellular carcinoma. This patient referred to this hospital 7 years ago in 2013 and he was diagnosed as chronic hepatitis-c and liver cir-

rhosis (genotype 3a). Treatment with pegylated interferon (pegasys-180mcg) once a week, ribavirin – 200 ng-daily dose of 1200 ng for 6 months and 24 weeks was continued. Treatment finished without any side effects but after 6 months (24 weeks) HCV RNA was detectable or patient relapsed. After two years in 2015 the patient was switched in elimination program and antiviral treatment combined with interferon (DAA-direct acting antiviral-sofosbuvir or sofosbuvir 400mg+ pegylated interferon alfa-2a 180 mcg+ ribavirin 200ng,6tablets during day for 12 months was started. Sustained viral response developed after continuing all these medications. Liver fibro scan or transient elastography had performed to investigate cirrhosis or other complications. laboratory data showed significantly increased levels of AFP (alpha-fetoprotein) of 475.80μ/l. Later abdominal ultrasound was done but could not reveal any lesion. Based on performed diagnostic tests MRI SCAN of abdomen with IV contrast was recommended. For evaluation of heart functions echocardiography was performed. For excluding any lung pathology chest X-ray was performed. Biopsy taken from 8th, 6th and 4rth segment and as a result 3rd grade hepatocellular carcinoma was identified.

Conclusion

1. Based on investigation from 57-year-old male and previous studies hepatocellular carcinoma is investigated due to hepatitis-c with cirrhosis in most cases however it is a rare incidence which arises due to chronic liver disease.
2. Patient admitted in 2013 and even after elimination of hepatitis-c hepatocellular carcinoma had detected after termination of treatment that's why it is necessary to check alpha-fetoprotein, liver enzymes (ALT, AST, GGT), total bilirubin, investigations like ultrasound every 6 months and liver function test for every patient who suffers from hepatitis-c virus or end stage liver disease to prevent morbidity and mortality because even after termination of treatment or elimination of disease later complications may arise such as hepatocellular carcinoma.

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Vasopressin improves the production of a conditioned two-way escape reflex

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Abstract

Vasopressin (Lvp) is neuropeptide produced largely in the hypothalamus. Lvp is released from paraventricular nucleus (PVN) and supraoptic nucleus (SON) magnocellular terminals located in the neurohypophysis [1]. Upon entering the systemic blood supply, they exert endocrine actions including uterine contraction and milk ejection. Furthermore, Lvp released from terminals of parvocellular neurons of the PVN influences adrenocorticotropic hormone synthesis and release from the adenohypophysis and, thus, modulates corticosteroid hormone levels and stress response [2,3,4]. The neurohypophyseal peptide Lvp play an important role in the regulation of such processes as learning and memory. The participation of these peptide in the processes of memory and learning have been confirmed by investigations in which neurohyphopiseal extract has been employed [5,6]. It is yet unclear exactly what role vasopressin has in the organization, development, and replication of long-term memory traces. We investigated the effect of modest dosages of vasopressin on the rate of conditional bilateral escape reflex elaboration in rats weighing 250-300 g for this purpose. The experiment consisted of two groups of animals: control and experimental. During 12 days, 15 minutes before testing, experimental animals were given 4 g/0.2 ml lysine 8-vasopressin (Gedeon-Rixter) intraperitoneally. The equal

quantity of saline was administered into the control animals. We employed the T Student criteria for statistical data analysis. It was shown that in experimental group the indices of correct responses, as a latent period of reaction of active avoidance, significantly lagged behind the control group. The level of conditional reflex on active defensive escape was checked during three days in two weeks, 1 month and 2 months after such termination of experiment in both control and experimental groups of animals. However, through the first and second month breaks, the level of fulfillment of conditional reflex reaction at the experimental animals statistically significantly (P <0,01) exceeded those of control group animals. Therefore, vasopressin promotes preservation of a trace of memory and had anti amnesic effect.

KEYWORDS: vasopressin; conditional reflex; memory; rat

Introduction

Learning and memory are essential requirements for every living organism in order to cope with environmental demands, which enable it to adapt to changes in the conditions of life. An aversive stimulus is used to develop an active avoidance reaction. Aversive stimuli are associated with the release of stress hormones and neuropeptides. Neuropeptides affect not only attention, motivation, concentration, and arousal or alertness, but also anxiety and fear. Thus, they are involved in learning and memory processes. Despite certain successes, achieved in researches, accumulated actual data frequently had inconsistent character and required further specialization. Till now it is not finally found out, what role vasopressin can play in organization, formation and reservation of memory at all a stage of its reproduction. Originally, the assumption about a possible role of hypophyseal hormones, (especially vasopressin) in organization of memory, was studied by Wied et al [7]. The aim of this study was to find out a lysine 8 – vasopressin role in process of consolidation, preservation and reproduction of long-term memory trace. Therefore, the influence of small doses of vasopressin in dynamics of conditional two-way escape reflex elaboration were studied.

Methods

The experiments were carried out in adult male laboratory albino rats (n=40), weighing 250-300 g. For study of conditional defense reflexes the model of bilateral

escape reaction was used. The experimental cage represented a box (dimensions – 30x50x30 cm) made of transparent organic glass. The box was divided into two equal compartments by a 10 cm height partition. The floor of the cage was made from metallic rods, by means of which a threshold electrical painful stimulation was rendered to the paws. The source of a conditional signal – 60 w electric bulbs – was placed in the center of the cage at a height of 60 cm, which illuminated the whole cage. If after presentation of a conditional signal the animal jumped in other compartment of the cage during 5 sec, the answer was considered correct and the animal fail of an electrical punishment, otherwise it was punished by an electrical current. Each experimental session was carried out 20 trails. During experiment the dynamics of elaboration and course of bilateral escape reaction were studied. The following indices were registered: duration of latent period of conditional signal; duration of latent period of conditional (bilateral escape reaction), and unconditional (escape) reaction. The general behavior of the animal was also observed.

For revelation of vasopressin influence on elaboration of conditional reflexes the experiments were carried out on two groups of animals. In experimental group (n=20) for 15-20 minutes prior to the beginning of experiments vasopressin (Lysine-vasopressin “Koch-Light, England) was administered intraperitoneally (4 mg/kg). In control group (n=20) for the similar time prior to the beginning of experiments same amount of saline was administered.

The degree of reproduction of the conditioned active-avoidance reflex was checked immediately, 2 weeks, 1 month, and 2 months after the end of the experiment in both the control and experimental groups of animals.

Results

It is shown that in the first day of experiment (20 couplings) the quantity of the correct answers in control group of animals reached 30%. In following days, this parameter grew and on the seventh experimental session (in limits of 140 couplings) critical level was reached. The indices of adequate reactions achieved 90%. This level was remained stable in further days also. After vasopressin administration the indices of correct responses of the animals did not exceed 5 %. In the subsequent days this parameter was gradually increased, but nevertheless much lagged behind from those at control group of the animals. The critical level by the experimental animals was achieved only for the 10-th day (200 couplings). At further stages of experiment quantity of correct reactions of experimental group did not give any difference (Fig.1).

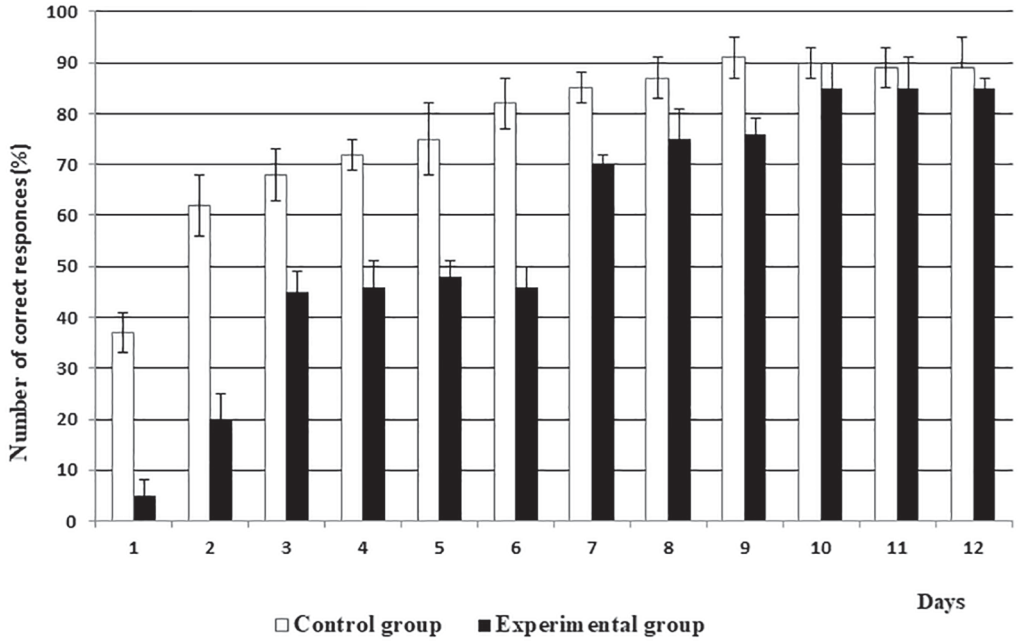

Fig.1. Effect of vasopressin on bilateral escape conditional reflex in rats.

During 12 days of elaboration of active defense reaction were revealed significant differences in the latent period of conditional reaction in control and experimental groups. In particular the latent period of conditional reaction changed in range of 1.9 – 2.4 sec and on the average made 2.1 sec. The minimal value of a similar parameter in experimental group of the animals has made 2.9 sec, and maximum – 3.6 sec. In general, during all period of elaboration of conditional reaction, latent period in experimental group of the animals statistically significant (P <0,05) exceeded those of control group of the animals. (Fig.2).

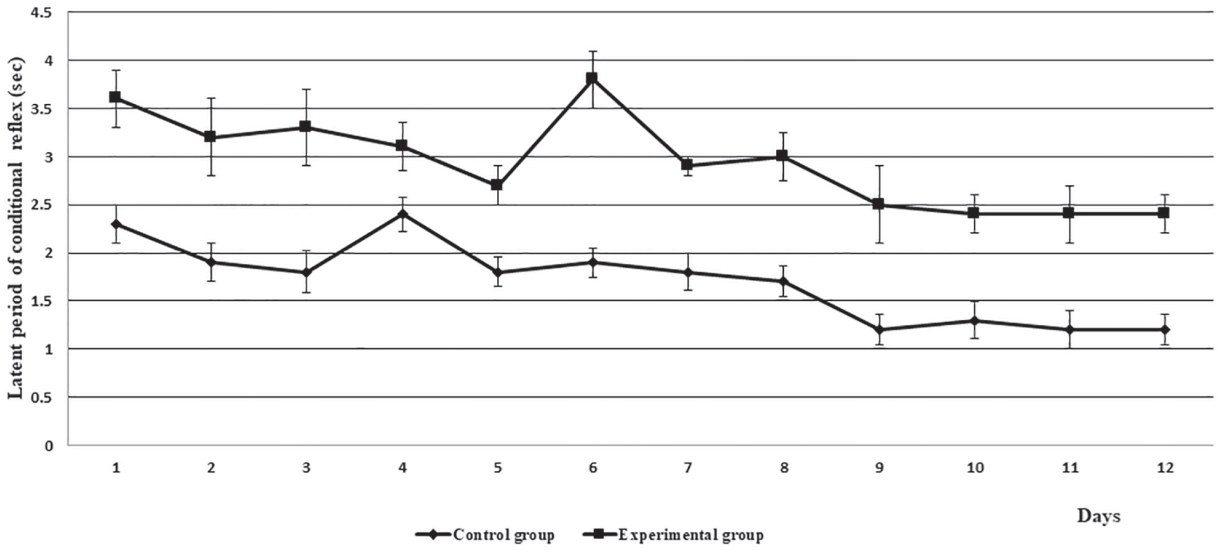

Fig.2. Latent period of bilateral escape conditional reflex in control and experimental groups.

The distinction between those two groups of the animals was marked also in latent period of unconditional escape reaction. In particular, during the first 9 days of elaboration of active escape defense reaction, latent period of escape in experimental group statistically significantly exceeded those in control group. During the three last days of experiments this distinction was kept, but statistically already was not significant. (Fig.3).

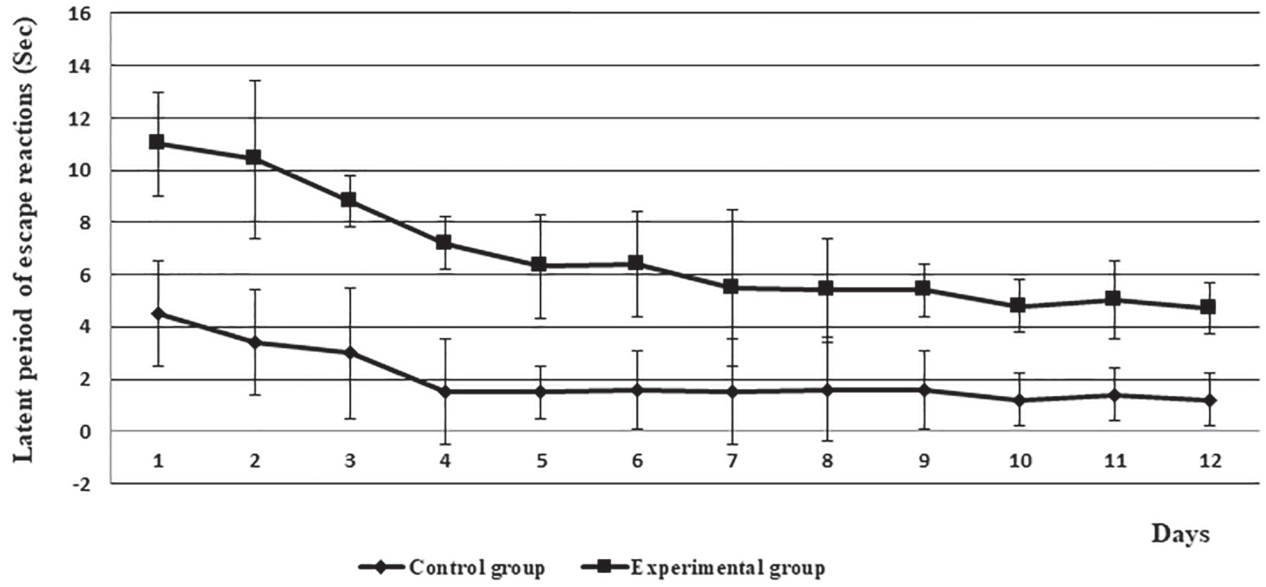

Fig.3. Latent period of unconditional escape reaction.

On basis of experiments it was established, that elaboration of adequate defense behavior for the animals' received vasopressin in comparison with the control animals much more couplings (80) were required.

As we mentioned above, the level of conditional reflex on active defensive escape was checked during three days in two weeks, 1 month and 2 months after such termination of experiment in both control and experimental groups of animals.

Two weeks after rest the distinction in a level of reaction on conditional reflex between the control and experimental animals was not found out. However, through the first and second month breaks, the level of fulfillment of conditional reflex reaction at the experimental animals statistically significantly ($P<0,01$) exceeded those of control group animals. In particular, on 20 conditional signals they adequately reacted 11 times (55%), and the conditional reactions were carried out on the verge of fortuity. At experimental group of the animals the level of the correct answers made 80-90%. (Fig.4).

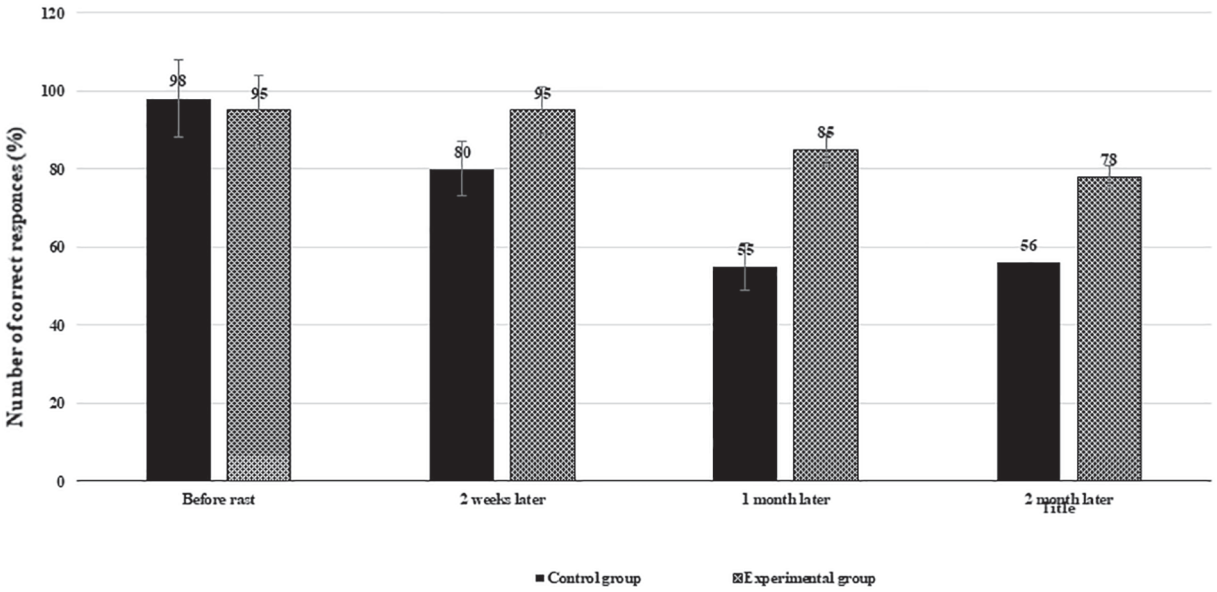

Fig.4. Effect of vasopressin on preservation and reproduction of active escape reaction. 1. Before rest; 2. Two weeks later; 3. One month later; 4. Two month later.

Discussion

We consider that such influence of lysine vasopressin on elaboration of conditional reflexes should be caused both by direct action of specified hormone on memory, and by alteration of motivational-emotional condition of the animal. The neuropeptide vasopressin might be affect motor performance in the early stage of formation conditional reflex (in order to maintain active avoidance extinction, the motor activity must be kept high) and this condition in its turn finds reflection during formation of memory [8,9,10]. Furthermore, vasopressin might be modulated the release of stress hormones such as epinephrine. In turn, catecholamines enhance memory consolidation. Vasopressin is co-localized with CRF in neurons from the paraventricular nucleus, which project to nuclei in the brainstem, involved in autonomic regulation [11-15]. These neuropeptides may act synergistically or in a concerted action aimed to learn to adapt to environmental demands. The effects induced by vasopressin is associated with central brain mechanisms which depends on the character of the reinforcing stimuli of the external environment.

The chronic administration of vasopressin promotes preservation of a trace of memory and its perfect reproduction.

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Evaluating the Impact of a Comprehensive HIV Education Lecture on Dental Students' Attitudes and Behaviors Towards Individuals Living with HIV: A Pre – and Post-Test Study

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Abstract

HIV infection remains a major public health challenge globally. Despite advancements in treatment and prevention, stigmatized attitudes towards individuals living with HIV can impact their accessibility to healthcare services, including dental care. Dental students, as prospective healthcare providers, have a crucial role in enhancing these individuals' quality of life. This study aimed to investigate the impact of an educational lecture on dental students' attitudes and behaviors towards individuals living with HIV. The study employed a pre – and post-test design to evaluate the effect of an educational lecture on dental students' attitudes and behaviors towards people living with HIV. A total of 123 dental students were surveyed before and after the lecture to assess changes in their knowledge, attitudes, and behaviors relating to HIV care. There was a significant increase in students' understanding of HIV, its transmission, and necessary support for

people living with HIV following the lecture. This improvement led to a positive shift in attitudes towards individuals living with HIV, including increased comfort discussing HIV, willingness to provide medical care to HIV patients, and readiness to interact socially with individuals living with HIV. Nonetheless, some reluctance and stigma persisted in certain social scenarios involving people living with HIV. Educational interventions, such as lectures, can substantially influence the understanding and attitudes of future dental professionals towards individuals living with HIV. However, targeted initiatives may still be necessary to address remaining areas of stigma and hesitance concerning social interactions with people living with HIV.

KEYWORDS: HIV; Dental Students; Attitudes; Educational Interventions; Stigma

Introduction

HIV infection continues to pose a significant global health challenge, affecting an estimated 38 million people worldwide [1]. Despite the strides made in its treatment and prevention, individuals living with HIV frequently encounter substantial obstacles to accessing quality healthcare, especially in resource-limited settings [2]. Medical and dental students, as prospective healthcare providers, hold a pivotal role in mitigating these challenges and enhancing care for those living with HIV. However, research suggests that these students can harbor stigmatizing attitudes towards individuals living with HIV, negatively influencing the quality of care [3]. Particularly disconcerting are findings from a study in Georgia, which revealed that a combination of negative attitudes and lack of knowledge about HIV/AIDS among practicing dentists and dental residents often led to a refusal to provide treatment to patients living with HIV [4].

Addressing these attitudes could potentially be achieved through focused education and training on HIV and AIDS [5]. Specifically, comprehensive lectures about services for HIV-infected patients can equip medical and dental students with the requisite knowledge and skills to deliver high-quality care to this demographic. However, there is a relative paucity of studies exploring the impact of such lectures on the attitudes and behaviors of these students towards people living with HIV. Prior studies have yielded inconsistent results, with some indicating positive attitudinal shifts post HIV education, [6] while others found no significant changes [7].

A viable strategy for evaluating shifts in medical and dental students' attitudes and behaviors towards people living with HIV following an educational intervention is a pre – and post-test design. This approach involves surveying students before and after an HIV services lecture to assess any changes in knowledge, attitudes, and behaviors pertaining to HIV care. While this method may not capture the full complexity of attitudes and behaviors towards HIV care, it offers a valuable initial measure of the impact of educational interventions on students' attitudes and behaviors.

Thus, this study aims to evaluate the effect of a lecture on services for HIV-infected patients on medical and dental students' attitudes and behaviors towards individuals living with HIV. Specifically, we will employ a pre – and post-test design to gauge shifts in students' knowledge, attitudes, and behaviors towards people living with HIV after attending the lecture. The findings of this study will contribute critical insights into the potential of educational interventions to counteract stigmatizing attitudes towards individuals living with HIV among medical and dental students.

Methods

Study Design:

We employed a pre – and post-test design for this study, which was carried out at a medical school situated in a resource-limited setting. Prior to initiating the study, we obtained necessary approval from the institutional review board.

Study Participants:

The study population comprised of 123 dental students in their clinical years, all of whom were enrolled in a mandatory course on infectious diseases, with a module on HIV. Only students who willingly provided informed consent were included in the study, ensuring their voluntary participation.

Intervention:

The core intervention for this study was a single lecture, with a duration of 90 minutes, focusing on services provided to HIV-infected patients. The lecture shed light on various aspects such as HIV's epidemiology and pathogenesis, the underlying prin-

ciples of antiretroviral therapy, the crucial role of consistent treatment adherence, and strategic measures for combating stigma and discrimination experienced by individuals living with HIV.

Data Gathering:

Prior to the lecture, participants were asked to fill out a questionnaire, which encompassed queries about their demographics, HIV-related knowledge, attitudes towards individuals living with HIV, and their perception of potential barriers hindering the provision of high-quality care to this patient group. In the immediate aftermath of the lecture, the participants were given a post-lecture questionnaire, mirroring the questions asked in the pre-lecture survey.

Data Examination:

We used descriptive statistics to encapsulate the demographic characteristics of the study group. For comparing the pre – and post-lecture scores on knowledge, attitudes, and behaviors in relation to individuals living with HIV, paired t-tests were utilized. All data analyses were carried out using the SPSS software. In this study, we considered a p-value of less than 0.05 as indicative of statistical significance.

Results

A positive shift in the understanding of HIV was observed after the lecture. Initially, 87.4% of the participants correctly identified HIV as a virus attacking the immune system. After the lecture, the correct understanding increased to 95.1%. Concurrently, misconceptions decreased. Those identifying HIV as bacteria fell from 5.8% to 1.6%. Similarly, the percentage of participants unaware of what HIV was, dropped from 6.8% to 2.4%. Only 26% of respondents reported having been tested for HIV before the lecture, suggesting that some may have been hesitant to get tested due to stigma or fear.

Awareness of HIV Transmission

There was an increase in the understanding of HIV transmission methods after the lecture. Those who identified all correct methods of transmission (unprotected sex,

sharing needles, and blood transfusions) increased from 81% to 88.6%. In comparison, individual understanding of unprotected sex as a mode of transmission dropped from 13.2% to 3.3%, suggesting a shift towards a comprehensive understanding.

Misconceptions about HIV

There was a decline in all reported misconceptions about HIV post-lecture. Of note, there were interesting gender differences in the misconceptions about HIV. Men recognized the importance of mental health support in dealing with HIV slightly more than women. However, responses from both genders indicated a shared understanding about common misconceptions of HIV.

Doctor-patient Relationship with HIV Positive Patients

The willingness to provide medical care to HIV patients increased following the lecture, with 51.2% definitely willing compared to 35.6% before the lecture. Those uncertain about providing care decreased from 26.3% to 7.3%. Notably, post-lecture, more women than men reported feeling more comfortable working with HIV patients.

Comfort Talking about HIV

The lecture increased the participants' comfort in discussing HIV, with 56.9% feeling more comfortable post-lecture. Interestingly, a higher percentage of males than females reported feeling more comfortable discussing HIV after the lecture.

Access to Services for People living with HIV

Following the lecture, there was a marked increase in the perceived importance of access to services (medications, mental health support, support groups) for people living with HIV, with 74% considering it very important. Particularly, more women than men thought it was 'very important' for people living with HIV to have access to these services.

Interactions with People living with HIV

After the lecture, the willingness to interact socially with someone living with HIV increased across various scenarios. Women were generally more willing than men to interact with people living with HIV. This was evident in the context of having them as a neighbor, having a close friend with HIV, and willingness to work closely with someone who has HIV. However, both genders showed some reluctance when it came to

scenarios like having a family member marry someone with HIV or renting a room in their house to someone with HIV. Despite the positive shifts in attitudes post-lecture, these areas suggest that there remains room for further growth in understanding and acceptance. (Refer to Table 1).

Table 1. Changes in willingness to interact socially with someone living with HIV after the lecture

Willingness to interact socially with someone living with HIV	Before lecture	After lecture
Not willing	63.5%	42.7%
Somewhat willing	24.5%	36.2%
Very willing	12%	21.1%

Conclusion

In conclusion, the lecture on HIV effectively increased the participants' understanding of HIV and debunked various misconceptions surrounding the disease. This enhanced understanding was not limited to the nature of the virus or its modes of transmission, but also extended to the necessary services and support for those living with HIV. This improvement in understanding translated into a positive shift in attitudes, with participants expressing an increased comfort level in discussing HIV, providing medical care to HIV patients, and interacting with people living with HIV.

However, disparities still exist based on gender, with women tending to express higher levels of empathy and willingness to interact socially with people living with HIV. These disparities underscore the necessity of tailoring education initiatives to address specific biases and misconceptions in different groups.

While the data shows clear progress, it also highlights the continuing stigma around HIV. The relatively low willingness of participants to rent a room to someone living with HIV or to accept a family member marrying someone with HIV suggests that more work is needed to address the stigma that people living with HIV face in their daily lives.

Overall, the lecture's impact underscores the importance and effectiveness of education in combating misinformation and stigma surrounding HIV. However, there is a continuing need for comprehensive and tailored strategies to fully bridge the gaps in understanding and attitudes, and to ensure that those living with HIV can lead lives free of discrimination and stigma.

Discussion

In light of the findings, the discussion will begin by reemphasizing the fact that the lecture effectively served its purpose of educating participants on HIV, by not only enhancing their understanding of the disease but also challenging and reducing misconceptions. The data clearly demonstrates this shift in knowledge, evidenced by a decrease in misconceptions and an increase in accurate understanding of HIV.

One possible explanation for these findings could be the comprehensive nature of the lecture, which might have covered areas of HIV understanding that are often overlooked or misunderstood. Furthermore, the lecture's effectiveness might also be attributed to its focus on debunking popular misconceptions, leading to a better overall understanding of the disease.

Putting our findings in the context of relevant evidence, it is well established that education plays a critical role in HIV awareness and stigma reduction. Our study adds to this body of evidence by demonstrating how a single lecture can significantly impact participants' understanding and attitudes towards HIV.

However, our study does have some limitations. The differences in responses based on gender, for instance, are intriguing but could be further explored. It's important to consider whether these differences are due to inherent biases, cultural factors, or a difference in how the material was interpreted by different genders. In future research, it might be valuable to investigate these factors further to develop tailored education initiatives.

While our findings showed an overall increase in the understanding of HIV, the willingness to accept closer social relationships with people living with HIV, such as having a family member marry someone with HIV or renting a room to someone with HIV, remained low. This shows that while educational interventions can be effective in reducing stigma, there is a need for further work to address deeper, perhaps unconscious biases.

From a policy perspective, our findings underscore the importance of incorporating comprehensive HIV education into broader health education programs. Such initiatives can significantly improve understanding and reduce stigma, thereby supporting improved health outcomes for people living with HIV.

In terms of clinical significance, while our study did not examine the direct impact of improved understanding on healthcare provision, we did observe an increased willingness to provide medical care to people living with HIV. Future studies could investigate how this increased willingness translates into clinical practice.

In conclusion, while our study supports the effectiveness of education in improving

HIV understanding and reducing stigma, it also highlights the need for further work in this area. Future studies should explore the complex interplay of factors that influence attitudes towards people living with HIV, including the role of gender, cultural factors, and deeper biases. New hypotheses to be considered include whether tailored educational initiatives can address specific misconceptions and biases more effectively, and how such education can translate into improved healthcare provision and policy.

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The effectiveness of ezetimibe and atorvastatin combination therapy related to low density cholesterol goal levels attainment in patients with acute coronary syndromes

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Abstract

The use of statins is essential for aggressive lipid-lowering treatment in acute coronary syndrome (ACS) patients. The purpose of the present study was to examine the impact of ezetimibe, a selective intestinal cholesterol transporter inhibitor, in ACS patients. We conducted a 16-week one-center, prospective, randomized, and open-label clinical trial, involving 323 patients who had been hospitalized for an acute coronary syndrome
within the preceding 14 days. They were received atorvastatin 20 mg during 28 days and after those 292 patients, who had low density cholesterol (LDL-C) levels ≥ 1.81 mmol/L, were randomized to ezetimibe 10 mg/day co-administered with atorvastatin therapy (EZE + Statin) or doubling their current atorvastatin dose. The primary efficacy end point was absolute reduction in LDL-C for ezetimibe plus atorvastatin versus atorvastatin-monotherapy treatment groups. At

16 weeks, the mean LDL cholesterol level during the study was 1.60 mmol per liter in the atorvastatine-ezetimibe group, as compared with 1.91 mmol per liter in the atorvastatin-monotherapy group (P<0.001). Patients receiving ezetimibe and statin were more likely to achieve target LDL-C after 16 weeks compared to patients doubling their statin dose. Ezetimibe/statin combination therapy was well tolerated among this ACS patients, without safety concerns.

KEYWORDS: Acute Coronary Syndrome; atorvastatin; ezetimibe; low-density lipoprotein cholesterol

Introduction

Aggressive lipid-lowering treatment is crucial to secondary prevention for patients with acute coronary syndrome (ACS) [1,2]. While statin therapy has been shown to be highly effective in lowering low-density lipoprotein cholesterol (LDL-C) and reducing cardiovascular disease risk [3,4,5]. many high-risk coronary heart diseases (CHD) and/or CHD risk-equivalent patients do not achieve their guideline-recommended LDL-C goals. [6,7]. Several studies have shown that while approximately two thirds of high-risk CHD patients achieve LDL-C levels of, 2.6 mmol/L, only about one third of these patients attain LDL-C ,1.81 mmol/L levels [6,8,9,10,11]. For these patients, clinical guidelines recommend more intensive LDL-C-lowering therapy, including statin uptitration to maximally tolerated doses, and/or combination therapy [4,5]. However, many patients may not be able to tolerate higher statin doses, and combination therapy may be a better alternative. In several clinical studies, the addition of ezetimibe to ongoing statin therapy has been shown to improve lowering of LDL-C as well as goal attainment more than statins alone and is generally well tolerated in various patient populations [12].

The purpose of this open-label randomized trial was to compare the effectiveness and tolerability of ezetimibe 10 mg/day coadministered with the existing statin regimen versus doubling of the current statin dose in patients at high CAD risk who had not achieved target LDL-C levels while on statin monotherapy.

Materials and methods

Study design

A 16-week one-center, prospective, randomized, and open-label clinical trial. involving 323 patients who had been hospitalized for an acute coronary syndrome (STEMI, NSTEMI, or UA) within the preceding 14 days. They were received atorvastatin 20 mg during 28 days, and after that 292 patients, who had LDL cholesterol levels of LDL-C ≥1.81 mmol/L, were randomized to ezetimibe 10 mg/day co-administered with atorvastatin therapy (EZE + Statin) or doubling their current atorvastatin dose. Statin-naive patients and patients unable to have their statin dose doubled due to maximal statin dosing already, or tolerability/safety concerns, were excluded. Additional exclusion criteria were: (i) treatment with bile acid sequestrants, niacin, or fibrates, and; (ii) active liver disease, uncontrolled endocrine illness, kidney disease, and creatine kinase (CK)>50% above the upper limit of normal (ULN). The study was approved by the Tbilisi Medical State University research ethics board. After providing informed consent, study participants attended 4 clinic visits. At screening (visit 1) the fasting lipid profile, and liver function parameters were assessed. eligible patients entered a four week stabilization phase during which they continued taking their current statin dose (Fig. 1). At Visit 2, eligibility for randomization was confirmed with another fasting lipid profile. Patients who remained eligible (LDL-C≥1.81 mmol/L) were randomized (1:1 ratio), using a computer-generated random table, to receive either ezetimibe 10 mg daily coadministered with current statin dosing (EZE + Atorvastatin) or doubling of current Atorvastatin dose. Bloodwork for exploratory marker (Creactive protein (CRP)) was obtained at Visit 2 and 4. After 8 weeks (Visit 3), a brief exam, blood draw for fasting lipid profile, liver panel, and review of any adverse events occurred. For EZE + Statin patients, if LDL-C levels were LDL-C ≥ 1.81 mmol/L, the statin dose was doubled for the next 8 weeks. For atorvastatin patients with LDL-C ≥1.81 mmol/L, the statin dose was again doubled for the next 8 weeks. At week 16 (Visit4), patients underwent a brief exam, review of adverse events, liver panel, and fasting lipid profile. If the atorvastatin-monotherapy patients were already at maximum statin dose (80mg) and LDL-C ≥1.81 mmol/L, ezetimibe 10 mg/day could be added at the physician's discretion.

Statistical analysis

Analysis of the results was carried out using the software packages SPSS 23, StatSoft Statisca 10 and SigmaPlot 12.5. mean group value and standard deviation

(SD) were determined for each quantitative index. Data are presented as M ± SD. All analyses were performed in the intent-to-treat (ITT) population including all patients who were randomized. For publication quality, figure 3 was derived from SigmaPlot 12.5. The independent-samples Student's t-test was used to assess between-group differences in LDL-C target achievement. All statistical tests were two-sided with an alpha level of 0.05. Sample size calculation was based on the primary outcome measure. It was calculated via StatSoft Statisca 10 (Independent sample t-test, H0: $Pi_1 = Pi_2$). From medical literature Pi_1=1mmol/l for atorvastatin + EZE and for atorvastatin monotherapy – Pi_2=0.4mmol/l. Population Sigma is about 0.8 mmol/l. In order to detect a similar magnitude of difference for this outcome, with 5% significance and 90% power, a total of 86 patients per group were required.

Results and discussion

Study participants: 351 acute coronary syndrome patients hospitalized in Bokhua Memorial Cardiovascular Center intensive coronary care unit, were informed of the purpose of the trial and had to give their signed informed consent before being enrolled. 5 patients declined to participate without giving a reason. From 346 patients 323 met eligibility criteria. From 323 patients screened, 292 met the inclusion/exclusion criteria and were randomized. The most common reason for exclusion was a Baseline LDL-C<1.81mmol/L. Among the 292 patients enrolled, 283 (97%) patients completed the 8-week assessment and 263 (90%) completed the 16-week assessment. During the course of the study, there were 16 patients who were prematurely discontinued (3 were lost to follow-up and 13 had adverse events) and 13 patients were died. Of the 127 statin of patients who completed 16 weeks treatment, 60 were eligible for a crossover since they had not achieved LDL-C target while treated with the maximum statin dose (80mg) for 8 weeks. All of them had ezetimibe 10 mg added to their statin treatment and were, therefore, crossed over to the EZE + Statin group after 16 weeks (End of study). 17 from the 136 EZE + Statin of patients, who completed 16 weeks treatment and had not achieved LDL-C target, doubled the statin dose (80 mg).

There were no clinically significant differences in baseline demographic or lipide level characteristics across the two treatment groups (Table 1 and 2). The were some differences in baseline coexisting diseases (Table 1 and fig. 2). At the time of randomization (at 4 weeks), the mean LDL-C4 cholesterol level was 2.83 mmol/l in atorvastatin + EZE group and 2.74 mmol/l in atorvastatin group (P = 0.170). Among

patients who had blood samples obtained at 16 weeks, the mean LDL-C16 cholesterol level was 1.91 mmol/l in the atorvastatin-monotherapy group and 1.60 mmol/l in the atorvastatin-ezetimibe group (P<0.0001) (Table 2).

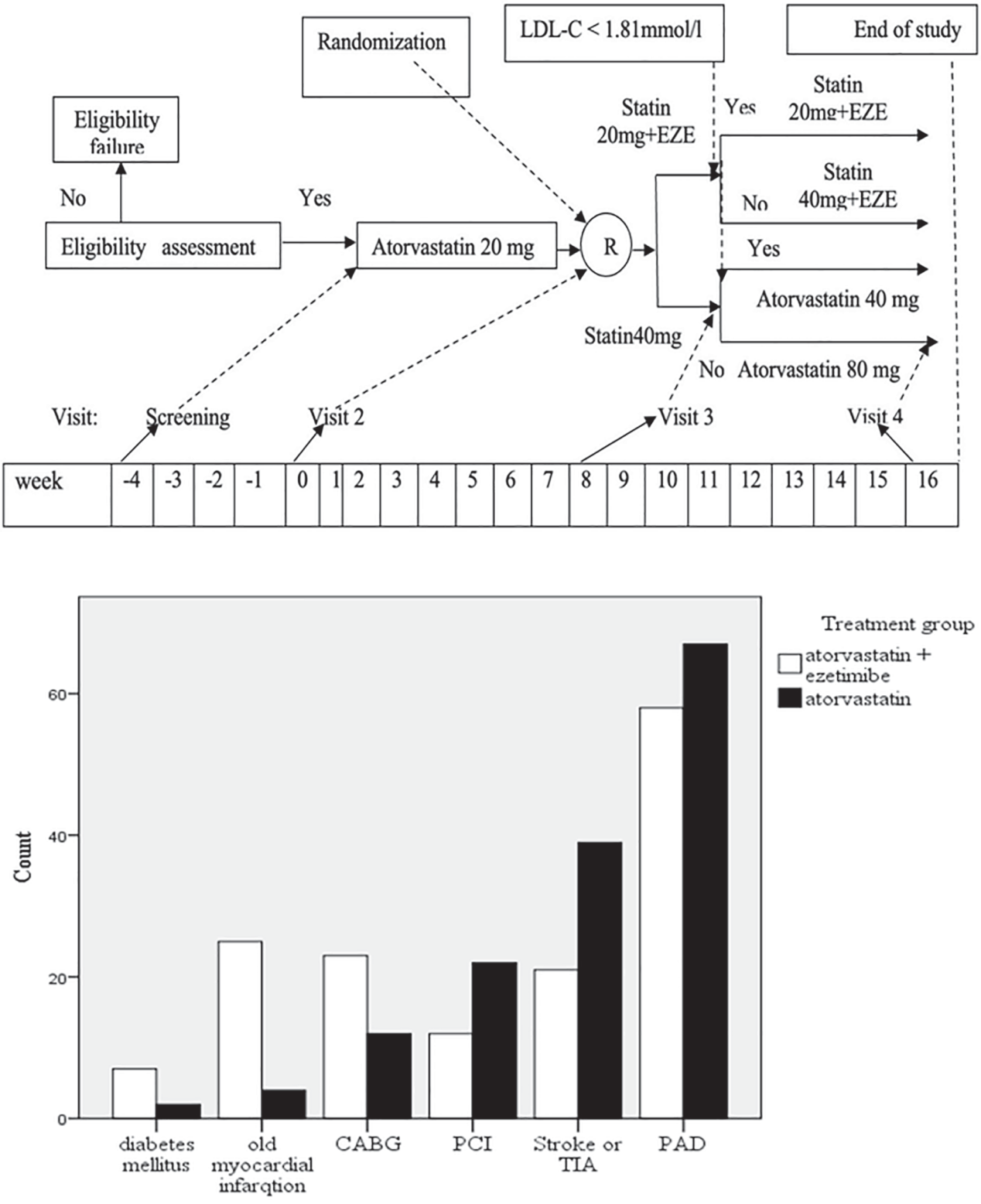

Fig. 2. History of coexisting conditions.

This difference of 0.31 mmol/l (P<0.0001) represented a 16% further lowering of LDL cholesterol level when ezetimibe was combined with atorvastatin than when atorvastatin was administered alone (fig.3). Some between-group differences were seen in the percentage of patients who had elevations in alanine aminotransferase levels that exceeded three times the upper limit of the normal range (ULN). There were 4 patients in the atorvastatin–ezetimibe group (2 patients had received atorvastatin 20 mg and 2 patients – atorvastatin 40 mg) with ALT, AST, or both ≥3× ULN. There were 9 patients in the atorvastatin group (5 patients had received atorvastatin 40 mg and 4 patients-atorvastatin 80mg) with ALT, AST, or both ≥3× ULN. All elevations in hepatic enzymes were asymptomatic, and no hepatitis, jaundice, or other clinical signs of liver dysfunction were reported. Discontinuation of study medication owing to the adverse event occurred in 6.2 % of the patients in the atorvastatin-monotherapy group and in 2.7 % of those in the atorvastatin–ezetimibe group. Although LDL-C goal attainment rates have recently improved overall through an increased awareness and use of lipid-lowering therapy, many high-risk CHD patients still do not meet guideline-recommended LDL-C goals on statin monotherapy [6,8,13,14]. Guidelines recommend that more intensive therapy, such as statin titration and/or combination therapy, may be needed for patients who are not at LDL-C goal [4,5]. While statins remain the first-line therapy for LDL-C reduction based on clinical trial data, many patients may not tolerate high doses required to achieve clinical targets. Combination therapy with ezetimibe plus statins has been shown to be safe and efficacious in numerous randomized, controlled clinical studies [12,15]. In our study, ezetimibe added onto atorvastatin therapy resulted in greater percent LDL-C changes from baseline (43%) compared with statin up titration (30%), consistent with the LDL-C reductions (30 %) observed previously in clinical studies in which ezetimibe was added onto ongoing simvastatin, atorvastatin, or rosuvastatin monotherapy [12,15]. Moreover, the significant additional 13% LDL-C reduction observed in our study with ezetimibe add-on versus statin uptitration is also in line with clinical studies in which the addition of ezetimibe to statin therapy significantly reduced LDL-C by 14% more than doubling the statin dose [12]. Multiple observational and randomized clinical studies have shown that statin uptitration and/or combination therapy with higher LDL-C-lowering efficacy is more effective than therapy for moderate-potency reducing LDL-C and improving goal attainment in high-risk patients [16,17,18,19,20,21,22]. A strength of our study is the assessment of the effects of lipid-lowering therapy in a real-world clinical practice setting. However, several limitations of our study should be considered. First, we evaluated patients who had had an acute coronary syndrome, and our results are most relevant to that population. Second, this trial had a particularly small duration of follow-up and the open-label study design may have biased the assessment or reporting of adverse events. It is worth to further evaluate the clinical effect of the combined therapy in larger population of ACS patients with enough longer follow-up.

TABLE 1. Baseline characteristics

Characteristic	EZE + Atorvastatin *n = 146*	Atorvastatin *n = 146*
Women, *n* (%)	67 (49.6)	68 (50.4)
Age, years, mean ± SD	62.21 ± 11.36	62.62 ± 11.03
body mass index, mean ± SD	25.22 ± 3.43	24.87 ± 2.88
Diabetes, *n* (%)	7 (77.8)	2 (22.2)
PAD, *n* (%)	58 (46.4)	67 (53.6)
Old MI, *n* (%)	25 (86.2)	4 (13.8)
CABG, *n* (%)	23 (65.7)	12 (34.3)
PCI, *n* (%)	12 (35.3)	22 (64.7)
Stroke or TIA, *n* (%)	21 (35)	39 (65)

TABLE 2. LDL-C at randomization and 16 weeks

Parameter	Atorvastatin + Ezetimibe n=146	Atorvastatin n=146	P value (between group)
Randomization, mmol/L (mean ± SD)			
LDL-C4	2.83±0.55 n=136	2.74± 0.64 n = 127	0.170
16 weeks,mmol/L (mean ± SD)			
LDL-C16	1.60 ± 0.39	1.91 ± 0.40	< 0.0001

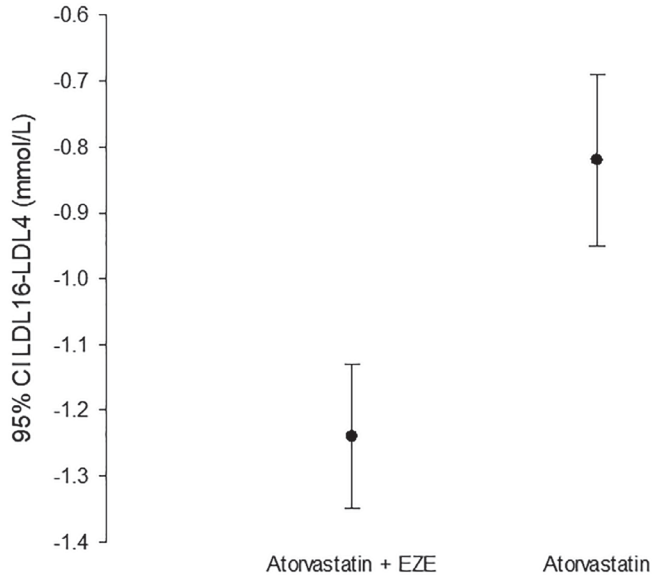

Fig. 3. Mean of LDL-C16-LDL-C4 at 16 weeks by treatment group.

TABLE 3. Absolute change in LDL-C parameters from randomization to 16 weeks

Parameter	Atorvastatin + Ezetimibe	Atorvastatin	P value (between group)
	n = 146	n =146	
mmol/L, (mean±SD), LDL-C16 – LDL-C4	– 1.24 ± 0.67	-0.82 ±0.76	< 0.0001

Conclusion

Ezetimibe coadministered with atorvastatin may enable more ACS patients to achieve recommended target LDL-C levels by offering greater LDL-C lowering with fewer dose titrations than uptitration of atorvastatin alone.

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Peculiarities of Blood Circulation and Rheological Properties During the Treatment of Cancer Disease

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Abstract

Neoplasms are characterized by an abnormal, altered stroma that facilitates cancer development by providing nutritional support and establishing a barrier for host defense mechanisms. During a malignant disease all physiological processes of destruction require structural changes, that manifest at different organization levels in organs, tissues, single cells, and cellular organelles. All of these structures have specific and significantly complex rheological parameters. In a given vessel within a tumor, blood flow fluctuates with time and can reverse its direction. Elevated geometric and viscous (rheological) resistance and other molecular and mechanical factors contribute to this spatial and temporal heterogeneity. Heterogeneity contributes to both acute and chronic hypoxia in tumors—a major cause of resistance to radiation and other therapies. adsorption-rheological properties of blood prognostic significance concerning lung neoplasm course and development of complications of chemoradiation respectively. Intravascular rheological changes are one of the most important factors to explain the radiobiological principles of SBRT. Laboratory studies suggest that the radiation

response for the high-dose single fractions used in radiosurgery is predominantly related to the supporting endothelial cells. The Linear Quadratic Model (LQ Model) applies to the calculation of iso-effect doses in treating with conventional EBRT. Based on the LQ and USC model, we estimated the Biologically Effective Dose (BED) and Equivalent Dose. When the fractional dose is higher than the Transient Dose, the LQ model is inappropriate to predict the effects induced by radiation. BED is calculated by the LQ formula if the dose per fraction is below the transition dose – DT and by the USC formula if the dose per fraction is higher than DT.

KEYWORDS: Stereotactic Body Radiation Therapy (SBRT); External beam radiation therapy (EBRT); Linear Quadratic Model (LQ Model); Universal Survival Curve (USC); Biologically Effective Dose (BED); Transition Dose (DT)

Introduction

Cancer development is usually associated with a genetic mutation causing pathological alterations of the cell cycle and invasive motility. Neoplasms are characterized by an abnormal, altered stroma that facilitates cancer development by providing nutritional support and establishing a barrier for host defense mechanisms [1]. cellular intrinsic traits and molecular factors within the tumor microenvironment significantly contribute to metastatic progression.

In solid tumors, proliferating cancer cells and activated fibroblasts deform the interstitial matrix, resulting in stretched collagen fibers, compressed hyaluronan, and deformed cells-all storing solid stress, a type of mechanical force transmitted by solid tissue components. This stress compresses intratumor blood and lymphatic vessels [2,3]. cancer-associated fibroblasts (CAFs) subsume at least two distinct cell types:

1. Cells with similarities to the fibroblasts that create the structural foundation supporting most normal epithelial tissues;
2. Myofibroblasts, whose biologic roles and properties differ markedly from those of the widely distributed tissue-derived fibroblasts [4,5].

Intussusception, wherein tumor vessels enlarge and an interstitial tissue column grows in the enlarged lumen, expanding the network; vasculogenesis, wherein endo-

thelial precursor cells mobilized from the bone marrow or peripheral blood contribute to the endothelial lining of tumor vessels; “sprouting” angiogenesis, wherein the existing vascular network expands by forming sprouts or bridges; co-option (not shown), wherein tumor cells grow around existing vessels to form “perivascular” cuffs [6, 7]. Tumor vasculature consists of both vessels co-opted from the preexisting host vasculature and vessels resulting from the angiogenic response of host vessels to cancer cells [8]. The former is invested in normal contractile perivascular cells, whereas the latter lack these perivascular cells or these cells are abnormal [9,10]. Macroscopically, four spatial regions can be recognized in a tumor:

- An avascular necrotic region
- A semi-necrotic region
- A stabilized microcirculation region
- An advancing front

During the malignant disease, all physiological processes destruction require structural changes, that manifest at different organization levels in organs, tissues, single cells, and cellular organelles [11,12]. All of these structures have specific and significantly complex rheological parameters. However, the association of structural elements to mechanical properties is especially difficult within the biological microenvironment and depends on the internal cell rearrangements and cellular interactions with molecules that compose the extracellular matrix (ECM) of stroma [13-15].

Rheological Properties

Average erythrocyte velocity can be an order of magnitude lower in some tumors as compared with that of normal host tissue. In a given vessel within a tumor, blood flow fluctuates with time and can reverse its direction [16,17]. Elevated geometric and viscous (rheological) resistance and other molecular and mechanical factors contribute to this spatial and temporal heterogeneity. Heterogeneity contributes to both acute and chronic hypoxia in tumors-a major cause of resistance to radiation and other therapies [18]. Pathological changes in stroma include an increase in ECM stiffness and an accumulation of stress gradients inside the tumor mass. Abnormal mechanical stresses can increase the invasive and metastatic potential and migration of cancer cells and tissue development [19,20].

An important pathogenetic link supporting the properties of lung cancer is neoangiogenesis (the formation of new vessels). Well simultaneously, the expression of protein products that are surfactants or possess surfactant properties in patients with lung neoplasm provides the processes of neoangiogenesis and the physicochemical interfacial state of blood serum [20,21].

Based on a randomized trial involving 115 patients, a rather interesting relationship between specific characteristics of lung cancer and rheological parameters was revealed.

There is a close relationship between the biochemical components and the functional activity of the cells in the tumor microenvironment, capable of secreting surfactants/insurfactants influencing biochemical processes, and thus the adsorption-rheological properties of blood (ARPB) – surface tension (ST), serum viscosity (SV), serum elasticity (SE), serum relaxation (SR), and viscoelasticity (VE) modulus. Surface-active, viscoelastic, and relaxation properties of blood correlate with the levels of tumor markers such as VEGF, TGFβ1, C-reactive protein, and α2-macroglobulin [22]. There are direct relations between the level of VEGF, which, in addition to the prognostic factor of high aggression of LC, is an important component in the development of neoangiogenesis in such patients. [23,24].

According to the final results, it was revealed that: Indices of VV are affected by the small-cell form of LC, the presence of compression pulmonary syndrome, adrenal metastases and the ribs, the number of metastases in lymph nodes per a patient; VE is affected by metastases in the spine and non-small cell LC; SV is affected by development of exudative pleurisy, tumor invasion in the ribs and metastasis in the brain; SE is affected by metastases in subclavian lymph nodes, the sternum, the humerus and the spinal column; ST is affected by the index of differentiation of LC; SR is affected by metastases in the spine and pancreas. VV and SV possess prognostic significance concerning lung neoplasm course and development of complications of chemoradiation respectively [25,26].

Rheological principles of SBRT radiobiology

Radiotherapy is one of the main methods of lung cancer management, mainly in the chemo-radiation mode. During the treatment aimed at radical cure, the convential, hyper fractionation dosage method is mainly used [27]. in some cases of non-small cell carcinoma, stereotactic radiosurgery is the best treatment option, for instance: in inoperable patients with initial stage, during the Recurrent neoplasm and/or lung metastatic disease [28-30]. Initial clinical experiences with SBRT show impressive results in terms of local tumor control and acceptable late complications rate [31].

Stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT), also known as stereotactic ablative radiotherapy (SABR), are novel and increasingly popular ways of delivering radiotherapy. This method can deliver, with high accuracy, a high dose of radiation to small and well-defined targets, utilizing either a single dose or a few fractions with a high degree of precision within the body [32,33]. High technology

modality requires a high degree of precision, accuracy, and reproducibility of the entire treatment delivery process. Maneuvers to limit the movement of the target volume and stereotactic localization of the lesion or image guidance are mandatory for target localization, minimization of margins, and dose delivery [34, 35].

Intravascular rheological changes are one of the most important factors to explain the radiobiological principles of SBRT. Laboratory studies suggest that the radiation response for the high-dose single fractions used in radiosurgery is predominantly related to the supporting endothelial cells [36]. Homeostatic factor, endothelial apoptosis regulates angiogenesis-dependent tumor growth, which only occurs at radiation doses above transition dose. High-dose radiation delivered by SABR increased vascular permeability and apoptosis through the ceramide pathway [37].

A simple way of modeling how radiation kills cells is the idea that there may be specific regions of the DNA that are important to maintaining the reproductive ability of cells.

These sensitive regions could be thought of as specific targets for radiation damage so that the survival of a cell after radiation exposure would be related to the number of targets inactivated [38]. DNA double-strand breaks (DSBs) are considered as the most lethal form of DNA damage and a primary cause of cell death and are induced by ionizing radiation during radiotherapy [39]. There are two methods of producing a double-strand break:

- One quantum of radiation damages both DNA strands (αD). This is referred to as a “double hit” because it damages two strands with one hit.
- Two quanta of radiation each breaking a single strand, produce a double-strand break (βD2). These are referred to as “single hits” because one strand is damaged with each hit.

The Linear Quadratic Model (LQ Model) applies to the calculation of iso-effect doses in treating with conventional EBRT. When the fractional dose is higher than the Transient Dose, the LQ model is inappropriate to predict the effects induced by radiation. introduced the Universal Survival Curve model (USC model), which integrated the LQ model with the multi-target model, and incorporated the effects of both low-dose and high-dose radiation [40].

The linear-quadratic (LQ) model, which derives from biological considerations of how cells could be killed by ionizing radiation, did fit the data at low doses, led to the replacement of this equation by the LQ equation as follows:

$$S(D) = e^{-(\alpha D+\beta D)}$$

D is the dose administered; S(D) is the fraction of cells to survive a given dose; αD is the probability of cell death arising from a single "double hit" producing a dou-

ble-strand break; βD2 is the probability of cell death arising from multiple "single hits," each generating single-strand breaks, close enough together to cause a double-strand break [39-42].

Experimental studies have shown that the LQ model overestimates cell killing at high single doses because it predicts a survival curve that continuously bends downward whereas the experimental data are consistent with a constant slope at high doses [43]. Therefore, there is concern that LQ model does not accurately predict tumor cell response at the higher doses per fraction used in SBRT. The response of tumors to radiation has been largely characterized in terms of factors that influence the ability of radiation to damage DNA, and that affect a population of cells in tumors to recover from such damage [44, 45]. The fundamental difference between these two models is based on five main radiobiological factors that are critical in determining the net effect of radiation therapy on tumors. These are:

- **Repair** compromises the efficiency of radiation and reduces the radiosensitivity of tumors. SABR induces more necroptosis than apoptosis
- **Repopulation** usually occurs in 2-3 weeks after conventional fractionated EBRT, depending on the fractionated radiation doses, total doses, and pathological types
- **Reoxygenation** may be reduced owing to the relatively short duration of SABR. Furthermore, tumor hypoxia may persist after vascular injury caused by SABR. Both oxygenated and hypoxic cells are ablated by high-dose radiation under SABR, resulting in highly efficient tumor-killing
- **Redistributions**: After irradiation, tumor cells at G0 stage of the cell cycle will accelerate into G2/M (radiation-induced G2/M arrest). The cell cycle is completely blocked at all stages after a single higher-dose ablation radiation
- **Radiosensitivity**: The clinical efficiency of SABR is greater than expected by the linear quadratic model and the conventional radiobiological principles of 4 Rs, may no longer be suitable to account for the killing effects of SABR. The underlying mechanisms of tumor response to radiation might also be involved in the intrinsic radiosensitivity and new radiobiological factors, e.g., vascular damage Cells differ in their intrinsic radiosensitivity. Radiosensitive cells include hematological cells and epithelial cells as well as hematological tumor cells [46,47].

Materials and Methods

The study presents the data of 9 people, of which 6 cases had residual non-small cell lung carcinoma, and 3 cases had metastatic lesions. In the residual tumor burden population, according to histological subtypes, adenocarcinoma was represented in 3 cases, squamous cell carcinoma in 2 cases, and large cell carcinoma in 1 case. The ratio of cases in men to women was 5:1. Localization of tumor was right-sided in 2 cases, left-sided – in 4, in the upper lobes of the lungs – in 2 cases, in the lower lobes-1, in the middle-upper – 2, the mediastinal – in 1. The central form of cancer occurred in 3 cases and the peripheral – in 3 cases. The maximal dimension of the tumor burden was estimated: in 1 case of squamous cell carcinoma – <3cm, 2 cases of adenocarcinoma and 1 case of large cell carcinoma – 3-4cm, and 1 case of adenocarcinoma da 1 case of squamous cell cancer – >4cm-<5cm. As for the patients with metastatic formation in the lung, in 1 case the metastases developed from rectal cancer, in 1 case from the head and neck squamous cell carcinoma, and in 1 case from breast invasive ductal carcinoma were detected. The maximal sizes of Secondary neoplasm were determined: head and neck cancer metastasis, breast and rectal were <2cm and 3-4cm respectively. The frequency of gender distribution represented: 1:2.

During the research we used 5 types single and multiple fractions SBRT dose schedules: For head and nack secondary formation (maximal size: <1,8cm) – 27 Gy in one fraction; for breast and rectal cancer cases (maximal dimension: 3-4cm) – 48 Gy in 3 fraction; for 2 upper lobe residual tumor (1 squamos cell and 1 adenocarcinoma, maximal dimension: 3-4cm) – 50Gy in 4 fraction; for lower lobe located adenocarcinoma residual cancer burden (maximal dimension 4,9cm) – 55 Gy in 5 fraction, also the same dosage for central located adenocarcinoma and large cell carcinoma (maximal size 4-5cm); for central/mediastinal located squamous cell carcinoma (maximal dimension 4,2cm) – 56 Gy in 8 fraction.

Based on the LQ model, we estimated the BED (biologically effective dose) and EQD2 (equivalent dose in 2 Gy fractions). the only parameter required to perform the calculations is the ratio.

1. $BED_{(\alpha/\beta)} = D \cdot (1 + d/\alpha/\beta)$ $BED_{10} = 27 \cdot (1 + 27/10) = 99.9$ Gy
   $EQD2 = D \cdot (d+\alpha/\beta)/(2+\alpha/\beta)$ $EQD2 = 27 \cdot (27+10/2+10) = 83.25$ Gy
   $d=2,2$Gy $\alpha/\beta=10$Gy
2. $BED_{10} = 51 \cdot (1 + 17/10) = 137.50$ Gy $EQD2 = 51 \cdot (17+10/2+10) = 114.75$ Gy
   $d=15$ Gy $\alpha/\beta=17$ Gy

3. $BED_{10} = 50 \cdot (1 + 12.5/10) = 112.5$ Gy $EQD2 = 50 \cdot (12.5+10/2+10) = 93.75$ Gy
   d=12.5Gy α/β=10 Gy
4. $BED_{10} = 55 \cdot (1 + 11/10) = 115.5$ Gy $EQD2 = 55 \cdot (11+10/2+10) = 96.25$ Gy
   d=11Gy α/β=10 Gy
5. $BED_{10} = 56 \cdot (1 + 7/10) = 95.2$ Gy $EQD2 = 56 \cdot (7+10/2+10) = 79.33$ Gy
   d=7 Gy α/β=10 Gy

Many authors believe that the use of the LQ model is inappropriate because it does not accurately explain the observed clinical data and ignores the impact of radioresistant subpopulations of cells. Also, the calculated equivalent doses are much higher than the actual effects.

Universal survival curve (USC) model was constructed to provide a superior approximation of the experimentally measured survival curve data in the high-dose range by hybridizing the LQ model survival curve for the low-dose range (the shoulder) and the multitarget model asymptote for the high-dose range. According to the USC model, DT is the transition dose from the LQ model to the multitarget model. The USC model depends on five radiobiological parameters: α, β, D_0, Dq, and D_T. According to the USC model, we calculated the (Biologically Effective Dose) BED_{USC}, (Single Fraction Equivalent Dose) SFED, and (Standard Effective Dose) SED. Estimated radiobiological parameters: α =0.33 Gy-1; D0 =1.25 Gy; D_q=1.80 Gy; D_T =6.2 Gy; α/β=10 Gy

$BED_{USC} = 1 /(\alpha \cdot D_0) \cdot (D - n \cdot D_q)$ $SFED = D - (n - 1) \cdot Dq$
$SED = (1/ (\alpha \cdot D_0)) \cdot (D_{sbrt} - n_{sbrt} \cdot D_q) / (1 + 2/\alpha/\beta)$

1. $BED_{USC} = (1/0{,}33 \cdot 1.25) \cdot (27 - 1.8) = 61.09$ SFED = 27 SED = 1/ (0.33 · 1.25)) · (27 − 1 · 1.8)/(1 + 2/10) = 50.91
2. $BED_{USC} = (1/0{,}33 \cdot 1.25) \cdot (51 - 3 \cdot 1.8) = 110.55$ SFED = 51 − (3 − 1) · 1.8 = 47.4 SED = (1/ (0.33 · 1.25)) · (51 − 3 · 1.8)/ (1 + 2/10) = 92.12
3. $BED_{USC} = (1/0{,}33 \cdot 1.25) \cdot (50 - 4 \cdot 1.8) = 103.76$ SFED = 50 − (4 − 1) · 1.8 = 44.6 SED = (1/ (0.33 · 1.25)) · (50 − 4 · 1.8)/ (1 + 2/10) = 86.46
4. $BED_{USC} = (1/0{,}33 \cdot 1.25) \cdot (55 - 5 \cdot 1.8) = 111.52$ SFED = 55 − (5− 1) · 1.8 = 47.8 SED = (1/ (0.33 · 1.25)) · (55 − 5 · 1.8)/ (1 + 2/10) = 92.93
5. $BED_{USC} = (1/0{,}33 \cdot 1.25) \cdot (56 - 8 \cdot 1.8) = 100.85$ SFED = 56 − (8− 1) · 1.8 = 43.4 SED = (1/ (0.33 · 1.25)) · (56 − 8 · 1.8)/ (1 + 2/10) = 84.04

In all SBRT schemes, the fractional dose was higher than the transit dose (>6,2 Gy). At high single fractional dose exposures (eg 27 Gray, 17 Gray) a very large difference between the effective and equivalent doses is noticeable.

Discussion

The prerequisite of LQ model application is complete oxygenation of tumor cells during radiation with a fractional dose of lower than 1–6 Gy. BED is calculated by the LQ formula if the dose per fraction is below the transition dose DT and by USC formula if the dose per fraction is higher than DT. SFED is defined as the dose delivered in one fraction that has the same biological effect as the tested dose-fractionation scheme. It should be noted that the closer the fractional dose is to the transition dose, the radiobiological parameters calculated by the LQ and the USC model are less differentiated from each other. Numerous experimental studies found obvious vascular injury under high-dose radiation, especially above 10 Gy, which induced hypoxia, acidification of tumor microenvironment, and indirect death of tumor cells [26,39,48]. High-dose radiation-induced blood vessel injury and ischemia, further leading to tumor necrosis. Radiobiological values estimated with high accuracy plays an important role for clinicians to effectively determine both clinical outcome and radiation-induced adverse events.

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Blood flow and rheological disorders in spinal vascular malformations

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Abstract

Malformation is a condition in which pathologically tortuous shunt vessels appear between arteries and veins instead of a network of capillaries. As a result of replacement of the capillary bed, the exchange of oxygen and nutrients between tissues and blood is disrupted, and oxygen starvation is experienced. Spinal vascular malformations are a rare and poorly studied pathology, which is characterized by significant diversity. There is no single hypothesis for the formation of malformations. Existing classifications do not always reflect the reality and prospects for the development of diseases. This work is an attempt to study the rheological properties and their contribution to fluidity failures during malformations with the aim of a comprehensive study of the problem.

KEYWORDS: aggregation; deformation; malformations; coagulation

Introduction

Spinal vascular malformations are a rare and poorly studied pathology, which is characterized by significant diversity [1-6]. Publications on this subject are mainly based on descriptions of individual observations [7-12]. Insufficient knowledge of this pathology is associated with the complexity of its diagnosis, which limits the development of differentiated methods of surgical treatment [7]. Great difficulties in this regard are caused by the lack of a clear structural-dynamic classification. Currently, the most widely used classification is according to which they distinguish: Dural arteriovenous fistulas (type I), glomus intracerebral (type II), juvenile or combined (type III), intradural perimedullary arteriovenous fistulas (type IV) [8,9]. Vascular tumors (hemangioblastomas, hemangiopericytomas, angiosarcomas, hemangioendotheliomas, hemangiomas, angiolipomas) and cavernous malformations are identified separately [2,12]. In 2002, R.F. Spetzler et al [12] proposed a new classification of spinal vascular pathology. However, this classification, despite its complexity, still does not cover the entire variety of types of spinal malformations. Therefore, we believe that a detailed systematization of spinal vascular malformations is necessary, which can contribute to the development of differentiated tactics of surgical interventions, taking into account the location, angio structural type and hemodynamic characteristics of the malformations, which will optimize treatment results.

The incidence of acute spinal circulatory disorders is about 1% of other forms of acute cerebrovascular accidents [7]. Among cerebrospinal circulation disorders, ischemic damage most often develops – myeloischemia; hemorrhages – hematomyelia – occur less often. All causes of myelischemia can be grouped into three main groups [13-15]. The first group includes lesions of the cardiovascular system itself: congenital (malformations of the spinal vessels – arteriovenous aneurysms, arterial aneurysms, varicose veins; coarctation of the aorta, hypoplasia of the spinal vessels) and acquired (atherosclerosis of the branches of the aorta, arteritis, phlebitis, thrombosis and embolism, insufficiency hemocirculation due to weakness of cardiac activity during myocardial infarction, atrial fibrillation, and hypertension). These causes are observed in 20% of patients with myelischemia. The second group consists of processes leading to compression of vessels from the outside: compression of the aorta and its branches by tumors and space-occupying formations of the thoracic and abdominal cavities (enlarged uterus due to pregnancy, lymph node packages in lymphogranulomatosis, tuberculosis, tumor metastases, etc.), compression of the radicular spinal arteries and radicular veins with prolapse of the intervertebral disc (the most common type of compression), epi – and subdural tumor, vertebral fragments due to trauma, epidural inflammatory infiltrate, thickened soft and arachnoid membranes (including atherosclerotic plaques

in them), etc. The third group consists of iatrogenic factors when myelischemia occurs as a complication of surgical interventions – radiculotomy with intersection of the radicular-spinal artery [5,7,16-20].

However, when describing blood circulation, it is necessary to recognize the very structure of the blood flow. The structure of the blood flow is the flow of elementary particles and plasma in the vessels. Red blood cells form a continuous structure, i.e., tend to aggregate and form in which cells touch their flat surfaces [21,22]

The aggregation of erythrocytes with their deformation properties is an important determinant that shapes the rheological properties of blood and the structure of blood flow. Two parallel models have been proposed to explain erythrocyte aggregation. According to the “bridging theory”, aggregation occurs when disaggregating forces are unable to resist the adsorption of macromolecules by nearby cells. “Depletion model”. With any consideration of the reason for the convergence of contacting particles, the contact area of the molecules is depleted, which leads to the formation of aggregates, overcoming factors such as the electrical charge of membranes, mechanical displacement, and Brownian motion. The formation of erythrocyte aggregates is the result of the action of osmotic forces and the formation of intermolecular bridges [20,23,24].

The blood supply to the spinal cord and spine is carried out from 3 pools – the subclavian arteries, the thoracic and abdominal aorta, and the internal iliac arteries. From all these vessels arise segmental arteries, from which in turn arise dorsal branches, which give rise to the spinal branches.

An increase in the aggregation ability of red blood cells during inflammation, stress and the development of other pathological processes is considered exclusively in a negative context. In particular, it is very popular to note the participation of the aggregation properties of erythrocytes in endothelial disorders, plaque formation and vascular injuries, when the main events develop near the walls of blood vessels, where the shear rate is greatest. Despite the ongoing interest in assessing the aggregation properties of erythrocytes, we will try to determine the feasibility of such studies [25-32].

Naturally, in the case of malformations, taking into account rheological pathologies is very important.

On the other hand, during vascular injury, destroyed red blood cells contribute to the formation of a platelet plug and fibrin clot due to the activation of erythrocyte coagulation factors (chemical role). They are capable of adsorbing and accumulating plasma coagulation factors, fibrinolysis and anticoagulants on their surface; fibrin threads are attached to their surface (mechanical role). Thus, the phenomenon of erythrocyte aggregation appears only when blood flow is completely stopped, but is still of theoretical and practical interest, because serves as a simple model for studying cellular interactions in body systems under normal conditions and especially during pathalgia, such as malformations.

If we consider the literature and epidemiological statistics, Arteriovenous malformation is a condition in which pathologically tortuous shunt vessels appear between arteries and veins instead of a network of capillaries – can occur anywhere, and is a clinically unfavorable disease. As a result of replacement of the capillary bed, the exchange of oxygen and nutrients between tissues and blood is disrupted, and oxygen starvation is experienced. The vessels have a thinner wall and are susceptible to rupture. The risk of rupture reaches 4% per year. Mortality in case of rupture is 30%, disability is 50% [7]. All these facts force doctors of all specialties and clinical rheologists to pay special attention to the diagnosis. It is still impossible to prevent the occurrence of malformation. However, fatal complications can be avoided if this pathology is diagnosed and treated in time.

According to our data, if an arteriovenous malformation is suspected, together with the technique of visualizing vessels to determine the tortuosity and shape of the vessels, it is necessary to register the aggregation ability of erythrocytes, which in turn can become a risk factor for complications and unfavorable outcomes.

We continue research in this direction, believing that experimental and clinical studies will provide new material for discussing problems associated with malformations.

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Beyond IPv4: Analyzing Barriers and Promoting Accelerated Adoption Strategies of IPv6

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Abstract

This discourse explores the factors influencing the gradual adoption of IPv6, the latest iteration of the Internet Protocol, despite its technological advantages over IPv4. IPv6's expansive address space, accommodating the anticipated surge in connected devices, makes it pivotal for sustained Internet growth. Notwithstanding, only 22% of websites have transitioned to IPv6 as of September. The analysis delves into key impediments, including IPv4 resilience technologies, compatibility challenges, costs, and ISP unreadiness. Additionally, potential solutions, such as government intervention, stakeholder collaboration, and thorough testing, are proposed to expedite IPv6 adoption for a resilient and technologically advanced Internet infrastructure.

KEYWORDS: IPv6, Internet Protocol; IPv4; Network; digital ecosystem; adoption barriers; connected devices; Internet growth; compatibility challenges; IPv6 adoption solutions

Introduction

IPv6, the latest iteration of the Internet Protocol, was conceptualized to address the inherent address-space constraints of IPv4, which have become exacerbated in the wake of the burgeoning digital ecosystem.

Despite the incremental integration of IPv6 by prominent entities such as Cisco, Tesla, SpaceX, Google, Meta, Microsoft, X/Twitter and YouTube, the broader implementation of this technologically advanced protocol has been characterized by a gradual pace. As of September, a mere 22% of websites have transitioned to IPv6. The elucidation of factors impeding the widespread adoption of IPv6 warrants a systematic exploration. This discourse endeavors to dissect potential causal factors and posit prospective remedial measures.

Methods

IPv6 is adopted primarily due to its 128-bit address format, which provides a significantly larger address space compared to its predecessor, IPv4. IPv4, utilizing a 32-bit address format, can accommodate only approximately 4 billion unique IP addresses. However, as the proliferation of devices is anticipated to escalate to around 30 billion by the year 2030, the constrained address capacity of IPv4 becomes inadequate.

In stark contrast, IPv6 offers an expansive address space, estimated at 340 undecillion (340 trillion[3]) unique addresses. This vast address pool renders IPv6 capable of accommodating the projected surge in the number of devices, providing a robust solution to address exhaustion challenges anticipated with the continued proliferation of networked devices.

Results

Table (table 1) succinctly compares the address capacities of IPv4 and IPv6. The data highlights the limited capacity of IPv4, which can accommodate approximately 4 billion devices, in contrast to IPv6, which boasts an expansive address space of 340 undecillion addresses, making it well-suited for the anticipated surge in the number of devices.

Table 1. Succinctly compares the address capacities of IPv4 and IPv6

IP Version	Address Capacity
IPv4	4 billion devices
IPv6	340 undecillion addresses

IPv6 exhibits notable enhancements beyond the mere expansion of address space, encompassing several facets of network architecture:

Streamlined Network Management: In stark contrast to IPv4's reliance on manual configuration or external servers like DHCP, IPv6 introduces the paradigm of stateless address autoconfiguration (SLAAC). This mechanism empowers devices to autonomously configure their IPv6 addresses. Particularly advantageous in sectors such as smart city infrastructure, agriculture, and finance, where diverse devices concurrently operate, this capability significantly diminishes the imperative for administrators to manually allocate IP addresses, thereby mitigating administrative overhead.

Efficient Routing and Packet Processing: IPv6 boasts a judiciously designed header structure, complemented by hierarchical addressing and prefix aggregation. These structural attributes collectively yield notable efficiencies in routing operations. The resultant reductions in packet processing costs, routing table sizes, and the number of IP prefixes contribute substantively to an augmented routing efficiency within IPv6 networks.

Support for Emerging Technologies: Foreseeing the advent of technologies like 5G and the Internet of Things (IoT), IPv6 is purposefully architected to accommodate these advancements. It affords advanced support for Quality of Service (QoS) functionalities, encompassing sophisticated features such as traffic shaping, packet classification, marking, and queueing. This heightened capability, orchestrated by class and traffic type, serves to optimize the end-user experience. Consequently, the intrinsic sophistication in handling network traffic positions IPv6 not only as compatible with but indeed highly efficient for, prospective technological innovations in device manufacturing.

The sluggish adoption of IPv6, despite its availability for over two decades and its demonstrable technical advantages over IPv4, can be attributed to several key factors. Exploring these reasons provides insight into the impediments hindering the widespread transition to IPv6.

IPv4 Resilience Technologies:

In response to the challenges posed by the scarcity of IPv4 addresses and to mitigate the immediate necessity for transitioning to IPv6, organizations and internet service providers (ISPs) have implemented various resilience technologies. These include:

IPv4 Leasing:

Definition: IPv4 leasing involves the temporary allocation of IPv4 address space by holders to entities in need, typically for a predetermined duration and at agreed-upon costs.

Purpose: This practice allows organizations to efficiently utilize available IPv4 resources by leasing out unused address space, thereby optimizing the allocation of IPv4 addresses.

Network Address Translation (NAT):

Definition: NAT is a technique where multiple device IP addresses from a private network are mapped to a single public IPv4 address during the transfer of packets between the private and public domains.

Purpose: NAT serves to alleviate the scarcity of public IPv4 addresses by enabling multiple devices within a private network to share a single public IP address when communicating with external networks.

Classless Inter-Domain Routing (CIDR):

Definition: CIDR is a methodology that removes traditional IP address class boundaries and facilitates the segmentation of IPv4 address spaces into subnets, allowing for more flexible and efficient allocation of IP addresses.

Purpose: CIDR enhances the utilization of IPv4 addresses by eliminating the rigid class-based structure, permitting the creation of subnets that cater to diverse addressing schemes.

The combined implementation of these technologies has significantly mitigated the urgency to transition to IPv6. By exponentially increasing the number of devices accommodated on a single IPv4 address, these measures have provided a measure of resilience against IPv4 address exhaustion. However, it is essential to acknowledge that these techniques introduce complexities in load balancing and traffic rerouting as the number of devices continues to grow.

Compatibility and Complexity:

Existing systems, including computers, networks, and routers, were primarily designed to function with IPv4. Regrettably, IPv6 lacks backward compatibility with these established systems and network devices. This predicament necessitates organizations to undertake a comprehensive network infrastructure upgrade to accommodate IPv6, a task fraught with complexity.

The Impact on Customers:

The transition to IPv6 may adversely affect customers whose devices are not compatible with IPv6. Fearing potential revenue loss due to customer migration to IPv4-compatible competitors, organizations exhibit hesitancy in embracing IPv6. Additionally, while Stateless Address Autoconfiguration (SLAAC) in IPv6 provides certain advantages, it lacks the necessary DNS information for seamless translation of domain names into IP addresses.

Costs Associated with Transition:

Transitioning to IPv6 entails significant costs, primarily attributed to compatibility gaps. This includes the acquisition and deployment of new, often expensive, network

infrastructure such as routers and switches. Moreover, the IT departments of most organizations, accustomed to IPv4 infrastructure, necessitate substantial investment in staff training and software migration to adapt to IPv6, especially for entities with intricate network configurations.

ISP Unreadiness:

Internet Service Providers (ISPs) play a pivotal role in the IPv6 transition. However, the challenges posed by IPv6 incompatibility and cost inefficiency are exacerbated by the slow adoption rates among ISPs. Given that ISPs control substantial portions of the network and its infrastructure, organizations might find it inefficient to transition to IPv6, particularly when many ISPs lack the facilities for effective implementation. The absence of robust IPv6 support from ISPs may result in connectivity issues or restricted access to IPv6-enabled websites, further hindering adoption.

Discussion

Ways to Encourage IPv6 Adoption:

Past attempts to expedite IPv6 adoption have encountered limited success. Six potential solutions for the future include:

Synergy between Technical and Financial Benefits:

Promoting the adoption of IPv6 by emphasizing its capacity to enhance technical capabilities while providing substantial financial gains. Scientific research by the National Institute of Standards and Technology estimated annual benefits of specific IPv6 use cases, serving as a persuasive motivator.

Prioritization of Pure/Native IPv6 Single Stack: Advocating for the prioritization of a pure IPv6 approach and phasing out IPv4/IPv6 workarounds to incentivize broad adoption. Highlighting the advantages of IPv6, including simplified hexadecimal addresses and improved routing efficiency.

ISP Support:

Acknowledging the critical role of ISPs in IPv6 provisioning and the need for substantial investment in skills enhancement for efficient deployment. Emphasizing the requirement for IPv6-compatible DNS infrastructure to ensure seamless connectivity between IPv6-enabled devices.

Government Intervention:

Highlighting the potential role of governments in driving IPv6 adoption through awareness programs, regulations, and financial incentives. Examining successful cas-

es, such as the U.S. government's mandates for federal agencies and initiatives in Taiwan and Germany.

Cross-Stakeholder Collaboration:

Recognizing the challenges posed by legacy systems and advocating for collaboration among ISPs, network operators, content providers, and equipment manufacturers. Facilitating the development of best practices, technologies, and documentation for IPv6 through knowledge-sharing initiatives.

Thorough Testing and Ongoing Community Support:

Emphasizing the importance of meticulous testing during IPv6 adoption to identify and resolve issues. Encouraging the formation of support communities for collective troubleshooting and innovation, as demonstrated by entities like the Internet Society (ISOC).

Conclusion

In conclusion, as the demand for IP addresses rises, the adoption of IPv6 becomes crucial for the sustainable growth of the Internet of Things (IoT). Organizations are urged to adopt IPv6 in a timely manner, showcasing their adaptability and technological leadership. However, successful transitions and accelerated adoption depend on collaborative efforts from governments and key internet players.

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Dynamics of β-glucosidase enzymatic activity in Yucca gloriosa L. leaves

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Abstract

The steroidal sapogenin tigogenin from Yucca gloriosa L. leaves is a raw material for the synthesis of steroidal hormonal preparations. Tigogenin is spirostan sapogenin. In the plant intact leaves are synthesized furostanol glycosides, which are transformed into spirostanol glycosides by the action of the enzyme **β-**glucosidase. The maximum of **β**-glucosidase enzymatic activity is observed in July and August. The results have a great significance for optimization of tigogenin production technology.

KEYWORDS: β-glucosidase; Yucca gloriosa L.; tigogenin; furostanol glycosides; spirostanol glycosides

Introduction

As early as in the 70s of the last century, I. Kutateladze Institute of Pharmacochemistry of the Georgian Academy of Sciences found that from all the species of the genus Yucca, introduced in our area for the decorative purposes, the leaves of Yucca gloriosa L. deserve particular attention. Leaves generally biosynthesize single aglycone-produced steroidal glycosides; this has simplified tigogenin isolation from the raw [1-4]. In cooperation with the All-Union Scientific Research Chemical-Pharmaceutical Institute, tigogenin was transformed into the initial products of the synthesis of steroidal hormonal drugs: 5α-pregnen-16-en-3β-20-oneacetate and 5α-androstan-3β-ol-17-ol acetate. The synthesis of a number of hormonal preparations was carried out from the latter: dihydrotestosterone and the ether derivatives thereof: Althesin, Dexamethasone, Mestranol, Methylandrostenol, anti-tubercular isonicotinic hydrazones and other 5α-steroids. Tigogenin from Yucca gloriosa was recognized as the most cost-effective industrial raw material for the synthesis of 5α-steroids [5-13].

The Institute of Pharmacochemistry developed a highly effective method of vegetative propagation of Yucca gloriosa; 200ha plantations were set up in Eastern Georgia in accordance with the elaborated agrarian recommendations [14].

As is known, steroidal glycosides are accumulated in plant in two forms: in furo – and spirostanol. For the isolation of tigogenin as a spirostanol aglycone from the plant, it is important that furostanols be converted into the spiro-form. This process in plant is carried out under the influence of β-glucosidase endogen enzyme. Our researches revealed that furostanolic glycosides in the leaves of Yucca gloriosa are localized in the epidermis of the leaf, while enzyme is active in the leaf mesophyll [15].

Two forms of β-glucosidase enzyme were found in the leaves of Yucca gloriosa: the first one catalyzes the hydrolysis of both, oligofurostanosides and 4-nitrophenyl-β-D-glucopyranoside synthetic substrate, while the second form shows the activity only towards the synthetic substrate. The first form of β-glucosidase exhibits a greater affinity for the natural substrate than for the synthetic substrate [16,17].

The purpose of the present paper was to study the dynamics of β-glucosidase enzyme activity in the leaves of Yucca gloriosa.

Materials and methods

The upper, middle and lower layers of the young Yucca gloriosa plant growing in Georgia were used as a research object. The dynamics was studied for 3 years during the vegetation period of the plant, in June, July and August. β-glucosidase activity was determined by the commonly known method [18]. The sum of furostanol glycosides of Yucca gloriosa isolated from Yucca gloriosa leaves through a commonly known method was used as a natural substrate [19]. 4-nitrophenyl-β-D-glucopyranoside by the Czech "La-Chema" company was used as a synthetic substrate.The amount of enzyme catalyzing 1nmol substrate hydrolysis per 1 minute was taken as a unit of glucosidase activity, while the specific activity was calculated per 1mg of protein. Enzyme activity was measured threefold. The results are presented in the table.

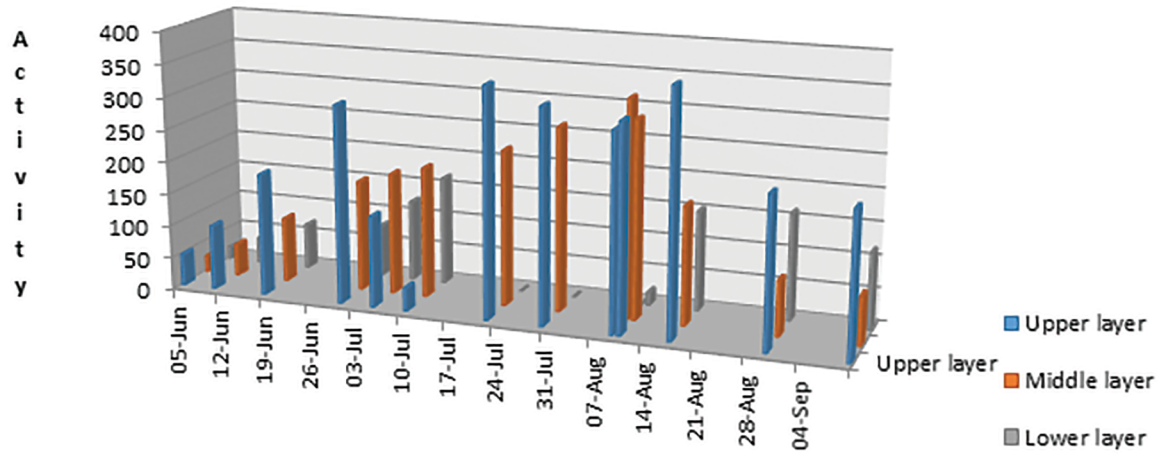
TABLE. The dynamics of β-glucosidase form 1 activity in Yucca gloriosa leaves during the plant vegetation period (the average of three parallel testing)

Date	Activity /Upper layer/	Activity /Middle layer/	Activity /Lower layer/
June 5	50	26	20
June 10	100	50	40
June 18	188	100	70
June 30	304	170	80
July 5	140	186	124
July 10	36	200	166
July 22	350	238	0
July 30	326	280	0
August 9	300	330	0
August 10	314	300	20
August 17	370	180	152
August 30	230	84	162
September 10	220	74	116

The table shows the three year data average.

Results and discussion

Experimental studies have shown that β-glucosidase form 1 specific activity in the leaves of Yucca gloriosa varies considerably during the plant vegetation period.



	05-Jun	10-Jun	18-Jun	30-Jun	05-Jul	10-Jul	22-Jul	30-Jul	09-Aug	10-Aug	17-Aug	30-Aug	10-Sep	
Upper layer	50	100	188	304	140	36	350	326	300	314	370	230	220	
Middle layer	26	50	100	170	186	200	238	280	330	300	180	84	74	
Lower layer	20	40	70	80	124	166	0	0	0	20	152	162	116	

Fig.1.The dynamics of β-glucosidase form 1 activity in Yucca gloriosa leaves during the plant vegetation period.

In the upper and lower layer leaves, the β-glucosidase form 1 activity increased several times in the period from May till August, while in the middle-layer leaves – it has abruptly increases during the mentioned period. Starting from September, the enzyme activity dropped and was practically not observed during the winter period. The maximum enzyme activity was reported in July-August.

The obtained results are of great importance for determining the period for collecting raw material, as well as for the fermentation conditions in order to achieve maximum tigogenin extraction.

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Optimizing Memory Usage in Python (Pandas)

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Abstract

This article explores Python's prominence in Data Science, Data Analytics, and Machine Learning, attributing its widespread adoption to its user-friendly nature, robust online community, and powerful data-centric libraries such as Pandas, NumPy, and Matplotlib. It delves into the challenges of managing extensive datasets and emphasizes the importance of memory utilization in navigating substantial data. The Pandas library's info() and memory_usage() methods are discussed as essential tools for assessing and optimizing dataframe memory consumption. The article demonstrates how changing data types, particularly for object columns, to the category datatype significantly reduces memory usage without altering the dataframe's appearance. The strategic adjustment of numerical column data types based on value range, illustrated with the age column as an example, is explored as a means of achieving precision and memory efficiency. The article highlights the considerable reduction in memory requirements by transitioning from float64 to float16 for columns containing floating-point numbers. Overall, this comprehensive exploration provides valuable insights into effective strategies for memory optimization in Pandas dataframes, catering to both categorical and numerical data, contributing to enhanced computational efficiency and significant memory savings.

KEYWORDS: Python Programming; Pandas Library; Memory Optimization; Data Science; Data Analytics; Machine Learning

Introduction

Python stands out as a highly prevalent programming language in the realms of Data Science, Data Analytics, and Machine Learning. Its widespread adoption can be attributed to its beginner-friendly nature, a robust online community of learners, and the presence of powerful data-centric libraries such as Pandas, NumPy, and Matplotlib. These libraries facilitate the seamless management and manipulation of extensive datasets. As a result, Python has emerged as the preferred language for professionals in the fields of Data Science and Data Analytics.

The Pandas library in Python provides a powerful capability for storing tabular data through a specialized data structure known as a dataframe. With a pandas dataframe, managing substantial amounts of tabular data becomes effortlessly accessible, thanks to its intuitive handling of row and column indices. This flexible structure accommodates data storage with hundreds of columns (fields) and thousands of rows (records).

Navigating substantial datasets requires a thoughtful approach to memory utilization. The challenge arises when confronted with an extensive volume of data, often leading to memory scarcity. Exhausting the available RAM may result in program crashes accompanied by the elusive MemoryError, posing a formidable challenge. Prioritizing memory management becomes paramount in such scenarios. Beyond the mitigation of potential crashes, streamlined memory usage enhances computational efficiency, ultimately saving valuable time.

Methods

The Pandas **info()** method serves as a quick gauge of a dataframe's memory consumption, offering a total memory overview. Simply by setting the **memory_usage** argument to "deep" within the **info()** method, we obtain the comprehensive memory allocation for the entire Pandas dataframe.

Nevertheless, when a more granular insight into memory usage per column is desired, the **memory_usage()** method comes to the rescue. This method delves into the specifics, providing a detailed breakdown of the memory consumed by each column in the dataframe. Executing the **memory_usage()** method returns a Pandas series, furnishing the memory space occupied by individual columns in bytes. Enriching this

with the deep argument set to True unravels the complete memory panorama of the dataframe's columns.

Typically, columns with an object datatype, such as gender, occupation, and zip code in our dataset, tend to consume substantial memory due to storing strings. Strings inherently occupy more space than numerical data types like integers and floating-point numbers, thereby inflating memory usage significantly.

A strategic solution involves converting select object columns to the category datatype. Consider the gender column, which inherently accommodates only two values, either "M" or "F". Switching the datatype from object to category optimizes storage by representing gender records as integer codes instead of strings. This simple alteration results in a remarkable reduction in memory usage—from 58,466 bytes to a mere 1,147 bytes, constituting a noteworthy 98% space-saving.

Extending this approach to other pertinent object columns in the dataframe yields substantial memory savings and acts as a preventive measure against potential MemoryError occurrences.

For numerical columns, an additional tactic involves tailoring the data type based on the value range. Take the age column in our dataset, where values span from 7 to 73. Recognizing that this range aligns with an 8-bit binary representation, we can efficiently store age as an 8-bit integer instead of the default 64-bit integer in newer Pandas versions. This strategic adjustment minimizes the required bits, resulting in a notable decrease in memory usage, particularly beneficial when dealing with large datasets.

Results

When transitioning the data type of the age column from int64 to int8, the space occupied by the column experiences a remarkable decrease-from 7544 bytes to 943 bytes, marking an impressive 87.5% reduction in space.

Furthermore, exploring alternative integer data types presents opportunities for optimization. Int16, accommodating a range of – 32,768 to +32,767, and int32, supporting a more extensive range from – 2147483648 to +2147483647, offer flexibility based on the required value range. The choice between int8, int16, or int32 hinges on the specific range of values within the dataset.

The following table outlines the complete spectrum of values representable by different integer data types:

Data Type	Range of Values
int8	-128 to +127
int16	-32,768 to +32,767
int32	-2,147,483,648 to +2,147,483,647
int64	-9,223,372,036,854,775,808 to +9,223,372,036,854,775,807

By aligning the data type with the appropriate range, we strike a balance between precision and memory efficiency, contributing to optimized storage in the age column.

Likewise, optimizing memory usage extends to columns containing floating-point numbers. Shifting from float64 to float16 as the data type introduces a substantial reduction in space requirements.

Discussion

This article delves into two key methods within Pandas for gauging dataframe memory consumption: the **info()** method and the **memory_usage()** method. Expanding on memory optimization strategies, we explored two effective approaches. The first involves transforming the data type of object columns to the category when dealing with categorical data. Despite maintaining the dataframe's appearance, this modification yields a noteworthy reduction in memory usage.

The second strategy revolves around adjusting the data type of numerical columns based on the value range, applicable to both integers and floating-point numbers. This proactive measure significantly contributes to memory efficiency.

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Polyphenol content, antioxidant and anti-inflammatory activities of Georgian wine and green tea

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Abstract

This comprehensive study explores the health-promoting properties of Georgian green tea and red wine, focusing on their antioxidant and anti-inflammatory activities, as well as polyphenol content. Utilizing the DPPH and FRAP methods, we observed impressive results, with green tea showcasing a remarkable FRAP activity of 61.2% of *ascorbic acid* activity set as 100 %, surpassing red wine at 18.2%. Comparative assessments against *ascorbic acid* for antioxidant activity and *Sodium diclofenac* for anti-inflammatory effects further underscored green tea's prowess. Intriguingly, green tea exhibited a substantial anti-inflammatory activity of 20 % of *Sodium diclofenac* also set as 100 %, outshining red wine at 3.7%. Polyphenol content, a key contributor to health benefits, revealed green tea's concentration at 7.5% (w/w), red wine's – 4.4% g/l. These findings highlight the potential of green tea and red wine as a potent source of bioactive compounds with implications for cellular health, inflammation mitigation, and chronic disease prevention. The results prompt a closer look at dietary choices, advocating for the incorporation of green tea to harness its multifaceted health benefits. As we delve into the molecular richness of these beverages, our findings provide valuable insights into the potential therapeutic avenues offered by these popular and culturally significant drinks.

Keywords: Antioxidants; Anti-inflammatory activity; DPPH; FRAP; Polyphenol content

Introduction

In an era where health-conscious choices steer lifestyles, the exploration of natural sources brimming with antioxidants and anti-inflammatory compounds has become a scientific pursuit of great significance. Among the potential candidates, green tea and red wine, especially Georgian red wine, stand out for their historical use and health benefits.

Green tea, derived from *Camellia sinensis* leaves, has been celebrated for centuries in traditional medicine for its significant health-enhancing properties [1]. Rich in polyphenols, green tea has become the subject of extensive research, with evidence suggesting potential benefits ranging from cardiovascular health to cancer prevention [2].

Antioxidants play a crucial role in neutralizing free radicals, which are unstable molecules that can cause damage to cells and contribute to various chronic diseases. Green tea and red wine have been widely studied for their potential health benefits due to their rich content of polyphenolic compounds [3].

The present study delves into the antioxidant activity assessed through the DPPH and FRAP methods, anti-inflammatory properties, and total polyphenol content of these beverages, aiming to shed light on their potential health benefits.

Materials and Methods

Extraction of Green Tea and wine materials

2 g commercially available Georgian green tea lives were added to 80 ml of boiling water and were steeped for 15 min. The infusion was cooled to room temperature in an ice bath and then centrifugated. The tea leaves were extracted a second time with 80 ml of boiling water and centrifugated again. Both fractions were combined.

The Georgian homemade red dry wine of *Saperavi* variety (harvisted in Kakheti region, left bank of riv. Duruji) fermented with whole skin for two weeks was used in the experiment.

Determination of antioxidant activity by DPPH – scavenging assay

The free radical scavenging activity of the green tea extract and Georgian red wine and also of standard solution (ascorbic acid) were investigated using 1,1-diphe-

nyl-2-picrylhydrazyl (DPPH) radical scavenging method. The free RSA of the diluted leaf extract of green tea and red wine was tested using a 1,1-diphenyl-2-picryl hydrazyl (DPPH) technique. A total of 24 milligrams of DPPH were dissolved in 100 mL of methanol for making the stock solution. In a test tube, 3 mL DPPH workable solutions were combined with 200 μL of wine and 1 ml of green tea extract and record. After that, the tubes were kept in complete darkness for 30 min. The absorbance was therefore measured using UV/Vis Spectrophotometer at 517 nm. The following formula was used to compute the percentage of antioxidants or RSA [4]:

% of antioxidant activity = [(Ac-As) ÷Ac] × 100

where: Ac-Control reaction absorbance; As-Testing sample absorbance.

Determination of antioxidant activity by FRAP (Ferric Reducing Antioxidant Power) method

Reagent – the FRAP reagent should be made immediately before use by mixing 2.5 mL of the 10 mM TPTZ stock solution, 25 mL of acetate buffer (300 mM, pH 3.6), and 2.5 mL of 20 mM $FeCl_3$ solution (1:10:1 v/v).

Instruction for FRAP method: Prapere Frap Reagent and warm up to 37^0C in water bath for 15 min. Add 30μL of sample to 3ml reagent blanc, record absorbance at 593 nm on the UV/Vis Spectrophotometer. Add 30 μL ascorbic acid to FRAP reagent and record absorbance at 593 nm. Compare FRAP values of samples to the ascorbic acid values [5].

Derermination of Anti-inflammatory Activity

Albumin denaturation inhibition.

The anti-inflammatory effect of green tea and red wine were tested using a modified form of the standard method [6]. The protocol was followed for inhibiting albumin denaturation. The reaction mixture was made up of an equal volume of green tea extract and red wine and 1 % aqueous egg albumin. The sample was incubated at 37^0C for 20 min before being heated to 51^0C for another 20 min. Finally, % inhibition of protein denaturation was calculated according the formula below:

Percent inhibition of protein denaturation=(Absorbance of control – Absorbance of test) x100/Absorbance of control.

The assay involved testing the samples against a known anti-inflammatory agent, Sodium diclofenac, as a reference.

Determination of polyphenol content in wine and green tea

Determination of total phenolics as gallic acid equivalent expressed in g/l was carried out using Folin-Ciocalteau method with minor modifications. Sample wine or green tea (400 μL), distilled water (1.8 μL), Folin-Ciocalteau reagent (200 μL) into the conical tube, wait 3 min for incubation before adding sodium carbonate (600 μL), mix and incubate at room temperature. After 2h of incubation, optical absorbance was read at 760 nm using UV/Vis Spectrophotometer, and the amount of total phenol calculated using gallic acid calibration curve [7]. For calibration per Gallic acid, we used 10 mg Gallic acid diluted in 1 ml MetOH. For different points take out appropriate volume from stock solution and dilute to definite amount. Makefurther dilutions with the double distilled or deionized water. Prepare the next dilutions: 0.1, 0.05, 0.025, 0.0125, 0.005 mg/ml. Diluting factors for samples was 100 times diluted wine in distilled water and 50 times green tea.

Determination of dry matters

Dry matter in green tea leaves was determined by express moisture meter.

Standards and reagents

All standards and reagents were of analytical grade.

2.8. Statistical analyses

The results are mean of five measurements ± standard deviation calculated.

Results

Polyphenol content

Georgian red wine boasted a polyphenol content of 4.4 ± 0.1 g/l, signifying a rich concentration and high quality of wine. Green tea, on the other hand, exhibited polyphenol content of 7.5 ± 0.2 % w/w, that corresponds to 0.94 ± 0.25 g/l in achieved

extract. Polyphenols are bioactive compounds abundant in both green tea and red wine. Polyphenols are known for their anti-inflammatory, antioxidant, and cardiovascular health benefits.

Antioxidant activity

Green tea exhibited a robust FRAP result of 61.2±1.2 % comparing with ascorbic acid set as 100 %, surpassing Georgian red wine at 18.2±0.5 %. DPPH result for green tea was 8.4±0.5 % of ascorbic acid, showcasing its substantial radical scavenging capacity, whereas wine displayed a lower but still significant antioxidant activity 3.7±0.1 %. The high FRAP result for green tea indicates its potent ability to reduce ferric ions, highlighting its superior antioxidant potential compared to Georgian red wine. Antioxidants play a crucial role in neutralizing free radicals, preventing oxidative stress, and reducing the risk of chronic diseases. Although red wine's FRAP result is lower, its DPPH result of 3.7±0.1 % suggests a commendable radical scavenging capacity. Both beverages exhibit antioxidant activity crucial for maintaining cellular health and preventing oxidative damage. According to scientific literature, Georgian red wines exhibited significantly higher antioxidant activity compared to West and Central European samples when assessed using the DPPH method. The highest antioxidant effect was particularly notable in wines derived from the Georgian cultivar *Saperavi*. These results underscore the exceptional antioxidant potential of Georgian red wine, highlighting their potential health-promoting properties [8].

Anti-inflammatory Activity

Upon conducting the experiments, we observed significant anti-inflammatory activity in both green tea and Georgian red wine. Paixão et al., showed that green tea exhibited a substantial anti-inflammatory effect, demonstrating a reduction in inflammation comparable to that of Sodium diclofenac [9]. Conversely, while red wine also showed anti-inflammatory activity, its efficacy was comparatively lower than that of green tea [10].

These results highlight the potential of both green tea and Georgian red wine as natural agents for mitigating inflammation. Further research into the specific mechanisms underlying their anti-inflammatory effects could provide valuable insights into their therapeutic applications for inflammation-related conditions.

Green tea demonstrated a substantial anti-inflammatory activity, 20% of Sodium diclofenac set as 100%, outshining red wine at 3.7%. Green tea's substantial anti-inflammatory activity underscores its potential in mitigating inflammation-related conditions. This surpasses the anti-inflammatory effect of red wine and even competes with Sodium diclofenac, a standard anti-inflammatory drug.

We expressed antioxidant, radical scavenging and anti-inflammatory activities of Georgian green tea and red wine in mmoles of ascorbic acid equivalents (AAE) and mg of Sodium diclofenac (SDF) equivalent per liter and the results are summarized in Table 1.

TABLE 1. Polyphenol content, antioxidant, radical scavenging and anti-inflammatory activities of Georgian green tea and red wine

Material	Polyphenols g/l	FRAP mmol AAE/l	Radical scavenging activity by DPPH mmol AAE/L	Anti-inflammatory activity mg of SDF/L
Georgian Green tea extract	0.94 ± 0.05	9 ± 0.2	1.2 ± 0.02	510 ± 5
Georgian Red wine	4.40 ± 0.10	43	0.52 ± 0.01	923 ± 8

Discussion

The results underscore the remarkable antioxidant potential of green tea, outperforming Georgian red wine in both DPPH and FRAP methods. This emphasizes green tea as a potent source of radical scavengers, potentially contributing to oxidative stress mitigation [11]. In terms of anti-inflammatory activity, green tea exhibited a substantial effect, surpassing the efficacy of Georgian red wine and even competing with Sodium diclofenac. This suggests a promising role for green tea in addressing inflammation-related conditions [12].

Total polyphenol content revealed that wine boasts a higher concentration compared to green tea. According to the data obtained, green tea with a lower content of polyphenolic compounds compared to wine, shows greater antioxidant and anti-inflammatory activity. This phenomenon is apparently associated with the content of different phenolic compounds in the products studied, as well as with differences in the activity of specific substances and also with their concentration. It is also worth taking into account the polymerization reactions of phenolic compounds that take place in wine depending on its aging. It is known that dimers and polymers are characterized by lower antioxidant activity than monomers of the same phenolic compounds.

Polyphenols are known for their health-promoting properties, and this disparity may contribute to the divergent effects observed in antioxidant and anti-inflammatory activities.

Conclusions

The achieved results suggest that both green tea and Georgian red wine exhibit health-promoting properties. Green tea stands out with its remarkable antioxidant and anti-inflammatory activities, as well as also significant polyphenol content. However, the higher polyphenol content does not suggest a greater activity potential for promoting health. These findings support the inclusion of green tea in a balanced and health-conscious diet. However, individual preferences and health goals should guide the choice between these beverages. The reasonable amounts of mentioned products for daily human consumption should be also taken into the account. Further research is needed to unravel the specific polyphenolic compounds responsible for these observed effects, paving the way for targeted nutritional interventions.

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Understanding individuals' well-being in higher education: A critical review of the Warwick-Edinburgh Mental Well-being Scale and its implications

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Abstract

This article presents a critical review of the Warwick-Edinburgh Mental Well-being Scale (WEMWBS) and its implications for understanding individuals' well-being in higher education. The review is structured into four main sections: the validation and psychometric properties of the WEMWBS, associations between student well-being and the WEMWBS, interventions and programs promoting student well-being, and a comparative analysis of the WEMWBS with the Mental Health Literacy Scale (MHLS). The first section focuses on the validation and psychometric properties of the WEMWBS, providing an in-depth examination of its development and validation process. This includes an exploration of the rigorous methodologies employed to establish the reliability, validity, and factor structure of the scale, ensuring its suitability for assessing mental well-being in diverse populations within the higher education context. Moving forward, the article investigates the associations between student well-being and the WEMWBS. This section offers valuable insights into the potential of the WEMWBS as a valuable tool for screening and assessing student well-being in higher education settings. The third section delves into interventions and programs aimed at promoting student well-being in higher education. It explores how the WEMWBS has been utilized in evaluating the effectiveness of these interventions,

shedding light on how the scale can inform the design and evaluation of initiatives that enhance student well-being. This section provides a comprehensive overview of the practical implications of the WEMWBS in fostering positive well-being outcomes among university students. Lastly, the article presents a comparative analysis of the WEMWBS with the Mental Health Literacy Scale (MHLS). By examining the similarities, differences, and potential complementarity between these two scales, this section offers insights into their respective strengths and limitations in capturing different aspects of individual well-being within the higher education context. It addresses the importance of considering multiple dimensions of well-being and mental health literacy when assessing and supporting the well-being of students in higher education.

KEYWORDS: WEMWBS; well-being; higher education; young adulthood; mental health

Introduction

The Warwick–Edinburgh Mental Well-being Scale (WEMWBS) is a widely recognized and validated instrument used to assess mental well-being on a population level. Consisting of 14 positively worded statements, the scale provides a comprehensive and holistic measurement of an individual's mental well-being across various domains [1]. The development and validation of the WEMWBS involved rigorous research methodologies and psychometric testing to ensure its reliability and validity. The scale has been validated through extensive studies and has demonstrated robust psychometric properties, making it a trustworthy tool for measuring mental well-being. By utilizing positively worded statements, the WEMWBS takes into account the positive aspects of mental health and well-being, focusing on individuals' positive emotions, functioning, and overall life satisfaction. The scale captures multiple dimensions of mental well-being, including positive affect, self-esteem, optimism, and positive relationships, among others. As a population-level measure, the WEMWBS is designed to assess mental well-being across diverse groups and can be used in various settings such as research studies, public health surveys, and program evaluations, in different languages [2]. Its validated nature ensures that the scale produces consistent and meaningful results when administered to large populations, allowing for comparisons and analysis at a broader level. Additionally, the WEMWBS has proven to be a valuable tool for monitor-

ing and evaluating mental well-being initiatives, informing policy decisions, and identifying areas for intervention and support. Its simplicity and brevity make it accessible and user-friendly, enabling efficient data collection and analysis [3].

Validation and psychometric properties of the WEMWBS

The measurement of mental well-being has been a subject of extensive debate, but there is an increasing consensus in favor of the conceptual framework underlying the Warwick-Edinburgh Mental Well-being Scale (WEMWBS) [4]. This framework recognizes that mental well-being encompasses both subjective feelings of positivity (Hedonia) and optimal psychological functioning (Eudaimonia). The WEMWBS is a widely used measure that assesses subjective well-being, encompassing both eudemonic and hedonic aspects [5]. Subjective well-being refers to an individual's evaluation of their own life satisfaction, happiness, and overall mental well-being. It goes beyond objective indicators of well-being, such as income or material possessions, and focuses on an individual's personal experiences and perceptions [6].

The development and validation process of the WEMWBS:

1. Development process: The WEMWBS was created by an expert panel that carefully considered current academic literature on mental well-being. They also conducted qualitative research with focus groups to gather insights from individuals regarding their experiences of well-being. Additionally, psychometric testing was conducted on an existing scale to refine and enhance the WEMWBS.
2. Validation on student and representative population sample: To establish the validity of the WEMWBS, it was administered to both a sample of students and a representative population. By including diverse groups of individuals, researchers aimed to ensure that the scale captured a wide range of experiences and perspectives related to mental well-being.
3. Content validity: Content validity, which refers to the extent to which the scale's items represent the construct being measured, was assessed by examining the frequency and distribution of responses to each item. This analysis helped determine if the items were capturing the intended aspects of mental well-being.
4. Confirmatory factor analysis: Confirmatory factor analysis was employed to test the hypothesis that the WEMWBS measured a single construct of mental well-being. This statistical technique helped determine the underlying structure of the scale and whether the items were measuring the intended construct.
5. Internal consistency: Internal consistency refers to the extent to which the items

within a scale are interrelated and measure the same construct. Cronbach's alpha, a commonly used measure of internal consistency, was calculated to assess the reliability of the WEMWBS. A higher Cronbach's alpha indicates greater internal consistency among the scale items.

6. Criterion validity: Criterion validity examines the extent to which the scale correlates with other established measures of well-being or related constructs. Researchers explored criterion validity by examining the correlations between the WEMWBS and other scales measuring mental health or well-being. Additionally, they tested whether the WEMWBS effectively differentiated between different population groups based on pre-defined hypotheses [7].
7. Test-retest reliability: Test-retest reliability assesses the consistency of scores over time. In the case of the WEMWBS, test-retest reliability was evaluated by administering the scale to participants and then re-administering it after a one-week interval. The intra-class correlation coefficients were calculated to determine the level of agreement between the two sets of scores.

By conducting a rigorous development and validation process, the creators of the WEMWBS aimed to ensure that the scale effectively measures mental well-being and provides reliable and valid results across diverse populations. The robustness of the scale's development process and validation procedures enhances its credibility and usefulness in research and practical applications related to mental well-being [5].

Associations between student well-being and WEMWBS

WEMWBS has been used to measure student well-being: One study examined how positive mental health and well-being are distributed and influenced by various factors in a sizable and diverse sample of tertiary-level students, utilizing the WEMWBS scale to assess mental well-being, aiming to provide insights into the factors that contribute to positive mental health among students. The study highlights the significance of a study that explores positive mental health and well-being scores specifically within a sample of students in higher education, using the WEMWBS. By focusing on the mental health and well-being of tertiary-level students, the study addresses a specific population that is often subject to unique stressors and challenges associated with academic pressures, transitions, and other factors related to university life. The findings of the study reveal a remarkable trend: students who possess a relatively adverse health and lifestyle profile—indicating that they may face health issues or engage in unhealthy lifestyle habits-demonstrate higher levels of mental health and well-being compared to the average student population. This unexpected finding challenges conventional assumptions that a healthier lifestyle

automatically corresponds to better mental health and well-being. It suggests that factors beyond physical health and lifestyle choices may influence mental well-being among students. Possible interpretations of the findings could include resilience and coping mechanisms developed by students facing adversity, a sense of personal growth and empowerment resulting from overcoming challenges, or the presence of other protective factors such as social support or a strong sense of purpose. The study's findings have implications for understanding the complex nature of mental health and well-being among students and highlight the need for a comprehensive perspective that goes beyond simplistic assumptions [8]. Further research is warranted to delve deeper into the underlying mechanisms and factors contributing to the higher mental health and well-being scores among students with an adverse health and lifestyle profile. Additionally, exploring the potential long-term effects on mental health and well-being outcomes for these students would provide valuable insights into their resilience and potential areas of support. Understanding the nuances of mental health and well-being among students is crucial for developing targeted interventions, policies, and support systems that promote positive mental health outcomes and overall well-being within the higher education context [9].

In addition, the COVID-19 pandemic had a detrimental effect on the university experience, leading to disruptions in teaching and well-being services. This disruption coincided with a significant decline in student well-being and a notable increase in the prevalence of clinical-level depressive symptoms, affecting over 30% of the student population [10]. A study utilizing the WEMWBS has demonstrated the substantial impact of the COVID-19 pandemic on the mental health of young individuals, including university students, and the findings suggest that the effects on mental health were particularly pronounced due to the data collection occurring during a later stage of the lockdown period, providing a more comprehensive understanding of the mental health consequences [11]. Consequently, mental health services should be ready to address an upsurge in mental health issues, with specific attention given to the needs of younger adults, women, and individuals residing in areas of higher deprivation. This highlights the importance of targeted support and interventions to mitigate the adverse mental health effects of the pandemic on these vulnerable populations [12].

Interventions and programs promoting student well-being

There has been a concerning trend regarding the mental health of university students, revealing a substantial increase in mental health concerns over the past decade. The statistic suggests that one in five university students currently face mental health

challenges [13]. The rise in mental health issues among university students has garnered attention from researchers, educators, and policymakers alike. Several factors contribute to this increase, including academic pressures, social and personal transitions, financial stress, and the overall demands of university life [14].

Many higher education institutions (HEIs) have dedicated welfare teams or departments that aim to provide support and resources to promote student well-being. These teams often consist of professionals such as counselors, therapists, and support staff who are trained to address the mental, emotional, and social needs of students. The rising demand for well-being services indicates a growing recognition of the importance of mental health and well-being among students. Factors such as academic pressures, personal challenges, and the transitional nature of university life can contribute to the need for additional support. The reported increase in demand by six in ten HEIs, exceeding 25% within a five-year period, indicates a substantial surge in the number of students seeking well-being services. This trend suggests that more students are recognizing the value of seeking support and are actively reaching out for assistance [15]. The reasons behind the increased demand for well-being services can be multifaceted. It may be attributed to a greater awareness and understanding of mental health issues, reduced stigma surrounding seeking help, and an overall increase in the prevalence of mental health concerns among the student population. The rising demand poses challenges for HEIs in terms of resource allocation, staffing, and ensuring timely access to support services. It highlights the need for institutions to continually assess and adapt their well-being support systems to meet the evolving needs of their students [16].

One recent study aimed to delve into students' experiences with well-being support services, with the overarching goal of understanding their engagement, identifying their specific well-being needs, and deriving concrete recommendations for the design and delivery of future interventions. To ensure that the interventions would be well-received and effective, the study adopted the Person-Based Approach, which places a central focus on the experiences and perspectives of the users themselves. By prioritizing the users' input, the study aimed to maximize the acceptability and effectiveness of the well-being resources. The research methodology consisted of an online survey involving 52 participants, followed by three focus groups with a total of 14 participants. The survey data were analyzed using a descriptive approach, providing an overview of the participants' responses. The qualitative data gathered from the focus groups underwent reflexive thematic analysis, which involved identifying recurring themes and patterns within the data. By integrating the findings from both the quantitative and qualitative data, the study revealed four key priorities expressed by students regarding well-being resources:

1. Ease of Access: Students emphasized the importance of easily accessible well-being resources. They highlighted the need for convenient and user-friendly platforms or services that can be accessed whenever they require support.
2. Inclusive and Preventative Approach: Students expressed a desire for well-being resources that cater to a wide range of needs and encompass a preventative approach. They emphasized the significance of interventions that address well-being proactively to promote mental health and prevent potential issues [17].
3. Sense of Community and Safe Space: Students emphasized the importance of fostering a sense of community and belonging within the well-being resources. They highlighted the need for a safe and supportive space where they can interact with peers, share experiences, and seek guidance without fear of judgment.
4. Application of Skills to Real-Life Contexts: Students expressed a desire for well-being resources that provide practical skills and strategies applicable to real-life situations. They emphasized the importance of interventions that equip them with actionable tools to navigate challenges and enhance their overall well-being [18].

The study's findings provide valuable insights into the factors influencing student engagement with well-being support services at universities. The resulting recommendations hold the potential to inform the development and improvement of future interventions, leading to the creation of well-being resources that are more acceptable, engaging, and effective for students. By aligning with students' needs and experiences, such interventions can better support their well-being throughout their university journey.

It is important to continue monitoring and addressing the mental health needs of university students through research, policy development, and the provision of accessible and effective support services. By prioritizing mental well-being, universities can create an environment that fosters academic success and personal growth while nurturing the overall health and well-being of their student population [19].

Comparative analysis of the WEMWBS with MHLS

Other measures such as the Mental Health Literacy Scale (MHLS) developed by O'Connor & Casey (2015) have also been implemented to assess individuals' well-being in Higher Education [20]. The evaluation of the methodological quality of the MHLS revealed substantial advantages over existing measures. These advan-

tages may include factors such as reliability, validity, sensitivity, and specificity in capturing and assessing mental health literacy. The MHLS offers a comprehensive framework for measuring mental health literacy, encompassing various dimensions such as knowledge of mental health conditions, beliefs and attitudes towards mental health, and understanding of available resources and help-seeking behaviors. By considering these multiple dimensions, the MHLS provides a more holistic and nuanced assessment of mental health literacy compared to other scales [21]. The use of the MHLS enables researchers, practitioners, and policymakers to assess individual and population-level differences in mental health literacy. It allows for the identification of gaps and variations in knowledge and awareness of mental health issues among different groups of individuals or communities. Furthermore, the MHLS serves as a valuable tool in evaluating the impact of programs and interventions designed to improve mental health literacy. By administering the scale before and after implementing such programs, researchers and practitioners can measure the effectiveness of these initiatives in enhancing individuals' mental health literacy. The MHLS can be utilized in various settings, including educational institutions, healthcare organizations, community centers, and public health campaigns. Its application can help inform the development and implementation of targeted interventions aimed at improving mental health literacy and promoting positive mental health outcomes. One recent cross-sectional study was carried out in ten universities in Egypt during the academic year 2022-2023 with the use of MHLS, which highlights the importance of inclusive mental health education, specifically targeting rural regions, and underscore the significance of personal connections in promoting mental well-being. Applying these findings has the potential to enhance mental health outcomes and diminish stigma associated with mental health in Egypt [22]. Overall, the methodological advantages of the MHLS make it a valuable tool for assessing and understanding mental health literacy at both individual and population levels. By utilizing the scale, researchers and practitioners can gain valuable insights into the knowledge, attitudes, and behaviors related to mental health, which can inform the design and evaluation of interventions and initiatives aimed at promoting mental well-being [23]. The WEMWBS and the MHLS are both assessment tools used in the field of mental health research. While they share a common goal of evaluating aspects of mental health, they differ in their specific focus and measurement objectives:

Table 1

	WEMWBS	MHLS
Focus	The WEMWBS primarily measures mental well-being or positive mental health. It assesses individuals' experiences of positive emotions, functioning, and psychological well-being.	The MHLS focuses on mental health literacy, which refers to individuals' knowledge, beliefs, and attitudes related to mental health issues. It assesses their understanding of mental health conditions, help-seeking behaviors, and the ability to provide support to others.
Measurement Approach	The WEMWBS utilizes a scale-based approach where respondents rate the frequency of specific thoughts, feelings, and behaviors related to well-being over a designated period. It provides a quantitative score reflecting the level of mental well-being	The MHLS also uses a scale-based approach, but it assesses mental health literacy through statements or questions related to various dimensions of mental health. Respondents indicate their level of agreement or disagreement, and the scale provides a quantitative measure of mental health literacy.
Scope	The WEMWBS captures a broad range of positive mental health aspects, such as positive affect, satisfaction with life, and personal functioning. It focuses on overall well-being rather than specific mental health literacy components.	The MHLS specifically targets mental health literacy and assesses knowledge, attitudes, and behaviors related to mental health. It measures specific aspects of mental health literacy, including knowledge of mental health conditions, beliefs about treatments, and help-seeking behaviors.
Application	The WEMWBS is often used in research studies, population surveys, and evaluations of mental health interventions to assess the impact of interventions on well-being outcomes.	The MHLS is commonly employed in studies and evaluations focused on mental health literacy, such as assessing the effectiveness of educational campaigns, interventions, or programs aimed at improving mental health literacy.

It's important to note that while both scales contribute to understanding mental health, they have distinct purposes and provide different insights. The WEMWBS emphasizes positive mental health outcomes, while the MHLS focuses on mental health literacy and knowledge. Researchers and practitioners may choose one or both scales based on their specific research objectives and the aspects of mental health they aim to assess [24,25].

Conclusion

The WEMWBS serves as a reliable and valid instrument for assessing mental well-being on a population level, contributing to a better understanding of mental health promotion and the overall well-being of individuals and communities. HEIs are responding to this increased demand by expanding their well-being services, implementing additional initiatives, and promoting mental health awareness on campus. They are working towards creating a supportive environment that fosters student well-being and strives to meet the growing demand for services [26]. In summary, this critical review contributes to our understanding of the WEMWBS and its implications for comprehending individuals' well-being in higher education. By examining its validation, associations with student well-being, interventions and programs, and comparative analysis with the MHLS, this article provides valuable insights for researchers, practitioners, and policymakers seeking to assess and promote well-being among individuals in the higher education setting.

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Post-COVID-19 symptoms: A case report and review

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Abstract

COVID-19 causes a number of symptoms associated with olfactory disorders and these clinical symptoms are widely reported in the current Literature. But more and more patients suffering from this disease turn to laryngologists with complaints of prolonged nasal obstruction in post-infection period. There is unclear connection between the nasal obstruction and the coronavirus disease 2019 (COVID-19). The study was performed in a clinic, among patients who had suffered from COVID-19 and which had complaints of nasal obstruction after recovery. The evaluation of the treatment results was carried out taking into account the anamnesis (subjective data) and the rhinoscopic picture (objective data). The case presentation is followed by a review of the potential causes and pathogenesis of nasal obstruction after COVID-19

KEYWORDS: COVID-19; nasal congestion; nasal breathing; chronic hyperotrophic rhinitis

Introduction

Coronavirus disease 2019 (COVID-19) was first detected in China in December, 2019, and declared as a pandemic by the World Health Organization (WHO) on March 11, 2020. [1]. The coronavirus disease 2019 (COVID-19) has become a serious pandemic. The reported symptoms of COVID-19 included cough (67.8%), fever (43.8%), increased sputum production (33.7%), sore throat (13.9%), and nasal congestion (4.8%) [2]. Some patients had only hyposmia and dysgeusia as their initial symptoms. Anosmia can occur alone or can be accompanied by other symptoms of COVID-19, such as a dry cough. Multiple cross-sectional studies have demonstrated that the incidence rate of olfactory dysfunction in COVID-19 patients varies from 33.9-68% with female dominance. [3]. In COVID-19 patients, the main manifestations were fever and cough and characterized by lymphocytopenia and ground-glass opacity changes on chest computed tomography [4]. Patients with severe infection can also develop neurological manifestations such as acute cerebrovascular diseases, skeletal muscle injury and impaired consciousness [5]. Besides, some patients may present with upper respiratory symptoms such as pharyngodynia, sore throat, nasal congestion, rhinorrhea and olfaction alterations [6, 7]. Olfactory dysfunction (OD), including anosmia and hyposmia, manifests itself particularly prominently among these symptoms in COVID-19 patients [8]. Covid 19 causes a number of symptoms, and all of these clinical symptoms are widely reported in the current literature.

In this article, we would like to consider the symptoms that are characteristic in pos-Covid period. The main complaint of most patients visiting laryngologists is similar to fatigue after severe acute respiratory syndrome (SARS). The most patients are turning to laryngologists with post-Covid-19 symptoms such as nasal congestion and difficulty in nasal breathing. The main complaints were lack of air and the resulting pain attack, general weakness, as well as frequent headaches. Hence, the aims of revue of cases to investigate and characterized the manifestations which appear after eradication of the coronavirus infection and its relation to disease severity.

Case Report

1. Patient Tamar G., 62 years old. In February 2020, she was diagnosed with Covid 19 (PSR test), the disease began with low-grade fever, loss of smell and taste (according to the patient's self-esteem), shortness of breath, general weakness. The disease was complicated by pneumonia,

the lung damage was estimated at 6-8 points. The patient was aware of the presence of COVID-19, which was confirmed by the PCR test. Adequate treatment was carried out, against which there was an improvement, the patient was discharged to an apartment, with the appropriate appointment and recommendations. After 2 months, the patient turned to the local doctor with respiratory complaints: shortness of breath, lack of air and connected with it the panic attack. The pneumatologist performed a complete examination of the respiratory and lung functions, as a result of which no changes were observed, and the patient was referred to the otorhinolaryngologist for further examination. Objective data: rhinoscopy – the nasal septum is slightly curved, both inferior turbinates are enlarged, the nasal passage is narrowed due to the hypertrophic of turbinates, the mucous membrane is light pink, the mucous membrane of the turbinates is more fermented. Oto-pharyngoscopy within normal limits. It is noteworthy that the patient had not previously complained of nasal congestion or any other rhinological symptoms (rhinorrhea, allergic rhinitis, etc.). The patient was diagnosed with turbinates hypertrophy and prescribed appropriate treatment (nasal corticosteroids (2-4 weeks) and montelukast with antihistamines for 20 days). The patients were reexamined 1 month later. There were no complaints about airlessness, nasal breathing was resumed, objectively – the inferior turbinates were moderately enlarged, the nasal passage was free.

2. Patient Anastasia F., 19 years old. In November 2020, she was diagnosed with Covid 19 (PCR COVID 19 – positive). He was treated on an outpatient basis, in self-isolation, under the supervision of a doctor. The disease was asymptomatic, with hyposmia (self-reported) for 3 days. After 2 weeks of self-isolation, the patient returned to a normal rhythm of life, but it was difficult for her to breathe through the nose, so she consulted an otolaryngologist. According to objective data: rhinoscopy – without curvature of the nasal septum, both inferior turbinates are enlarged, the mucous membrane is light pink. Oto-pharyngoscopy within normal limits. The patient is diagnosed with nasal turbinates hypertrophy. After taking topical corticosteroids for 2 weeks, breathing improved, the turbinates decreased in size, approached the norm, but the olfactory function did not recover.

Discussion

There can be many reasons for nasal breathing difficulties. Sometimes a stuffy nose without a runny nose does not look like a disease, but simply causes discomfort. This condition can really go away with a flu or a cold, if it was caused by these diseases. But completely different circumstances, if the congestion has arisen as a result of an allergic reaction or infectious processes have become chronic.

Rhinitis is defined as the presence of at least one of the following: nasal congestion, rhinorrhea, sneezing and itchy nose. There are two main classifications: allergic rhinitis and non-allergic rhinitis, a disease caused by an infection or allergy that causes nasal congestion [17].

Non-allergic rhinitis is a group of non-IgE-mediated diseases that share the common symptoms of nasal congestion, rhinorrhea, sneezing, and/or postnasal discharge, but not the itching that is characteristic of allergic rhinitis. Non-allergic rhinitis can be divided into two broad categories: inflammatory and non-inflammatory etiology. Inflammatory causes include post-infectious (viral and bacterial) rhinitis associated with nasal polyps and non-allergic rhinitis with eosinophilia, where eosinophils are present in nasal swabs but skin tests for air allergens are negative. Non-inflammatory causes include idiopathic non-allergic rhinitis (formerly called vasomotor rhinitis or, colloquially, „overly reactive nose “, which involves the involvement of the nerve, glandular and vascular pathways; however, this term is misleading because it implies a true understanding of the underlying pathophysiology of the disease. when it has not been definitively established [18]); medication rhinitis, which is medication-induced rhinitis; hormonally related (pregnancy); associated with a systemic disease (severe hypothyroidism); and associated with a structural defect (curvature of the septum, head trauma causing cerebrospinal fluid rhinorrhea). The classic symptoms of idiopathic non-allergic rhinitis are nasal congestion, post-nasal fluid and sneezing caused by irritating odors, perfume, wine, and changes in the weather [13].

With non-allergic rhinitis, both inflammatory and non-inflammatory etiology, the lumens of the nasal passages narrow, which causes nasal congestion without a runny nose; frequent or constant exposure to the nasal mucosa of any allergens or irritants. This circumstance leads to dysfunction of the mucous membrane and can cause chronic edema. A blocked nose leads to breathing through the mouth, which is believed to destabilize the upper airway and aggravate the condition.

Three conditions can be considered as a cause of obstruction of nasal breathing: anatomical conditions of the nose (deviation of the septum, hypertrophy of the inferior turbinates), chronic rhinosinusitis (CRS) and chronic nasal inflammation

caused by allergic or non-allergic rhinitis [12].

The nose and sinuses share common vascular and anatomical pathways, which explains why rhinitis coexists with sinusitis. Acute viral rhinitis is the most common form of upper respiratory tract infection and is usually caused by viral rather than bacterial agents [14,15]. Common causes of viral rhinitis include rhinovirus, coronavirus, adenovirus, influenza virus, parainfluenza virus, respiratory syncytial virus, and enterovirus [15,16]. These viruses cause damage to the tight junctions between epithelial cells, destroy their membranes, penetrate into epithelial cells and dominate the metabolic activity of the host cell, using it for their development and causing destruction and death of the host cell. Usually, the symptoms of infectious rhinitis resolve on their own, and there is no need for drug therapy as an initial approach to the disease [16]. Antibiotics are not indicated for viral rhinitis if there is no bacterial superinfection [14,15].

Chronic rhinitis is a long-term, sluggish inflammatory process in the structure of the mucous membranes of the nasal cavity, resulting from contact with infectious agents, allergens, or due to changes in the tone of the vessels located in the submucous layer of the shells. The main manifestation of the disease is persistent difficulty in nasal breathing, in severe cases, it may be completely absent.

The term chronic rhinitis refers to 3 forms of rhinitis: catarrhal, hypertrophic and atrophic. Chronic rhinitis is defined as rhinitis that persists for 2-3 months. It has been established that patients with chronic rhinitis suffer from concomitant diseases such as asthma, conjunctivitis, otitis media, sinusitis, eczema, food allergies, migraines and depression [9]. Chronic rhinitis can cause migraines due to inflammation, mast cell degranulation, and autonomic dysfunction [10]. Chronic hypertrophic rhinitis can cause nasal obstruction and interfere with breathing, and prolonged nasal blockage can cause sleep apnea [11].

It is known that in chronic rhinitis, especially in the hypertrophic form, thickening of the mucosa, submucosa, seromucinous glands, periosteum and bone is characteristic. Changes are more noticeable on the turbinates – this is one of the objective signs of chronic rhinitis. With this form of the disease, there is an active proliferation of the mucous membrane of the nasal passages. The violation causes permanent nasal congestion, which is mechanical in nature and is not sufficiently relieved by vasoconstrictor drugs. Common causes of hypertrophic rhinitis are recurrent nasal infections, chronic sinusitis, chronic irritation of the nasal mucosa from smoking, industrial irritants, prolonged use of nasal drops, vasomotor and allergic rhinitis.

The predominant symptom is nasal congestion. Nasal discharge is thick and sticky. Some complain of headache, heaviness in the head, or transient anosmia.

In the cases examined by us, the predominant symptom in post-infection period was nasal congestion and obstruction of nasal breathing, in the absence of discharge or the discharge were minor. One of the characteristic symptoms of coronavirus infec-

tion is loss of smell, that which was also present in both cases. During illness, swelling of the nasal mucosa occurs, which not only causes mechanical obstruction of nasal breathing, but also disrupts access to the olfactory receptors in the upper part of the nasal mucosa. In addition, prolonged edema can cause degradation of receptors and nerve tissue, which explains in some cases the duration of anosmia.

As for the objective data, the analysis of the study showed: anterior rhinoscopy revealed an increase in the inferior turbinates, which is characteristic of chronic hypertrophic rhinitis. The mucous membrane of the turbinal is thick. When taking vasoconstrictor drugs, there is a slight shrinkage. The maximum changes were observed in the inferior turbinate: the size of the turbinate was exaggerated completely or only at the anterior end, posterior end, or along the inferior border. Characteristic changes were observed mainly in the period after COVID-19 and were not observed in the subjective and objective data of the patients examined before this disease.

In both cases, the process of nasal obstruction was short-lived, I believe that hypertrophic changes mainly affected the mucous and submucosal layers and did not affect the bone.

This is also confirmed by the fact that under the influence of drugs, in particular the use of vasoconstrictors, in both cases the inferior turbinates decreased in size. As a treatment, it is proposed to regularly irrigate the nasal cavity with saline solutions. The use of nasal steroids, which are topical, are not absorbed into the bloodstream and are not addictive, also has a positive result in eradicating symptoms.

This allowed us to use topical corticosteroids, which soon had a positive effect on patients, although this did not exclude the possibility of surgical treatment.

Concluding Remarks

Nasal congestion and difficulty in nasal breathing is one of the symptoms that develop in the post-covid period, which is often the cause of insufficient breathing and a panic attack. Symptoms are similar to those of chronic hyperotrophic rhinitis. The reasons are not entirely clear, but the methods of treatment are almost identical to the medical treatment of chronic rhinitis. In conclusion, we must be concern about many conditions that mimic chronic rhinitis. Attention to the detail of history and physical examination should be considered. These cases showed the role of maintaining differential diagnosis for a common complaint, which were congestion and difficulty in nasal breathing at pos-COVID period.

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Electromagnetic field, conduct cross in the open field and neurochemical correlate blood and urine on the background of the supply of oils of grape seeds

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Abstract

The influence of an electromagnetic field (EMF) – network frequency causes minimal CNS dysfunction in Wistar rats in ontogenesis, which is expressed by a decrease of the levels of glutamate and aspartate, methionine and serine, in the blood – lysine, taurine, tyrosine, catecholamine and serotonin, an increase GABA and glycine in the blood, proline and cysteine in the urine. The ratio of excitatory/inhibitory mediator amino acids is significantly reduced. The ratio of essential/non-essential amino acids and the total level of amino acids also decrease in the blood. Against the background of taking the herbal preparation (grape seed oil), the identified changes disappear or smooth out, which is manifested in the behavior of rats in the open field – the animals are characterized by a smaller number of urinations and boluses, an increase in the total time of grooming and a small number of translocations.

KEYWORDS: EMF; amino acids; rat behavior

Introduction

Among the effects associated with exposure to an electromagnetic field (EMF), neurotropic and psychotropic effects occupy a special place, since the nervous system, along with the endocrine, cardiovascular and reproductive systems, is one of the most sensitive to the effects of EMF [1]. In connection with the ecological crisis, special attention is paid to finding ways to protect against the effects of chronic low-frequency EMF exposure in natural conditions [2,3]. As protection against EMF, it is possible to use biologically active substances of natural origin that can activate the body's protective resources, affecting mainly the neurohumoral and immune-hematopoietic systems. The general nonspecific resistance of the body increases, the endogenous background of resistance is stimulated (a complex of endogenous biologically active compounds: amines, thiols and other antioxidants that perform protective functions and suppress the accumulation of a destructive excess of peroxidation products). Due to the absence (or low) toxicity and good tolerance, products of natural origin are recommended as food additives that increase the overall nonspecific resistance of the body, stimulating protective, antioxidant reserves. Among the biologically active substances of natural origin, representatives of bioflavonoids – oligomeric proanthocyanidins – antioxidants that prevent cell degeneration occupy the central place. They also contain vitamin E. It should be noted that many components of plants are included in the list of medicinal herbal raw materials [4]. The pharmaceutical market today advertises many medicinal compositions containing special dietary supplements with antioxidant action. It is generally accepted that natural substances exhibit a much more optimal therapeutic and prophylactic effect than synthetic counterparts do.

In this aspect, grape seed oil (oleum Vitini Vini Pezae) deserves special attention. A number of researchers [5,6] convincingly showed that among the majority of known oils recommended as food additives, the highest content of essential fatty acids is found in grape seed oil, the physicochemical constants and biological activity of which depend on climatic and geographical conditions [7,8].

Studies related to the action of network frequency EMF on Wistar rats before and after feeding with a food supplement from grape seeds in Georgia have not been carried out.

The aim of the study is to determine the nature of the action of the dietary supplement from the Saperavi grape seed oil on some biochemical correlates of blood plasma and urine, as well as the behavior of rats in an open field before and after exposure to EMF of the network frequency. Studies of this nature contribute to the search for optimal ways of active prevention of EMF exposure in urban environments.

Materials and Methods

The experiments were carried out on two-month-old Wistar rats weighing 76-85 g. The animals were bred in the nursery of our Center and kept under the same conditions of care and free access to water and stable food (barley, corn, sunflower, cabbage, carrots and bread with milk. They were also given a multivitamin “Undevit”).

The animals were divided into three groups of 10 rats each. Control group A ate a standard diet. Experimental group B also had a standard diet and was subjected to a continuous magnetic field for 30 days. Experimental group C received a standard diet and peritoneal 0.5 ml of a 5% solution of grape seed oil (Natural Extra) “Saperavi” for 10 days before exposure to a magnetic field.

The electric field was applied using an original induction coil (coil diameter 750 mm, length 2200 mm). The coil had several sections of turns and a control unit of two types. The first of them made it possible to influence the high voltage of a stationary EMF of the mains frequency, and the second was universal – for the impact of a stationary and simulated frequency. The large dimensions of the coil made it possible to study complex forms of behavior and their ethological correlates even directly during the action of an EMF. Groups C and B were exposed to an electromagnetic field with a frequency of 50 Hz, 1.5 MT.

As behavioral comparison criteria, ethological parameters were used, determined by the method of the so-called “Open Field”, which was a round chamber with a diameter of 80 cm, divided into 32 identical sectors. It was illuminated from a height of 1 m with a 200-watt lamp. The duration of each rat in the “Open Field” was 180 seconds. The results were transmitted by a video camera to a computer equipped with a special Rat Watcher program. The program was a significantly improved version of the Pole-91 program previously developed at our Center [9]. It is provided for personal computers such as IBM PC and runs on the Windows operating system.

The following parameters were recorded: animal motor activity (by which the time spent to leave the central circle was noted), the number of sector lines crossed, the number of translocation cycles and time spent, and the average line crossing speed. Orientation-exploratory activity was assessed by the number of vertical standing up, according to the average time spent on one standing up. The idea of emotional activity was assessed by the number of boluses and urinations. Stereotypical activity was judged by the number of grooming cycles, the amount of time spent on them, etc. Attention was paid to the number of cycles of immobility, the average time spent on one cycle.

The level of free amino acids in plasma and urine was determined by high-performance liquid chromatography on an RTS-1 chromatograph (Woters, USA) according to

the method [10], and catecholamines on the same device according to the method [3]. Blood was taken from the distal part of the tail after appropriate treatment.

The results of the study were subjected to statistical processing using Student's criteria for the computer program SPSS version 13 ANOVA.

Saperavi grape seed oil was obtained by pressing at low temperatures [11]. This method is the most gentle, as it is carried out without additional heating of the oil. An increase in pressure in the mixture is accompanied by a natural increase in temperature up to 35°C, which does not adversely affect the quality of the oil. The oil obtained in this way has a pronounced aroma and taste, and biologically active substances (vitamins, polyunsaturated fatty acids, pigments, etc.) are almost completely preserved. The oil is not subjected to refining, which significantly reduces its quality. The considered method does not allow to obtain oil in a large volume, it is called "Natural Extra". After the end of the first phase of the process, the pressings are separated, the residue is mixed and pressed again. Obtained after the secondary extraction is filtered, it is also of high quality and is not subjected to refining. It's called Natural Delicate Oil.

Results

After exposure to EMF group B, a distinct change in the level of amino acids is observed – namely, compared with the control, there was a decrease in the blood plasma of proline, methionine, tyrosine, glutamic acid, and aspartic acid. The content of asparagine, glutamine, valine, tryptophan and threonine also decreased. The content of leucine and cysteine did not change. Amino acids in the urine are increased. Compared to the control, the level of glycine, asparagine, aspartic acid and tryptophan decreased. The level of valine, glutamine, threonine also moderately decreased, the content of tyrosine and phenylalanine did not change, the level of cysteine, proline, leucine and alanine.

The effect of EMF on rats treated with a food supplement (group C) turned out to be significantly different.

Out of the plasma monoamino monocarboxylic amino acids, the levels of alanine and leucine did not change, valine and threonine increased and glycine decreased, while in the urine the level of valine and glycine increased, leucine, threonine decreased, and alanine did not change. Out of the monoamino dicarboxylic acid amino acids in plasma and urine, the levels of aspartic and glutamic acids, as well as asparagine and glutamine, increased significantly. Among sulfur-containing amino acids, plasma and urinary methionine levels increased, while plasma cysteine levels

increased and remained unchanged in plasma. In the group of aromatic amino acids, plasma tyrosine levels increased, while plasma and urine phenylalanine levels did not change. The content of heterocyclic amino acids (proline and histidine) in plasma remained unchanged, while in urine it increased and decreased respectively. Tryptophan levels in plasma and urine increased.

As a result of exposure to EMF, significant changes were observed in relation to biogenic amines. In plasma, there was a decrease in the level of adrenaline, norepinephrine and dopamine, while in the urine only a decrease in dopamine.

And the levels of norepinephrine and adrenaline significantly increased (A-B). The content of serotonin in plasma decreased, in urine it did not change, but the level of 5-indoacetic acid increased significantly.

The effect of the magnetic field on rats treated with a food supplement (group C) turned out to be significantly different.

The levels of dopamine, norepinephrine, adrenaline and serotonin in plasma increased significantly in group C rats compared to group B, while the content of dopamine, adrenaline and 5-indolacetic acid in the urine increased. Serotonin levels have not changed.

The following observations were made in the “open field”. Comparative analysis of the behavior of control (A) and grape-seed oil-fed rats (B) groups in the “open field” showed a difference in motor activity. The latent period of exit from the central circle changed, which turned out to be shorter in the rats of the control group (1.9±0.8 instead of 3.2±0.6 seconds). For group B, the number of crossed lines is much higher compared to the rats of the control group A (48.6±2.0 and 42.8±5.0 seconds). The difference is significant both in the time spent on translocation and in the percentage of time spent on translocation in relation to the total time spent on the experiment. From this it follows that the rats of group B move faster compared to the control ones and spend on average less time to overcome the cells – 30.0±4.2% instead of 35.6±4.0%. This conclusion is confirmed by the number of cycles of immobility. The table shows that in rats of the control group these indicators are higher (13.2±0.2 sec.) than in animals of group B (4.1±0.5 sec). In addition, the rats of groups A and B also differ in their orientational activity in the open field. The number of vertical rises was 17.0±1.01 (group A), and in group B rats it was 22.1±0.5. The average time of vertical risings for control animals was 0.8±0.2 sec., and for group B it was 1.6±0.3 sec. An increase in the number of vertical standing and a significant increase in the time spent on orientation while in one or another compartment means that the rats are examining the compartment in which they are located. Comparison of the stereotypical activity of rats of groups A and B in the open field showed that, although the number of grooming cycles in animals differs little, the rats of group B spend 9.7±0.3 seconds per cycle, and the control rats – 4.9±0.1 seconds.

Thus, based on the data obtained, it can be concluded that rats treated with grape seed oil are characterized by lower anxiety, which is manifested in fewer urinations and boluses, a high number of total grooming times, and a small number of translocations. As a result of exposure to a magnetic field (group C), the behavior of rats in the open field changed significantly compared to the indicators of the control group A.

The exit time from the central circle significantly decreased (1.2±0.5 sec 1.9±0.8 sec, respectively), the number of crossed cells significantly decreased (34.4±2.9 and 42.8±5.0 sec, respectively), and the number of immobility cycles also decreased (10.1±1.8 and 13.2±0.2 sec), increased the specific time of immobility during the testing period (50.2±4.0 and 30.3±4.7%) and translocation during the testing period (38.0±3.5 and 35.6±4.0%), respectively. Thus, they move more slowly, as a result of which the number of crossed cells decreases. Also in group C, there is a very low number of rises to the paws, which is especially reduced in the middle circle and adjacent cells (9.8±1.0 and 17.0±1.01, respectively). This may be due to a decrease in the activity of the central nervous system, as a result of which the number of orientation reflexes decreases, and the number of urination and boluses increases sharply (2.5±0.1 and 8.0±0.2). the average number of grooming cycles (4.5±0.7) compared with group A (11.1±0.2) drops sharply against the background of an increase in its total time (6.8±0.1 sec). Behavior of group D rats in a magnetic field and those fed with grape seed oil significantly differs from the behavior of group C animals. The data indicate low anxiety. The specific time spent on translocation for group C animals is 38.0 ±3.5, and for group D animals it is 45.8 ± 0.6%. The specific time of immobility in rats of group C was 50.2±4.0% sec, and for animals of group D it was 35.9±0.7%, while the number of immobility cycles increased significantly (16.8±0.3), the time to exit from the central circle (3.8±0.4 sec) and the number of crossed lines (40.9±0.5). The rats of group D outperformed group C with a significant increase in the number of vertical standings (14.8±0.6) and their duration (1.9±0.5 sec), as well as in the average number of grooming cycles (7.4±0.5) and their total time (9.6±0.3 sec). The mean number of boluses (1.2±0.4) and frequency (1.5±0.4) appeared to be reduced.

Thus, as a result of exposure to EMF in blood plasma and urine, a certain change in the level of individual amino acids is observed, which themselves or through derivatives affect the functional state of the central nervous system. Increased levels of GABA and glycine. It is accompanied by a decrease in serotonin levels. These shifts not only affect the processes of activation of the brain, but also contribute to the emergence of dysfunction of behavioral processes, which manifests itself in a change in the activity of animals and a decrease in plasma glutamate and aspartate with a parallel decrease in GABA and glycine. Of great importance is a significant change in the qualitative ratio of the amino acid composition of the

plasma, followed by a change in the balance of functionally opposite mediators, the pathogenetic significance of which is the regulation of the functional activity of the central nervous system. In plasma, there is a decrease in the level of serotonin, in the urine only 5-hydroxyindoleacetic acid. The ratio of the levels of dopamine and norepinephrine to serotonin revealed a significant increase in this indicator, which convincingly indicates a decrease in the relative amount of serotonin, that is, there is a pronounced activation of the kynurenine pathway of tryptophan metabolism, which leads to an imbalance of functional processes. Deviation from the optimal level and ratio of biogenic amines and free amino acids, caused by the influence of a magnetic field, changes the biochemical and physiological processes directly or indirectly associated with the implementation of behavioral acts. The change in the level of amino acids and their derivatives in biological fluids and tissues is one of the most important causes of multiple pathology, which manifests itself not only in the dysfunction of the nervous system, but also contributes to the development of a number of nervous and mental disorders as a result of the action of EMF, especially in ontogenesis [12,13].

A food supplement (grape seed oil) contributed to a certain regulation of the changes caused by exposure to EMF. In the group of rats irradiated with EMF and treated with a food supplement, there is an increase in plasma glutamate and aspartate, which is accompanied by a decrease in GABA and glycine, which helps to optimize the ratio of activating/inhibiting amino acids. Obviously, a change in the balance of functionally opposite mediators contributes to the process of regulating metabolic shifts. The above problems of the effect of EMF and food additives on the level of individual biochemical constants of the organism and the holistic behavior of animals require further study. Meanwhile, multiorgan lesions characteristic of EMT, according to modern data are largely associated with the primary violation of the functional processes of the CNS, including primary cerebrovascular disorders [14,15]. In this regard, the study of the impact of the electromagnetic field on various forms of behavior against the background of food additives can be of practical importance.

Discussion

The data obtained indicate that the decrease in anxiety after a certain time after the use of the herbal preparation is due not only to the residual effects of organic changes in the brain structures associated with the organization of behavior, in particular, spe-

cific glutaminergic neurons of the “attack center” of the hypothalamus but also with the activation the entire adaptive-compensatory system in the process of restitution from exposure to EMF. The clarification of these issues will deepen the current understanding of the chronic effects of industrial EMF (frequency 50 Hz, inductance 1.5 MT) and the effect of grape seed oil on neurochemical correlates and dysfunction of the nervous system of animals.

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