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PUBLIC HEALTH

REVIEW OF POLICIES AND ACTIONS ON TACKLING GLOBAL CLIMATE CHANGE - COP26 - IS THIS THE LAST CHANCE?

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Abstract

The world is facing the visible and potential consequences of climate change. No place on the Earth is immune to these changes. Current policy applied worldwide anticipates global warming of about 2.7°C compared to pre-industrial level by the end of the century. By implementation of Nationally Determined Contributions (NDCs), warming will be kept to 2.4°C. If long-term commitment targets or net-zero targets are included, then warming would be kept to about 2.1°C above the pre-industrial levels. The warming projections dropped by 0.3°C after the made pledges and established targets by the USA and Peoples' Republic of China. According to the "optimistic" scenario, if the 140 analysed countries reach the zero emission targets, then the average warming will be 1.8°C, or below 2°C. There is a significant gap between the pledges made by the governments and the total level of actions they have undertaken so far. With the new economic challenges, it is clear that we are at a crossroads. The impact of COVID-19 crisis will be crucial for the future of the climate policy. Climate changes will not wait. Their threat is over our heads and each and every day we face them. Every individual has a role to play in dealing with global climate change and we all can contribute to this threat if we all work together in a synchronous way. A greater political involvement is needed along with collective actions taken by all social actors. Over the last two years, the World Health Organization has advocated for greater inclusion of health authorities and services in Nationally determined contributions through activities to reduce the implications on health by climate change.

ЈАВНО ЗДРАВЈЕ

ПРЕГЛЕД НА ПОЛИТИКИ И АКЦИИ ЗА СПРАВУВАЊЕ СО КЛИМАТСКИТЕ ПРОЕМЕНИ- КОП 26 - ДАЛИ Е ТОА ПОСЛЕДНАТА МОЖНОСТ?

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Клучни зборови: КОП26, климатски промени, политики, акции

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Печатарски права: ©2023 Михаил Кочубовски, Гордана Ристовска, Александра Петрова, Џансун Буковец, Кристи Дишо, Томислав Хаџи Тошев, Александар Петрески. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираат оригиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Светот се соочува со видливи и потенцијални последици од климатските промени. Нема место на Земјата кое не е зафатена од овие промени. Сегашната политика што се применува ширум светот предвидува глобално затоплување од околу 2,7°C во споредба со прединдустриското ниво до крајот на векот. Со имплементација на националните одредени придонеси (NDCs), затоплувањетоќе се одржи на 2,4°C. Доколку се вклучат долгорочни цели или целите на "net-zero", тогаш затоплувањето би се задржало на околу 2,1°C над прединдустриските нивоа. Проекциите за затоплување се намалија за 0,3°C по дадените ветувања и воспоставените цели од страна на САД и Народна РепубликаКина. Според „оптимистичкото" сценарио, доколку 140-те анализирани земји ги достигнат целите за нулта емисија на штетни гасови, тогаш просечното затоплување ќе биде 1,8°C или под 2°C. Постои значителен јаз помеѓу ветувањата дадени од страна на владите и вкупното ниво на активности што тие ги презеле досега. Со новите економски предизвици, јасно е дека сме на крстопат. Влијанието на КОВИД-19 пандемијата ќе биде клучно за иднината на политиката поврзана со климатските промени. Климатските промени нема да чекаат. Нивната закана е над нашите глави и секој ден се соочуваме со нив. Секој поединец има улога во справувањето со глобалните климатски промени и сите ние можеме да придонесеме за отстранување на оваа закана ако сите работиме заедно на синхронизиран начин. Потребно е поголемо политичко вклучување како и колективни активности преземени од сите општествени чинители. Во текот на последните две години, Светската здравствена организација се залагаше за поголемо вклучување на здравствените власти и услуги во Национално одредени придонеси преку активности за намалување на импликациите врз здравјето од климатските промени.

Introduction

The world is facing the visible and potential consequences of climate change. No place on the Earth is immune to these changes. The latest paper of Lynas et al. from 2021, clearly states that 99.9% of climate changes have been caused by humans. People all over the world are aware of this, but nonetheless the actions taken and their success are debatable[1].

Did we have to wait until 2021 to initiate discussion on this issue? No! In 1896, Svante Arrhenius estimated that with increased CO2 emission, the Earth's temperature would increase for 5°C by 2100[2].

In 1963, for the first time ever, an expert meeting was held and majority of climate change implications were presented[3]. In 1970, again for the first time, the Earth Day was celebrated and eco-campaigns were globally initiated to increase the awareness for environmental protection[4].

The first World Climate Conference was held in 1979 in Geneva. It is considered a harbinger of the foundation of Intergovernmental Panel on Climate Change (IPCC) in 1988.

The Secretariat of the United Nations Framework Convention on Climate Change (UNFCCC) was established in 1992 as an entity of the UN located in Bonn, Germany. The Secretariat provides technical expertise and helps in the analysis and review of information about climate change reported/submitted by each country. Today, the Convention is ratified by 196 countries, among them the Republic of North Macedonia[5].

The aim of this paper was to make a review of the policies and actions taken to tackle climate change, the accent being on COP2[6].

COP as a significant turning point

After the UN Framework Convention on Climate Change (UNFCCC) was ratified in 1994, the next year the first Conference of the Parties in Berlin (COP) was held. Since 1994, COP meets every year and it is the supreme decision-making body of UNFCCC. All states of UNFCCC review the implementation of the decisions and recommendations, undertake measures and necessary decisions to promote the implementation of the Convention[5].

The Kyoto Protocol was adopted in 1997 and it entered into force in 2005. According to this Protocol agreed at COP3, the industrialized countries for the first period of the Protocol committed to limit and reduce emissions of carbon dioxide, methane, nitrous oxide, hydrofluorocarbons, perfluorocarbons, and sulfur hexafluoride during the five-year period of 2008-2012 to at least 5% in comparison to the level of these gases in 1990. The EU and its Member States committed to an 8% decrease in their emissions in that period[6].

The Kyoto Protocol was not ratified by the United States of America and Canada, so this Protocol entered into force in the 36 remaining countries. According to Shishlov *et al.*, the average annual emissions in the period 2008-2012 were 24.4% below the emissions from 1990. If hypothetically the USA and Canada participated, it would have reduced these emissions by 11.8%. Another reason mentioned in this paper was the collapse of the Eastern Bloc and financial crisis in

the period of 2007 and 2008 that significantly contributed to reduction of greenhouse gas emissions[7].

Specifically, the EU countries, without Cyprus and Malta that did not have targets, succeeded in reducing the emissions of around 19% without counting the additional reductions coming from carbon and trading systems for greenhouse gas emissions[8].

Unfortunately, this does not present the real picture in the world. According to The Emissions Gap Report 2012, the other countries increased the emissions so much that the increase of global emissions was 32% from 1990 to 2010[9].

In spite of the international agreements on fight against climate change, countries do not implement the recommendations and assignments and even if they participate, they do not accomplish ambitious goals[10].

In 2009, COP15 was held in Copenhagen, Denmark, and for the first time the objective of 1.5 to 2°C was established, and at COP16 held in Cancun, Mexico, industrialized countries pledged 100 billion dollars per year by 2020 for fight against global climate change[11].

As a continuation of the previous agreements, the Paris Agreement was adopted on 12 December 2015. A total of 193 countries were Parties of the Agreement, and the Republic of North Macedonia ratified it on 9 January 2018[12].

The objectives of the Paris Agreement are:

1. To reduce global warming below 2 and preferably to 1.5°C compared to pre-industrial levels;
2. To increase the ability to adapt to the negative impacts of climate change and to encourage climate resilience and development of low greenhouse gas emissions in a way that it does not threaten food production;
3. To prepare financial projections (flows) in compliance with the new climate plans and climate-resilient changes[12].

The adoption of the Nationally Determined Contributions (NDCs) and their update every five years can be considered as one of the greatest benefits of the Paris Agreement.

Article 6 from the Paris Agreement anticipates implementation of NDCs of the Parties through voluntary international cooperation in order to stimulate cleaner technologies and an overall transition towards a low-carbon economy. Countries with low emissions will be allowed to sell the excess capacity to countries with higher emissions by an overall restrictions of greenhouse gas emissions providing their net reduction. Demand and supply of allowed emissions will lead to formation of a carbon global price that will connect the negative external effects of greenhouse gas emissions and the pollutants. In other words, by paying the price for the carbon the countries that exceed their NDCs would bear the expenses for global warming[13].

It is indisputable that the goal to reach a healthier world depends on fulfillment of the above-mentioned aims. Also, greenhouse gas emissions should be reduced as soon as possible and to reach net zero by the middle of the 21st century. By 2020, each country that adopted the Agreement had to submit its plans for actions regarding reduction of greenhouse gas emissions. According to

this Agreement, developing countries with their financial and technological capacity have to be leaders in accomplishing the objectives. With the establishment of Enforced Transparency Framework (ETF), starting in 2024, countries should report transparently on actions taken to fight climate change[14].

However, according to the paper published in *Nature*, in addition to Intended Nationally Determined Contributions (INDCs), a median warming of 2.6-3.1 degrees Celsius is expected by 2100[14].

No consensus was achieved at the COP25 in Madrid on the issue of common time frames for mutual implementation of climate plans. In general, there was no progress in mitigation, adaptation and finance to deal with climate crisis[15]. There was no governing body that could ensure implantation of these agreements and hence, the Conference was considered unsuccessful[16].

United Nations Environment Programme for 2020 expected that by the end of this century global mean temperatures would rise for more than 3°C. Having in mind that the COVID-19 pandemic contributed to reduction of CO2 emission, if countries succeed to recover from the pandemic with low carbon emission, and in line with the pre-pandemic estimations, then greenhouse gas emissions would be reduced by 25% until 2030[17].

Six years after the adoption of the Paris Agreement, climate actions became a key part of the plans for recovering from COVID-19 pandemic. But, in spite of this, having in mind the incomplete implementation of previous plans and agreements, there was no true hope for adherence to the next plans and agreements. Therefore, under the slogan *Uniting the world to tackle climate change*, COP26 was held.

On 25-26 July 2021, more than 50 ministers and UN representatives discussed about the implementation and goals of COP26. The agenda consisted of five topics: boost adaptation, keeping 1.5°C alive, loss and damage, finalizing the Paris Rulebook – focusing on Article 6, and mobilizing finance[18].

One month prior to COP, as usual, Pre-COP was held. It took place in Milano (Milano Convention Center) from 30 September to 2 October 2021. In fact, Pre-COP was the last official multilateral event where participants from more than 50 countries, representatives of UNFCCC Secretariat, civil society representatives were present, before the meeting in Glasgow in November[19].

Within the frameworks of Pre-COP, it is very important to emphasize the participation of young people, their perspectives, commitments and recommendations presented in the Youth Manifesto that delivers 4 key messages:

- Increased financial support for the young and their engagement and participation in the decision-making processes regarding climate change.
- Energy transition by 2030 that prioritizes keeping 1.5°C alive. Urgent use of diverse means available for adaptation and alleviation of damages, especially for the most vulnerable groups and regions. Recognition of tourism's vulner-

ability by the impacts of global climate change and building capacities, monitoring, investment and decision-making processes towards resilient recovery of blue and green tourism.

- Support participation of young entrepreneurs, artists, farmers, and athletes, particularly those from marginalized groups (ethnic minorities, indigenous people, persons with disabilities, etc.). Enhance ecological transparency and accountability. Abolishing the fossil fuels by 2030 at the latest. All non-states actors, including UN bodies, fashion, sport, art, entrepreneurship, agricultural entities etc. must not accept any fossil fuels investment, lobbying activities from this industry, especially in relation to international negotiations.
- Raising public awareness, mobilization of more people and active involvement in issues addressing climate change. Informing the entire population in an accessible and understandable way, starting with education of children and students at all levels through a unique and integrated system[18,19].

Body language, interpersonal communication, the mood, possibility for direct discussion, shared workspaces, establishment of international cooperation and building confidence – all of these greatly affect conference outcomes[20].

In 2021, the 26th meeting of COP was held in Glasgow (Scottish Event Campus), Scotland, UK. The Conference took place between 31 October and 13 November 2021. The Summit was hosted by the UK in partnership with Italy. It was attended by 120 country leaders, 197 representatives and more than 40,000 participants from governments, a large number of representatives of non-governmental organizations and youth movement, activists and media.

The official negotiations happened within a two-week period. Primarily technical issues were discussed in the first week, and the second week, meetings on high level were held and final negotiated decisions were made[21].

Quote

"1. Secure global net zero by mid-century and keep 1.5 degrees Celsius within reach.

To deliver on these targets, countries will need to:

- accelerate the phase-out of coal
- curtail deforestation
- speed up the switch to electric vehicles
- encourage investment in renewable sources.

2. Adapt to protect communities and natural habitats

At COP25 we need to work together in order to enable and encourage countries affected by climate change protect and restore ecosystems.

3. Mobilise finance

International finance institutions must play their role and we need work towards unleashing the trillions in private and public sector finance required to secure global net zero.

4. Work together to deliver

We can only respond to challenges of the climate crisis by working together."

These targets must be translated into action in order to accomplish them as soon as possible. We have to halve emissions over the next decade and reach net zero carbon emissions by the middle of the century[22].

In line with the UK conditions, the Summit patrons had to give real contribution to global climate change and to agree with the COP26 targets. In fact, to accomplish them businesses are obliged to net zero commitments by 2050 or earlier with a reliable short-term action plan.

Many believed that Glasgow 26 was "the last chance" to put under control global climate change. Although there is agreement for keeping global warming below 2°C compared to the pre-industrial era, and preferably to 1.5°C, and despite the implementation of Nationally Determined Contributions (NDCs), we are not approaching these goals.

At the very beginning of COP26, the leaders by Leaders' Declaration stated that they would engage themselves in conservation and restoration of forests and other terrestrial ecosystems, decrease in vulnerability, sustainable agriculture, and if necessary, redesign agricultural policies and programmes.

The most vulnerable are at the greatest risk from climate change, but their contribution has been the smallest in causing it. Therefore, COP26 suggested action on adaption to make plans and allocate more finance for improvement of early warning systems, defence from floods and building resilient infrastructure and agriculture to avoid further loss of life, livelihoods and natural habitats[23].

COP26 PLEDGES

Glasgow Food and Climate Declaration has confirmed the necessity of all parties involved in food systems to bring decisions on sustainable and righteous transition and coordinated decision-making for all involved parties. Development and implementation of integrated food policies as key elements in the fight against climate change, reduction of greenhouse gas emissions and appeal to governments to establish policies for support of these objectives.

Food systems currently account 21-37% of total greenhouse gases, and extreme inequalities are spread throughout the food system and disproportionately affect communities.

A total of 130 countries have promised to end deforestation by 2030. Furthermore, they committed to zero emission cars and vans transition by 2040, and no later than 2035 in leading markets[24].

Finance as a huge challenge

The amount and access to finance are very important for implementation of the Paris Agreement and play a key role in reaching "the green" recovery from the COVID-19 pandemic. Participants concluded that the amount of climate finance was increasing as well as the challenges in accessing available finance from the climate funds, including Green Climate Fund (GCF). Participants emphasized that political will was necessary to direct and simplify approaches and that greater individual and collective actions would be necessary to overcome the current and future catastrophic effects of global climate change[25].

Presidency asked the Canadian and German governments to lead the 100 billion dollars delivery plan. Within UK's Clean Green Initiative, finance would be provided for supporting the deployment of sustainable infrastructure and green technology in developing countries[26].

Developed countries agreed to continue with providing 100 billion dollars annually as financial support to developing countries until 2025[27].

In order to reach Nationally determined contributions, South Africa as the world's largest carbon-intensive producer of electricity would be given 8.5 billion dollars over the next 3-5 years. However, trillion of dollars of additional investment annually would be needed to provide a safe future with low carbon and to support countries that already live with the devastating impacts of climate change. Also, the United States, the European Commission and United Kingdom committed to work together with other countries to support a green recovery from COVID-19 and to increase financial support for clean, green infrastructure in developing countries[28].

The anticipated 20 trillion US dollars should be shifted to infrastructure from fossil fuels to renewable sources and energy efficiency by 2050[29].

At least 23 countries undertook new commitments to gradually discontinue the usage of coal energy. On the other hand, major international banks committed to end the entire international public financing of coal power by the end of 2021. At least 25 countries and public finance institutions committed to stop international public support of fossil fuels energy sector by the end of 2022. If these commitments are fulfilled, it is clear that COP26 meant gradual ending of coal energy as the major cause of climate change. Furthermore, it was planned to end the support for new coal power plants[30].

Governmental steps are concentrated on economic support. Will the high-emission reduction be a priority or the recommendations from the Paris Agreement and all its previous heralds will be ignored? In spite of the fact that World Bank (2020), International Monetary Fund (IMF) (2020), International Energy Agency (IEA) (2020) and International Renewable Energy Agency (IRENA) (2020) have developed guidelines and recommendations for sustainable recovery, they have no political support.

By completion of the Paris Rulebook and how the Paris Agreement is being delivered, for the first time the developing countries and at the same the most vulnerable ones to climate change agreed to gradually end the use of fossil fuels[29].

At COP26, six years after the Paris Agreement, no resolved issues on financing global climate action, transparency and mutual frameworks for climate commitments were approved. In fact, this refers to Article 6 of the Paris Agreement. Thus, the pathway to full implantation to the Agreement was opened[31].

Now the resolute implementation of the contributions and targets remains to be seen.

Assessments and expectations

Current policy applied worldwide anticipates global warming of about 2.7°C compared to pre-industrial level

by the end of the century. By implementation of NDCs, warming will be kept to 2.4°C. If long-term commitment targets or net-zero targets are included, then warming would be kept to about 2.1°C above the pre-industrial levels. The warming projections dropped by 0.3°C after the made pledges and established targets by the USA and Peoples' Republic of China. According to the "optimistic" scenario, if the 140 analysed countries reach the zero emission targets, then the average warming will be 1.8°C, or below 2°C.

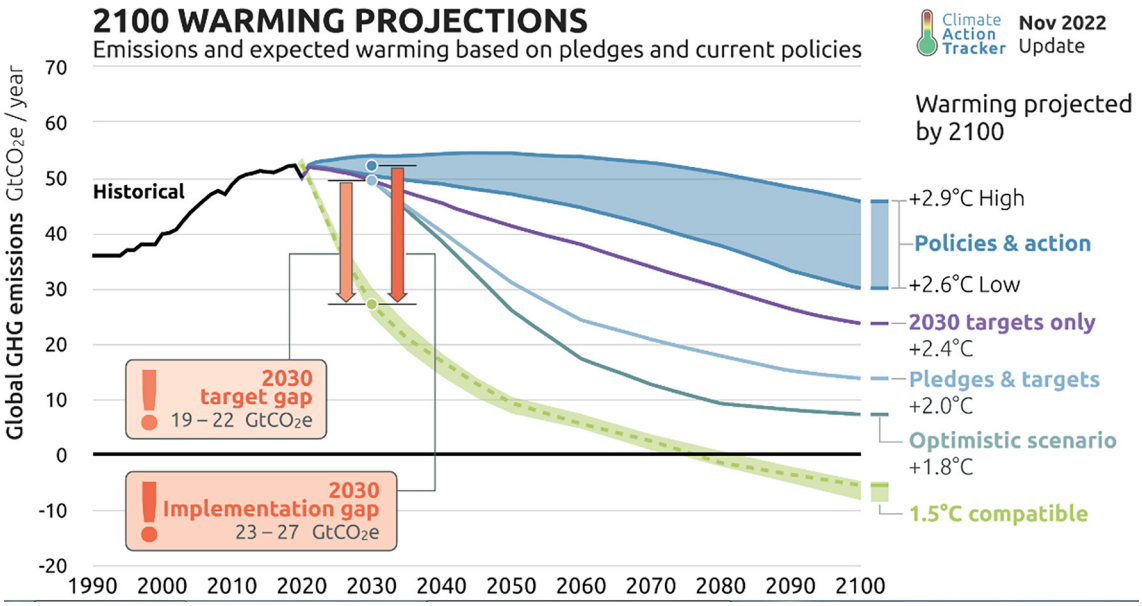

Chart 1. Warming projections until 2100
Available at: https://climateactiontracker.org/global/temperatures/

There is a significant gap between the pledges made by the governments and the total level of actions they have undertaken so far. To accomplish limiting warming to 1.5°C above pre-industrial levels means that greenhouse gas emissions should be reduced rapidly in the next years and decades and reach zero around the middle of the century[32].

It is estimated that natural causes such as changes in solar radiation or volcanic activity are estimated to contribute to less than plus or minus 0.1°C to total warming between 1890 and 2010[33].

EU member states, although considered to be the leaders in implementation of climate change promises, have not reached the targets required by the Paris Agreement[34].

According to the National broadcasting system of the UK (BBC), after long negotiations, despite the expressed disappointments, "the countries agreed to phase down rather than phase out coal"[35].

With the new economic challenges, it is clear that we are at a crossroads. Although COP26 did not deliver the full range of ambitions necessary to tackle climate change, COP26 must start now by a persistent, strenuous fight for our lives[36].

Conclusions

The impact of COVID-19 crisis will be crucial for the future of the climate policy. Climate changes will not wait. Their threat is over our heads and each and every day we face them. Every individual has a role to play in dealing with global climate change and we all can contribute to this threat if we all work together in a synchronous way. A greater political involvement is needed along with collective actions taken by all social actors. Over the last two years, the World Health Organization has advocated for greater inclusion of health authorities and services in Nationally determined contributions through activities to reduce the implications on health by climate change.

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PUBLIC HEALTH

RISK FACTORS FOR CARDIOVASCULAR DISEASES IN PROFESSIONAL DRIVERS

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Abstract

Aim of the paper was to determine the presence of risk factors for cardiovascular diseases (CVD) such as arterial hypertension, hyperlipidemia, hyperglycemia, overweight, smoking; and (ii) to analyze the link between the requirements of their job and the resources available to them. Materials and methods: A descriptive and analytical cross-sectional study was conducted involving 210 professional drivers who underwent a medical examination at the Institute for Occupational Health of the Republic of North Macedonia. The examination was done in order to assess their ability to drive a motor vehicle; they were also given a questionnaire to fill in so as to compare the requirements of the job and the resources available to them for doing their job. Results: One third of the respondents had increased levels of triglycerides, glycemia and cholesterol in their blood (33.3%, 28.1%, and 21.4%, respectively); almost half (44.2%) of them were active smokers. One third of the respondents (31.9%) were obese, with BMI >30 (kg/m2). The resources available to the professional drivers for doing their job exceed the requirements of the job and this situation has a protective effect on the occurrence of risk factors for CVD. Conclusion: The high prevalence of risk factors for CVD among professional drivers can lead to development of CVD and increased incidence thereof, which can negatively impact on their ability for safe driving. Hence the need for interventions to prevent these risk factors, including the need to invest in the resources available to professional drivers for doing their job.

ЈАВНО ЗДРАВЈЕ

ФАКТОРИ НА РИЗИК ЗА ПОЈАВА НА КАРДИОВАСКУЛАРНИ БОЛЕСТИ КАЈ ПРОФЕСИОНАЛНИТЕ ВОЗАЧИ

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Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Целта на трудот беше да се детерминира присуството на факторите на ризик за појава на кардиоваскуларни болести (КВБ): артериска хипертензија, хиперлипидемија, хипергликемија, зголемена телесна тежина, пушачки статус, и да се анализира нивната поврзаност со барањата и ресурсите на работното место. Материјал и методи: дескриптивно-аналитичка студија на пресек, во која кај 210 професионални возачи беа анализирани дел од резултатите добиени при здравствениот преглед спроведен во Инситутот за медицина на трудот на РСМ при оценката на способноста за управување со моторно возило и резултатите за барањата и ресурсите на работното место добиени со соодветен прашалник. Резултати: Една третина од испитаниците имаа покачени вредности на триглицеридите во крвта (33,3%); гликемијата беше зголемен кај 28,1%, холестеролот во крвта беше зголемен кај 21,4% и речиси половина (44,2%) од испитуваните професионални возачи беа активни пушачи. Третина (31,9%) од испитаниците беа обезни со BMI >30 (кг/м2). Ресурсите на работното место со кои располагаат испитуваните професионални возачи беа поголеми од барањата на работното место и овој модел има протективно дејство врз појавата на испитуваните фактори на ризик за КВБ. Заклучок: Високата преваленција на факторите на ризик за КВБ кај професионалните возачи може да придонесе за зачестена појава и развој на КВБ што, пак, може да влијае врз нивната способност за безбедно управување со моторно возило. Оттаму, произлегува потребата од интервенции за нивна превенција вклучително и инвестиција во ресурсите на работното место.

Introduction

Human activity in modern living and working conditions cannot be imagined without traffic. The term traffic refers to the transfer of people, goods, news, energy from one place to another[1]. Professional drivers transport material goods or passengers and driving is their primary occupation which provides their livelihood. Pursuant to the Rulebook on the health criteria to be met by drivers of motor vehicles arising from the Law on Traffic Safety and Article 3:

*"**professional driver** is a candidate for driver/driver of a motor vehicle of the categories: B+E, C, C+E, D, D+E as well as categories A, B, F, G and M to whom driving a motor vehicle is his/her primary occupation"*[2].

Road traffic can be freight, passenger and specific traffic. Professional drivers in freight and passenger traffic, in terms of whether they transport material goods or passengers, can be professional truck/heavy truck drivers, bus drivers and taxi drivers.

Several factors, such as continuous time pressure, sitting position of the body during the entire working hours, excessive stimulation from the external environment, problematic interactions with other road users, lack of social support at work and shift work (rotations) 3,4 are defined as stress-related factors that simultaneously increase the occurrence of negative effects on drivers' health, safety and driving performance[5-7].

The working conditions of professional drivers can affect their health and well-being[8,9]. Professional drivers are constantly exposed to environmental impacts (e.g., noise, smog, variable light conditions)[10] and poor ergonomic conditions[5].

In the available literature, the most common health problems faced by professional drivers as a result of exposure to occupational harms at the workplace are: arterialhypertension[11-13], musculoskeletal disorders[14-16], gastrointestinal [17], metabolic disorders[18], chronic fatigue[19,20,] and mental health problems[21,22]. However, the main health conditions that professional drivers suffer from are: cardiovascular diseases, gastrointestinal disorders and musculoskeletal problems[7]. Tse *et al*. found that bus drivers have problems with arterial hypertension and work-related stress[5].

The health of professional drivers is an important aspect related to traffic safety. Cardiovascular diseases are a leading cause of morbidity and mortality in the general population. Most studies indicate that the risk of cardiovascular disease is higher in professional drivers than in the general population [23-27]. Platek, Anna E. *et al*. point out in their study that professional drivers are exposed to many risk factors for cardiovascular diseases due to certain job characteristics such as: working hours, work-related stress, low physical activity and unhealthy dietary habits[28].

There are health conditions that have obvious implications or pose a risk to the safe operation of a motor vehicle. With these health conditions, there is a risk of unexpected

weakness and inability to safely operate a motor vehicle, which confirms the importance of the link between health and traffic safety. Health conditions in which there is a risk of unexpected weakness and inability to safely operate a motor vehicle include: sudden cardiac and cerebrovascular episodes[29], neurological diseases[30], narcolepsy[31], or hypoglycemic episodes of type I or II diabetes[32], disorders of the sensory organs for sight and hearing.

Arterial hypertension, hyperlipidemia, hyperglycemia, increased body weight and smoking status are described in the available literature as significant risk factors for cardiovascular diseases in professional drivers that can affect the ability to safely operate a motor vehicle. The obtained results are a baseline for further research and analysis of the influence of work-related factors (job demands and resources) on the occurrence of risk factors for cardiovascular diseases.

The aim of this paper was to determine the presence of risk factors for cardiovascular diseases, such as: arterial hypertension, hyperlipidemia, hyperglycemia, increased body weight and smoking status, and to analyze their link with the job demands and resources of professional drivers.

Materials and methods

A descriptive and analytical cross-sectional study involving 210 professional drivers was conducted in the Institute for Occupational Healthof the Republic of North Macedonia in the period from June 2020 until October 2021.

The data on the studied risk factors for cardiovascular diseases in professional drivers were obtained using the medical record for evaluation of the psychophysical ability to operate a motor vehicle and the clinical tests (laboratory tests and ECG) as part of the medical examination of the studied group of professional drivers in order to evaluate their ability to operate a motor vehicle, which is carried out in accordance with the "Rulebook on the method of performing medical examination of drivers of motor vehicles, the criteria regarding the staff and the equipment for performing medical examination, as well as the method and procedure for issuing a health certificate for psychophysical ability to operate a motor vehicle"33and the "Rulebook on the health criteria that must be met by candidates for drivers of motor vehicles"2. The data on the studied risk factors for cardiovascular diseases were obtained through medical examination performed by an occupational medicine specialist and refer to the following: anamnestic data on selected health conditions of interest (arterial hypertension, hyperlipidemia, diabetes) diagnosed by a doctor and presentation of positive findings obtained during the examination for the following parameters: laboratory tests (hyperglycemia, increased cholesterol and triglyceride levels in the blood), clinical parameters (ECG findings, blood pressure), habits (smoking status) and with the help of data on body weight, body height and age,

the body mass index was calculated using a calculator.

The following instruments were used to obtain data in the current study: Medical record for evaluation of the psychophysical ability to operate a motor vehicle (medical record) and Questionnaire on job demands and resources.

Electrocardiography – The analysis of the electrocardiogram was performed based on the characteristics of: heart rate, rhythm, QRS axis, signs of left ventricular hypertrophy and signs of coronary disease[34].

Arterial hypertension (HTA) is defined as a blood pressure (BP) with values >140/90 mmHg in population >18 years of age. These values correspond to BP of >135/>85 mmHg in case of home measurement, i.e., average value of >125-130/>80 mmHg in case of ambulatory measurement[35]. Blood pressure was measured in the doctor's office with a mercury sphygmomanometer on the right arm in a sitting position, after a 5-minute rest, and the measurement was repeated after 2 to 5 minutes, with mandatory measurement on the contralateral arm as well. Elevated blood pressure is confirmed if values of >140/90 mmHg are measured at least twice during two or three consecutive visits. According to the 2013 Guidelines for the management of arterial hypertension, the European Society of Arterial hypertension (ESH) and the European Society of Cardiology (ESC) classifies blood pressure: optimal blood pressure (<120/80mmHg), normal blood pressure (120-129/80-84 mmHg), high normal blood pressure (130-139/85/89 mmHg), grade 1 arterial hypertension (140-159/90-99mmHg), grade 2 arterial hypertension (160-179/100-109 mmHg) and grade 3 arterial hypertension (>180/110 mmHg)[36].

Smoking status – the classification of respondents according to smoking status was made according to the WHO recommendations for defining smoking status.Respondents who during the study smoked at least one cigarette per day weredefined as active smokers[37].

Laboratory tests – Cholesterol (reference value <5.2 mmol/L) and triglycerides (reference value <1.9 mmol/L) were examined according to the Chod-PAP-cholesterol peroxidase method[38,39].

Body mass index (BMI) is a tool that shows the relationship between body weight and height, of course, taking into account the age and the gender. It is calculated simply by using a calculator, which provides a certain index that indicates whether the body weight is appropriate in relation to other parameters.

Job demands and resources were analyzed by using the modified Questionnaire for job demands and resources designed on the basis of "Questionnaire on the impact of working conditions on the health of healthcare workers – violence and work-related stress", which refers to the job demands and resources, taken from the School of Occupational Medicine, University of Zaragoza, Spain[40]. This study

used the section with questions referring to the job demands and resources that were modified for the needs of this study. The first part of the questionnaire consists of five questions referring to the job demands to which the respondent provided answers on a Likert scale (never - very often) to the following questions: at work I feel tense, uncomfortable; my job has a negative impact on my physical or mental health; I have a lot of things to finish in an unrealistically short amount of time; the pressure from work affects my family, i.e. private life, and on a Likert scale (easy – very difficult) I tell my opinion to my superiors. The following seven questions refer to job resources to which the respondent had to provide an answer on a Likert scale (never - very often) to the following questions: I am able to completely finish my work duties; I am sufficiently financially rewarded for my work; I have enough advancement opportunities at work; and on a Likert scale (completely false - very true) to the following questions: I can adequately apply my knowledge and skills at work; the workplace is safe; I have enough funds for maintenance of the vehicle and for fuel and the vehicle I drive is roadworthy.

The validation of the questionnaire was performed with the reliability analysis, by measuring the internal consistency of the questionnaire. The analysis determined the following reliability coefficients – Crombach alpha for job demands was 0.704, and for job resources 0.688, which indicated their good and acceptable reliability.

The respondents, i.e., the professional drivers, were informed about the objectives of the study and each respondent signed a written consent for voluntary participation in the study.

Data obtained were statistically processed with the SPSS programme. Continuous variables are expressed as mean values with standard deviation, and nominal variables as absolute numbers and percentages.

Limiting factors in the study can be errors due to no response as a result of professional drivers refusing to answer questions related to their health status or answers not being completely honest and complete and referring to health conditions that can question their ability to operate a motor vehicle. To minimize these errors, before starting to answer the questions, the respondents were informed about the motive, objectives and method of the study, as well as the confidentiality of the obtained data.

Results

Demographic characteristics

The current study included 210 male professional drivers. The average age of professional drivers was 46.31±9.45 years, with a min/max age of 23/67 years. Most of the respondents 164 (78.6%) have completed secondary education.

Table 1. Analysis of the sample according to work experience

Work experience	N	Mean±SD	Min/Max	Median (IQR)	[1]p
Years of services as a professional driver					
Taxi driver	51	12.08±7.44	1/30	10 (6-18)	$X^2(2)=2.019$; p=0.3644
Truck/heavy truck driver	133	14.61±9.05	1/40	12 (7-20)	
Bus driver	26	15.04±12.01	1/38	13.5 (4-26)	
Total	210	14.59±9.08	1/40	12 (7-20)	
Working hours per week					
Taxi driver	51	45.09±8.18	30/70	40 (40-50)	$X^2(2)=4.589$; p=0.1008
Truck/heavy truck driver	133	42.22±5.05	30/70	40 (40-45)	
Bus driver	26	40.23±3.98	30/46	40 (40-40)	
Total	210	42.67±6.03	30/70	40 (40-45)	
[1]Kruskal-Wallis H test *significant by p<0,05					

The representation of taxi drivers in the study was 51 (24.28%) persons with an average of 12.08±7.44 years of service; min/max of 1/30 years and 50% of them with less than 10 years of service for Median IQR =10 (6-18). There were 133 (63.33%) truck/heavy truck drivers with an average of 14.61±9.05 years of service; min/max of 1/40 years and 50% with less than 12 years of service for Median IQR=12 (7-20).The smallest number of professional drivers in the sample were bus drivers, namely 26 (12.38%) with an average of 15.04±12.01 years of service; min/max of 1/38 years and 50% of them with less than 13.5 years of service for Median IQR=13.5 (4-26). For p>0.05, there was no significant difference between the three types of professional drivers regarding the length of service (Kruskal-Wallis H test:$X2_{(2)}$=2,019; p=0,3644 (Table 1).

Years of service – The average total years of service of professional drivers in the sample was 14.59±9.08 years with min/max of 1/40 years and 50% with less than 12 years of service for Median IQR=12 (7-20) (Table 1).

Working hours per week – The average number of working hours per week for the entire sample of respondents was 42.67±6.03 with min/max of 30/70 hours. For 50% of professional drivers, regardless of the type of motor vehicle they drive, the number of working hours per week was less than 40 for Median=40 (Table 1).

The average number of working hours per week for taxi drivers, truck/heavy truck drivers and bus drivers separately was 45.09±8.18 *vs.* 42.22±5.05 *vs.* 40.23±3.98, respectively. The minimum number of working hours per week for all three types of professional drivers was 30 hours and the

maximum number was the smallest for bus drivers and it was 46 hours, and for taxi drivers and truck/heavy truck drivers it was 70 hours each. For p>0.05, there was no significant difference between the three types of professional drivers regarding the number of working hours per week (Kruskal-Wallis test: X2(2)=4.589; p=0.1008 (Table 1).

Table 2. Data on selected risk factors for CVD (anamnestic data on health conditions diagnosed by a doctor: arterial hypertension, hyperlipidemia, diabetes)

Number	**Diseases of interest	N (%)
1	Arterial hypertension – HY	17 (8.09%)
2	Hyperlipidemias – HL	11 (5.24%)
3	Diabetes – DB	18 (8.57%)

Regarding the data related to diseases diagnosed by a doctor for which they receive chronic therapy, professional drivers included in this study with regards to selected risk factors for cardiovascular diseases stated that 8.1% suffered from arterial hypertension, and 8.6% from diabetes. A smaller percentage (5.2%) of the tested professional drivers stated that they had elevated levels of fat in the blood.

Table 3. Data on selected laboratory and clinical parameters

Laboratory and clinical parameters	N (%)
Laboratory parameters	
Glycemia - increased values in the blood	59 (28.09%)
Cholesterol (total) – increased values in the blood	45 (21.43%)
Triglycerides – increased values in the blood	70 (33.33%)
Cardiac parameters	
ECG findings – pathological changes	9 (4.28%)
Blood pressure – high blood pressure measured during the examination by the occupational medicine specialist	28 (13.33%)
Habits – smoking status	
*	

According to the laboratory and clinical tests, the highest percentage (33.3%) of the tested professional drivers had elevated triglycerides levels in the blood. Blood sugar levels were elevated in 59 respondents or 28.09%, while total cholesterol was elevated in 45 respondents or 21.4% of the studied professional drivers.

From the results shown in Table 3, we can see that in 9 (4.3%) respondents pathological changes were found on the ECG, while in 28 (13.3%) respondents the blood pressure was high, i.e., above 140 mmHg for systolic pressure and above 90 mmHg for diastolic pressure.

Regarding the smoking status, 92 respondents stated that they smoked at least one cigarette per day, which was 44.2% of the tested professional drivers.

Table 4. Results for Body Mass Index (BMI)

BMI (kg/м^2)			
<25 (kg/m^2)	N (%)	62 (29.52%)	p=0.0001*
≥25 (kg/m^2)		148 (70.48%)	
WEIGHT STATUS			
Underweight(UW)	N (%)	5 (2.38%)	NW/OB: p=0.198 NW/OW: p=0.004* OW/OB: p=0.104
Normal weight (NW)		55 (26.19%)	
Overweight (OW)		83 (39.52%)	
Obesity (OB)		67 (31.90%)	
[1]Difference test significantly * p<0,05			

The results of the calculated values of BMI showed that more than half of the respondents, as high as 70.5%, wereovernourished and had a BMI greater than 25 (kg/m^2), of which 31.9% were in the obese category with BMI greater than 30 (kg/m^2). Less than one third of the respondents, 26.2%,were normally nourished with a BMI in the interval of 18.5 (kg/m^2) -24.9 (kg/m^2).

Table 5. Results for mean values of job demands and resources (job demands and resources scale)

[1]JRD (domains / questions)	JRD score					
	Number (N)	Mean±SD	Min/ Max	Percentiles		
				25th	50th (Median)	75th
Job demands						
At work I feel tense, uncomfortable	210	0.45±0.76	0/4	0	0	1
I think that my job has a negative impact on my physical/mental health:	210	0.28±0.72	0/4	0	0	0
I have a lot of tasks to complete in an unrealistically short amount of time	210	0.82±0.96	0/4	0	1	1
I tell my opinion about work to the superiors	210	0.42±0.93	0/4	0	0	0
The pressure I feel from work also affects my family and/or private life	210	0.23±0.70	0/4	0	0	0
Average TOTAL score	210	0.44±0.56	0/3.4	0	0.3	0.6

Job resources						
I am able to completely finish my work duties	210	2.99±0.35	1/4	3	3	3
I am sufficiently financially rewarded for my work	210	2.39±1.14	0/4	2	2	3
I have enough advancement opportunities at work	210	2.75±1.06	0/4	2	3	4
I can adequately apply my knowledge and skills at work	210	3.64±0.77	0/4	4	4	4
My work environment is safe (passengers, traffic)	210	3.54±0.99	0/4	4	4	4
I have enough funds for maintenance of the vehicle and for fuel	210	3.78±0.60	0/4	4	4	4
The vehicle I drive is roadworthy	210	3.87±0.42	1/4	4	4	4
Average TOTAL score	210	3.28±0.48	1.3/4	3	3.3	3.6
[1]Job Demand -Resource						

The results presented in the above table show that the respondents (professional drivers) had higher mean values for job resources (mean value on the scale of job resources 3.280 SD 0.482) than the mean values for job demands (mean value on the scale of job demands 0.425 SD 0.546).The greatest job resources pointed out by the respondents were the vehicle's road worthiness (mean value 3.87 SD 0.421), the possibility to maintain the road worthiness of the vehicle and had a sufficient fuel supply (mean value 3.79 SD 0.601), the possibility to adequately apply knowledge and skills (mean value 3.64 SD 0.774), as well as the job safety (mean value 3.55 SD 0.982).Respondents perceived the time pressure as the most stressful factor of the job, while driving a roadworthy vehicle was the most valuable resource of the job, which gave them a sense of safety in the traffic.

Table 6. Analysis of the relationship between the occurrence of risk factors for cardiovascular disease and the mean values of job demands

Risk factors for CVD		Job demands		*t* (p)
		Average	SD	
Arterial hypertension	No	0.436	0.554	*1.032* (0.30)
	Yes	0.294	0.424	
Diabetes	No	0.439	0.556	*1.312* (0.19)
	Yes	0.258	0.379	
Hyperlipidemias	No	0.422	0.541	*-0.297* (0.77)
	Yes	0.472	0.646	
Blood pressure	No abnormality detected:	3.277	0.546	*0.260* (0.79)
	High BP	3.306	0.552	

Glycemia	No abnormality detected:	0.460	0.583	*1.49* (0.14)
	Hyperglycemia	0.334	0.426	
Cholesterol	No abnormality detected:	0.440	0.525	*0.778* (0.43)
	Hypercholesterolemia	0.368	0.617	
Triglycerides	No abnormality detected:	0.411	0.518	*0.496* (0.62)
	Hypertriglyceridemia	0.451	0.600	
Smoking status	Non-smokers	0.422	0.583	*-0.077* (0.93)
	Smokers	0.428	0.498	
Body Mass Index	BMI < 25	0.465	0.605	*0.690* (0.49)
	BMI >25	0.408	0.520	

The analysis of the obtained data regarding the impact of job demands on the occurrence of the studied risk factors for cardiovascular diseases did not show any statistically significant relationship.

Table 7. Analysis of the relationship between the occurrence of risk factors for cardiovascular diseases and the mean values of job resources

Risk factors for CVD		Job demands		*t* (p)
		Average	SD	
Arterial hypertension	No	3.268	0.49	*-1.245* (0.21)
	Yes	3.420	0.26	
Diabetes	No	3.273	0.490	*-0.792* (0.43)
Yes		3.369	0.367	
Hyperlipidemias	No	3.294	0.457	*1.719* (0.08)
	Yes	3.039	0.795	
Blood pressure	No abnormality detected:	3.277	0.485	*-0.297* (0.78)
	High BP	3.306	0.466	
Glycemia	No abnormality detected:	3.301	0.485	*1.01* (0.31)
	Hyperglycemia	3.226	0.472	
Cholesterol	No abnormality detected:	3.286	0.476	*0.323* (0.74)
	Hypercholesterolemia	3.260	0.505	
Triglycerides	No abnormality detected:	3.305	0.410	*1.028* (0.36)
	Hypertriglyceridemia	3.232	0.598	
Smoking status	Non-smokers	3.254	0.511	*-0.872* (0.38)
	Smokers	3.313	0.442	
Body Mass Index	BMI < 25	3.339	0.460	*1.132* (0.25)
	BMI >25	3.256	0.490	

The job resources available to the tested professional drivers were greater than the demands, which contributed to having a commitment to the job, job safety, and they did not have any statistically significant relationship with the occurrence of CVD risk factors.

Discussion

The current study included 210 male professional drivers, at an average age of 46 years and most of them with completed secondary education .These demographic data match the demographic characteristics of professional drivers worldwide who have a distinct set of demographic characteristics and have undergone selective processes regarding their physical, psychological, and educational standards 41.

According to the anamnestic data of the respondents, 17 professional drivers or 8.1% of the respondents suffered from arterial hypertension for which they regularly received therapy. The values obtained from the measured blood pressure showed a greater representation of this phenomenon among professional drivers; in 28 professional drivers measured values were higher than 140 mmHg for systolic pressure or higher than 90 mmHg for diastolic pressure, which was 13.3% of the respondents. This may be the result of a newly discovered condition or a condition that some of the respondents didn't want to share. Similar values regarding the prevalence of arterial hypertension in professional drivers were observed in the study conducted by Nadia Tigha-Bouaziz *et al.* (2016), among 128 male professional drivers with work experience longer than 5 years, where the prevalence of arterial hypertension was 8%. It was established that obesity and prolonged sitting were important risk factors for cardiovascular diseases and 40% of those who had arterial hypertension were in the obese category with a BMI greater than 30[42].

Arterial hypertension is a serious condition that can cause stroke, heart failure, peripheral artery disease and kidney failure. In order to evaluate the ability to drive, the focus must be put on the potential relationship between arterial hypertension and sudden collapse, and the functional disturbances that arterial hypertension can cause that affect visual acuity and brain function.

With regards to the safe operation of a motor vehicle, arterial hypertension may be the reason for the driver's incapacity in the case of malignant arterial hypertension. This condition includes a syndrome of severe elevation of arterial blood pressure (diastolic blood pressure usually > 140 mmHg) with vascular damage, especially retinal hemorrhages, exudates and/or papilledema, which may lead to sudden onset of blurred vision. Malignant arterial hypertension can also be complicated by cerebral hemorrhages that can affect cognitive or physical abilities, restricting these patients from driving. In addition to this extreme condition, grade 3 arterial hypertension according to the ESH/ESC Guidelines – classification of arterial hypertension[36] is strongly and proportionally associated with the occurrence of a stroke which has an annual incidence of over 0.3% when systolic blood pressure is > 180

mmHg. Therefore, professional drivers should not be allowed to drive until their arterial hypertension is under control. According to the same ESH/ESC Guidelines ,grade 1 or grade 2 arterial hypertension can be considered as a cardiovascular risk without immediate consequences on driving safety. It should be treated, but should not be a reason to restrict driving[43].

Professional drivers included in this study with regards to hyperlipidemia provided anamnestic data that 11 of them had elevated blood fat values, or 5.2% of the respondents. However, the laboratory blood tests showed that blood cholesterol was increased in 45 respondents, which was 21.4% of the respondents, while triglycerides in the blood were increased in 70 respondents, or 33.3%. Hyperlipidemia as cardiovascular risk factors was also identified in a study conducted by Hirata RP. *et al.* along with obesity, arterial hypertension, and hyperglycemia in a young male population of professional bus drivers[44].

Hyperglycemia, the increased level of blood sugar in professional drivers is one of the most common findings in the process of evaluating the ability to operate a motor vehicle. Also in the current study, laboratory tests showed increased levels of blood sugar of over 6.1mmol/L in 59 professional drivers, i.e., in 28.1% of the respondents, while 8.6% of the respondents reported that they were suffering from diabetes. Increased blood sugar levels in professional drivers occur due to the sedentary way of work and long-term driving, fast food, reduced physical activity, stressful situations related to other road users, and the increased blood sugar levels are detected during regular medical examinations that are mandatory for professional drivers every 24 months.

Izadi N. *et al.*, in their study of 1903 drivers who applied for a driver's license, found hyperglycemia in 52.1% of the drivers, 9.1% of whom were in the diabetic phase. Overweight was observed in 65.6% of the studied population, 44.8% were diagnosed with overweight and 20.8% with obesity. Obesity among professional drivers can also be noted among professional drivers in the current study in which 71.2% of professional drivers had a BMI over 25 and even 32.2% were in the obese category with a BMI over 30[45].

A study published by Ronna et al. described that in the United States professional drivers must undergo a medical examination in order to become a licensed driver of a commercial motor vehicle. This certificate is valid for up to 24 months; however it can be issued for less than 24 months when monitoring a health condition, such as arterial hypertension. However, medical examinations of professional drivers have shown that drivers have poor overall health and a higher prevalence of risk factors for cardiovascular diseases, especially tobacco use, arterial hypertension, and obesity, compared to the general population[46]. Regarding the smoking status, the percentage of smokers is high and in the current study, as many as 44.2% of respondents were active smokers. Poor health of truck drivers is often attributed to lifestyle including diet, physical inactivity and prolonged sitting.

Analysis of the mean values of job demands and resources showed higher values of job resources compared to the mean values of job demands and the occurrence of risk factors for car-

diovascular diseases. According to job demands and resources model, high values of job resources lead to increased productivity and motivation at work.T his process was demonstrated in the critical review of the Job Demands-Resources Model (JD-R model) presented by Schaufeli *et al.* in 2014, according to which high job demands led to impaired health (health impairment process), while high job resources led to increased motivation and higher productivity (motivational process). This model also explains the relationship between job demands and health disorders that can occur as a result of high job demands, while job resources are associated with motivational processes and work productivity[47].

The high prevalence of overweight, high blood pressure and hyperlipidemia are risk factors for the possible occurrence of cardiovascular diseases in professional drivers, as indicated by the fact that 4.3% of professional drivers were found to have pathological changes in the ECG.

The current study provided data regarding the frequency of occurrence of certain cardiovascular risk factors, which will be further used to analyze the effect of job-related factors on their occurrence and their impact on the safe operation of a motor vehicle by applying the model of an integrated approach to the influence of work environment and health condition of professional drivers on the safe operation of a motor vehicle.

Conclusion

Lifestyle and work through job demands and resources of professional drivers may have an impact on the increased occurrence of risk factors for cardiovascular diseases. The high prevalence of risk factors for cardiovascular diseases in professional drivers may contribute to the frequent occurrence and development of CVD that may affect drivers'ability to safely operate a motor vehicle. Fortunately, risk factors for cardiovascular diseases that have been examined in this study are preventable health conditions and lifestyle habits and it is necessary to create interventions for their timely diagnosis and treatment, with the aim of preventing the occurrence of cardiovascular diseases among professional drivers. One of the preventive approaches, also, includes investing in increased job resources for professional drivers.

The results of the current study showed an increased occurrence of risk factors for cardiovascular diseases in professional drivers. The high prevalence of obesity and the high percentage of smokers among the respondents, together with the occurrence of hyperlipidemia, hyperglycemia, arterial hypertension and diabetes are risk factors for cardiovascular diseases in the studied group of professional drivers. Job demands and resources may influence the occurrence of risk factors for CVD. In the current study, greater job resources compared to job demands had a protective effect on the occurrence of risk factors for CVD. Investing in job resources and in developing a model where job resources will be greater than job demands, as it is the case in the current study, will contribute to the prevention of CVD. In order to improve the ability for operation of a motor vehicle, timely diagnosis and treatment of CVD in professional drivers is required.

It is necessary, by applying the model of integrated approach, to analyze the impact of work environment on the occurrence of risk factors for cardiovascular diseases and their impact on the safe operation of a motor vehicle, in order to propose preventive measures regarding diet, work conditions (working hours, breaks during driving), introduction of regular physical activity for timely prevention of risk factors for cardiovascular diseases.

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PUBLIC HEALTH

CHARACTERISTICS OF THE JOB DEMANDS OF HEALTHCARE WORKERS IN DIFFERENT SEGMENTS OF THE HEALTHCARE SECTOR

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Abstract

Healthcare workers are exposed to various demands at their workplace (physical, psychological, social or organizational aspects of work) that impose constant physical and/or psychological effort on a worker. The aim of this study was to determine the characteristics of the job demands of healthcare workers in different segments of the health sector in RNM, categorized into three groups: healthcare workers in hospital activity, healthcare workers in outpatient activity and technical support and administrative staff.Material and methods: This is a cross-sectional descriptive-analytical study, in which 418 employees participate, classified into three groups according to their work tasks in health institutions: healthcare workers in hospital activity, healthcare workers in outpatient activity and technical supportand administrative staff. The statistical analysis has been done in statistical programs: STATISTICA 12.0; IBM SPSS Statistics 20.0, and the processed data are presented in tabular forms. Results: The difference among the three groups of respondents in terms of the following demographic characteristics and job characteristics: gender, marital status, type of employment contract, total years of service, length of service at thecurrent workplace and number of working hours per week, is insignificant, i.e. the three groups of respondents are homogeneous on these issues. The average value of the physical job demands at the level of the entire analyzed sample is significantly higher compared to the average values of all other job demands. The most common job demands for each of the groups (physical, organizational, emotional and cognitive job demands) have been determined, and a comparison has been made among the three groups of respondents regarding the most significant job demands. Conclusions: The difference registered in the physical job demands in relation to the three groups of respondents is statistically significant. Healthcare workers in hospital activity, compared to the technical supportand administrative staff and the healthcare workers in outpatient activity, are more exposed to the different types of job demands. The higher average values of the physical job demands among respondents employed in hospital activity and outpatient activity in relation to technical support and administrative staff are also highlighted.

ЈАВНО ЗДРАВЈЕ

КАРАКТЕРИСТИКИ НА БАРАЊАТА НА РАБОТА КАЈ ЗДРАВСТВЕНИТЕ РАБОТНИЦИ ВО РАЗЛИЧНИ СЕГМЕНТИ НА ЗДРАВСТВЕНИОТ СЕКТОР

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Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Здравствените работници се изложени на различни барањана работното место (физички, психолошки, социјални или организациски аспекти на работата) кои на работникот му наметнуваат постојан физички и/или психолошки напор.Целта на истражувањето беше да се детерминираат карактеристиките на барањата на работното место кај здравствени работници во различни сегменти во здравствениот сектор во РСМ, категоризирани во три групи: здравствени работници во болничка дејност, здравствени работници во вонболничка дејност и помошно-технички и административен персонал. Материјал и методи: Трудот претставува дескриптивно-аналитичка студија на пресек, во која учество земаат 418 вработени класифицирани во три групи според нивните работни задачи во здравствените установи: здравствени работници во болничка дејност, здравствени работници во вонболничка дејност и вработени кои не се здравствени работници (помошно-технички и административен персонал). Статистичката анализа е направена во статистички програми: STATISTICA 12.0; IBMSPSS Statistics 20.0, а обработените податоци се прикажани табеларно. Резултати: Разликата помеѓу групите во однос на следните демографски карактеристики и карактеристики на работното место: пол, брачен статус, вид на договор за вработување, вкупен работен стаж, должина на работен стаж на сегашното работно место и број на работни часови во текот на неделата е несигнификантна, односно по овие прашања групите се хомогени. Просечната вредност на физичките барања на работното место на ниво на испитуваниот примерок е сигнификантно повисока во споредба со просечните вредности на сите други барања-организациски, емоционални и когнитивни. Добиени се сознанија за најчестите барања на работното место за секоја од групите (физички, оргнизациски, емоционални и когнитивни), а направена е и споредба меѓу трите групи во врска со најзначајните барања на работното место. Заклучок: Разликата која се регистрира кај физичките барања на работното место во однос на трите групи испитаници е статистички сигнификантна. Здравствените работници во болничката дејност споредено со помошно-техничкиот и административен персонал и здравствените работници од вонболничка дејност се повеќе изложени на различните видови барања на работното место. Се истакнуваат и повисоките просечни вредности на физичките барања на работното место кај испитаниците вработени во болничка дејност и вонболничка дејност во однос на помошно-техничкиот и административен персонал.

Introduction

Due to the fact that healthcare workers are people engaged in specific activities with the primary goal of preserving and improving people's health may provide direct patient care and service delivery (doctors, nurses, psychologists, social workers, laboratory technicians, etc.) or indirect care (accountants, drivers, administrators, foremen, equipment maintainers, drug distribution, service planners, and even medical waste management)[1]. According to the Law on Health Protection, health care is an activity of public interest, which is carried out in health facilities as a public service that provides health care[2]. Healthcare workers are the key actors in the process of implementation of health care measures and activities in order to provide health services to the patients according to their needs, as well as best medical practice in different health care settings[3]. They have a great responsibility towards human life and health, and at the same time, they are exposed to various psychosocial risks that come from the requirements and conditions of the workplace. These risks include various aspects of work and the work environment, such as the organizational climate or culture, interpersonal relationships, and the design and content of workplace activities[3]. Psychosocial risks at the workplace are related tostress occurrence, burnout syndrome, harassment (mobbing), and violence at the workplace. At the same time, the negative consequences are present not only at an individual level (e.g. psychosomatic disorders in the worker) and at an organizational level (level of work productivity, absenteeism, and presenteeism, increased number of injuries and accidents at work, etc.) but also at the level of social community and national economies (economic losses)[4].

It is important to note that in the last few years the pressure on medical personnel, especially on doctors, has increased in many countries as a result of various healthcare reforms that affect the autonomy of doctors, imposing more administrative burdens and professional requirements for continuous improvement[5].

Job demands and job resources are the main elements of the Job Demand-Resources Model (JD-R)[6-8] which is used in this research. The central assumptionof the JD-R Model is that whereas every occupation has its own specific job risk factors (characteristics) that affect organizational outcomes, including employee well-being, these characteristics can be classified into these two general categories—job demands and job resources. The JD-R model has been proven to have a high predictive value for employee health and well-being[6-9].

Job demands, actually, refer to various physical (e.g, high levels of noise or crowding), psychological, social (e.g. interpersonal conflicts, abusive supervision) or organizational aspects of the job (e.g. interpersonal conflicts) that require prolonged physical and/or psychological (cognitive and emotional) efforts and

therefore they are associated with certain physiological and/or psychological costs in workers. Job demands are not necessarily negative, but high job demands lead to excessive strain when the invested personal efforts are high, which depletes the energy of the worker (emotional exhaustion) and it affects the reduced engagement of the individual at work (energy overload process)[7-9].

On the other hand, job resources as mental, physical, social and organizational aspects of work that provide functionality in the achievement of work goals, reduce job demands and related physical and/or psychological costs and stimulate personal growth, learning as well asemployee development. Lack of resources at work can lead to changes in behaviour manifested as distancing/negative attitude towards work or cynicism (depersonalization) and disengagement from the work process (motivational process). When the organizational context is presented through adequate work resources, such as proper feedback, supervisor and co-worker support as well as teamwork, high levels of work engagement can be observed among employees, as well as low levels of depersonalization. On the other hand, in the context of reduced job resources (e.g. inadequate feedback, low salary, job insecurity, inadequate supervisory coaching, and poor teamwork), job demands are particularly detrimental[6-9]. Hence, job satisfaction and good interpersonal relationships can have a protective function against the impact of stress[10].

Additionally, the problem of psychosocial risks among healthcare workers has worsened as a result of the global public health crisis caused by the COVID-19 pandemic. Research has shown that during the COVID-19 pandemic, stress and burnout syndrome among healthcare workers increased[11]. Lack of health personnel, long working hours without adequate rest periods, and shortages of personal protective equipmentlead-to fatigue and non-adherence to infection prevention and control measures.[12] Somestudies suggest that infection prevention and control measures reduce the autonomy of healthcare workers and contribute to their exhaustion and occurrence of burnout syndrome[13].

The aim of this paper is to determine the characteristics of the requirements of the workplace for employees in different segments of the health sector in RNM, categorized into three groups depending on their work tasks in health institutions: healthcare workers in hospital activity, healthcare workers in outpatient activity and employees who are not healthcare workers (technical support and administrative staff).

Material and methods

The paper is a cross-sectional descriptive-analytical study. Employees in health facilities in RNM were surveyed through Google Forms (a cloud-based data management tool used for designing and developing

online questionnaires). The survey was conducted during June - October 2022. Participants were asked to complete the questionnaires online and were encouraged to invite new respondents from their contacts. A total of 418 employees in health facilities filled out questionnaires. The respondents were categorized into three groups depending on their work tasks in health institutions: healthcare workers (doctors, specialist doctors, nurses/technicians/laboratory workers) in hospital activity - 200 respondents, healthcare professionals (doctors, specialist doctors, nurses/technicians/laboratory technicians) in outpatient activity -166 respondents and employees in the hospital activity and in outpatient activity who are not healthcare professionals, i.e. technical support and administrative staff)- 52 respondents. The respondents were informed about the objectives of this research, and their participation was anonymous as well ason a voluntary basis.

In order to determine the demographic characteristics and job characteristics of employees in different segments of the health sector in RNM, specially designed questionnaires were used to obtain relevant data of research interest.

The data on the demographic characteristics, as well as the job characteristics of the respondents, i.e. gender, age, education degree, marital status, profile description of the workplace, type of activity, type of institution where they work,total years of service, length of service at the current workplace, type of employment contract, number of working hours per week, night shift work, work with patients infected with COVID-19, have been obtained from the Questionnaire on demographic characteristics and job characteristics specially designed for the needs of the research through analysis of the literature and the methods used in other similar studies, consisting of 14 questions.

Data on job demands have been obtained with the help of Job Demands Questionnaire specially designed for conducting research through a review and analysis of instruments that have been used in studies in this field[14], consisting of 28 questions relating to different types of job demands: physical (the fast pace of work, the responsibility for a large number of patients, the lack of personnel, the lack of equipment and materials for work, the burden of administrative activities and additional tasks in the conditions of the COVID-19 pandemic), organizational (the strict hierarchical arrangements of superiors, poor communication between departments, unclear and ambiguous roles and work tasks, frequent changes to rules and regulations in the health facility, the unfair management in the department, the influence of the media on the bad image of healthcare workers from the specific facility and problematic communication among departments in the context of the COVID -19 pandemic), emotional (lack of coopera-

tion with colleagues, high competition among colleagues, problems in communication with patients, inadequate handling of negative feelings during work, fear of making a mistake during work and conflict between demands home and work environment, inadequate handling of negative feelings during the COVID-19 pandemic) and cognitive job demands (lack of feedback on work results, decision-making under time pressures, insufficient participation in decision-making, obligation to train new employees, as well as decision-making during lack of necessary information and decision-making under time pressures during the COVID-19 pandemic). In doing so, the respondents gave points for each statement according to a Likert scale on which there are five ratings from 1 for "hardly ever" to 5 for "always". The scores given for the statements have been summed and an average value was calculated for the physical, organizational, emotional, and cognitive job demands.

The statistical analysis has been done in statistical programs: STATISTICA 12.0; IBM SPSS Statistics 20.0, and the processed data are presented in tabular form.

Results

The average age of all respondents included in the survey is 41 years with a standard deviation of 10.9. Among the respondents, the percentage representation of the female gender is higher at 81.8% compared to the male respondents at 18.2%. Most of the participants in this study have university degrees-120 (28.7%). Most respondents are married or they live with their partner - 301 (72%). In terms of job position, i.e. the profile, the most represented healthcare workers are nurses with 45.7%, compared to doctors with 25.4%. According to the type of activity performed by most of the respondents, 200 (47.9%) engaged in hospital activity. A large part of the respondents work at University Clinics 134 (32.1%) and they mostly work in internal medicine (101). The largest percentage of participants in the study are employed with a contract for an indefinite period of time (90%), provide direct patient care (57.9%), and do not work in night shift (69.1%). Most respondents worked with patients infected with COVID-19, i.e. 285 (68.2%). The average value length of total years of service among the respondents is 15.8 years, the average value length of service at the current workplace is 11.2 years, and the average number of working hours among the respondents per week is 41 hours.

Table 1. Differences among the three groups of respondents in terms of the average values of age, total years of service, years of service at the current workplace, and the number of working hours per week

Q1 age	average	standard deviation	
technical support and administrative staff	43.1	10.02478	F=2.250028 p=0.106681
healthcare workers in outpatient activity	41.8	11.90639	
healthcare workers in hospital activity	40.0	10.34842	
Q8 total years of service			
technical support and administrative staff	16.9	10.14649	F=0.482186 p=0.617780
healthcare workers in outpatient activity	16.0	11.77178	
healthcare workers in hospital activity	15.3	10.38351	
Q9 length of service at the current workplace			
technical support and administrative staff	11.2	8.54753	F=0.021899 p=0.978340
healthcare workers inoutpatient activity	11.3	10.03802	
healthcare workers in hospital activity	11.1	9.70520	
Q10 number of working hours per week			
technical support and administrative staff	39.4	7.018909	F=2.596865 p=0.075717
healthcare workers in outpatient activity	40.6	6.627504	
healthcare workers in hospital activity	41.9	8.912478	

The difference between the three groups of respondents in terms of the average age is insignificant, it is 43.1±10.0 for technical support and administrative staff, as well as it is the lowest among healthcare workers in hospital activity -40.0±10.3 (table 1).

The longest total length of years of service is registered among respondents who work in technical support and administrative staff 16.9±10.1, the shortest among healthcare workers in hospital activity15.3±10.4, the difference among the three groups of respondents in relation to the average value of length of total years of service is insignificant (table 1).

The difference that is recorded between the three groups of respondents in terms of the average value of the length of serviceat the current workplace is in significant. It is 11.2±8.5referring to technical support and administrative staff, healthcare workers in hospital activity-11.1±9.7 and healthcare workers in outpatient activity -11.3±10.0 (table 1).

The largest number of working hours per week is registered among healthcare workers in hospital activity -41.9±8.9, and the lowest number of working hours per week is observed among respondents who are technical support and administrative staff 39.4±7.0, the difference among the three groups of respondents in terms of the average value of the number of working hours per week is insignificant (table 1).

Table 2. Display the demographic characteristics of the respondents in the three groups

Q2 gender	technical support and administrative staff	healthcare workers in the outpatient activity	healthcare workers in hospital activity	Pearson Chi-square p
male	11	27	38	0.80873 p=.667399
female	41	139	162	
Q3 education degree				
Secondary vocational education	17	26	43	61.6617 p=0.0000
Three-yearvocational studies	3	19	64	
University degree	21	50	49	
Specialization	2	55	32	
Master's degree/Ph.D.	9	16	12	
Q4 marital status				
not married	8	40	45	6.34015 p=0.386184
married/ not married, but you live with your partner	38	118	145	
divorced	5	6	6	
widow/er	1	2	4	
Q11 type ofemployment contract				
indefinite period of time	45	152	179	0.579874, p=.748311
definite period of time	4	9	14	
Q13 night shifts				
yes	1	26	102	76.3952, p=0.0000
no	51	140	98	
Q14 work with patients infected with COVID-19				
yes	14	105	166	62.9048 p=0.000
no	38	61	34	

The three groups of respondents (healthcare workers in hospital activity, healthcare workers in the outpatient activity, and technical support and administrative staff) do not differ significantly from each other in terms of gender, marital status, and type of employment contract (p=0.667399, p=0.386184,p=0.748311) (table 2).

But they differ significantly from each other in terms of the level of education, night shifts, as well as work with patients infected with COVID-19 (table 2).

Table 3. Average values of the key variables in the total sample - job demands

Job demands	average	standard deviation	
physical demands	3.335825	0.848541	F=142.4379 p=0.00
organizational demands	2.546480	0.902322	
emotional demands	2.153110	0.741874	
cognitive demands	2.558214	0.892616	

In general, referring to the level of the entire examined group, the average value of physical demands is 3.3 and it is significantly higher compared to the average values of all other job demands – organizational (2.5), emotional (2.1), and cognitive (2.6) for $p< 0.05$ (table 3).

The average value of emotional demands (2.1) is significantly lower versus the average values of all other job demands - physical, organizational, and cognitive for $p<0.055$ (table 3).

Table 4. Differences among the three groups of respondents in terms of job demands

physical demands	Average	standard deviation	
technical support and administrative staff	2.983173	0.795217	F=11.97362 p=0.000009
healthcare workers in outpatient activity	3.213855	0.882281	
healthcare workers in hospital activity	3.528750	0.786757	
organizational demands			
technical support and administrative staff	2.357143	0.847046	F = 2.279282 p=0.103638
healthcare workers in outpatient activity	2.501721	0.954725	
healthcare workers in hospital activity	2.632857	0.864827	
emotional demands			
technical support and administrative staff	2.038462	0.754931	F=1.627208 p=0.197728
healthcare workers in outpatient activity	2.111876	0.709350	
healthcare workers in hospital activity	2.217143	0.762273	
cognitive demands			
technical support and administrative staff	2.368590	1.036027	F=1.749684 p=0.175109
healthcare workers inoutpatient activity	2.539157	0.895728	
healthcare workers in hospital activity	2.623333	0.845760	

The average value of the physical job demands at the workplace is the highest among healthcare workers in hospital activity (3.5, sometimes), and the lowest among technical support and administrative staff (2.9, rarely). The difference that is registered in the physical demands in relation to the three groups of respondents (healthcare workers in hospital activity, healthcare workers in outpatient activity and tech-

nical support and administrative staff) is statistically significant for p>0.05 (table 4).

The average value of organizational demands is the highest among healthcare workers in hospital activity (2.6, rare), and the lowest among technical support, and administrative staff (2.3, rare). The difference registered in the organizational demands in relation to the three groups of respondents is statistically insignificant for p>0.05 (table 4).

The average value of emotional job demands is the highest among healthcare workers in hospital activity (2.2, rare), and the lowest among technical support and administrative staff (2.0, rare). The difference registered in the emotional demands in relation to the three groups is statistically insignificant for p>0.05 (table 4).

The average value of cognitive job demands is the highest among healthcare workers in hospital activity (2.6, rare), and the lowest among healthcare workers in outpatient activity (2.5, rare). The difference registered in the cognitive demands in relation to the three groups of respondents is statistically insignificant for p>0.05 (table 4).

Table 5. Presentation of the average values of the physical job demands in relation to the three groups of respondents

	responsibility for a large number of patients			the fast pace of work			a health facility is in a very noisy area			burdened of administrative activities		
	average	N	SD.	average	N	SD.	average	N	SD.	average	N	SD.
technical support and administrative staff	2.5	52	1.4	3.2	52	1.3	2.8	52	1.3	4.0	52	1.2
healthcare workers in outpatient activity	3.4	166	1.6	3.5	166	1.3	2.8	166	1.4	3.8	166	1.2
healthcare workers in hospital activity	4.1	200	1.2	4.0	200	0.9	3.2	200	1.3	3.6	200	1.4
	lack of personnel			lack of supplies necessary for work			lack of equipment and materials for work			additional tasks in the conditions of the COVID-19 pandemic		
technical support and administrative staff	3.4	52	1.4	2.8	52	1.2	2.5	52	1.3	2.5	52	1.4
healthcare workers in outpatient activity	3.4	166	1.5	2.9	166	1.4	2.6	166	1.3	3.4	166	1.5
healthcare workers in hospital activity	3.9	200	1.2	3.2	200	1.3	2.8	200	1.2	3.3	200	1.5

The average values of the answers of all respondents for the statements within the framework of the physical job demands are ordered according to their importance for the respondents: in the first place are the fast pace of work and the burden of administrative activities, then comes the responsibility for a large number of patients and the lack of staff, the additional tasks in the conditions of the COVID-19 pandemic, the lack of supplies necessary for work, the lack of equipment and materials for work (table 5).

As the most significant physical job demands within the group of technical support and administrative staff, the following stand out: the burden of administrative activities, the lack of personnel, and the fast pace of work (table 5).

According to the obtained results, within the group of healthcare workers in outpatient activity, the most significant physical job demands stand out the burden of administrative activities, the fast pace of work and the responsibility for a large number of patients (table 5).

As the most significant physical demands within the group of healthcare workers in hospital activity, the following stand out: the responsibility for a large number of patients, the fast pace of work, and the lack of supplies necessary for work (table 5).

The average values of the physical jobdemandsin relation to the three groups of respondents (healthcare workers in hospital activity, healthcare workers in outpatient activity and technical support and administrative staff), are significantly higher among respondents employed in hospital activity and in the outpatient activity compared to technical support, and administrative staff (table 5).

Table 6. Presentation of the average values of the organizationaljob demands in relation to the three groups of respondents

	strict hierarchical arrangement of superiors			poor communication among departments			unclear and ambiguous roles and work tasks			frequent changes to rules and regulations in the health facility		
	average	N	SD.	average	N	SD.	average	N	SD.	average	N	SD.
technical support and administrative staff	2.3	52	1.3	2.5	52	1.3	2.0	52	1.2	2.2	52	1.2
healthcare workersin outpatient activity	2.3	166	1.3	2.5	166	1.4	2.1	166	1.3	2.5	166	1.4
healthcare workers in hospital activity	2.6	200	1.3	2.4	200	1.3	2.1	200	1.2	2.5	200	1.3

	unfair management in the department			influence of the media on the bad image of healthcare workers from the specific facility			problematic communication among departments in the context of the COVID-19 pandemic		
technical support and administrative staff	1.9	52	1.9	3.3	52	0.9	2.2	52	1.1
healthcare workers in outpatient activity	2.1	166	2.1	3.4	166	1.2	2.5	166	1.4
healthcare workers in hospital activity	2.2	200	2.2	3.9	200	1.1	2.8	200	1.4

The average values of the answers of all respondents to the statements within the organizational job demands are ordered according to their significance for the respondents: the influence of the media on the bad image of the healthcare workers from the specific facility, problematic communication among departments in the context of the COVID-19 pandemic, the frequent changes of the rules and regulations in the health facility, the strict hierarchical arrangement of superiors, poor communication among departments, the unclear and ambiguous roles and tasks and unfair management in the department (table 6).

The most significant organizational job demands within the group of technical support and administrative staff stand out: the influence of the media on the bad image of healthcare workers from the specific institution, poor communication among departments, and frequent changes to the rules and regulations in the health institution (table 6).

According to the results obtained within the group of healthcare workers in outpatient activity, the most significant organizational job demands stand out: the influence of the media on the bad image of healthcare workers from the specific institution, problematic communication among departments in the conditions of the COVID-19 pandemic and poor communication among departments (table 6).

The following stand out as the most significant organizational job demands within the group of healthcare workers in hospital activity: influence of the media on the bad image of healthcare workers from the specific facility, problematic communication among departments in the conditions of the COVID-19 pandemic, poor communication among departments and the frequent changes of the rules and regulations in the health facility (table 6).

The average value of the difference of the organizational job demands is insignificantly higher among healthcare workers in hospital activity compared to technical support and administrative staffand healthcare workers in outpatient activity. The difference in the organizational demands is significantly higher among healthcare workers in hospital ac-

tivity compared to technical support and administrative staffand healthcare workers in outpatient activity about these organizational demands: influence of the media on the bad image of healthcare workers from the specific facilityand problematic communication among departments in the context of the COVID-19 pandemic (table 6).

The average values of the responses of all respondents to the statements within the emotional job demands are ordered according to their importance for the respondents: the conflict between demands in the home and work environment, the high competition among colleagues, inadequate handling of negative feelings during the COVID-19 pandemic, the problems in communication with patients, the fear of making a mistake during the work and the lack of cooperation with colleagues.

As the most significant emotional job demands within the group of technical support and administrative staff, the following stand out: the conflict between demands in the home and work environment, the high competition among colleagues, and the fear of making a mistake during the work.

According to the obtained results, within the group of healthcare workers in outpatient activity, the most significant emotional job demands stand out: the conflict between demands in the home and work environment, the high competition among colleagues and the problems in communication with patients.

The most significant emotional job demands within the group of healthcare workers in hospital activity stand out: the conflict between demands in the home and work environment, the high competition among colleagues and the inadequate handling of negative feelings during the COVID-19 pandemic.

The average value of the differences in emotional job demands are insignificant among healthcare workers in hospital activity, technical support and administrative staffand healthcare workers in outpatient activity. The difference is significant in the emotional job demands and it is significantly higher among healthcare workers in hospital activity compared to healthcare workers in outpatient activity in terms ofemotional job demand - problems in communication with patients.

The average values of the responses of all respondents to the statements within the cognitive job demands are ordered according to the importance of the respondents: the obligation to train new employees, decision-making under the time pressures, decision-making under time pressures during the COVID-19 pandemic, the lack of feedback on work results, anddecision-making in the absence of necessary information and insufficient participation in decision-making.

As the most significant cognitive job demands within the group of technical support and administrative staff, the following are highlighted: the obligation to train new employees, making decisions under time

pressure and the lack of feedback on work results.

According to the results obtained within the group of healthcare workers in outpatient activity, the most significant cognitive job demands stand out: the obligation to train new employees, decision-making under time pressures during the COVID-19 pandemic, decision-making under the time pressuresand making decisions in the absence of the necessary information.

As the most significant cognitive demands of the workplace within the group of healthcare workers in hospital activity, the following stand out: the obligation to train new employees, decision-making under time pressures during the COVID-19 pandemic, and decision-making under time pressures.

The difference in the average value of the cognitive job demands is insignificant among healthcare workers in hospital activity, technical support and administrative staff,and healthcare workers in outpatient activity. The difference is significant in the cognitive job demands and is significantly higher among healthcare workers in hospital activity compared to technical support and administrative staff about these cognitive demands: obligation to train new employees and make decisions under thetime pressures during the COVID-19 pandemic.

Discussion

The difference among the groups in terms of the following demographic characteristics and job characteristics: gender, marital status, type of employment contract, total yearsof service, length of service at the current workplace, and number of working hours per week is insignificant, i.e. the three groups of respondents on these issues are homogeneous.

Healthcare workers play a central role in health systems, which is certainly confirmed mainlyduring the Covid-19 pandemic, referring tothe lack of health personnel reported as the most common cause of disorders in providing basic health services[15].Vulnerability in the medical profession stems from psychosocial health problems, organizational requirements, and health care requirements[16,17].

Employees in the different segments of the health sector are faced with different types of job demands. The types of job demands and job resources depend on the characteristics of the healthcare institution (e.g. University Clinic, Clinical Hospital, General Hospital, Health Center, etc.) and the job characteristics, i.e. the profile of the worker (e.g. a doctor, a nurse, technical support and administrative staff, etc.). The fact that some worker profiles provide direct patient care and service delivery and are in everyday immediate communication with patients, and others are not, refers to differences in the work process, workplace tasks, work organization, and different disadvantages and risks to which different workers' profiles are exposed[18].

Employees deal with the following job demands on a daily basis: physical, emotional, organizational, and cognitive. Thus, the results of a study by Mijakoski conducted in two hospitals (University Surgery Clinic and General Hospital) in RNM show the presence of the highest average values for all types of job demand among the surgeons and operating room nurses from both analyzed health institutions[18]. In a similar study conducted to examine differences in burnout, job demands, and teamwork between Macedonian and Croatian hospital nurses, Croatian nurses have reported higher levels of organizational job demands (e.g.strict hierarchy, ambiguous roles, problematic communication) and emotional job demands (e.g.lack of cooperation, high competitiveness among colleagues, emotional involvement in work), while Macedonian nurses have reported higher levels of physical job demands (e.g. excessive workload, time pressure, lack of staff and materials) which is obviously a consequence of their difficult goal - workload (Croatian hospital - 250 beds with 250 employed nurses, while the Macedonian hospital - 500 beds and 230 employed nurses)[19].

In this context, the findings of the current study, show that at the level of the entire examined group, the average value of physical job demands (3.3, sometimes) is significantly higher compared to the average values of allother job demands – organizational, emotional, and cognitive. Furthermore, it has been established that the average value of emotional job demands (2.1) is significantly lower versus the average values of all other job demands - physical, organizational, and cognitive for $p < 0.055$.

The average values of the answers of all respondents for the statements within the framework of the physical job demands are ordered according to their importance for the respondents: in the first place are the fast pace of work and the burden of administrative activities, then comes the responsibility for a large number of patients and the lack of staff, the additional tasks in the conditions of the COVID-19 pandemic, the lack of supplies necessary for work, the lack of equipment and materials for work (table 5). In the three groups of respondents (healthcare workers in hospital activity, healthcare workers in outpatient activity and technical support and administrative staff) as the most significant physical job demand is the fast pace of work, but the groups differ in terms of the exposure to the other physical job demands. The difference registered in the physical job demands in relation to the three groups of respondents is statistically significant for $p > 0.05$.

The average values of the physical job demands in relation to the three groups of respondents are significantly higher among respondents, healthcare workers in hospital activity and healthcare workers in outpatient activity compared to technical support and administrative staff, which means that healthcare workers in hospital activity and

healthcare workers in outpatient activity experience the physical job demands more seriously compared to the technical support and administrative staff. This confirms the differences in the characteristics of job demands depending on which segment of the healthcare sector the respondents are involved in.

The average values of the answers of all respondents to the statements within the organizational job demands are ordered according to their significance for the respondents: the influence of the media on the bad image of the healthcare workers ofthe specific facility, problematic communication between departments in the context of the COVID-19 pandemic, the frequent changes of the rules and regulations in the health facility, the strict hierarchical arrangement of superiors, poor communication among departments, the unclear and ambiguous roles and tasks and unfair management in the department (table 6). In the three groups of respondents (healthcare workers in hospital activity, healthcare workers in outpatient activity and technical support and administrative staff) the most significant organizational job demand is the influence of the media on the bad image of the healthcare workers from the specific facility. The difference registered in the organizational job demands in relation to the three groups of respondents is statistically insignificant for $p>0.05$.

The average value of the difference of the organizational job demands is insignificantly higher among healthcare workers in hospital activity compared to technical support and administrative staff and healthcare workers in outpatient activity. The difference in the organizational demands is significantly higher among healthcare workers in hospital activity compared to technical support and administrative staff and healthcare workers in outpatient activity about these organizational demands: influence of the media on the bad image of healthcare workers from the specific facility and problematic communication among departments in the context of the COVID-19 pandemic (table 6).

In the following, the average values of the responses of all respondents to the statements within the emotional job demands are ordered according to their importance for the respondents: the conflict between demands in the home and work environment, the high competition among colleagues, inadequate handling of negative feelings during the COVID-19 pandemic, the communication problems with patients, the fear of making a mistake during the work and the lack of cooperation with colleagues. In the three groups of respondents (healthcare workers in hospital activity, healthcare workers in the outpatient activity and technical support and administrative staff) the most significant emotional job demands are the conflict between the demands in the home and work environment as well as the great competition among colleagues. The difference registered in the emotional job demands in

relation to the three groups of respondents is statistically insignificant for p>0.05.

The average value of the differences in emotional job demands is insignificant among healthcare workers in hospital activity, technical support and administrative staff, and healthcare workers in outpatient activity. The difference is significant in the emotional job demands and it is significantly higher among healthcare workers in hospital activity compared to healthcare workers in outpatient activity in terms of emotional job demand - communication with patients.

In the end, the average values of the responses of all respondents to the statements within the cognitive job demands are ordered according to their importance to the respondents: the obligation to train new employees, decision-making undertime pressures, decision-making undertime pressures during the COVID-19 pandemic, the lack of feedback on work results and decision-making in the absence of necessary information and insufficient participation in decision-making.

In the three groups of respondents (healthcare workers in hospital activity, healthcare workers in outpatient activity, and technical support and administrative staff) the most significant cognitive job demand are the obligation to train new employees, decision-making under the time pressures during the COVID-19 pandemic and decision-making under the time pressures. The difference registered in the cognitive job demands in relation to the three groups of respondents is statistically insignificant for p>0.05. The difference in the average value of the cognitive job demands is insignificant among healthcare workers in hospital activity, technical support and administrative staff, and healthcare workers in outpatient activity. The difference is significant in the cognitive job demands and it is significantly higher among healthcare workers in hospital activity compared to technical support and administrative staff about these cognitive demands: obligation to train new employees and make decisions under the time pressures during the COVID-19 pandemic.

These findings lead to the conclusion that healthcare workers in hospital activity are more exposed to the different types of job demands compared to technical support and administrative staff and healthcare workers in outpatient activity, therefore that healthcare workers in hospital activity and healthcare workers in outpatient activity are more exposed to the physical job demands compared to technical support and administrative staff.

Hence, it follows that the physical job demands should not be neglected, because of the findings similar to those in the current study have also been obtained in other studies. In that context, in research conducted in two hospitals (University Surgery Clinic and General Hospital) in RNM, the physical job demands among respondents of the university surgical clinic are sig-

nificantly higher compared to other job demands, and they are also significantly higher compared to the physical job demands among respondents of the general hospital. Another study, also study conducted in RNM in order to examine differences in burnout, job demands, and teamwork among healthcare workers employed in a general hospital, during two periods oftime (2011 and 2014) showed that the levels of physical jobdemands (increased workload, increased number of patients served and complex administration procedures) were consistently higher compared to the levels of other job demands[20].

As has been stated previously, high job demands drain workers' mental and physical resources resulting in emotional exhaustion.These job demands affect employee well-being and performance. Various studies confirm the relationship between job demands and reduced productivity[21] and work-related stress, increased medical malpractice[22] as well as mental health disorders in healthcare workers, mainly depression and anxiety[23-25].

Conclusions

The results of this study show that the difference among the examined groups in terms of demographic characteristics and job characteristics are insignificant, that is to say, the three groups of respondents are homogeneous in terms of these issues.

Regarding the most common job demands, the findings show that at the level of the entire examined group, the average value of physical job demands is significantly higher compared to the average values of all other job demands – organizational, emotional, and cognitive. The difference registered in the physical job demands in relation to the three groups of respondents is statistically significant for $p>0.05$.

These results indicate higher average values of the physical job demands among healthcare workers in hospital activity and healthcare workers in the outpatient activity compared to technical support and administrative staff.

The knowledge that has been obtained about the characteristics of job demands of healthcare workers in different segments of the healthcare sector is the basis for proposing and developing strategies as well as preventive measures at organizational and individual levels.

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CLINICAL SCIENCE

CORRELATION OF PLASMA D-DIMERS WITH STAGES OF LIVER CIRRHOSIS AND ITS COMPLICATIONS

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Key words: liver cirrhosis, D-dimer, hyperfibrinolysis, Model for End-Stage Liver Disease, Child-Pugh-Turcotte

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Abstract

Aim of the study: To investigate plasma D-dimer levels in correlation with Child-Pugh-Turcotte (CTP) and Model for End-Stage Liver Disease (MELD) scores in patients with liver cirrhosis (LC) of different severity, as well as the correlation with LC-associated clinical, biochemical parameters and complications. Material and methods: Fifty patients with LC were divided in three groups according to LC severity using the CTP Score (CTP-A, CTP-B, CTP-C). The levels of D-dimer were measured in sodium-citrate plasma on Siemens, BCS XP Blood Coagulometer. Kruskal-Wallis test was used to compare D-dimer levels between the groups. Mann-Whitney U test was used to evaluate the difference of D-dimer levels in groups with different MELD score, and to evaluate the difference in D-dimer levels in patients with presence or absence of ascites and the difference of D-dimer levels in patients with or without spontaneous bacterial peritonitis (SBP). Pearson's coefficient of correlation was used to evaluate the correlation between D-dimer levels with MELD score and the correlation between D-dimer levels and the concentration of LC-associated biochemical, clinical parameters and complications. Results: D-dimer levels increased with severity of the disease as assessed with CTP and MELD scores, with a statistically significant difference between the groups (p=.0000 and ***p***=.0001, respectively). Group CTP-C demonstrated the highest D-dimer levels, followed by groups B and A. Patients with SBP had significantly higher levels of D-dimers than patients without SBP (p=.0006). A significant positive correlation between D-dimers and CTP and MELD score was detected (r= 0.74 and r=0.44, respectively; ***p***<.001). A correlation between D-dimer levels and several biochemical parameters characterizing progressive liver dysfunction was observed. From all investigated biochemical parameters, the highest significant correlation was detected between D-dimer levels and the concentration of serum albumin (r= -0.65, ***p***<.001). Conclusions: Plasma D-dimer levels are tightly correlated with the degree of liver dysfunction and LC-associated complications. Therefore, D-dimer levels could be utilized as a prognostic stratification marker and adjunctive diagnostic marker in LC-associated complications.

КЛИНИЧКИ ИСТРАЖУВАЊА

АСОЦИЈАЦИЈА НА ПЛАЗМА Д-ДИМЕРИТЕ СО СТАДИУМИТЕ НА ЦРНОДРОБНА ЦИРОЗА И НЕЈЗИНИТЕ КОМПЛИКАЦИИ

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Клучни зборови: цироза на црн дроб, Д-димери, хиперфибринолиза, Model for End-Stage Liver Disease, Child-Pugh-Turcotte

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Печатарски права: ©2023. Анче Волкановска, Виолета Дејанова, Владимир Андреевски, Мери Трајковска, Даница Лабудовиќ. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираат оригиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Цел на студијата: Да се испита нивото на Д-димери во плазма во корелација со клиничките скорови: Child-Pugh-Turcotte (CTP) и Model for End-Stage Liver Disease (MELD) кај пациенти со црнодробна цироза со различна тежина, како и нивна корелација со клинички, биохемиски параметри и компликации поврзани со црнодробна цироза. Материјали и методи: Вкупно 50 пациенти со цироза на црн дроб беа поделени во три групи според тежината на цироза на црниот дроб врз основа на CTP Score (CTP-A, CTP-Б, CTP-C). Концентрацијата на Д-димерите беше одредена во плазма со натриум цитрат користејќи го Siemens, BCSXP крвниот коагулометар. Kruskal-Wallis тестот беше користен за да се спореда нивоата на Д-димери помеѓу CTP групите. Mann-Whitney U тестот беше направен за да се одреди разликата во нивоата на Д-димерите помеѓу групите со различен MELD скор, и за да се оцени разликата во нивоата на Д-димерите кај пациенти со присуство или отсуство на асцит и разликата во нивоата на Д-димерите кај пациенти со или без спонтан бактериски перитонитис (SBP). Pearson-овиот коефициент на корелација беше користен за да се оцени корелацијата помеѓу нивоата на Д-димери со MELD скорот и корелацијата помеѓу нивоата на Д-димери и концентрацијата на биохемиски, клинички параметри и компликации поврзани со црнодробна цироза. Резултати: Концентрацијата на Д-димерите се зголеми со тежината на болеста проценета со CTP и MELDскорот со статистички значајна разлика помеѓу групите (***p***=,0000 и ***p***=,0001, соодветно). Групата CTP-C покажа највисока концентрација на Д-димери, по што следуваа групите Б и А. Пациентите со SBP имаа значително повисока концентрација на Д-димери во споредба со пациентите без SBP (***p***= ,0006). Беше утврдена значителна позитивна корелација помеѓу Д-димерите и CTP и MELD скорот (коефициент на корелација r= 0,74 и r= 0,44, соодветно; ***p***< ,001). Дополнително, резултатите покажаа дека постои поврзаност меѓу плазма концентрацијата на Д-димерите со клиничките и биохемиски параметри кои карактеризираат прогресивна дисфункција на црниотдроб. Од сите испитувани биохемиски параметри, највисока статистички значителна корелација беше утврдена меѓу нивоата на Д-димерите и концентрацијата на серумските албумини (r = - 0,65, ***p***< 0,001). Заклучок: Плазматската концентрација на Д-димерите е тесно поврзана со степенот на дисфункција на црниотдроб и компликациите поврзани со цироза на црн дроб. Затоа, нивоата на Д-димерите може да се користат како прогностички маркер за стратификација и дополнителен дијагностички маркер во компликациите поврзани со цироза на црн дроб.

Introduction

Plasma D-dimers are the end products of fibrinolysis, the process which regulates fibrin degradation and prevents thrombosis or hemorrhage. In combination with clinical probability assessment, D-dimers are routinely used in clinical practice for ruling out pulmonary embolism[1,2], as well as for deciding on anticoagulant therapy in patients with risk of recurrent venous thromboembolism[3]. Liver cirrhosis (LC) is associated with changes in hemostasis[4], and accelerated hyperfibrinolysis may be one of the mechanisms that can contribute to serious coagulopathy which can occur in LC in different settings.

Incidence of hyperfibrinolysis and its association with clinical parameters of LC has not been extensively evaluated[5]. Plasma D-dimers give precise insight in the presence of fibrinolysis and elevated levels reflect overactive coagulation and fibrinolysis *in vivo*. Previous studies have shown elevated levels in association with liver dysfunction[6], presence of ascites[7], development of spontaneous bacterial peritonitis (SBP)[8], and in occurrence of portal vein thrombosis[9]. Consequently, it has been suggested that they may have a prognostic value for LC-associated outcomes[9,10].

In our study we aimed to evaluate plasma D-dimers in patients with LC with varying degree of liver dysfunction using the Child Turcotte Pugh (CTP) and Model for End-Stage Liver Disease (MELD) scores. Additionally, we assessed the relationship between hyperfibrinolytic state with different biochemical and clinical parameters in LC at different stage of the disease.

Materials and methods

This was a cross-sectional study conducted at the University Clinic for Gastroenterohepatology in Skopje between June 2021 and December 2022. Patients consecutively admitted to the Clinic or evaluated at the outpatient level were enrolled. The inclusion criteria were as follows: 1) diagnosis of LC of different etiology (based on clinical presentation, routine laboratory tests and ultrasound examination of the abdomen); 2) patients at the age of 18 years and older; 3) a voluntary signed informed consent by patients or their family. Exclusion criteria were as follows: 1) presence of sepsis; 2) acute bleeding; 3) use of vitamin K antagonists, oral therapy with direct anticoagulants or antithrombotics; and 4) presence of malignant disease (hepatocellular carcinoma included). The present study was approved by the Ethics Committee at the Faculty of Medicine, Ss. Cyril and Methodius University in Skopje.

The following data were analyzed: age, gender, etiology of LC, presence of ascites, presence of SBP [defined as an elevated absolute fluid polymorphonuclear neutrophil (PMN) count in the ascites (>250/mm3) without an evident intra-abdominal surgically treatable source of infection], spleen diameter, portal vein diameter, red blood cell (RBC) count, hemoglobin (Hb) level, white

blood cell (WBC) count, platelet level (PLT), C-reactive protein (CRP), total bilirubin (TBIL), albumin (ALB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine (Cr), urea, prothrombin time (PT), international normalized ratio (INR), D-dimer levels, CTP and MELD scores. Blood samples for laboratory and hemostatic assessment were obtained before initiation of therapy for the hospitalized patients and at a regular follow-up. Patients were divided in 3 groups according to their LC severity and expected survival using the CTP score (CTP A - 5-6 points, CTP B – 7-9 points and CTP C – 10-15 points)[11,12]. Laboratory hemostatic assessment was according to already adopted protocols and standard practice using Siemens' fully automated coagulometer - Dade Behring BCS® XP System, hematological analyzer MEDONIC and Xprecia Stride analyzer which uses single-use test strips with reagents (Dade® Innovin®) at the Institute for Transfusion Medicine.

Categorical data are presented as mean ± standard deviation, and were compared using the Mann-Whitney U test. The comparison of D-dimer levels (reference range: 0-500 ng/ml) with the CTP score was evaluated using the Kruskal-Wallis test and Multiple Comparison test, while the comparison of D-dimer levels between patients according to MELD score, presence of ascites and SBP was made with Mann-Whitney U test. Boxplots were also constructed to demonstrate the difference in the D-dimer levels among various Child-Pugh classes (namely A-C) and MELD (namely scores >15 or <15). Scatterplots were constructed for displaying the correlation between evaluated variables and correlation was assessed with Pearson's coefficient of correlation. A two-sided P-value of <0.05 was considered to indicate a statistically significant difference. All statistical analyses were performed using the IBM SPSS Statistics[20].

Results

Patients

In total, 50 patients with LC fulfilling the inclusion criteria were enrolled in the study. Patient characteristics are demonstrated in Table 1.The mean age in group CTP-A was 56.9±10.4 years with 38.9 % being men; in group CTP-B the mean age was 54.0±16.7 years with 50 % being men, and in group CTP-C the mean age was 51.6±14.4 years with 81.3% being men. The most common etiology of LC was alcoholic liver disease (13/50; 26%).

Table 1. Demographic and clinical characteristics of patients.

Variables	CTP-A	CTP-B	CTP-C	p
Number of patients (n)	18	16	16	
Age (mean±SD)	56.9±10.4	54.0±16.7	51.6±14.4	
Gender, %				
Male	7/38.9	8/50.0	13/81.3	
Female	11/61.1	8/50.0	3/18.7	
Etiology (n)				
Viral hepatitis	6	3	4	
Alcohol	2	5	8	
Autoimmune	6	3	/	
MAFLD*	3	2	/	
Others	1	3	4	
Albumin, g/L (mean±SD)	42.1±5.9	34.0±5.9	26.6±4.4	.0000
Bilirubin, mol/L (mean±SD)	15.5±8.6	43.3±28.8	143.2±139.5	.0000
Ascites, %	4/22.22	12 /75	16 /100	
SBP^, %	0	0	8/50	
Hepatic encephalopathy, %	0	2/12.5	10/62.5	
CRP‡, mg/L(mean±SD)	7.1±9.6	9.1±8.7	50.8±46.5	.0000
PT, s (mean±SD)	12.2±0.9	14.3±2.3	20.0±4.0	.0000
INR (mean±SD)	1.1±0.1	1.3±0.2	1.8±0.4	.0000
D-dimers, ng/ml (mean±SD)	670.2±419.1	2972.0±3815.7	6393.6±3086.1	.0000
MELD score† (mean±SD)	8.7±3.1	12.3±3.6	24.6±7.4	.0000
Patients with LC-associated complication that led to death, %	/	3/18.75	7/43.75	

**MAFLD: metabolic-associated fatty liver disease; ^SBP: spontaneous bacterial peritonitis; ‡CRP: C-reactive protein; †MELD score: Model for End-Stage Liver Disease score*

D-dimer and CTP Score.The mean value of D-dimer was lowest in group CTP-A (670.2±419.1ng/ml), and progressively increased in group CTP-B (2972.0±3815.7ng/ml) and group CTP-C (6393.6±3086.1ng/ml) as shown in Fig.1. The difference in D-dimer levels among the groups was statistically significant (H(2) = 26.99, p = .0000) (Table 1). Furthermore, significant differences were observed between the different groups (A *vs.* B, *p*= .037; A *vs.* C, *p* = .0000; B *vs.* C, *p* = .026). The mean values of D-dimers in patients who died of LC-associated complication at least 2 weeks after being enrolled in the study were 4837.97±3480.124ng/ml. A significant strong positive correlation was demonstrated between D-dimer levels and CTP score (r= 0.74, *p*< .00001).

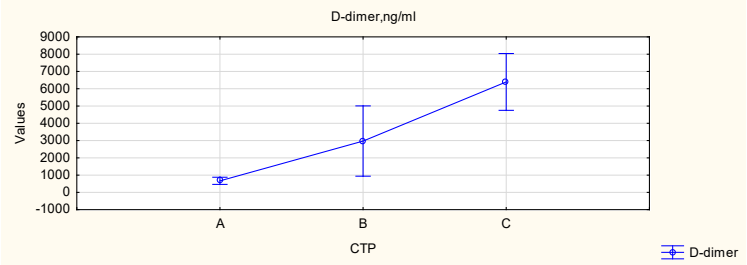


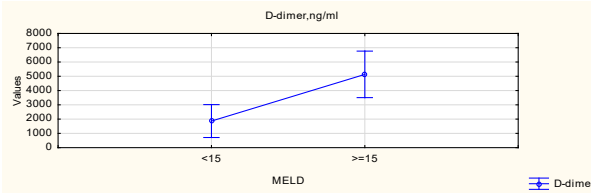
Figure 1. Average levels of D-dimers within different stage of LC according to CTP score

D-dimer and MELD score.

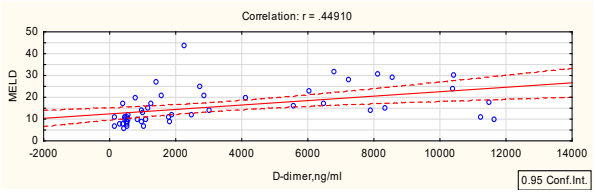
The mean value of D-dimer levels in MELD < 15 group was 1864.4±3027.781ng/ml, while in MELD group > 15 was significantly higher, 5135.6±3580.157ng/ml (Table 2). There was a statistically significant difference between the groups (z =-3.73, *p*=.0001). As shown in Fig. 2-b, D-dimer levels were positively correlated with the MELD score (r= 0.44; *p* =.001).

Table 2. D-dimer levels in patients according to MELD score

MELD score	Number of patients, n	D-dimer (mean±SD), ng, mL
< 15	29	1864.4±3027.781
> 15	21	5135.6±3580.157



a



b

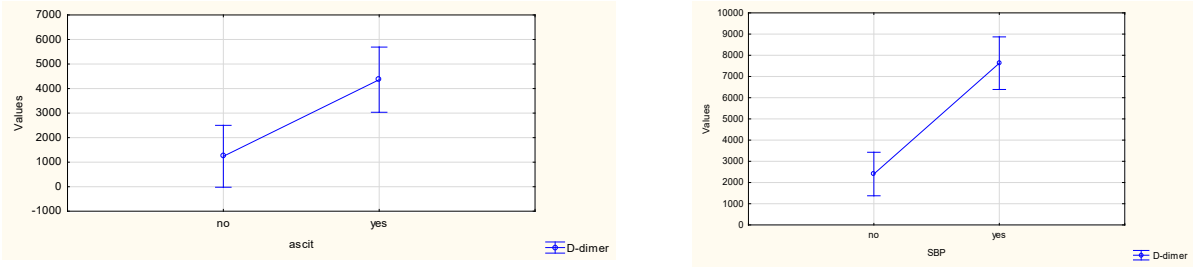
Figure 2. D-dimer levels and MELD score. a) average levels of D-dimers in patient with MELD score < 15 and > 15; b) correlation of D-dimer levels with MELD score

D-dimer and ascites

The mean values of D-dimers in patients with ascites were 4362.7±3687.4 ng/ml, which were significantly higher than those in patients without ascites, 1239.2±2537.6 ng/ml (Table 3 and Fig. 3-a). This difference was statistically significant (z =4.07, *p*=.00004). Additionally, the mean values of D-dimer levels were significantly higher in patients with large volume ascites (6196.9±3498.7 ng/ml), compared to patients with small amount ascites (1306±929.9 ng/ml) (Table 3). The difference between these groups of patients was statistically significant (z =6.41, *p*< .00001).

Table 3. D-dimer levels in presence or absence of ascites and the amount of ascites

Ascites	Number of patients (n)	D-dimers (mean±SD, ng/mL
< 15	29	1864.4±3027.781
> 15	21	5135.6±3580.157
Small amount ascites	12	1306±929.9
Large volume ascites	20	6196.9±3498.7



a **b**

Figure 3. D-dimer levels in: a) patients without and with ascites; b). patients with and without SBP

D-dimers and SBP

The mean value of D-dimers in patients with SBP was 7630.2±1483.5 ng/ml compared to patients without SBP (2401.7±3291.7 ng/ml), which was statistically significantly higher (z =-3.42, *p*=.0006) (Table 4 and Fig. 3-b). Likewise, the comparison of the mean value of D-dimers between patients with ascites but without SBP (3273.6±3564.4 ng/ml) and patients with ascites and SBP (7630.2±1483.5) showed a statistically significant difference (z = -2.85,*p* = .004).

Table 4. D-dimer levels in patients without and with SBP

	Number of patients (n)	D-dimers (mean±SD, ng/mL
Absence of SBP	42	2401.7±3291.7
Presence of SBP	8	7630.2±1483.5
Ascites without SBP	24	4362.7±3687.4
Ascites with SBP	8	7630.2±1483.5

D-dimers and other LC-associated clinical and biochemical parameters.

The evaluated LC-associated clinical and biochemical parameters (age, Hb, Hct, PLT, WBC, CRP, ALT, AST, albumin, bilirubin, blood urea nitrogen, serum creatinine, PT, INR, fibrinogen, etiology of disease, spleen diameter and portal vein diameter) showed a significant moderate positive correlation between D-dimer levels and WBC (r =0.55, *p* = .0000), CRP (r= 0.42, p = .0023), PT (r= 0.44, *p* = .001) and INR (r =0.44, *p* = .001) (Fig. 4). A significant moderate negative correlation of D-dimer levels was registered for albumin (r= -0.65, *p*< .00001) (Fig. 4).

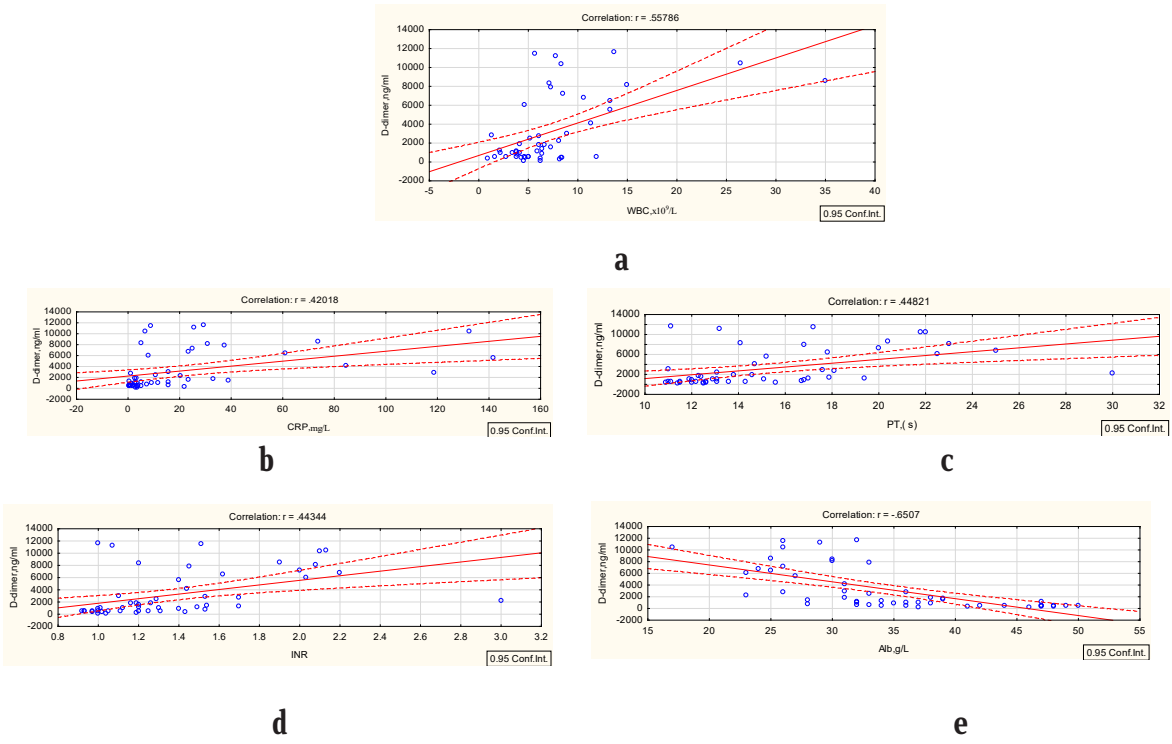


Figure 4. Significant moderate positive correlation of D-dimer levels with WBC, CRP, PT and INR (a-d) and significant moderate negative correlation with albumin (e).

Discussion

In our study we demonstrated that the increase of D-dimer levels throughout different stage of LC was in correlation with CTP and MELD scores. This finding was in line with previous studies. In our study, D-dimer levels in healthy subjects and subjects with non-cirrhotic chronic liver disease were not assessed, but in the study of El-Sayed *et al.*[13] a substantial difference in D-dimer levels between these groups of patients was demonstrated. The authors observed significantly higher D-dimer levels in patients with Child-Pugh class A and B compared to non-cirrhotic patients with chronic liver disease, and also compared to healthy controls. Similar results were demonstrated in two independent studies in which progressive increase of D-dimers among Child-Pugh class A, B and C was registered[14,15]. In a study evaluating the correlation of D-dimers with esophageal variceal bleeding in patients with LC, classified according to their

CTP and MELD scores, a significant increase was detected in patients in advanced stage of the disease, more specifically in Child-Pugh class C (with and without bleeding) and in those with MELD score > 17 with bleeding[16]. The results of our study correspond to the afore mentioned studies and has clearly demonstrated that as LC progresses, the levels of D-dimer progressively increase. Additionally, our study confirmed that between different stages of LC according to CTP score, there was a significant difference in D-dimer levels that was statistically significant (p = .0000, p < .05). The same result was obtained when evaluated with MELD score showing a positive correlation with D-dimer levels. Based on current guidelines, patients with LC and a MELD score of 15 or greater should be referredfor liver transplantation evaluation[17]. The group of patients with MELD score > 15 had significantly higher values of D-dimers compared to the group with MELD score < 15, with a statistically significant difference (p = .0001, p < .05). These findings support the tight correlation of accelerated fibrinolytic activity, i.e., hyperfibrinolysis with the degree of liver dysfunction as assessed by the CTP and MELD scores.

When comparing patients with LC without and with ascites in our study, we registered a significant difference between the two groups. D-dimer levels in patients with ascites were significantly higher than in those without (p = .00004, p < .05). Furthermore, there was a statistically significant difference (p <.00001) in D-dimer levels when evaluating the amount of ascites (Table 3). These results are also to be expected given that patients with ascites, especially those with higher amounts of ascites have more advanced LC, i.e., are common in the CTP-B and CTP-C class. But some studies suggest that the elevated D-dimer levels can also be the result of the ascitic fluid itself, as a fibrinolytic activity of the ascitic fluid has been demonstrated[18]. Still, this is controversial as not all studies have confirmed this finding[19,20]. Another finding that supports the role of developing ascites in the LC-associated hyperfibrinolysis, is the reduction of D-dimer level with treatment and resolution of ascites (medicamentous or with ascitic fluid paracentesis) [7,21,] though D-dimers are still higher than in patients with LC but without ascites [7,22].

The difference in D-dimer levels was even more accentuated in patients with SBP compared to patients with LC without ascites or with ascites and no SBP. We demonstrated a significant difference (p = .0006) between D-dimer levels in patients with LC and without SBP and patients with SBP. This difference was also significant (p=.004) when comparing patients with LC and ascites but without SBP. These findings were confirmed in other studies[8,23]. Hence D-dimers can be an adjunctive diagnostic tool in identifying LC patients with SBP, and possibly differentiating patients with ascites, but without bacterial infection. This is of importance in the clinical management of these patients since

SBP has a subtle presentation and a high index of suspicion is needed for diagnosis and prevention of LC deterioration[24]. SBP is a serious LC-complication and leads to worsening of prognosis in patients with LC with short-term mortality of about 15-40%[25].

In our study we found a significant but moderate positive correlation of D-dimer levels with WBC, CRP, PT and INR, and a significant strong negative correlation with serum albumin. This correlation confirms once again that higher levels of D-dimers are present in advanced liver cirrhosis and reflect liver dysfunction.

Although our study did not evaluate the role of D-dimers as a predictor of mortality rate, we detected a marked increase of D-dimers in patients with LC-related death up to 2 weeks after inclusion in the study. The mean values of the D-dimers in this group of patients were4837.97±3480.12 ng/ml.D-dimers were evaluated as a possible predictive and prognostic marker in patients with LC. Primignaniet al. evaluated the association of D-dimers with the 6-week mortality rate in cirrhotic patients with esophageal variceal bleeding 16. Hyperfibrinolysis was present in 67% of non-survivors compared to 11% of survivors, and the odds ratio for D-dimer level for predicting 6-week mortality was 16[16]. Another study of 703 patients with LC showed that D-dimers can predict in-hospital mortality with sensitivity of 86.84% and a specificity of 49.17% for the cut off value of 0.28 μg/ml10.

The limitation of our study is the small sample and the fact that it was performed in a single institution. Additionally, this was a cross-sectional study and a follow-up of the patients would have added to the strength of D-dimers as diagnostic markers for liver dysfunction and diagnosis of SBP as well as a prognostic factor for LC-related mortality.

Conclusion

Hyperfibrinolysis and D-dimer levels are correlated with the degree of liver dysfunction. Furthermore, a significant increase in plasma D-dimers in the presence of ascitic fluid is highly correlated with SBP, thus it represents a promising marker for early detection of SBP. Our study suggests that higher D-dimer levels should further be investigated and validated as predictor of increased in-hospital mortality and thus, in the future can present a prognostication parameter for patients with advanced liver disease.

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CLINICAL SCIENCE

CENTRAL OBESITY: WAIST CIRCUMFERENCE, WAIST-TO-HIP RATIO AND WAIST-TO-HEIGHT RATIO IN 13-YEAR-OLD CHILDREN

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Key words: childhood obesity, central obesity, waist circumference, waist-to-hip ratio, waist-to-height ratio.

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Competing Interests: The author have declared that no competing interests

Abstract

Obesity in children is a growing worldwide health problem, with a tenfold increase over just four decades. The aim of this study was to determine the prevalence of obesity and to identify central obesity in children aged 13 years from southwestern part of North Macedonia. Materials and methods: This cross-sectional study included a total of 178 healthy children of both sexes (boys 98, girls 80) aged 13 years living in Tetovo, North Macedonia. Results: The prevalence of categorized BMI according to CDC in all 13-year old children (n=178) was 4.5% underweight, 20.2% overweight and 16.3% obese. Among boys, the total prevalence of underweight, overweight and obese was consistently 4.1% vs. 19.4 %vs. 15.3%, while girls had statistically insignificant higher prevalence of underweight, overweight and obese 5% vs. 21.2% vs. 17.5%. At a comparison of the central obesity parameters like WC,WHR, WHtR showed statistically significant differences between sexes ($p<0.003$, $p<0.0001$, $p<0.011$). In the entire sample, the prevalence of high risk for waist-to-hip ratio (WHR) was 34.3% and the prevalence of high risk for waist-to-height ratio (WHtR) was 31.5%. In boys, the prevalence of high risk for WHR was 51% and for WHtR was 35.7% while in girls for WHR was 13.8 % and for WHtR 26.2%. A significant association of male gender with high risk for WHR ($X2=27.161$; $df=1$; $p=0.0001$) was found while for WHtR ($X2=1.830$; $p=0.176$) there was no statistically significant sssociation. It is important to underline that in boys the risk of central obesity was 6.53 times higher compared to girls of the same age [OR=6.53 (3.08–13.83) 95% CI. Conclusions: In our study girls had a higher BMI prevalence of general overweight and obesity vs. boys, and a significant association of male gender with high risk for WHR was detected. Additionally, healthcare professionals should always consider assessing the measurements and risk of central obesity in obese or overweight children, and seek for the unique risk factors associated with each type of obesity and tailor interventions accordingly.

КЛИНИЧКИ ИСПИТУВАЊА

ЦЕНТРАЛНА ДЕБЕЛИНА: ОБЕМ НА ПОЛОВИНА, ОДНОС ОБЕМ НА ПОЛОВИНА И КОЛКОВИ, ОДНОС ОБЕМ НА ПОЛОВИНА И ВИСИНА КАЈ 13-ГОДИШНИ ДЕЦА

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Клучни зборови: детска дебелина, централна дебелина, обем на половината, однос на половина и колк, однос на половина и висина

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Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Дебелината во детска возраст е сè поголем јавноздравствен проблем глобално, со десеткратно зголемување во текот на последниве четири децении. Целта на оваа студија беше да се процени преваленцијата на дебелината и да се идентификува централната дебелина кај децата на возраст од 13 години во северозападниот дел на Р.С. Македонија. Материјали и методи: Во оваа студија на пресек беа вклучени вкупно 178 здрави деца од двата пола (момчиња 98, девојчиња 80) на 13-годишна возрастод Тетово, Северна Македонија. Резултати: Преваленцијата на катагоризираниот БМИ според CDC кај сите 13-годишни деца (n=178) беше 4,5% потхранети, 20,2% натхранети и 16,3% дебели. Кај момчињата вкупната преваленција на потхранети, натхранети и дебели беше 4,1%; 19,4%; 15,3%, додека кај девојчињата имаше статистички незначителна поголема преваленција на потхранети, натхранети, и дебели 5%; 21,2%; 17,5%. При споредбата на параметрите за централна дебелина како WC, WHR, WHtR истите покажаа статистички значајни разлики помеѓу половите ($p<0,003$, $p<0,0001$, $p<0,011$). Кај целиот примерок, преваленцијата на висок ризик за WHR беше 34,3%, додека преваленцијата на висок ризик за WHtR беше 31,5%. Кај момчињата, преваленцијата на висок ризик за WHR беше 51%, а заWHtR беше 35,7% додека кај девојчињата за WHR беше 13,8%,а за WHtR 26,2%. Утврдивме статистички сигнификантна поврзаност на машкиот пол со висок ризик за WHR ($X2=27.161$; $df=1$; $p=0,0001$), додека за WHtR ($X2=1.830$; $p=0.176$) не постои статистички значајна поврзаност. Важно е да се нагласи дека кај момчињата ризикот од централна дебелина беше 6,53 пати поголем во споредба со оној кај девојчињата на истата возраст [OR=6,53 (3,08-13,83) 95% CI]. Заклучок: Оваа студија покажа дека девојчињата во споредба со момчињата имаа повисока преваленција на БМИ, потхранетост и дебелина, а беше регистрирана значајна поврзаност на машкиот пол со висок ризик за WHR. Здравствените работници треба секогаш да размислуваат за проценка и на ризикот од централна дебелина кај дебели и натхранети деца, како и идентификување на факторите на ризик поврзани со секој тип на дебелина и соодветно приспособување на понатамошните интервенции.

Introduction

Obesity in children is a growing public health problem worldwide. According to the World Health Organization, the number of children and adolescents who are overweight or obese has increased dramatically in recent years, which is more than ten-fold increase in the prevalence of obesity over just four decades.[1]

The causes of the increase in childhood obesity are complex and multifactorial, such as genetics, socioeconomic status, cultural factors, and factors such as changes in dietary habits and reduced physical activity.[2] Childhood obesity can lead to a range of health problems, including type 2 diabetes, high blood pressure, cardiovascular diseases, but it can also have a negative impact on children's mental and emotional well-being as it can lead to social stigma and discrimination.[3,4,5]

The standard and widely used method for measuring, screening and diagnosing obesity in children is the body mass index (BMI). In children, the calculation of BMI also takes into account their age and sex. However, there are other anthropometric measurements that can be used to assess central obesity, also known as abdominal obesity or visceral obesity in children, which is associated with an increased risk of several chronic diseases. Measuring waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) are the most common ways to measure central obesity.

The aim of this study was to determine the prevalence of obesity and to identify central obesity in children aged 13 years from southwestern part of North Macedonia.

Material and methods

This cross-sectional study conducted between February and April 2022 included a total of 178 healthy children of both sexes (boys 98, girls 80) aged 13 years living in Tetovo, North Macedonia.

To collect data for the purpose of assessing obesity and central obesity, the following anthropometric measurements were taken: height, weight, waist circumference and hip circumference. Additionally, these measurements were used to calculate various indices of obesity, including BMI, waist-to-hip ratio, and waist-to-height ratio.

Height is measured using a stadiometer and weight is measured using a calibrated scale. The children were asked to remove their shoes, any heavy clothing or accessories, and stand straight with their feet together on the stadiometer and the scale. The measurement is recorded in centimeters (cm) for height and kilograms (kg) for weight.[6]

Children's BMI calculated by using the formula BMI=weight (kg) / height (m)2 was compared with children's BMI to age- and sex-specific BMI charts to determine if children were underweight, normal weight, overweight, or obese.

In our study we used the CDC 2000 (Center for Disease Control and Prevention) BMI charts for age and sex. The weight status was categorized based on age and sex -BMI percentile of 85th to less than 95th is considered overweight, while BMI percentile of 95th or greater is considered obese.[7]

For accessing central obesity, WC is measured with stretch-resistant tape around the narrowest point of the waist, typically just above the belly button and HC is measured around the widest part of the hips, both of them with a precision of 1 mm.[8]

Waist-to-hip ratio (WHR): WHR is calculated by dividing the waist circumference by the hip circumference. A higher >=90th percentiles WHR indicates a higher proportion of fat stored around the waist and is associated with a higher risk for obesity-related health conditions. Waist-to-height ratio (WHtR): WHtR is calculated by dividing the waist circumference by the child's height. A WHtR of 0.5 or higher indicates increased health risks associated with excess abdominal fat.9 The data obtained in this study were analyzed with the SPSS software package, version 22.0 for Windows. Numerical (quantitative) series were analyzed with measures of central tendency (average, median, minimum values, maximum values, interactive ranks), as well as with measures of standard deviation. The prevalence of the investigated parameters of interest was presented as a ratio between the representation and the whole mass expressed in percentages. The LMS method was used to create the specific percentile display tables of the selected parameters according to age and sex. A two-sided analysis with a statistical significance valueof $p<0.05$ was used to determine a statistical significance.

Results

An analysis of the distribution of the mean value and standard deviation of the height (cm), weight (kg) and BMI (kg/m2), WC (cm), HC (cm), WHR, WHtR in 13-year-old boys and girls was made. In the entire sample (n=178) the mean values of body height was 157.5 ±8.2 cm, of weight 52.9± 13.3 kg, of BMI 21.2 ± 4.4 kg/m2, of WC 74.79 ± 11.35 cm, of HC 86.61± 11.74 cm,of WHR 0.90±0.44 and of WHtR 0.47±0.06. The mean values in boys (n=98) were: height 158.7± 9.3 cm, weight 53.8± 13.6 kg, BMI 21.02±4.2 kg/m2, WC 77.47±12.21 cm, HC 85.60 ± 12.76 cm, WHR 0.98 ±0.83 and WHtR 0.49±0.07. The mean values in girls (n=80) were: height 156.4± 7.1 cm, weight 53.8± 13.1 kg, BMI 21.2±4.6 kg/m2, WC 77.47±10.50 cm, HC 87.62 ± 10.73 cm, WHR 0.82 ±0.05 and WHtR 0.46±0.06 (Table 1).

With the Mann-Whitney U Test, for $p<0.05$, height, weight, BMI and HC showed no statistically significant differences between sexes ($p>0.05$), while a comparison of the central obesity parameters like WC,WHR, WHtR showed statistically significant differences between sexes ($p<0.003$, $p<0.0001$, $p<0.011$) (Table 2).

Table 1. Mean and standard deviations, sex-specific differences

Age 13 years	N	Height (cm)	Weight (kg)	BMI (kg/m2)	WC (cm)	HC (cm)	WHR	WHtR
		MEAN± SD	MEAN± SD	MEAN± SD	MEAN± SD	MEAN± SD	MEAN± SD	MEAN± SD
All	178	157.5±8.2	52.9 ±13.3	21.2±4.4	74.79±11.35	86.61±11.74	0.90±0.44	0.47±0.06
Boys	98	158.7±9.3	53.8±13.6	21.2±4.2	77.47±12.21	85.60±12.76	0.98±0.83	0.49±0.07
Girls	80	156.4±7.1	52.1±13.1	21.2±4.6	72.12±10.50	87.62±10.73	0.82±0.05	0.46±0.06

Values are mean ±SD=Standard deviation for height, weight, BMI=body mass index, WC= waist circumference, HC= hip circumference, WHR= waist-hip ratio WHtR= waist-height Ratio

Table 2. Height, weight, BMI,WC,HC,WHR,WHtR – comparison sex-specific differences

	Height	Height (cm)	BMI	WC	HC	WHR	WHtR
Z		Weight	(0.208)	(2.983)	(0.794)	(7.120)	(2.541)
P		0.406	0.836	0.003	0.427	0.0001	0.011

Z=Mann-Whitney U Test P= significance($p<0.05$)

The prevalence of categorized BMI according to CDC in all 13-year-old children (n=178) was 4.5% underweight, 20.2 % overweight and 16.3% obese. Among boys, the total prevalence of underweight, overweight and obese was consistently 4.1% vs. 19.4%vs. 15.3%, while in girls a statistically insignificant higher prevalence of underweight, overweight and obese was found (5% vs. 21.2% vs. 17.5%).

Table 3. Percentile indicators

	PERCENTILES									
	N	3th	5th	10th	25th	50th	75th	90th	95th	97th
BMI										
BOYS	98	14.89	15.71	15.93	17.96	20.70	23.71	27.81	29.91	31.81
GIRLS	80	14.28	15.01	15.99	17.73	20.40	23.97	28.12	30.17	31.06
WC										
BOYS	98	60.07	61.59	64.28	68.10	74.45	83.20	98.44	103.71	103.93
GIRLS	80	57.59	59.11	60.32	62.93	70.10	80.10	89.28	91.68	92.63
HC										
BOYS	98	67.78	69.99	73.19	79.38	85.20	92.48	101.34	103.75	105.50
GIRLS	80	70.66	71.91	74.17	79.50	86.50	95.93	103.04	104.68	108.09
WHR										
BOYS	98	0.79	0.81	0.81	0.84	0.89	0.93	0.97	1.01	1.11
GIRLS	80	0.72	0.73	0.77	0.79	0.82	0.85	0.89	0.91	0.94
WHtR										
BOYS	98	0.39	0.40	0.41	0.43	0.47	0.52	0.61	0.65	0.67
GIRLS	80	0.37	0.38	0.39	0.41	0.45	0.51	0.56	0.60	0.60

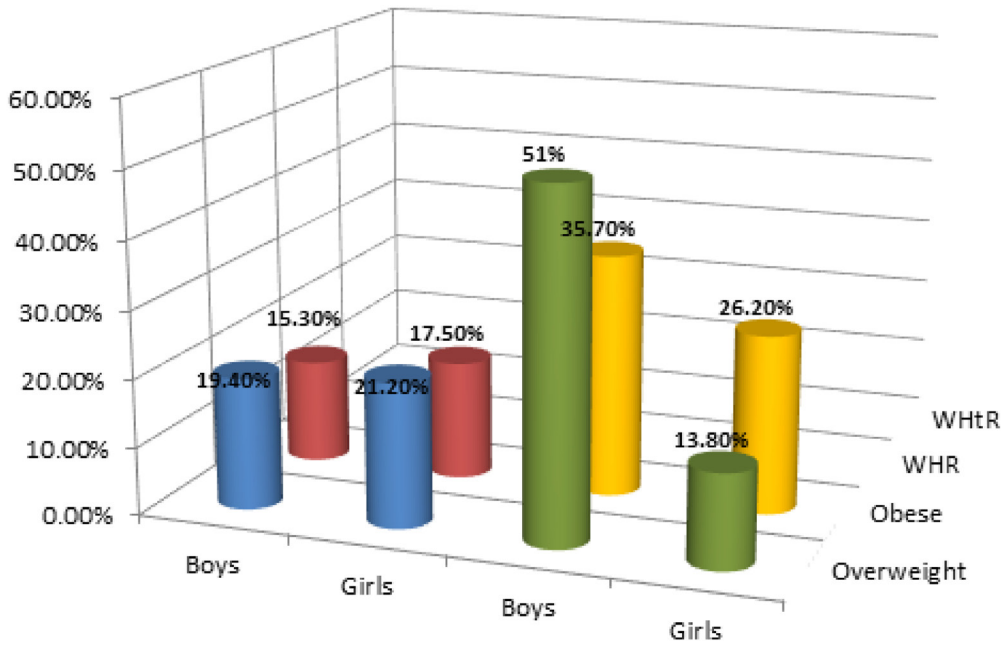

Figure 1. Distribution of overweight, obese, WHR and WHtR

Additionally, sex- and age-specific parameters for BMI and central obesity, WC, HC, WHR, and WHtR were analyzed with LMS method separately for boys and girls for 9 percentile indicators (3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, and 97th).

WHR and WHtR parameters were classified into groups with low and high risk for central obesity. A value ≥0.5 was considered a high risk of central obesity for WHtR, and for WHR the 90th percentile value distribution as cut off was taken.

In all children, the prevalence of high risk for WHR was 34.3% and the prevalence of high risk for WHtR was 31.5%. In boys, the prevalence of high risk for WHR was 51% and for WHtR 35.7%, while in girls the prevalence of high risk for WHR was 13.8 % and for WHtR 26.2%. A significant association of male gender with high risk for WHR (X2=27.161; df=1; p=0.0001) was found, while high risk for WHtR (X2 =1.830; p=0.176) showed no statistically significant differences. It is important to underline that the risk of central obesity was 6.53 times higher in boys compared to girls of the same age [OR=6.53 (3.08–13.83) 95% CI].

Discussion

General and central obesity are two distinct types of obesity with different health implications. General obesity refers to the accumulation of excess body fat all over the body, while central obesity refers to the accumulation of excess fat around the waistline and abdomen. These two types of obesity are associated with different health outcomes and have been the focus of numerous studies.

Brambilla *et al.* assessed the relationship between anthropometric measures such as waist circumference and visceral fat by magnetic resonance imaging in children aged

7 to 16 years. According to their data, waist circumference can be considered a good predictor of visceral adipose tissue.[10]

According to Yoo, WHtR is an index with a high specificity for central obesity that can be used in different genders and ethnic groups for central obesity in children aged ≥6 years.[11]

A study by Chung showed that metabolic syndrome was more common in overweight adolescents with a WHtR of ≥0.5 than in those with a WHtR of <0.5.[12]

According to our study, girls had a higher BMI prevalence of general overweight and obesity *vs.* boys with 21.2 % vs.19.4 % for overweight and 17.5%vs. 15.3% for obese, while a significant association of male gender at a comparison of the central obesity parameters like WC,WHR, WHtR ($p<0.003$, $p<0.0001$, $p<0.011$) and high risk for WHR was detected. In all children, the prevalence of high risk for WHR was 34.3%, and the prevalence of high risk for WHtR was 31.5%. In boys, the prevalence for WHR was 51% and for WHtR 35.7% while in girls the prevalence of high risk for WHR was 13.8 % and for WHtR 26.2%.

Grigirakis *et al*. in a study for assessment of central obesity in children from the third and fifth grades in Greece classified 33.4% of childrenat risk of central obesity. Central obesity was significantly more prevalent in boys than in girls (36.0% *vs.* 30.7%).[13]

Another Greek study detected higher values in height, weight, BMI, HC in children of both sexes, however, the study also revealed that Greek children had lower values in waist circumference and WHtR than values determined in our sample of 13-year-old children.[14]

The comparison with 13-year-old peers from Bulgaria revealed lower values of BMI and WC (20.67) in boys and in girls (20.89) as well as lower values of WC inboys (70.1±9.7) and in girls (67.7±8.63).[15]

The results obtained in our study also showed higher values for BMI, WC, WHtR compared to earlier studies conducted in the Balkans (Croatia, Turkey, Cyprus), and in Europe (Switzerland, Germany and Poland)16-21, but our results indicated a higher risk of central obesity prevalence. However, it is important to note that our study was conducted in a period after the COVID-19 pandemic, due to which-related restrictions in recent lifestyle changes and physical activity levels, may have further contributed to the rise of obesity in children.

It is crucial to continue monitoring trends in central obesity prevalence and associated metabolic risks in our children. Overall, the research on general and central obesity in children highlights the need for prevention and management strategies to address these health concerns. These strategies should focus on promoting healthy eating habits, regular physical activity, and reducing sedentary behaviors.

Conclusion

In conclusion, both general and central obesity can have significant health implications in children, including an increased risk of developing chronic diseases. In our study, girls had a higher BMI prevalence of general overweight and obesity vs. boys, while a significant association of male gender at a comparison of the central obesity parameters like WC, WHR, WHtR and high risk for WHR was detected.

Additionally, healthcare professionals should always consider assessing the measurements and risk of central obesity in obese or overweight children and seek for unique risk factors associated with each type of obesity and tailor interventions accordingly.

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CLINICAL SCIENCE

EFFECT OF VACCINATION AND NUMBER OF DOSES ON DISEASE SEVERITY AND MORTALITY IN COVID-19 POSITIVE HOSPITALIZED PATIENTS

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Abstract

The COVID-19 pandemic, caused by the novel SARS-CoV-2 virus, started in December 2019 in the city Wuhan, province Hubei in the Republic of China. The disease quickly became pandemic and infected 48.539.872 people and had a mortality of 1.232.791 in 215 countries all over the world resulting in economic and healthcare collapse. On 11-th of March the World Health Organisation declared COVID 19 as pandemic. SARS-CoV-2 (severe form of acute respiratory syndrome coronavirus 2) as the cause of COVID 19 is the member of the coronavirus family along with MERS-CoV and SARS-CoV-1which cause severe respiratory infections that are highly contagious and have very high mortality. The pandemic character, the high morbidity and mortality and rehabilitation resulted in a massive vaccine production as an attempt to control the spread of the SARS CoV-2 virus and reduce the morbidity and mortality, especially in the most vulnerable population groups. The aim of the study was to evaluate the association between vaccination status, number of doses and disease severity, length of hospital stay and mortality. Material and Methods: In this case-control study we included 230 male and female patients admitted in the Covid Centre in Acibadem Clinical Hospital in Skopje from March 2021 to February 2022. Patients were divided in two groups according to their vaccination status. Data about patients demographics, comorbidities, vaccination, number of doses received, type of oxygen and ventilation support, length of stay and patient outcome were collected. Results: A total of 230 COVID-19 positive hospitalized patients participated in the study. 50.4% of them were vaccinated, of which 86.2% received two doses, 11.2% received one and 2.6% received three doses of vaccines. A significant association was registered between lethal outcome and vaccination (PearsonChi-square: 5.32523, p=.021019), association with number of doses of vaccination (PearsonChi-square: 7.66262, p=.043524), association with type of ventilation - NIV, HFO, IMV (PearsonChi-square: 177.399, df=3, p=0.00000), associationwithcomorbidity (3.90770, p=.048065). Conclusion: Vaccination against Covid-19 and number of doses have a significant impact on disease severity, progression and outcome of the disease.

КЛИНИЧКИ ИСТРАЖУВАЊА

ВЛИЈАНИЕТО НА ВАКЦИНАЛНИОТ СТАТУС И БРОЈОТ НА ДОЗИ НА ТЕЖИНАТА НА КЛИНИЧКАТА СЛИКА И СМРТНОСТА ОД COVID-19

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Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

COVID-19 како инфективно заболување за првпат се појави во декември 2019 година, а првите заразени беа во градот Вухан, област Хубеи во Н.Р.Кина. Болеста доби пандемиски карактер и за брзо доведе до 48.539.872 заразени луѓе и предизвика 1.232.791 смртни случаи во 215 земји во светот, доведувајќи до глобален здравствен и економски колапс на светското население. На 11 март 2020 година Светската здравствена организација прогласи COVID-19 пандемија. SARS-CoV-2 (тешка форма наакутен респираторен синдром коронавирус 2) како предизвикувач на COVID-19 претставува корона вирус кој што исто како и останатите два корона вируси MERS-CoV и SARS-CoV-1 се одговорни за предизвикување на акутни респираторни инфекции кои се многу контагиозни по природа и доведуваат до висок морталитет. Пандемискиот карактер на болеста, високиот морбидитет, морталитет и долгата рехабилитација доведоа до масовно производство на вакцини со цел превенирање и спречување на инфекција со SARS-CoV-2 вирусот,намалување на морбидитетот и морталитетот, особено кај ранливата популација со имунокомпромитираност и имунодефицит. Целта на оваа студија беше да се испита поврзаноста помеѓу вакцинлниот статус и бројот на примени дози против COVID-19 и тежината на болеста, должината на болничкиот престој и смртноста. Материјали и методи: Во оваа студија беа вклучени 230 пациенти од машки и женски пол, кои беа третирани во Covid центарот при Инфективниот оддел на Клиничката болница Аџибадем Систина во периодот од март 2021 година до февруари 2022 година. Пациентите беа поделени во две групи според вакцинлниот статус. Податоци за демографските карактеристики, коморбидитетите, вакцинацијата, бројот на примени дози, типот на кислородна и вентилаторна поддршка, должината на престој во болница, исходот од лекувањето беа следени и забележани. Резултати: Во студијата учествуваа 230 хоспитализирани COVID-19 позитивни пациенти. Вакцинирани беа50,4% од хоспитализираните, од кои 86,2% примиле две дози, 11,2% примиле една и 2,6% примиле три дози вакцини. Беше регистрирана значајна поврзаност помеѓу смртоносниот исход и вакцинацијата (PearsonChi-square: 5.32523, p=.021019), поврзаноста со бројот на дози на вакцинацијата (PearsonChi-square: 7.66262, p=.043524), поврзаноста со типот на вентилација (PearsonChi-square: 177.399, df=3, p=0.00000), и поврзаноста со присуството на коморбидитети (3.90770, p=.048065). Заклучок: Вакцинлниот статус и бројот на примени дози во нашата студија покажа значителен заштитен ефект за развој на тежок облик на болеста и летален исход.

Introduction

SARS-CoV-2 is a member of the coronavirus family, a group of enveloped single-stranded RNA viruses. First reported infections were in 2019, and since then the SARS-CoV-2 virus (COVID-19) pandemic has spread globally in almost every country in the world[1]. Although most commonly attacking the respiratory system, all systems can be affected. Signs and symptoms can differ from asymptomatic, mild illness to very severe and critical disease requiring intensive care unit admission and death[2].

COVID-19 mortality and morbidity are affected by many different factors, i.e., gender, age and several chronic diseases such as chronic respiratory disease/asthma, heart arrhythmias, hypertension, coronary disease, diabetes and neoplasma[3]. Vaccination against SARS-CoV-2 has become crucial for limiting disease transmission and reducing its severity, hospitalization and mortality[4]. More specifically, data from systematic reviews underline the efficacy of vaccination in terms of clinical severity and mortality[5]. Despite universal acceptance, vaccine hesitancy is still significant[6]. Finally, the occurrence of the new variants can change all previous data in relation to previous emerging virus strains. In light of all these factors, analysis of real-world data concerning disease severity and mortality of COVID-19 and vaccination is important for making future national health policy.

The aim of the study was to evaluate the association between vaccination status, number of doses and disease severity, length of hospital stay and mortality of COVID-19.

Materials and Methods

After receiving an approval from the local Ethics Committee, we performed a case-control study, including 230 male and female Covid-19 positive patients, aged from 34 to 90 years admitted to the Covid center at the Clinical Hospital Acibadem, Skopje from March 2021 to February 2022. Patients were either on oxygen support with 5-15 liters of oxygen per minute, high-flow oxygen support (HFO), non-invasive mechanical ventilation (NIMV) or invasive mechanical ventilation (IMV) and were divided in two groups according to their vaccination status: Group 1 included 116 patients vaccinated with 1, 2 or 3 doses of vaccine against SARS-CoV-2 regardless of the manufacturer at least 14 days before admission, and Group 2 was the control group with 114 unvaccinated patients.

All patients tested positive to PCR test for SARS-CoV-2 virus. Patients' data regarding age, sex, vaccination, number of doses, comorbidities, symptoms, duration of disease and therapy were collected from questionaries submitted by the patients or their families, and from the CEREBRAL patient system at Clinical hospital Acibadem from Skopje.

Results

A total of 230 COVID-19 positive hospitalized patients participated

in the study, of which 54.3% were men and 45.7% women. The percentage difference registered between the sexes was statistically non-significant for p>0.05 (Difference test, p=0.0651) (Table 1).

50.4% of the hospitalized patients were vaccinated, of which 86.2% received two doses, 11.2% received one and 2.6% received three doses of vaccines (Table 1).

Comorbidities were registered in 84.8% of patients, with more than two comorbidities registered in 40.0%. Cerebrovascular disease (CVD) was registered in 69.1%, endocrine diseases (diabetes mellitus, Addison's disease, hypothyroidism) in 36.5%, immunocompromising conditions in 10.0%, chronic obstructive pulmonary disease (COPD) and asthma in 8.7% and obesity in 6.1% (Table 1).

In the largest percentage (72.2%), patients ended up on oxygen support with face mask, 26.9% on non-invasive ventilation and high-flow oxygen support and 0.9% (two patients) on mechanical ventilation (Table 1).

The average age of males was 62.4±13.9 (minimum32, maximum 92 years), and of females 66.3±11.7 (minimum34, maximum 90 years) (Table 1). The difference registered between the average age according to gender was significant, for <0.05 (t-test=2.27101, p=0.024080).

Table. 1. Demographic characteristics and comorbidities of participants

Gender	Number	Percent
M	125	54.3
F	105	45.7
Vaccination		
no		
yes		
Dose		
I	13	11.2
II	100	86.2
III	3	2.6
Comorbidity		
yes	195	84.8
no	35	15.2
comorbidity>=2		
yes	92	40.0
no	138	60.0
CVD		
yes	159	69.1
no	71	30.9

DM, hypotireosis, Adison's disease		
yes	84	36.5
no	146	63.5
HBI, HD		
yes	10	4.3
no	220	95.7
Immunocompromising		
yes	23	10.0
no	207	90.0
COPD, asthma		
yes	20	8.7
no	210	91.3
Obesity		
yes	14	6.1
no	216	93.9
Type of oxygen support		
OM	166	72.2
NIV/HFO	62	26.9
	2	0.9
MV		
age	***Average***	***SD***
M	62.4	13.9
F	66.3	11.7

Table 2. Patient characteristics according to vaccination status

Vaccination	**yes**		**no**	
sex	Number	Percent	Number	Percent
M	65	56.0	60	52.6
F	51	44.0	54	47.4
age				
>67	61	52.6	53	46.5
<67	55	47.4	61	53.5
Comorbidity				
yes	98	84.5	97	85.1
no	18	15.5	17	14.9
Oxygen support type				
OM	93	80.2	73	64.0
NIV/HFO	23	19.8	39	34.2
IMV	0	0	2	1.8

No gender difference in vaccination status was registered, for p>0.05 (PearsonChi-square: 0.268343, p=0.604445). 52.6% of vaccinated patients were older than 67 years, and 46.5% of unvaccinated. There was no association between the age above and below 67 years and the vaccination status, for p>0.05 (PearsonChi-square: 0.854422, p=0.355304). Comorbidity was registered in 84.5% of the vaccinated, and 85.1% of the unvaccinated. There was no association between registration of comorbidity and vaccination status, for p>0.05 (PearsonChi-square: 0. 016310, p=0.898379). 80.2% of the vaccinated patients were on oxygen mask, 19.8 % on NIV/HFO. None of the patients in vaccinated group were on IMV. 64.0% of the unvaccinated were on an oxygen mask; 32.4% were on NIV/HFO and 1.8% on IMV. An association was registered between the type of ventilation and the vaccination status, for p<0.05 (PearsonChi-square: 8.53979, p=0.0360).

Table 3. Length of hospitalization according to vaccination

Mean yes	Mean no	t-test	df	p	Valid N yes	Valid N no	Std.Dev. yes	Std.Dev. no
8.775	11.403	-3.402	228	0.0007	116	114	4.852	6.724

Vaccinated patients were hospitalized for an average of 8.8±4.8 days, and those who were not vaccinated were hospitalized for 11.4±6.7 days; the difference between the average length of hospitalization was significant, for p<0.05.

Vaccinated patients with one dose were hospitalized for 9.3±8.4 days, with two doses 8.7±4.3 days and with three doses 7.7±4.0 days. According to the Analysis of Variance test, the difference between the average hospitalization between unvaccinated and those vaccinated with three doses was significant, for p<0.0 (F=3.901, p=0.0095).

21.7% (50) of hospitalized patients died. The profile of patients who had fatal outcome were men, not vaccinated, or vaccinated with only one dose, with registered comorbidities; they had ended on NIV, HFO, IMV, and they were with anaverage age of 67 years, i.e., 50% were older than 67.5 years (mean=67.5 years) (Table4).

A significant association was registered between lethal outcome and vaccination status (Pearson Chi-square: 5.325, p=.0210), association with number of doses of vaccination (PearsonChi-square: 7.662, p=.0435), association with type of ventilation - NIV, HFO, IMV (PearsonChi-square: 177.399, df=3, p=0.000), association with comorbidity (3.907, p=.0480).

Table 4. Age, gender, vaccination and type of ventilation in patients with fatal outcome

Gender	Number	Percent
M	28	56.0
F	22	44.0
Vaccination		
no	32	64.0
yes	18	36.0
Dose		
I	32	64.0
II	4	8.0
III	14	28.0
Comorbidity		
yes	42	84.0
no	8	16.0
Ventilation type		
NIV/HFO/MV	48	96.0
MV	2	4.0

age	*Average*	*SD*
live	63.4	13.0
deceased	66.9	13.0

Accordingto the binary logistic regression, non-vaccination was a predictor of lethal outcome in hospitalized patients (Table 5).

Table 5. Binary logistic regression

Variables in the equation

Vaccination		B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	no	.754	.330	5.201	1	.023	2.125	1.112	4.060
	Constant	-1.695	.256	43.669	1	.000	.184		

a. Variable(s) enteredonstep 1: ref.yes

Variables in the equation

sex		B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	no	.085	.322	.070	1	.791	1.089	.580	2.046
	Constant	-1.328	.240	30.660	1	.000	.265		

a. Variable(s) enteredonstep 1: female

Variables in the equation

Type of ventilation		B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]				.000	3	1.000		.000	
	MV	42.406	28591.418	.000	1	.999	260975880129586330 0.000		
	NIV/HFO	22.676	3119.579	.000	1	.994	7049344222.542	.000	
	Constant	-21.203	3119.579		1	.995			

a. Variable(s) enteredonstep 1: ref.OM

Variablesintheequation

Comorbidities		B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	no	-.076	.439	.030	1	.862	.926	.392	2.189
	Constant	-1.216	.403	9.131	1	.003	.296		

a. Variable(s) enteredonstep 1: yes

Variablesintheequation

age		B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	>67	.227	.321	.502	1	.479	1.255	.669	2.352
	Constant	-1.397	.233	35.992	1	.000	.247		

Variable(s) enteredonstep 1: ref.<67years

Discussion

COVID-19 is the first disease where a large number of institutions and companies have been engaged in research to produce effective multiplatform vaccines. By the end of 2020, more than 60 vaccines had entered clinical trials, of which 13 were in phase 3 clinical trials[7]. Among them, mRNA vaccines (Pfizer-BioNTech, Moderna), recombinant adenoviral vectored vaccines (AstraZeneca, Cansino, Gamaleya, Johnson Pharma) and inactivated vaccines (Sinopharm, Sinovac) achieved the fastest progress. By the end of 2020, nine candidate vaccines have been approved for human use in many countries[8–15]. The first generation of COVID-19 vaccines developed for emergency use showed promising results for controlling the pandemic 16. The SARS-CoV-2 virus during the several waves showed a large number of mutations, some of which were marked as “of concern”,

because they could have an impact on health policies of public interest, monitoring and immunization strategies[17]. In addition, the development of vaccines in such a short period of time has also led to doubts about the safety and efficacy of vaccines. Several studies have examined the efficacy and safety of vaccines. In a recent systematic review of 42 original studies, the authors analyzed the efficacy of various licensed vaccines and concluded that vaccines successfully reduce the number of infections, the severity of the disease, the need for hospitalization, the number of hospital days and mortality. The Pfizer-BioNTech vaccine is the most studied of the available vaccines and shows an effectiveness greater than 90%, followed by Moderna with an effectiveness greater than 80%[18].

In our case-control study, it was shown that unvaccinated patients had higher in-hospital mortality than vaccinated ones. It was also shown that vaccination and vaccine dose were significantly associated with shorter hospitalization compared to unvaccinated patients. The incidence of comorbidities was similar in the groups of vaccinated and unvaccinated patients. No significant statistical difference was found in terms of sex, age and vaccination status of patients. We found an association with unvaccinated status and type of oxygen support and the need for invasive mechanical ventilation.

There are studies that examined the effect of vaccination against COVID-19 and their impact on the clinical picture and the outcome of hospitalization, with results that are similar or coincide with ours. José M. Ruiz-Giardin et al. conducted a retrospective comparative studyof 500 hospitalized patients,of which 15.4% fully vaccinated, 17.2% partially vaccinated and 67.4% unvaccinated COVID-19 positive patients. They showed that complete vaccination was associated with a milder form of COVID-19 and a shorter hospital stay[19].

Papaioannou et al. in their prospective study including 166 vaccinated and 416 unvaccinated COVID-19 positive patients showed that the mean number of days of hospitalization was higher in unvaccinated compared to vaccinated patients [7.0 (95% CI: 7.0-8.0) vs. 6.0 (95%CI: 5.0-7.0),p=0.02]. Also, age-adjusted analysis showed that hospitalized unvaccinated patients had a significantly higher risk of mortality compared to hospitalized vaccinated patients[20].

Giacomo Grasselli et al. in their Lombardy cohort study of 10 million inhabitants, during the study period analyzed 553 patients that required admission to an intensive care unit, of which 139 (25.1%) were vaccinated, while 414 (74.9%) were unvaccinated. Vaccinated patients were older, with more comorbidities and mostly men. Vaccinated patients had a significantly lower risk of intensive care unit admission than unvaccinated patients, but there was no significant difference in hospital and intensive care unit mortality[21].

Robert Whittaker et al. included 716 fully vaccinated and 2487 unvaccinated COVID-19 positive patients in their cohort study. Using cox proportional hazard model adjustment, they showed that vaccinated patients had a shorter hospital stay and a lower risk of intensive care admission compared to unvaccinated patients. On the other hand, when they were admitted to the intensive care unit, the length of stay and mortality was not significantly different[22].

Athina A. Samara's study conducted from June 1, 2021 to February 1, 2022 included 760 consecutive patients diagnosed with COVID-19 infection. Of them, 38.7% were vaccinated, and 11.7% were diagnosed with a severe form of the disease. Vaccination against the SARS-CoV-2 virus had a significant protective effect against the development of a severe form of the disease and mortality, but the comparison of the length of hospital stay was not statistically significantly different between vaccinated and unvaccinated patients[23].

The existence of comorbidities, hypertension, diabetes, chronic lung disease, heart disease and malignant tumors are associated with the development of a severe form of the disease[24]. Additionally acute and chronic renal failure, COPD, diabetes, hypertension, cardiovascular disease, malignancy, high d-dimers, high ferritin, age, male gender, obesity, and smoking are factors associated with higher mortality from COVID-19[25,26].

However,of particular importance is the fact that in certain studies it has been observed that vaccination modifies or reduces the association of these risk factors and the development of a severe form of the disease and death[22,23,27]. On the other hand,in the multicenter prospective study of Anna Motos et al. From Spain during the study period 1585 patients were admitted to the intensive care units of seven hospitals due to COVID-19. Of them, 1314 (82.9%) were unvaccinated, 161 (10.2%) had not completed the vaccination protocol, and 110 (6.9%) were fully vaccinated. Data from 81 (73.6%) fully vaccinated patients were available for analysis. Among fullyvaccinated patients, 45 (55.6%) were on mechanical ventilation, and only one patient required extracorporeal membrane oxygenation. In-hospital mortality was 34.6%, the meantime on mechanical ventilation was 19.0 (9.0–28.0) days, and the mean number of hospital-days was 11.0 (7.0–30.0)[28]. The main conclusion of this study according to the authors was that patients with specific comorbidities despite being fully vaccinated could develop a severe form of COVID-19. Important to say that only 7% of patients with severe COVID-19 were fully vaccinated. A comparison between vaccinated and unvaccinated patients with severe COVID-19 requiring intensive care showed a two-to three-fold higher prevalence of immunosuppression, chronic lung disease, diabetes, kidney disease, and hypertension. Similar results have been published by Tal Brosh-Nissimov et al.in their study of 152 COVID-19 positive patients from Israel requiring hospitalization[29].

Only 4% of patients had no comorbidities. Even 40% of patients were immuno compromised. Mortality in their study was 22% (34/152). The authors conclude that although in a small percentage of patients with COVID-19 who are fully vaccinated, the development of a severe form of the disease and death is possible, especially in those with multiple comorbidities. Compared to unvaccinated group of patients, these patients have more comorbidities and are immunocompromised.

The analysis of patients with a fatal outcome in our study also showed an association with the existence of comorbidities. Patients with a fatal outcome were mostly men over the age of 65, had more comorbidities, and were unvaccinated or vaccinated with a single dose. The association of age and gender as risk factors for a severe form of the disease and death outcome has also been shown in other studies. In a 2020 population-based cohort study from Sweden, the authors analyzed 758,932 patients. Patients were couples, men and women, with an age difference of no more than 5 years and living together. The authors concluded that men had a higher risk of developing severe, intensive care unit admission, developing complications, and death compared to women, and that risk varied with age and was greatest inp atients aged 50 to 59 years 30. The relationship between age, sex and vaccination status and the number of doses received has been shown in other-studies as well[31,32].

Conclusion

Data from our study suggest that vaccination against Covid-19 and booster doses provide protection against the development of a severe form of COVID-19 and death. In addition, vaccination and the number of doses received affect the type of oxygen support and the need for mechanical ventilation. Vaccinated patients have a shorter hospital stay and a faster recovery from the sequelae of the disease.

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CLINICAL SCIENCE

PHYSICAL TREATMENT OF POSTTRAUMATIC ELBOW CONTRACTURES IN CHILDREN – OUR EXPERIENCE

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Abstract

The most common complications of elbow trauma are contractures and neurovascular injuries. The complications can be a result of the initial injury, but they can also be a result of a surgical treatment. In addition to orthopedic treatment of elbow fractures, physical therapy and rehabilitation play a significant role in treatment of posttraumatic contractures. The aim of this study was to determine the effects of physical therapy and rehabilitation of posttraumatic elbow contractures in children. Materials and Methods: This was a retrospective cross-sectional study conducted in the University Clinic for Physical Medicine and Rehabilitation, Skopje in the period 01.01.2021 – 01.07.2022. A total of 52 children were included, at the age between 2 and 13 years who had a posttraumatic elbow contracture, limited range of motion, pain and/or limitations in accomplishing daily activities. Depending on the clinical finding, children underwent a relevant physical therapy (kinesitherapy, functional therapy, electrotherapy, thermotherapy, hydrotherapy and magnetotherapy) in duration of three weeks. For assessing the effects of the rehabilitation therapy, the range of motion of the elbow and forearm was examined along with the Flynn's scale in all children, prior to and after completion of the physical treatment. Results: Applied physical treatment resulted in a significant improvement in all analyzed movements such as: elbow flexion (p=0.00001), elbow extension (p=0.00001), forearm pronation (p=0.00001), forearm supination (p=0.0000) and Flynn's scale (p=0.0000). After completion of the rehabilitation treatment, excellent results were registered in 41 (85%) children, moderate in 10 (19.23%) and favorable in 1 (1.92%). Conclusion: Timely and adequate application of physical therapy and rehabilitation can significantly improve the final outcome in treatment of posttraumatic elbow contractures in children. A combination of different physical procedures adequately applied and personalized can significantly improve the range of motion of the elbow.

КЛИНИЧКИ ИСПИТУВАЊА

ФИЗИКАЛЕН ТРЕТМАН НА ПОСТРАУМАТСКИ КОНТРАКТУРИ НА ЛАКОТ КАЈ ДЕЦА – НАШЕ ИСКУСТВО

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Печатарски права: ©2023 Марија Гоцевска, Ериета Николиќ Димитрова, Валентина Коевска, Билјана Митревска, Цветанка Ѓеракароска Савевска, Билјана Калчовска, Маја Манолева, Лазар Тодоровиќ. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираат оригиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Најчестите компликации на траумата на лактот се контрактури и невроваскуларни повреди. Компликациите може да бидат резултат на иницијална повреда, но може да бидат и резултат на хируршки третман. Покрај ортопедскиот третман на фрактури на лактот, физикална терапија и рехабилитација играат значајна улога во третманот на посттрауматски контрактури. Целта на оваа студија беше да се утврдат ефектите од физикална терапија и рехабилитација на посттрауматски контрактури на лактот кај децата. Материјали и методи: Ова беше ретроспективна студија на пресек спроведена на Универзитетската клиника за физикална медицина и рехабилитација, Скопје во периодот 01.01.2021 – 01.07.2022 година. Вклучени се вкупно 52 деца, на возраст меѓу 2 и 13 години кои имале посттрауматска контрактура на лактот, ограничен опсег на движења, болка и/или ограничувања во извршувањето на секојдневните активности. Во зависност од клиничкиот наод, на децата им беше извршена соодветна физикална терапија (кинезитерапија, функционална терапија, електротерапија, термотерапија, хидротерапија и магнетотерапија) во времетраење од три недели. За проценка на ефектите од терапијата за рехабилитација, опсегот на движење на лактот и подлактицата беше испитувана и Флиновата скала кај сите деца, пред и по завршувањето на физичкиот третман. Резултати: Применетиот физикален третман резултираше со значително подобрување на сите анализирани движења како што се: флексија на лактот (p=0,00001), екстензија на лактот (p=0,00001), пронација на подлактицата (p=0,00001), супинацција на подлактицата (p=0,0000's) и Флинова скала (p=0,0000). По завршувањето на рехабилитационит третман, одлични резултати се забележани кај 41 (85%) дете, умерени кај 10 (19,23%) и поволни кај 1 (1,92%). Заклучок: Навремената и адекватна примена на физикална терапија и рехабилитација може значително да го подобри крајниот исход во третманот на посттрауматски контрактури на лактот кај децата. Комбинацијата на различни физички процедури соодветно применети и персонализирани може значително да го подобри опсегот на движење на лактот.

Introduction

Elbow fractures account for about 16% of all skeletal injuries in childhood. Supracondylar humerus fractures are the most common fractures in children and they comprise about 60% of all pediatric fractures; the largest number of these fractures occur in children in their first decade of life.[1] The incidence of elbow fractures in children is variable and depends on many factors, and is opposite to the relatively small incidence of elbow fractures in adults. Elbow fracturesare usually a result of trauma. Falling from a height is the cause of 70% of cases.[2] The largest number of supracondylar fractures in children happen due to fall on an outstretched hand, and hence, this mechanism is frequently named with the acronym FOOSH.[3] It means that the extended elbow suffers a severe compression, especially the distal humerus. Flexion injury hasa direct impact on the olecranon of the flexed elbow. Immature bone is subject to twisting, but absorbs a lot of energy before breaking. In childhood, there is a much higher percentage of cartilage than in adulthood, and consequently this percentage diminishes as the child grows. Therefore, there are significant differences in bone fractures between children and adults.[4,5]

The impact of different factors related to injury as well as therapeutic intervention on bone, soft-tissue and other structures in the elbow area can cause posttraumatic elbow contracture as a recognized sequelae in these injuries. Posttraumatic elbow fractures with different range of motion can happen even after adequately realized orthopedic treatment.[6]

Elbow fractures are manifested with clear and obvious deformities to hidden and barely seen radiological changes. Complications in elbow injuries can be a result of the initial trauma, but they can also be a result of the surgical treatment. The most common complications of elbow trauma are angulation deformities and neurovascular injuries.[7,8] The incidence of complications primarily depends on the severity of the injury, and can be reduced by prompt and adequate treatment. Early diagnosis and treatment significantly improve the clinical outcome.

In addition to the orthopedic treatment in elbow fractures, physical therapy and rehabilitation also play an important role in treatment of posttraumatic elbow contractures and their related complications.9 For management of pain and swelling and prior to initiation of kinesiotherapy, several forms of physical procedures can be used. Different physical agents are applied, and they influence on physiological and functional regeneration of tissues, creation of biologically active materials, improvement in circulation and cellular metabolism. They are combined with kinesitherapy, hydro-kinesitherapy, functional therapy and thermotherapy. Various heat procedures (paraffin therapy) act on pain relief; they reduce the increased muscle tonus and improve elasticity and extensibility of fibrous tissue around the elbow. From phototherapy modalities infra-red and ultraviolet rays are used, and from electrotherapeutic procedures the following are applied: interferen-

tial currents, diadynamic currents, electrophoresis with drugs and galvanic current.

The goal of the physical treatment in elbow fractures is complete bone consolidation, achievement of painless and full range of motion by eliminating the present contracture, improvement in muscle strength and stability of the joint. By application of physical therapy and rehabilitation, onset of deformities is prevented and children can return to their daily activities.

The aim of this study was to determine the effects of physical and rehabilitation treatment of elbow contractures in children.

Materials and methods

This was a retrospective cross-sectional study conducted in the University Clinic for Physical Medicine and Rehabilitation in Skopje in the period 01.01.2021 - 01.07.2022. The sample consisted of 52 children with posttraumatic elbow contracture, limited range of motion, pain, reduced stability in the joint and/or limitation in performing daily activities. Following primary surgical/conservative intervention, children were treated on an outpatient basis at the University Clinic for Physical Medicine and Rehabilitation in Skopje.

Inclusion criteria for participation in the study: age from 2 to 13 years, regardless of gender, with limited range of motion of the elbow in any angle, limited range of motionof the adjacent joints, damage to the nerve structures, regardless of previous treatment by ansurgery doctor. Exclusion criteria: blood vessels lesion, open fractures and age >13 - <2.

Anamnestic data comprised: age, gender, side of injury, type of fracture, time elapsed from injury to initiation of rehabilitation therapy.

Physical therapy was started after removal of cast immobilization, with/without removal of osteosynthetic material. Children included in the study were examined by a Physiatrist, and physical therapy in duration of three weeks was recommended. Depending on the clinical finding, children were involved in a relevant physical therapeutic program.

All children underwent kinesitherapy and functional therapy, and therapeutic choice for the other procedures of physical therapy (interferential currents, diadynamic currents, electrophoresis with KJ, galvanic currents, magnetotherapy, cryotherapy, paraffin therapy and hydrotherapy) was recommended in line with the clinical and radiographic findings. Kinesitherapy consisted of active, active-assisted, active and active exercises with individual resistance that was progressively increased depending on the clinical finding. Having in mind the age of the child and local finding, functional therapy included different techniques and activities to increase the range of motion of the joint, to improve the muscle strength and to improve the functional status. Therapeutic program was individually adapted in line with the results obtained during therapy. At the same time, we educated and trained the parents to implement the exercises with their children at home.

Parameters for assessment of the rehabilitation treatment effects were: range of flexion and extension of the elbow, pronation and supination of forearm on the side of the elbow fracture. Plastic goniometer with a minimum deviation of 1o was used. Measurements were done in all children prior to and after completion of the physical treatment.

The range of motion of the elbow on admission and after completion of therapies was also assessed with the Flynn's four-degree scale for each patient as follows: a) grade/score 3 = full range of motion of the elbow or limitation of 5o; b) grade 2 = limitation of the range of motion of 5 to 10o; c) grade 1 = limited amplitude of motion of 10-15o; d) grade 0 = poor therapeutic result with limited range of motion of more than 150.[10]

Statistical analysis

Data obtained were analyzed with the SPSS software package, version 22.0 for Windows. Qualitative series were analyzed with the coefficients of relations, proportions and rates, and quantitative series with measures of central tendency (average/mean, mediana, minimal and maximal values), as well as with measures of dispersion (standard deviation). Shapiro-Wilk W test was used for determination of the normal distribution of frequency of the examined variables. Pearson Chi-square test was used for determination of the association between certain attributive dichotomous features. Difference test was used to compare the proportions. Wilcoxon Signed Ranks test was used for analysis of numerical variables between two measurements. To define the statistical significance, a two-way analysis was used with a level of significance of $p<0.05$.

Results

The study included 52 children with posttraumatic elbow contracture, 39 (75%) were boys and 13 (25%) were girls and the ratio between genders was 3:1, with a significant female preponderance (Difference 50% [(31.32-63.81) CI 95%]; p=0.0001).

The mean age of the entire group was 6.72±2.72 years with min/max of 2/12 years, and 50% of them were at the age <6.5 years for median (IQR)=6.5 (5-9). The mean age of boys was 6.41±2.59 years with min/max 2/12 years and median (IQR) = 6 (5=9). The mean age of girls was 7.77±2.95with min/max 4/12 years and median (IQR) = 8 (5-10). There was no significant difference between genders and age (Mann-Whitney U Test: Z=-1.405; p=0.1599).

The most frequent type of fracture was supracondylar, found in 30 children (57.69%), and the rarest was the fracture of the medial condyle, found in only one child (1.92%). There was no significant percentage difference in the frequency of previous surgical/conservative treatment and in the affected left/right hand, for consequently p=0.6961 vs. p=0.4345. Only 6 (11.54%) children with elbow contracture suffered from involvement of a peripheral nerve (Table 1).

Table 1. General and clinical parameters

General parameters	N (%)	p
Gender		
boys	39 (75%)	p=0.0001*
girls	13 (25%	
Type of fracture		
supracondylar	30 (57.69%)	-
olecranon	3 (5.67%)	
radial head	5 (9.61%)	
proximal forearm	2 (3.85%)	
lateral condyle	11 (21.15%)	
medial condyle	1 (1.92%)	
Treatment		
surgical	25 (48.07%)	p=0.6961
conservative	27 (51.92%)	
Hand		
left	24 (46.15%)	p=0.4345
right	52 (53.85%)	
Peripheral nerve lesion		
no	46 (88.46%)	p=0.0001*
yes	6 (11.54%)	
Affected peripheral nerve		
n.medianus	1 (16.67%)	
n.radialis	2 (33.33%)	
n.ulnaris	3 (50%)	
1 Difference test; *significant for p<0.05		

The average number of days from injury to rehabilitation in all children was 28.54±9.86 days with min/max of 15/60 days, and in 50% of children with <28 days for median (IQR)=28 (20.5-30). This period was 28.05±8.75 vs. 30±12.93 in boys vs. girls, respectively, without a significant difference between genders (Mann-Whitney U Test:Z=-0.032; p=0.9747).

The number of rehabilitation days after posttraumatic elbow contracture ranged from minimum 10 to maximum 20 days. On average, rehabilitation lasted 16.15±2.55 days, without a significant difference between genders (Mann-Whitney U Test: Z=-0.063; p=0.9494). In 75% of children the rehabilitation length was <20 days.

In children with posttraumatic elbow contracture, after completed rehabilitation compared to the condition prior to its initiation, there was a significant improvement in all analyzed movements such as: elbow flexion (p=0.00001), elbow extension (p=0.00001), forearm pronation (p=0.00001), forearm supination (p=0.00000) and Flynn's scale (p=0.00000) (Table 2).

Table 2. Comparison of movements prior to/after rehabilitation of posttraumatic elbow contracture

Intergroup comparison	Comparison of movements at two time points after posttraumatic elbow fracture					P
	Number (N)	Mean± SD	Min/Max	Median (IQR)	Mean Rank	
Elbow flexion						
before treatment	52	105.38±12.-5	35/145	110 (95-120)	0.00	Z=-6.105; p=0.00001*
after treatment	52	130.19±15.53	85/165	135 (120-140)	25.00	
Elbow extension						
before treatment	52	-24.33±19.45	-70/0	-20 (-40-10)	0.00	Z=-5.991; p=0.00001*
after treatment	52	0.19±1.39	0/10	0 (0-0)	24.00	
Forearm pronation						
before treatment	52	71.63±19.91	10/90	80 (52.5-90)	0.00	Z=-4.471; p=0.00001*
after treatment	52	83.94±7.69	50/90	85 (80-90)	15.00	
Forearm supination						
before treatment	52	77.88±13.98	30/90	82.5 (70-90)	0.00	Z=-4.487; p=0.00001*
after treatment	52	86.35±6.27	50/90	90 (85-90)	13.50	
Flynn scale						
before treatment	52	0.56±0.78	0/3	0 (0-0)	0.00	Z=-.001; p=0.00001*
after treatment	52	2.77±0.47	1/3	3 (3-3)	26,00	
Wilcoxon Signed Ranks Test*significant for p<0.05						

The additional analysis showed that none of the children with posttraumatic elbow contracture who underwent physical treatment experienced exacerbation in movements after treatment compared to pre-treatment. Unchanged condition before/after physical treatment was registered in 3 children in elbow flexion, 23 children in forearm pronation, 26 children in forearm pronation and in 1 child with unchanged score on Flynn's scale (Table 3).

Table 3. Changes in movements after physical treatment in children with posttraumatic elbow contracture

Determined change	Comparison of movements at two time points after posttraumaticelbow fracture				
	before/after Flexion - elbow	before/after Extension - elbow	before/after Pronation–forearm	before/after Supination - forearm	before/after Flynn scale
	after<before - 0 after>before - 49 after=before - 3	after<before - 0 after>before - 47 after=before -5	after<before - 0 after>before -29 after=before -23	after<before - 0 after>before -26 after=before -26	after<before - 0 after>before - 51 after=before - 1
SIgn Test					

Table 4. Analysis on Flynn's scale of mobility before/after rehabilitation treatment

Flynn scale score	Before treatment N (%)	After treatment N (%)
3 = excellent	1 (1.92%)	41 (85%)
2 = good	6 (11.54%)	10 (19.23%)
1 = favorable	14 (26.92%)	1 (1.92%)
0 - unsatisfactory	31 (59.61%)	-
Total		

Prior to physical treatment, unsatisfactory range of mobility was determined in majority of children with posttraumatic elbow contracture – 31 (59.61%). After completion of the rehabilitation treatment, excellent results were registered in 41 (85%) children, good in 10 (19.23%), and favorable in 1 (1.92%). There was no unsatisfactory mobility in none of the children after physical therapy (Table 4).

Discussion

Although the elbow is one of the most stable joints in the human body, posttraumatic contractures to elbow area are common. Posttraumatic elbow contractures that appear as a sequelae of elbow trauma in pediatric population are of different degrees of limitation in the elbow joint. These contractures can be a result of the injury type, diagnostic examination, modalities of treatment, and they certainly pose a significant therapeutic problem. After accomplishment of orthopedic and surgical treatment, physical therapy and rehabilitation play an important role in improvement of the elbow range of motion and overall functional improvement in patients.[11] The application of kinesitherapy, functional therapy in combination with the other physical procedures has a favorable impact on the outcome in treatment of posttraumatic contractures.[12]

Elbow fractures in children happen in their first decade of life, most often in children aged 3-10 years, withthe peak incidence in the 5- to 8-year-olds.[13,14] In our investigation, the mean age of children with elbow contracture was 6.72±2.72, which was in agreement with literature data.

In our sample, 75% of children with posttraumatic elbow contracture were boys, and in all patients the injury was a result of a fall on the elbow area, which was in correlation with the results presented by other authors.[15,16] In the literature, fall has been reported as a cause of supracondylar fractures in 90% to 95% of children. Contracture in the elbow area can also appear secondary as a consequence of a surgical intervention, manipulation of fractured fragments and prolonged physical therapy.[17]

Therefore, the success of treatment depends on various factors including the choice of physical modalities as well as the response of the tissue to physical therapy.

Many authors have reported their results with regards to treatment of elbow fractures, but without precise presentation of the ratio between the time when injury happened and start of rehabilitation. However, all authors have agreed that there is certain limitation in the elbow range of motion after removal ofcast immobilization. In our sample, the average number of days from injury to rehabilitation was 28.54 days, and the average length of outpatient treatment was 16.15 days. The limitation of this study was no long-term follow-up when there still might be a certain degree of elbow contracture in spite of the applied physical therapy and rehabilitation. A very small number of authors have reported on the dynamics of regaining range of motion of the treated elbow.[18,19,20,21] Orthopedic surgeons recommend physical therapy after removal of the immobilization in elbow fractures.[22,23] Contrary to this, some authors consider physical therapy not necessary after treatment of supracondylar humerus fractures.[24] Other authors advise physical therapy only in case of severe limitation in the elbow range of motion, in which the range of motion is unsatisfactory after certain postoperative period.[25]

In his study, Keppler assessed the effects of physiotherapy in improving the range of motion of the elbow after supracondylar humerus fractures in children. He examined 51 patients who had been surgically treated. One of the conclusions in his study was that physical therapy enabled a more rapid returnof normal elbow range of motion in the first 20 weeks after trauma.[18]

The incidence of specific nerve injuries varies in the literature. Primary lesions are a direct result of the trauma, whereas the secondary lesions appear during surgery, management of fractured fragments and onset of edema in the adjacent tissue.[26] In general, it is considered that the most common are median nerve injuries (28%-60% of all nerve injuries), followed by radial and ulnar lesions.[27,28] In our investigation, peripheral nerve lesion was encountered in 11.54% of children and the prevailing was ulnar nerve injury.

The final result of treatment of elbow contractures with physical therapy in children included in our study was excellent. After completed rehabilitation compared to the condition prior to its initiation, a significant improvement in the elbow range of motion was observed in all movements (flexion, extension, pronation and supination). Also, regarding the Flynn's scale excellent results were achieved in 85% of children. There were no unsatisfactory results. These results are similar to those of treatment outcome in supracondylar elbow fractures in studies with long-term follow-up.[29,30]

Our results also showed that kinesitherapy, functional therapy and hydro-kinesitherapy in combination with the other physical agents appropriately adjusted to the time period that corresponds to the clinical findings can be of substantial importance in treatment and outcome of treatment of posttraumatic elbow contractures in children. Elbow frac-

tures might cause functional morbidity and restricted range of motion, hence great attention should be paid to these fractures when establishing the diagnosis and conducting the treatment. Prompt diagnosis and appropriate orthopedic treatment as well as timely and adequately applied physical procedures within the overall treatment can significantly improve the final outcome of treatment.

A combination of various physical procedures adequately applied and adjusted can significantly improve the range of motion of the elbow.

Conclusion

Any delay in rehabilitation of an elbow fracture can cause disability and can have a negative impact on further mental and physical development of a child. Therapeutic approach to posttraumatic elbow fractures should be personalized and adequately adjusted, employing huge patience of all the involved parties.

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CLINICAL SCIENCE

DESIGN OF FEASIBILITY STUDY FOR THE ESTABLISHMENT OF PRODUCTION OF ZIRCONIUM-89 RADIOISOTOPE AND IMPLEMENTATION OF ^{89}ZR-RADIOPHARMACEUTICALS IN CLINICAL PRACTICE IN THE REPUBLIC OF NORTH MACEDONIA

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Abstract

In the last decade, the application of radiopharmaceuticals based on zirconium-89 (^{89}Zr) radiometal has increased in both preclinical and clinical studies. The most frequently used ^{89}Zr-radiopharmaceutical is ^{89}Zr-trastuzumab used in the management of patients with breast cancer. Breast cancer is the most common cancer among women in North Macedonia and the most common cause of death from malignant neoplasms in this population; therefore, the introduction of new nuclear medicine procedures in these patients might improve the management of this disease. However, the introduction of radioisotope and radiopharmaceutical production requires significant investments, both manpower and financial. The purpose of this work is to present the design conceptualization of a feasibility study for the establishment of production of zirconium-89 radioisotope and implementation of ^{89}Zr-radiopharmaceuticals in clinical practice in the Republic of North Macedonia and to present the initial results from the first phases of the study. This feasibility study is designed to include preliminary analysis, market research, technical feasibility analysis, economic analysis, review and analysis of all data and feasibility conclusion. The evaluation of the data from the analyses conducted in all study phases is needed to identify the favourable and unfavourable factors and circumstances in order to make a final assessment of the feasibility of establishing the zirconium-89 radioisotope and ^{89}Zr-radiopharmaceuticals production and implementation of ^{89}Zr-trastuzumab use in nuclear medicine practice.

КЛИНИЧКИ ИСПИТУВАЊА

ДИЗАЈН НА ФИЗИБИЛИТИ СТУДИЈА ЗА ВОСПОСТАВУВАЊЕ НА ПРОИЗВОДСТВО НА ZIRCONIUM-89 РАДИОИЗОТОП И ИМПЛЕМЕНТАЦИЈА НА ^{89}ZR-РАДИОФАРМАЦЕВТИЦИ ВО КЛИНИЧКАТА ПРАКСА ВО РЕПУБЛИКА СЕВЕРНА МАКЕДОНИЈА

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Клучни зборови: физибилити студија, zirconium-89 радиоизотоп, ^{89}Zr-радиофармацевтици, производство, ^{89}Zr-trastuzumab

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Печатарски права: ©2023 Катерина Колевска, Марија Атанасова-Лазарева, Маја Чочевска, Маја Величковска, Филип Јолевски, Тони Трипуноски, Шабан Мемети, Ана Угринска, Бистра Ангеловска. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираат оригиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Во последната деценија, радиофармацевтските препарати што содржат zirconium-89 (^{89}Zr) радиоизотоп имаат зголемена примена како во претклиничките, така и во клиничките студии. Најчесто користен ^{89}Zr-радиофармацевтик е ^{89}Zr-trastuzumab кој се применува во насока на планирање на терапија на пациенти со рак на дојка. Ракот на дојката е најчестиот карцином кај жените во Северна Македонија и најчеста причина за смрт од малигни неоплазми кај оваа популација, затоа воведувањето нови дијагностички процедури во нуклеарната медицина може да придонесе за подобро планирање на терапијата кај овие пациенти. Сепак, воспоставувањето на производство на радиоизотопи и радиофармацевтици бара значителни инвестиции, финансиски и кадровски. Целта на овој труд е да го претстави дизајнот на физибилити студијата за воспоставување на производство на zirconium-89 радиоизотоп и имплементација на ^{89}Zr-радиофармацевтици во клиничката пракса во Република Северна Македонија, како и да ги претстави резултатите од почетните фази на студијата. Оваа физибилити студија е дизајнирана така што вклучува прелиминарна анализа, истражување на пазарот, анализа на техничка изводливост, економска анализа, преглед и анализа на сите податоци и заклучок за физибилност. Евалуацијата на податоците од анализите во рамки на сите фази на студијата е потребна за да се идентификуваат поволните и неповолните фактори и околности за да се донесе конечна проценка на физибилноста за воспоставување на производство на zirconium-89 радиоизотоп и ^{89}Zr-радиофармацевтици и воведување на ^{89}Zr-trastuzumab во нуклеарно-медицинската пракса.

Introduction

Radiopharmaceutical preparations or radiopharmaceuticals are medicinal products which, when ready for use, contain one or more radionuclides (radioactive isotopes) included for a medicinal purpose to diagnose, stage a disease, monitor treatment, or provide therapy.[1,2]

Regarding the radiopharmaceuticals used for positron emission tomography (PET) imaging, the application of radiometals in nuclear medicine worldwide is progressing steadily. Short-lived radiometals are suitable for combination with ligands that exhibit rapid pharmacokinetics (e.g., small molecules or peptides), while long-lived radiometals are suitable for visualizing slow biological processes, such as antibody biodistribution (immuno-PET).[3]

Zirconium-89 is one of the radiometals that in the last decade has been increasingly used in both preclinical and clinical studies.[3,4] The zirconium-89 half-life of 78.4 h corresponds to the biological half-life of monoclonal antibodies, making this radioisotope suitable for immuno-PET imaging.[3-5] Immuno-PET combines the sensitivity of PET with the specificity of antibodies. The use of ^{89}Zr is promising for monitoring antibody-based cancer therapies and a number of studies have been conducted to investigate the feasibility of ^{89}Zr immuno-PET imaging for predicting the efficacy of radioimmunotherapy and antibody therapies, imaging target expression, detecting target-expressing tumors, and monitoring of anti-cancer chemotherapies.[4] There are literature data on more than 90 clinical studies, of which already completed studies involve more than 20 antibodies labelled with ^{89}Zr.[6]

A common method for obtaining zirconium-89 radioisotope is by irradiating solid target material with accelerated protons in medical cyclotrons, typically using energies of 10–18 MeV.Due to the easy availability of the target material in natural form, ^{89}Y(p, n)^{89}Zr is considered to be the best nuclear reaction for the production of ^{89}Zr in medical cyclotrons.[5,7-9]

Having in mind all the above, the potential of ^{89}Zr-radiopharmaceuticals to expand the possibilities in terms of cancer management and research development in North Macedonia, as well as the fact that the only cyclotron in the country is within the University Institute of Positron Emission Tomography (UI PET), the idea of preparing a feasibility study for the establishment of zirconium-89 radioisotope and ^{89}Zr-radiopharmaceuticals production in this institute is rational.

The cyclotron at UI PET, GE PET trace 800 16.5 MeV, according to its technical characteristics belongs to the group of cyclotrons, which can produce the radioisotope ^{89}Zr. UI PET is the only site for producing PET radioisotopes and radiopharmaceuticals in the country and also it is a centre for molecular diagnostics where 2,000 oncology patients are scanned annually.

This study aims to present the design of the feasibility study for the establishment of zirconium-89 radioisotope production and the implementation of ^{89}Zr-radiopharmaceuticals in clinical practice in the Republic of North Macedonia and to present the initial results from the first phases of the study. The design is conceived

originally and structured taking into consideration several aspects. The results of the feasibility study will provide an objective insight into all aspects of the feasibility of this proposed idea, as well as a conclusion regarding the impact that radiopharmaceuticals based on this radioisotope may have on making clinical decisions in the management of the malignancies in the country.

Materials and Methods

The feasibility study to establish the production of zirconium-89 radioisotope and ^{89}Zr- radiopharmaceuticals is designed to cover the following phases:

- preliminary analysis;
- market research;
- technical feasibility analysis;
- economic analysis (financial analysis and pharmacoeconomic analysis);
- review and analysis of all data;
- conclusion on feasibility.

Preliminary analysis

The preliminary analysis includes:

- review of statistical data regarding malignant diseases in North Macedonia;
- review of clinical applications data of ^{89}Zr-radiopharmaceuticals.

The review of malignant disease statistics is performed by literary search of reference databases, international (Global Cancer Observatory) and domestic (Mortality Register and Cancer Register of Institute of Public Health).[10-12] These databases display statistics of malignant diseases, such as total new cases per year, most common cancers among new cases - sex distribution, and mortality from malignant diseases in Macedonia (mortality rate and primary localization).

The review of the application of ^{89}Zr-radiopharmaceuticals in clinical trials is based on a literature search, that is, a reference database for clinical trials. (ClinicalTrials.gov, a Web-based resource maintained by the U.S. National Library of Medicine).[6]

Market research

Within this step, searches are conducted regarding:

- the distribution of medical cyclotrons in Europe;
- zirconium-89 radioisotope production sites in Europe;
- zirconium-89 radioisotope price, and
- the potential possibilities for placement of the produced radioisotopes at a cost-effective price.

The information on the distribution of medical cyclotrons is obtained from the International Atomic Energy Agency (IAEA) Cyclotron Distribution Database.[13] The research on the production sites of zirconium-89 radioisotope in Europe is based on a literature search of studies published in scientific journals, data on the production of these radioisotopes presented at professional symposia and congresses, as well as media available data from radioisotope manufacturers. The zirconium-89 radioisotope price information is based on data obtained from

manufacturers. The research of the potential possibilities for placement of the produced radioisotope at a cost-effective price is based on the obtained data on the needs and possibilities for use for clinical purposes in our country and the region.

Technical feasibility analysis

The estimation of technical feasibility is based on the analysis of the technical capacities of UI PET in terms of space and equipment necessary for the implementation of the production of zirconium-89 radioisotope and ^{89}Zr-radiopharmaceuticals. As part of this phase of the feasibility study, it is also verified whether additional equipment/apparatus is needed to realize the production.

Economic analysis

The assessment of economic feasibility is conducted in two phases and includes financial analysis and pharmacoeconomic analysis. Firstly, the costs are defined (direct and indirect), and then they are calculated according to data obtained by a literature search, as well as data from UI PET.

For performing pharmacoeconomic analyses, data collected by a literature search of clinical trials conducted with these radiopharmaceuticals have been applied. In order to cover the initial clinical data and to simulate the patterns of real practice, meta-analysis is applied which is a systematic method for finding, evaluating and combining the results of different scientific studies.[14] A cost-effectiveness analysis is performed, which is a systematic method that compares two or more alternative treatments by measuring the cost of money (MKD) and the health outcomes over the years, based on the utility results presented in the literature. The cost-benefit analysis compares the net production costs of both preparations with the benefits arising from their use expressed in monetary terms.[15-17] Depending on the literature data obtained during the research, the two analyses can be combined.

Review and analysis of all data

The processing of the results of analyses is one of the phases of the feasibility study, during which the data from all previously conducted analyses are evaluated: preliminary analysis, market research, technical feasibility analysis and economic analysis.

Conclusion on feasibility

After conducting all the analyses, as well as after reviewing all the obtained data, a conclusion is made about the feasibility of the proposed idea, i.e., whether the process of establishing production of zirconium-89 radioisotope and ^{89}Zr-radiopharmaceuticals in UI PET is feasible.

Results

Given that the feasibility study is ongoing, this paper presents the results of the analyses already done, the preliminary analysis and the market research (distribution of medical cyclotrons in Europe and zirconium-89 radioisotope production sites in Europe).

Preliminary analysis

- Malignant diseases on a national level

Neoplasms are the second leading cause of death in Macedonia, after circulatory system diseases. In 2020, 24.25 % of deaths in the population aged 1 to 64 years and 12.68 % of deaths in the population over 64 years were due to malignant diseases.[11]

In the period from 2011 to 2020, the average mortality rate from malignant neoplasms in both sexes was 180 per 100,000 population. For the same ten-year period, the average mortality rate from malignant neoplasms in men was 215 and in women 146 per 100,000 population. From 2011 to 2020, the most common cause of death from malignant neoplasms in men was malignant neoplasm of the bronchi and lungs (average mortality rate 63.9 per 100,000 men), and in the same period, the most common cause of death from malignant neoplasms in women was malignant breast neoplasm (average mortality rate 29.07 per 100,000 women).[12]

In the period from 2011 to 2020, there were an average of 6,808 new cases of cancer per year or 328 cases per 100,000 inhabitants. About 87.8 % of cancer cases were among the population over the age of 50, of which 19.3 % were between the ages of 50 and 60 years. The most common cancer diagnoses in the period of ten years (2011-2020) in the entire population were malignant neoplasms of the bronchi and lungs with 13.12 % of the total reported cases, followed by malignant neoplasms of the breast, other malignant neoplasms of the skin, colon, stomach, prostate, liver and intrahepatic bile ducts, rectum, bladder, corpus uteri etc. In the male population, the most common cancers in the period of 2011- 2020 were malignant neoplasms of the bronchi and lungs with 18.80 % of the total reported cases, followed by malignant neoplasms of the prostate, other malignant neoplasms of the skin, stomach, colon, bladder, liver and intrahepatic bile ducts, rectum, larynx, pancreas, etc. In the same ten years period, the most common cancers in females were malignant neoplasms of the breast with 25.29 % of the total reported cases, followed by non-melanoma malignancies of the skin, malignant neoplasms of corpus uteri, bronchi and lungs, colon, cervix uteri, stomach, ovaries, rectum, liver and intrahepatic bile ducts, etc.[12]

According to the Global Cancer Observatory database, among 7,632 new cases of cancer in 2020, the five most common cancers in both sexes, with the exception of non-melanoma skin cancer, were cancers of the lung (14.9 %), breast (12.9 %), colorectum (12.4 %), prostate (10.3 %), corpus uteri (4.8 %). Among women, the most common new cases in 2020 were cancers of the breast (29.2 %), colorectum (14.4 %), corpus uteri (10.9 %), lung (7.2 %), cervix uteri (3.3 %), and in men, the most common were cancers of the lung (21 %), prostate (18.5 %), colorectum (10.9 %), bladder (7.0 %), stomach (5.2 %). Regarding the mortality rate from malignant diseases in 2020, the first ten malignancies were cancers of the lung (23.3 %), breast (7.5 %), prostate (7.1 %), stomach (6.6 %), pancreas (6.4 %), colon (6.0 %), brain, central nervous system (6.0 %), rectum (5.8 %), liver (4.4 %), and bladder (3.1 %).[10]

- ^{89}Zr-radiopharmaceuticals in clinical trials

According to ClinicalTrials.gov, as of May 9, 2021, there have been a total of 93 clinical trials involving ^{89}Zr-radiopharmaceuticals, of which 48 studies have status completed, terminated, or unknown. Most clinical studies were conducted in the Netherlands (28 studies), followed by the United States (16 studies), Belgium and China with 2 studies each, and one clinical study each in Australia, Sweden, Denmark, Korea, France and Spain.[6]

^{89}Zr-radiopharmaceuticals used in these clinical trials were ^{89}Zr-bevacizumab (9 studies), ^{89}Zr-trastuzumab (6 studies), ^{89}Zr-Df-IAB2M (3 studies), ^{89}Zr-cetuximab (3 studies), ^{89}Zr-pembrolizumab, ^{89}Zr-J591, ^{89}Zr-panitumumab, ^{89}Zr-girentuximab, ^{89}Zr-DFO-pertuzumab each in 2 clinical trials and ^{89}Zr-Df-IAB22M2C, ^{89}Zr-KN035, ^{89}Zr-MMOT0530A, ^{89}Zr-AMG211, ^{89}Zr-ABT806, ^{89}Zr-daratumumab, ^{89}Zr-Cripec Docetaxel, ^{89}Zr-GC1008, ^{89}Zr-durvalumab, ^{89}Zr-GSK3128349, ^{89}Zr-GSK2849330, ^{89}Zr-BI754111, ^{89}Zr-GSK2398852, ^{89}Zr-RO5429083, ^{89}Zr-TAK-164, 89Zr-nanocoll, ^{89}Zr-DS-8895a, ^{89}Zr-RO5479599 each in one clinical study.[6]

Market research

- Distribution of medical cyclotrons in Europe

A total of 1,266 cyclotrons are registered in the International Atomic Energy Agency (IAEA) cyclotron database, of which 356 are located in Europe, Turkey and the Russian Federation (including its Asian part). In Europe, the largest number of cyclotrons is in Italy - 45 cyclotrons, followed by Germany - 43, France - 32, the United Kingdom - 28, Spain - 21, the Netherlands - 13, Belgium - 13, Denmark - 10, etc. There are 59 cyclotrons on the entire territory of the Russian Federation, and 20 in Turkey. As for the Balkan Peninsula, Bulgaria and Romania have 4 cyclotrons each, Greece two and North Macedonia and Croatia have one cyclotron each.[13]

- Zirconium-89 radioisotope production sites in Europe

In the Netherlands, there is GMP (Good Manufacturing Practice)-compliant production of ^{89}Zr for the research community. Research in-house productions are registered in Germany, Great Britain, Italy, Turkey, Belgium and Russia.

Technical feasibility analysis

The cyclotron at UI PET, PETtrace 16.5 MeV GE Healthcare Cyclotron, according to its technical characteristics is convenient for the production of ^{89}Zr radioisotope. There are commercially available ^{89}Zr purification and labelling modules which compatibility with existing UI PET systems is being evaluated.

Discussion

A feasibility study is an analysis of the viability, that is, the sustainability of a given idea. The feasibility study aims to objectively and rationally reveal the strengths and weaknesses of the proposed venture, the opportunities and threats present in the environment, the necessary resources to realize the idea and finally the prospects for success. The

feasibility study assesses the project's potential for success; therefore, perceived objectivity is an important factor in the credibility of the study. For this reason, feasibility studies should be conducted with an objective, unbiased approach to provide information on which decisions can be based. The goals of feasibility studies are to thoroughly understand all aspects of a given project, concept or plan; to identify any potential problems that may arise during the implementation of the project; to determine whether, after considering all the important factors, the project is feasible that is, worth undertaking. Feasibility analysis covers several aspects of feasibility: technical, economic, financial, regulatory, operational, temporal, etc. The aspects covered in the study, i.e., the design of the feasibility study itself are based on the characteristics of the project/idea that is proposed.[18] A preliminary analysis is also often performed to determine if the project/idea concept is justified.

However, the current literature is very scarce regarding comprehensive feasibility studies in the field of radiopharmacy. There are literature data for some radiopharmaceuticals regarding the analysis of technical feasibility for their production, but there are no data about feasibility studies that also analyze the effect of their potential implementation in routine clinical practice and further research. As a result of technological development, the designing and development of new radiopharmaceuticals are progressing rapidly, with a continuous expansion of perspectives regarding their use. For developing countries, their introduction into healthcare practice is a challenge, and therefore an objective assessment is needed that takes into account not only the economic aspect but also the clinical impact and development of research potential.

This feasibility study for the establishment of the production of zirconium-89 radioisotope and ^{89}Zr-radiopharmaceuticals is designed originally and it includes preliminary analysis, market research, technical feasibility analysis, economic analysis (financial and pharmacoeconomic), review and analysis of all data and feasibility conclusion.

The preliminary analysis aims to assess whether there is a field for the application of ^{89}Zr-radiopharmaceuticals in our country and for that purpose it includes a review of statistical data regarding malignant diseases on a national level and a review of clinical applications data of ^{89}Zr-radiopharmaceuticals.

The market research is conducted in order to define the geographical impact of the market. The market competitiveness and the transport cost are factors that affect the price of the product - radioisotope. This is especially important considering the nature of radioactive preparations, i.e., their short shelf life. The longer geographic distance of the production site to the site of use hugely contributes to a higher price of the radioactive product. As the results show, there is no ^{89}Zr production in the Balkan countries.

The technical feasibility analysis focuses on the technical resources available to the organization implementing the proposed idea and includes an assessment of the hardware, software and other technical requirements of the proposed sys-

tem. In the framework of this feasibility study, the technical feasibility analysis is being performed to determine whether the production process of zirconium-89 radioisotope and ^{89}Zr-radiopharmaceuticals in UI PET is technically feasible in terms of space and equipment.

The financial analysis, as the first phase of the economic feasibility analysis, is carried out to determine the initial investment for the establishment of zirconium-89 radioisotope production; financial investments (costs) in the process of production of zirconium-89 radioisotope and ^{89}Zr-radiopharmaceuticals as well as the price of the product (radioisotope and radiopharmaceutical products).

The pharmacoeconomic analysis, as the second phase of the economic analysis, aims to assess the justification for the implementation of ^{89}Zr-radiopharmaceuticals in clinical practice. The subject of the pharmacoeconomic analysis is ^{89}Zr-trastuzumab, a radioimmunoconjugate containing the recombinant humanized monoclonal antibody trastuzumab radiolabeled with zirconium-89. ^{89}Zr-trastuzumab was selected as the subject of pharmacoeconomic analysis on the basis of the preliminary analysis results. As per statistics related to malignant diseases, breast cancer is the most common cancer among women in Macedonia and the most common cause of death from malignant neoplasms in this population. On the other hand, ^{89}Zr-trastuzumab is one of the most common ^{89}Zr-radiopharmaceuticals in clinical trials.

^{89}Zr-trastuzumab binds to the extracellular domain of human epidermal growth factor receptor 2 (HER2), enabling visualization and quantification of HER2-expressing tumour cells, by positron-emission tomography.[4,19] According to the literature data, PET imaging with ^{89}Zr-trastuzumab supports clinical decision-making in patients with breast cancer when HER2 status cannot be determined by standard workup.[20,21] ^{89}Zr-trastuzumab has the potential to characterize the HER2 status of the complete tumour burden in patients with breast cancer, thus obviating repeat or multiple tissue sampling to assess intrapatient heterogeneity of HER2 status.[22] HER2-PET imaging with ^{89}Zr-trastuzumab shows excellent tumour tracer uptake and can be used to detect HER2-positive breast cancer metastases and quantify ^{89}Zr-trastuzumab uptake, non-invasively.[23] PET scanning after administration of ^{89}Zr-trastuzumab at appropriate doses allows visualization and quantification of uptake in HER2-positive lesions in patients with metastatic breast cancer.[19]

After completion of all the feasibility analyses, a review of all the data is needed in order to identify favourable and unfavourable factors and circumstances (internal and/or external), that is, to determine the favourable opportunities and/or limitations for the implementation of the proposed idea, as well as the benefits of eventual realization. In the end, after data evaluation, a conclusion on feasibility is made.

Conclusion

When designing feasibility studies, the aspects important for the realization of a given idea should first be evaluated and consequently, based

on them, the necessary analyses should be defined. We have designed a feasibility study for the establishment of production of zirconium-89 radioisotope and ^{89}Zr-radiopharmaceuticals that covers the elements of feasibility related to the technical and financial aspects of the production process, research potentials, but also includes an assessment of the clinical impact of the eventual implementation of ^{89}Zr-radiopharmaceuticals in the management of patients with malignant diseases in the Republic of North Macedonia.

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CLINICAL SCIENCE

PAIN ASSESSMENT AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION WITH AUTOGRAFT: QUADRUPLED M.SEMITENDINOSUS VERSUS M.SEMITENDINOSUSANDM.GRACILIS

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Abstract

Anteriorcruciate ligament (ACL) tear is one of the most common sports injuries. The all-inside technique (AIT) for anterior cruciate ligament reconstruction (ACLR) is gaining popularity as a more anatomic, less invasive technique with the potential for more rapid recovery. With the recent advances in the field of sports medicine, the all-inside technique is reported to have less postoperative pain as compared to the conventional transportable procedure. The purpose of this research is to determine the differences in acute pain levels between undergoing ACL reconstruction hamstring autograft m. Semitendinosus and m.gracilis versus hamstring autograft quadrupled m.semitendinosus in first and second postoperative day. Materials and Methods: A total of 80 patients in period of two years who underwent primary ACL reconstruction using either HS autograft m.semitendinosus and m.gracilis or HS autograft quadrupled m.semitendinosus consented to participate. The primary outcome of the study was postoperative pain levels that were collected after surgery at first and second day. For the quantification of the intensity of pain after the surgery the patients were offered a Visual Analogue Scale (VAS scale), numbered from 0 to 10 (0 means no pain, 10 is the strongest pain). This part of the research shows the results obtained by processing patients with ACL, treated at the Department of Orthopaedics and Traumatology in the City General Hospital „8th of September" in Skopje. Results: The average postoperative score one day after surgery for patients with a standard method using a graft in the form of a duplication of m.semitendinosus and m.gracilis based on the VAS scale was 7.70 +0.9 and the score second day after surgery was 4.75 + 1.1.The average postoperative score a day after the surgery for patients treated with the method where only m.semitendinosus is used as a graft and that in the form of quadruplication based on the VAS scale was 3.90 +3.1and the score second day after surgery was 2.70 +2.7. Conclusion: A significant reduction in acute postoperative pain was found when performing ACL reconstruction with HS quadrupled m.semitendinosus compared to HS m.semitendinosus-m.gracilis.

КЛИНИЧКИ ИСПИТУВАЊА

ПРОЦЕНКА НА БОЛКА ПО РЕКОНСТРУКЦИЈА НА ПРЕДЕН ВКРСТЕН ЛИГАМЕНТ СО АУТОГРАФТ:КВАДРИПЛИКАТУРА НА M.SEMITENDINOSUS НАСПРОТИ M.SEMITENDINOSUSИМ.GRACILIS

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Цитирање: Несторовски З, Вангеловска З, Илиева АМ. Проценка на болка по реконструкција на преден вкрстен лигамент со аутографт: квадрипликатура на m.semitendinosus наспроти m.semitendinosusim.gracilis. Арх J Здравје 2023;15(1). 105:113.

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Клучни зборови: преден вкрстен лигамент, контрола на болка, артроскопија на колено, реконструкција на предниот лигамент, аутографт

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Извадок

Повредата на предниот вкрстен лигамент (ПВЛ) е една од најчестите спортски повреди. Техниката all-inside (AIT) за реконструкција на предните вкрстени лигаменти (РПВЛ) се здобива со популарност како повеќе анатомска, помалку инвазивна техника со потенцијал за побрзо закрепнување. Со неодамнешниот напредок во областа на спортската медицина, техниката „all-inside" е регистрирана дека има помала постоперативна болка во споредба со конвенционалната транспортна процедура. Целта на овој труд е да се утврдат разликите во нивоата на акутната болка помеѓу аутографтот на тетивата за реконструкција на ПВЛ со m.semitendinosus и m.gracilis наспроти аутографт на тетива со квадрипликатура на m.semitendinosus во првиот и вториот постоперативен ден. Материјали и методи: Вкупно 80 пациенти во период од 2 години кои беа подложени на примарна реконструкција на ПВЛ со користење на аутографт на HS (m.semitendinosus-m.gracilis) или HS аутографт (m.semitendinosus) учествуваа во ова студија. За квантификација на јачината на болка по извршената оперативна интервенција на пациентите им беше понудена ВАС скала, нумерирана од 0 до 10, при што 0 значи нема болкаа 10 најсилна болка.Во ова истражување прикажани се резултатите на пациенти со повреда на преден вкрстен лигамент, лекувани во Градската општа болница „8-ми Септември" на Одделението за ортопедија и трауматологија. Резултати: Просечниот постоперативен резултат еден ден по операцијата за пациенти хируршки третирани со стандардна метода користејќи графт во форма на дуплирање на m.semitendinosus и m.gracilis врз основа на Visual Analogue Scale(VAS) скалата беше 7,70 +0,9, а резултатот од вториот ден по операцијата беше 4,75 +1,1. Просечниот постоперативен резултат еден ден по операцијата за пациенти хируршки третирани со метода, каде што само m.semitendinosus се користи како графт и тоа во форма на квадрипликатура врз основа на VAS скала изнесуваше 3,90 + 3,1, а резултатот од втор ден по операцијата изнесуваше 2,70 +2,7. Заклучок: Значително намалување на акутната постоперативна болка беше забележано при изведување на реконструкција на ПВЛ со HS со квадрипликатура на (m.semitendionosus) во споредба со реконструкција со HS (m.semitendinosus-m.gracilis).

Introduction

Anterior cruciate ligament (ACL) tear is one of the most common sports injuries. ACL rupture is a common type of knee ligament injury that is more common atphysically active people than at non-active people[1]. This ACL injury may result in pain, functional limitations, osteoarthritis after knee trauma, and a lower quality of life[2]. Surgical reconstruction is the most commonly used treatment after high grade ACL injuries[3]. The all-inside technique (AIT) for anterior cruciate ligament reconstruction (ACLR) is gaining popularity as a more anatomic, less invasive technique with the potential for more rapid recovery[4]. ACL tear is a common injury caused by sports accidents or other knee injuries, with little distinction between regions and countries, prevalent among working-age patients. Traditional literature has generally supported ACL reconstruction over ACL repair, considering to be the current 'gold standard' treatment for an ACL tear[5]. The use of hamstring tendons for anterior cruciate ligament reconstruction has become more accepted in recent years. The use of a doubled semitendinosus tendon grafts versus a quadrupled semitendinosus tendon graft is still a matter of contention[6].Anterior cruciate ligament reconstruction using the hamstring tendon autograft is a well-recognised and commonly performed procedure across the world. The 'all-inside' ACL reconstruction technique is a new development which is gaining popularity due to its unique features of using a single tendon autograft as compared to two tendon autografts used in the conventional technique. Many studies have alluded to the good functional results of the all-inside techniquealong with its other advantages for example, its bone preserving nature, reduced postoperative pain and smaller skin incision. The all-inside technique (AIT) for anterior cruciate ligament reconstruction is gaining popularity as a more anatomic, less invasive technique with the potential for more rapid recovery. This systematic review aims to critically assess components of the technique its safety profile, outcomes and complications[7]. The goal of the all-inside method is to minimize surgical trauma. This has also affected clinical outcomes by decreasing pain and morbidity, speeding up recovery and return to activities, more cosmetically attractive results, and finally better stability and overall knee function. All these potential theoretical advantages must be validated in clinical trials[8].

The purpose of this research is to determine the differences in acute pain levels between undergoing ACL reconstruction hamstring autograft m. semitendinosus - m. gracilis versus hamstring autograft quadrupled m. semitendinosus in first and second postoperative day.

Materials and methods

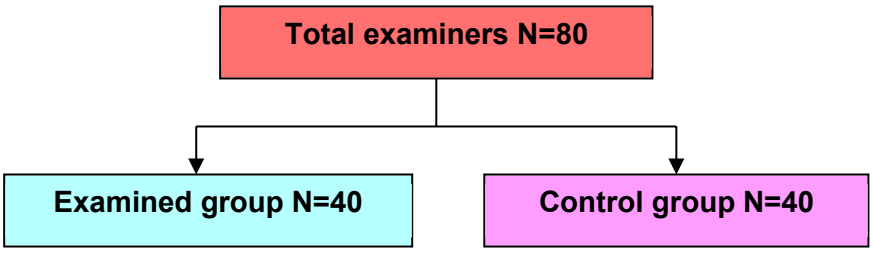
We performed a retrospectively analysis of patients' analysis undergoing ACL reconstruction surgery in early postoperative pain compare HS autografts quadrupled (m.semitendinosus) vs HS autografts (m.semitendinosus-m.gracilis). A total of 80 patients who were surgically treated at City General

Hospital "8th of September" were included in this study in period of two years. Inclusion criteria included patient from 18 to 35 years with complete rupture of ACL and patient without before surgery of the knee. Exclusion criteria were patient under 18 years, patient with other surgery of the knee and patient with partial rupture of ACL. Patients consented for inclusion in the study underwent arthroscopically assisted ACL reconstruction using HS autografts quadrupled (m.semitendinosus) or HS (m.semitendinosus vs m.gracilis). For the purpose of quantifications of strength of the pain in the first and second postoperative days the patients were offered a VAS scale, numbered from 0 to 10 (0 means no pain, 10 is the strongest pain). For statistical analysis, SPSS v19.1 was applied and all data was collected in digital tables. The nonparametric Mann-Whitney U test for independent samples was used to analysedifferences in mean VAS scores between the two patient groups. Intragroup variability for the same subjects was examined using a Wilcoxon matched-pairs test in two measurements on all-inside technique compared to the conventional transportable procedure. Statistical significance was assumed at $p < 0.05$.

Results

80 patients had ACL reconstruction and they were divided in two groups (picture 1). First group (40 patients) consist of control group (CG) and they were operatively treated with standardmethod with hamstrings autograft with depicture od m.semitendinosus and m.gracilis. Second or examined group (40 patients) consist of initial group (IG) operatively treated with hamstring autografts of quadrupled m.semitendinosus.

Fig. 1. Participants of study



Gender difference between the 2 groups is presented in Table 1. Demographic structure of the respondents included 71.2% (N=57) male and 28.8% (N=23) female. Men patients dominated in both groups. Specifically,67.5%(N=27) in examiner group were male and 75%(N=30) in control group. Tested difference for distribution of male and female patient between examiner and control group gave no significant statistical difference (p=0.46). According to the gender distribution, we may conclude that the two groups were homogeneous.

Table 1. Gender of patients

Gender	Groups			p-level
	N (%)	CG* N (%)	IG** N (%)	
Male	57 (71.3)	27 (67.5)	30 (75)	$\chi 2$ =0.55
Female	23 (28.7)	13 (32.5)	10 (25)	p=0.46
Total	80 (100)	40 (100)	40 (100)	ns

Note: *CG (graft from m.semitendinosus), ** IG (grafts from m.semitendinosus and m.gracilis)

Also, concerning the patients age from the both groups they were homogenous,i.e., there was no significant differences concerning the age (p=0.77). Patients from CG were of age between 20 and 52, the mean age was 32.2 ± 9.8 age; patients from IG were of age between 20 to 58 age old, the median age was 31.5 ± 9.0.

According to Table 2 first day after the operation patient in CG have grade the pain with average score of 7.70 ± 0.9 and the patient IG average of 3.90 ± 3.2. More than half of the patients in CG in the day of the intervention had pain which they have graded with 8, otherwise half of the patients with IG had pain with strength larger than 3. Statistical analyses of signification have confirmed stronger pain by patients treated with graft m.semitendinosus-m.gracilis compare with patients who have used graft form m.semitendinosus (p<0.01).

Table 2. VAS first day post-operations

Group	Post-operations clinical examinations			p-level
	Descriptive Statistics			
	mean ± SD	min – max	median (IQR)	
CG	7.70 ± 0.9	6 – 9	8 (7 – 8)	Z=4.93*
IG	3.90 ± 3.2	1 – 10	3 (1 – 7)	p=0.000001 sig

Note: *Z (Mann-Whitney U Test)

Table 3 shows distribution of the scores for VAS scale in both groups of patients, one day after the surgery procedure. In CG the most patients' intensity of pain has been graded with 7 (N=12; 30%) while patients with IG pain have graded the pain with the weakest grade or score (N=13; 32.5%).

Table 3. VAS scale in both groups

First day post-operation	Groups		
	Total	CG* n (%)	IG** n (%)
1	13	0	13 (32.5)
2	6	0	6 (15)
3	6	0	6 (15)
4	1	0	1 (2.5)
5	2	0	2 (5)
6	5	4 (10)	1 (2.5)
7	15	12 (30)	3 (7.5)
8	20	16 (40)	4 (10)
9	8	8 (20)	0
10	4	0	4 (10)

Note: *CG (graft from m.semitendinosus), ** IG (grafts from m.semitendinosus and m.gracilis)

After second day of the surgery, VAS scale has presented higher scores of CG versus of IG (Table 4). Namely, mean score was 4.75 ± 1.1 in examination group versus 2.70 ± 2.7 incontrol group.Statistics analysis shows that CG patients received higher VAS scores on the second postoperative day compared to IG patients ($p<0.01$). We can conclude that on the second postoperative day, patients operated with HS (m.semitendinosus-m.gracilis) have significantly stronger pain than patients treated with HS quadrupled (m.semitendinosus).

Table 4. VAS scale second post-operation day

Group	Post-operations clinical examinations			p-level
	Descriptive Statistics			
	mean ± SD	min – max	median (IQR)	
CG	4.75 ± 1.1	2 – 7	5 (4 – 6)	Z=4.65*
IG	2.70 ± 2.7	1 – 10	1 (1 – 3.5)	p=0.000003 sig

Note: *Z (Mann-Whitney U Test)

Distribution of score from VAS scale, two days after surgery presented at the CG patients have been scored with intensity of pain 4(N=14;35%) while more than half of the patients in IG second postoperative day don't feel pain (N=23;57.5%) (Table 5).

Table 5. Second post-operation day

First day post-operation	Groups		
	Total	CG* n (%)	IG** n (%)
1	23	0	23 (57.5)
2	5	1 (2.5)	4 (10)
3	6	3 (7.5)	3 (7.5)
4	15	14 (35)	1 (2.5)
5	14	11 (27.5)	3 (7.5)
6	11	9 (22.5)	2 (5)
7	3	2 (5)	1 (2.5)
10	3	0	3 (7.5)

Note: *CG (graft from m.semitendinosus), ** IG (grafts from m.semitendinosus and m.gracilis)

Regarding the VAS scores at CG and IG, evaluation by Wilcoxon Matched Pairs Test showed that there was significant difference between the first and second post-operation day (p>0.01).

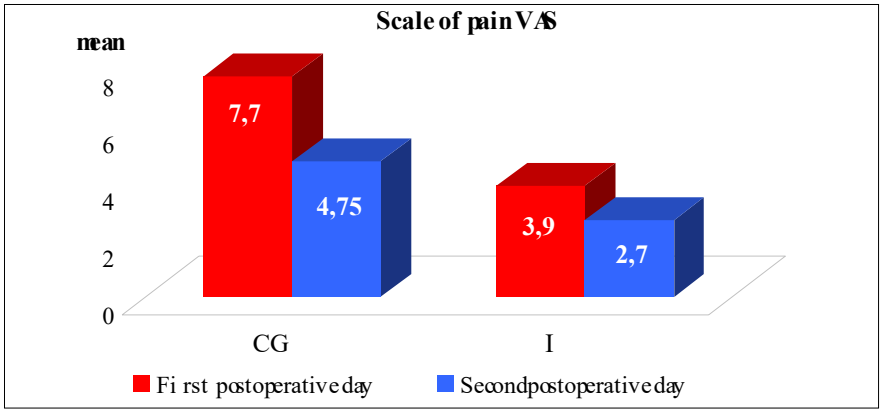
Table 5. Difference between first and second day

Scale of the pain VAS	Groups	
	CG mean ± SD	IG mean ± SD
Scale of the pain VAS	7.70 ± 0.9	3.90 ± 3.1
Second post-operation day	4.75 ± 1.1	2.70 ± 2.7
p-level	Z=5.51 p=0.0000 sig*	Z=3.92 p=0.0000 sig*

Note: *p(Wilcoxon Matched PairsTest)

From Figure 2 it can be seen that IG patients have a lower score on the VAS scale on the first and second postoperative day (3.90 ± 3.1) than CG (7.70 ± 0.9).

Figure 2. Mean difference on VAS



Discussion

Although it is difficult to anticipate the future, historically, sports medicine and arthroscopy are developing to be increasingly less invasive. With the advantages of less trauma (only semitendinosus muscle or allogeneic tendon), less early pain (preservation of bone cortex and periosteum) and reliable fixation effect the All-inside technique has become an increasingly popular approach of ACLR. This technique has limitations as well as a long learning curve and affects proprioception and vascularization since it is unfit for reconstruction through stump preservation.

Also, the titanium plates may lead to bone tunnel enlargement and graft loosening[9]. The literature review did not identify a significant difference in post-operative functional outcomes between AIT and TP group.

Many studies have compared the outcomes between single bundle and double bundle grafts in ACL reconstruction and overall found no significant differences in clinical and functional outcomes. The optimal outcome scoring system for evaluating the outcome of ACLR is still a controversial issue in which various subjective or objective scoring methods such as IKDC, Lysholm, KSS, SF-12, KOOS and VAS scoring systems were used among the studies.

Chorea Benea et al., reported the results of a randomized controlled trial conducted between December 2010 and September 2011. The primary outcome measure analysed was pain score at one month. The results show that postoperative pain was slightly better with the all-inside technique. The difference in postoperative pain between the two groups at one month was at the limit of statistical significance because the study was underpowered.

In particular, a study of 37 patients by Toan D. Duong et al. evaluated postoperative clinical and patient-reported outcomes who underwent total internal arthroscopic anterior cruciate ligament reconstruction with IBLA using semitendinosus tendon autografts. Their results recorded good to excellent patient outcomes in terms of patient-reported outcomes. The mean postoperative Lysholm Knee score at 1 year reached 94.03 +- 3.65 (range 86 to 98), with 24 cases (64.8%) rated as excellent and 13 cases (35.2%) as good.

Sahu SK and Ganesh A compared the All-Inside technique with the conventional transportable reconstruction of the ACL in cases of ACL injuries and evaluated the functional outcome in patients admitted to Imsand Sum Hospital, Bhubaneswar from July 2017 to June 2019. Lysholm and VAS scores were calculated at minimum follow-up of 1, 3, 9 months. The response to VAS shows that the two group show no significant difference as far as the level of satisfaction with their respective operations is concerned.

McDonald et al., compared VAS pain scores and medication consumption in patients undergoing ACL reconstruction with either a single or double-bundle technique. A total of 88 patients who were treated with SB and 41 who underwent DB ACLR were included in the study. After analysing the results, they found a significant difference in pain at 1 hour after surgery, with a lower mean pain score in the SB group than the DB group.

However, post-operative VAS pain scores and complications rates was lower AIT group compared to the TP group in studies directly comparing the two techniques prospectively suggesting AIT as a good alternative method, especially when treating athletes with ACL injury.10.

Less postoperative pain is an evidence-bases advantage of all-inside. This was shown first in Level 1 randomized controlled trial with allograft comparing all-inside reconstruction to a full tibial tunnel.It was then proven again using semitendinosus autograft with the Graft-Linktechnique. Given the trend for outpatient surgery and accelerated rehabilitation after ACL reconstruction less postoperative pain is an advantage for patients.11 Differences in postoperative pain between various surgical options should be discussed with patients before a treatment plan is made.Postoperative pain after ACL reconstruction in an individualized patient experience that contributes significantly to patient -perceived outcome. Post discharge pain after any outpatient surgery is known to delay return to normal daily activities and thus rehabilitation.

Conclusion

The early postoperative period is frequently marked by severe pain after anterior cruciate ligament (ACL) reconstruction. Therefore, postoperative pain control is still a major issue in ACL reconstruction in order to increase preoperative patient satisfaction. The all-inside technique with quadrupled semitendinosus graft appears to be equivalent to the classic interference screw technique with a semitendinosus-gracilis grafts in terms of outcomes and failure rates. Based on our results we have stronger pain by patients treated with autograph tm.semitendinosus and m.gracilis compare with patients which has used autograft form m.semitendinosus.

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BASIC SCIENCE

EVALUATION OF SEMEN QUALITY IN YOUNG MEN IN REPUBLIC OF NORTH MACEDONIA

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Abstract

Research data show that in the last 50 years (1938-1991) there has been a trend of decreasing sperm concentration in the male population in Europe by 2.3% and in the USA by 0.8%. The reasons for such negative trend are not known, but it is assumed that lifestyle and environmental factors have an influence on genetic factors. Aim of this study was to evaluate sperm quality in young, healthy men in our country, and to compare sperm quality in our population with others in the world. Material and methods: Ejaculates from 203 healthy male subjects, aged 18-32, were stored in a thermostat at 36^{0}C and analyzed manually on a native slide and hematoxylin-eosin-stained slides, under a phase contrast microscope. Sperm motility was assessed at two-time intervals, group A, 60 minutes after ejaculation and group B, 120 minutes after ejaculation, while sperm concentration and sperm morphology were assessed at one time interval. Results:Semen analysis showed an average volume of ejaculate3.45 ± 1.5 ml, sperm concentration in 1 milliliter62.4 ± 39.2 x10(6) /ml, while total sperm concentration was 211.2 ± 173.2 x10(6). In group A, values for progressive spermatozoa were 48.6 ± 18.1 x10(6) /ml and in group B, values for progressive spermatozoa were 47.9 ± 17.3 x10(6) /ml. There was no statistically significant difference between the two time intervals (group A and group B) when interpreting sperm motility, p>0.005. Analysis of morphology of spermatozoa showed a mean value of 6.9% for morphologically normal spermatozoa. Conclusion: The quality of ejaculate in young men in North Macedonia is in the range of reference values according to WHO, and also our results are similar to those from Germany, Turkey, Bulgaria, Faroe Islands.

БАЗИЧНИ ИСТРАЖУВАЊА

ЕВАЛУАЦИЈА НА КВАЛИТЕТОТ НА ЕЈАКУЛАТ КАЈ МЛАДИТЕ МАЖИ ВО РЕПУБЛИКА СЕВЕРНА МАКЕДОНИЈА

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Клучни зборови: подвижност на сперматозоидите, концентрација на сперматозоидите, морфологија на сперматозоидите.

***Кореспонденција:** Ирена Костадинова Петрова, Институт за медицинска хистологија и ембриологија, Медицински факултет, Универзитет „Св. Кирил и Методиј" во Скопје, РепубликаСеверна-Македонија.

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Печатарски права: ©2023 Ирена Костадинова-Петрова, Лена Какашева-Маженковска, Елида Митевска, Љубица Ташева, Наташа Стојковска. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираат оригиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Истражувачките податоци покажуваат дека во последните 50 години (1938-1991) постои тренд на намалување на концентрацијата на сперматозоиди кај машката популација во Европа за 2,3% и во САД за 0,8%. Причините за ваквиот негативен тренд не се познати, но се претпоставува дека начинот на живот и факторите на околината имаат влијание врз генетските фактори. Целта на оваа студија беше да се оцени квалитетот на ејакулатот кај млади, здрави мажи во нашата земја, за да можеме да го споредиме квалитетот на ејакулатот кај нашата популација со другите популации во светот. Материјал и методи: Ејакулите од 203 здрави машки испитаници, на возраст од 18-32 години, беа складирани во термостат на 36^{0}C и рачно анализирани на нативен препарати препарати обоени со хематоксилин/еозин, под фазно-контрастен микроскоп. Подвижноста на сперматозоидите беше проценета во два временски интервала, група А, 60 минути по ејакулацијата и група Б, 120 минути по ејакулацијата, додека концентрацијата и морфологијата на сперматозоиди беа анализирани во еден временски интервал. Резултати: Анализата на ејакулатите покажа просечен волумен на ејакулатот 3,45 ± 1,5 ml, концентрација на сперматозоиди во 1 милитар 62,4 ± 39,2 x10 (6) / ml, додека вкупната концентрација на сперматозоиди беше 211,2 ± 173,2 x10 (6). Во групата А, вредностите за прогресивни сперматозоиди беа 48,6 ± 18,1 x10 (6) /ml, во групата Б, вредностите за прогресивни сперматозоиди беа 47,9 ± 17,3 x10 (6) /ml. Немаше статистички значајна разлика помеѓу двата временски интервала (група А и група Б) при интерпретација на подвижноста на сперматозоидите, p>0,005. Анализата на морфологијата на сперматозоидите покажа вредност од 6,9% за присуство на морфолошки нормални сперматозоиди. Заклучок: Квалитетот на ејакулатот кај младите мажи во Северна Македонија е во опсегот на референтните вредности според СЗО. Нашите резултати се слични на оние од Германија, Турција, Бугарија, Фарските Острови.

Introduction

World literature points to the fact that in many developed countries there is a trend of declining fertility among the male population[1]. The quality of the ejaculate reflects the fertile ability of the male individual in the fertilization process. Numerous factors influence the achievement of this task. The amount of seminal fluid, the number of spermatozoa, their quality in terms of shape, vitality, motility are some of the characteristics that reflect the ability to fertilize[2]. However, many other factors, influence this complex process.

Research data show that in the last 50 years (1938-1991) there has been a trend of decreasing sperm concentration in the male population in Europe by 2.3% and in the USA by 0.8%[3]. It is considered that between 19 - 29 years the concentration of spermatozoa is constant, but after that, decreased values have been observed mainly in sperm concentration[4,5].

Laboratories and centers for *in vitro* fertilization which study this issue, use data given by the WHO as reference values[6,7]. Those values are obtained from studies of people from different parts of the world in which there are different climatic conditions, different way of life, working conditions, diet, religious customs, traditions and so on. Studies have shown that there is a difference in the same age groups of respondents from different countries[8,9,10]. The reasons for such regional differences are not known, but it is assumed that regional, lifestyle and environmental factors have an influence on genetic factors[11,12]. Low spermatogenic capacity may be associated with developmental disorders of the male reproductive system such as cryptorchidism, hypospadias, and testicular germ cell carcinoma, which are components of testicular dysgenesis syndrome (TDS). There is an increasing trend of TDS over the past decades in western countries. The explanation is sought in the exposure of the testicles of fetuses to environmental factors, mostly chemical ones, which lead to endocrine disorders[13].

Lifestyle factors also affect spermatogenesisand sperm quality. These factors include smoking, drinking, drug abuse, diet, obesity, chemicals, pesticides, use of cell phones and laptops. Each of these factors has negative correlation with the quality of the sperm and fertile potential in men if the person is overexposed[14].

The aim of this study was to evaluate sperm quality in young, healthy men in our country, and to compare sperm quality in our population with others in the world.

Material and methods

Participants

The study was conducted in the Laboratory for Analysis of Human Ejaculate at the Institute of Histology and Embryology, at the Faculty of Medicine in Skopje, in the period 2018-2020. Human ejaculates from 203 healthy male subjects were analyzed. Respondents included in this study were young men and students from the Faculty of Medicine (I-VI

year), Faculty of Dentistry (I-V year) and University School for physiotherapists, medical technicians, x-ray technicians (I-III year), all at the Ss. Cyril and Methodius University in Skopje.

All respondents were voluntarily included in this study and were properly informed about the entire procedure.

The study was conducted according to the following protocol, which foresees the following stages and procedures:

- The respondent signs an informed consent that he consciously and voluntarily approaches to this research
- The respondent fills out a questionnaire that contains useful data about the subject of thestudy
- The respondent receives information about conditions that must be met before delivering the material for analysis.

This research was approved by the Committee for Ethical Issues at the Faculty of Medicine in Skopje.

Materials and methods

After delivering, the material for analysis was stored in a thermostat at temperature of 36^0C. Firstly, the method of observation was used, and then microscopic analyses were performed according to the WHO Laboratory manual for the examination and processing of human semen (5^{th} edition). The analyses included procedures that determined qualitative and quantitative parameters of the ejaculate:

- Macroscopic examination of the ejaculate:
  - volume
  - liquefaction
  - pH
  - viscosity

- Microscopic examination of the ejaculate:

Initial microscopic analysis was performed using a phase-contrast, light microscope, with magnification X40, X60 and X100, on native and hematoxylin-eosin stained slides. On native slides, we analyzedsperm motility and sperm concentration. On hematoxylin-eosin stained slides, we analyzed sperm morphology. Sperm vitality was assessed using the eosin-nigrosin method of staining.

- Sperm motility

  Sperm motility was determined in at least 5-10 fields of view (progressive spermatozoa, non-progressive spermatozoa and immotile spermatozoa, by counting a minimum of 200 spermatozoa, according to standard procedures (WHO, 5th edition). Sperm motility was analyzed at 2-time intervals, after 60 and 120 minutes from ejaculation (group A - 60 minutes and group B - 120 minutes).

- Sperm vitality

  The percentage of vital spermatozoa in the ejaculate was determined using eosin-nigrosin method of staining, according to standard procedures (WHO, 5th edition).

- Sperm concentration

  Number of spermatozoa in 1 ml and in the entire volume of the ejaculate was determined by counting spermatozoa in an Improved Neubauer chamber according to standard procedures (WHO, 5th edition).

- Sperm morphology

  Differential morphological analysis was performed on permanent histological slides, stained with hematoxillin-eosin, by which the morphological appearance of spermatozoa was qualitatively and quantitatively determined, with a percentage representation of normal and deviant spermatozoa. On the deviant spermatozoa, we quantitatively determined the percentage of deviations of the head, midpiece, tail of the spermatozoa and presence of cytoplasmic residue (WHO, 5th edition, Kruger's strict criteria).

The obtained macroscopic and microscopic results were processed using a descriptive statistical method and t-test to present the difference between the groups. Statistical analysis was performed using SPSS 17.0 software; $p<0.05$ was considered as significant.

Results

This study analyzed human ejaculates from 203 respondents, aged 18 to 32 years, with the average age of 24.3 ± 4.2 years.

Macroscopic examination of the ejaculate showed that the average ejaculate volume was 3.45 ± 1.5 ml; the smallest measured volume was 1 ml, the maximum measured volume was 9.2 ml. 159 (78.3%) ejaculates had a normal volume, 23 (11.3%) respondents had an ejaculate with a decreased volume.

pH values ranged from 6.7 to 8, the average pH value was 7.5 ± 0.2; 188 (92.65) ejaculates had a normal pH value, 12 (5.9%) ejaculates had a pH value lower than 7.2; 3 (1.5%) ejaculates had a pH value higher than [7,8].

Liquefaction time ranged from 15 to 240 minutes, an average of 34.5 ± 17.7 minutes. In 151 (74.4%) respondents, the liquefaction time was shorter than 30 minutes, while in 50 (24.6%) respondents the liquefaction of the ejaculate was longer than 30 minutes.

Viscosity of the ejaculate was normal in 185 (91.1%) respondents, while in 18 (8.9%) respondents it was increased.

Table 1. Macroscopic characteristics of the ejaculate

Parameter	Values	WHO 5 – reference values
Age (mean ± SD) (min – max)	(24.3 ± 4.2) (18 – 33)	
Volume / ml (mean ± SD) (min – max)	(3.45 ± 1.5) (1 – 9.2)	≥1.5
volume (%) normal (2 – 5 ml) decreased increased	 159 (78.32) 23 (11.33) 21 (10.35)	
pH (mean ± SD) (min – max)	(7.5 ± 0.2) (6.7 – 8)	7.2
pHn (%) normal (7.2 – 7.8) decreased increased	 188 (92.61) 12 (5.91) 3 (1.48)	
Liquefaction /minutes (mean ± SD)	(34.5 ± 17.7) (15-240)	30 minutes
Liquefaction n (%) <30minutes ≥30minutes	 151 (74.38) 50 (24.63)	
Viscosity		
Viscosity n (%) normal increased	 185 (91,13) 18 (8,87)	

The average sperm concentration was 62.4 ± 39.2x10(6)/ml; the lowest value of sperm concentration in 1 ml of ejaculate was 1 million spermatozoa, while the highest value of sperm concentration was 150x10(6)/ml. Lower sperm concentration than 15x10(6)/ml was detected in 36 (17.7%) of the ejaculates.

The total number of spermatozoa in the ejaculate ranged from 1 to 1196x10(6); the average value of the total number of sperm in the ejaculate was 211.2 ± 173.2 x10(6). Total sperm count in the ejaculate was decreased (<39x10(6)) in 30 (14.8%) respondents.

The number of progressive spermatozoa in 1ml ranged from 0.01 to 693x10(6)/ml; average 38.4 ± 52.8x10(6)/ml. Decreased number of progressive spermatozoa (<10x10(6)/ml) was detected in 37 (18.2%) ejaculates.

The total number of progressive spermatozoa in the ejaculate averaged 119.1 ± 106.5x10(6); the lowest total number of progressive spermatozoa was 0.038x10(6), while the highest was 660x10(6). In 36 (17.7%) ejaculates, the total number of progressive spermatozoa was decreased, it was less than 30x10(6) (Table 2).

Table 2. Sperm concentration and sperm motility

Parameter	n (%)	WHO 5 – reference values
Sperm concentration/x10(6) /ml (mean ± SD) (min – max)	(62.4 ± 39.2) (1-150)	≥ 15 x10(6)/ml
Sperm concentration (/ml)n (%) <15 >15	36 (17.73) 167 (82.27)	
Total sperm concentration/ x10(6) (mean ± SD) (min – max)	(211.2 ± 173.2) (1 – 1196)	≥39 x10(6)
Total sperm concentration/ x10(6)n (%) <39 >39	30 (14.78) 173 (85.22)	
Progressive spermatozoa/ x10(6)/ml (mean ± SD) (min – max)	(38.4 ± 52.8) (0.01 – 693)	≥ 32%
Progressive spermatozoan (%) <15 >15	37 (18.23) 164 (80.79)	
Total progressive spermatozoa/ x10(6) (mean ±SD) (min – max)	(119.1 ± 106.5) (0.038 – 660)	
Total progressive spermatozoan (%) <30 >30	36 (17.74) 165 (81.28)	

In the analysis performed in the first 60 minutes after ejaculation, the number of progressive spermatozoa ranged from 3 to 88%, average 48.6 ± 18.1%; the number of non-progressive spermatozoa ranged from 1 to 23%, average 6.5 ± 3.4%; the number of viable spermatozoa ranged from 9 to 97%, average 43.1 ± 17.2%. In these analyses, in 91 (44.8%) ejaculates a reduced percentage of progressive spermatozoa was observed (<50%), in 17 (8.4%) ejaculates an increased percentage of non-progressive spermatozoa was observed (>10%), while in 115 (56.65%) ejaculates an increased percentage of possessive spermatozoa (> 40%) was observed.

In the analysis performed in the second hour (120 minutes) after ejaculation, the number of progressive spermatozoa ranged from 2 to 87%, average 47.9 ± 17.3%; the number of non-progressive spermatozoa ranged from 1 to 30%, average 6.8 ± 3.2%; the number of possessive spermatozoa ranged from 11 to 100%, average 44.3 ± 17.4%. In these analyses, in 100 (49.3%) ejaculates, a reduced percentage of progressive spermatozoa (<50%) was observed, in 13 (6.4%)

ejaculates an increased percentage of non-progressive spermatozoa (>10%) was observed, while in 115 (56.65%) ejaculates an increased percentage of possessive spermatozoa (> 40%) was observed (Table 4). In 14(6.7%) ejaculates spermatozoa had reduced vitality (<45%) (Table 4).

When progressive spermatozoa were compared at 60 and 120 minutes (group A and group B), there was no statistically significant difference between the two groups, t=0,4028; p=0.6873;p>0.005 (Table 3).

Table 3. Comparison of progressive sperm motility at 60 and 120 minutes

	$(\bar{x})$	(Σ)	St.error	95% confidence interval of difference		t	df	p
Group 1 (60 min) – group 2 (120min)	48.250	17.500	1.738	-2.716	4.116	0.4028	404	0.6873

Table 4. Sperm motility and sperm vitality

	n (%)	WHO 5 - reference values
Progressive spermatozoa (60minutes) (mean ± SD) (min – max)	(48.6 ± 18.1) (3 – 88)	≥ 32%
Progressive spermatozoa (60 minutes)n (%) ≥ 32% <32%	 109 (53.69) 91 (44.83)	
Non-progressive spermatozoa (60 minutes) (mean ± SD) (min – max)	(6.5 ± 3.4) (1 – 23)	≤ 8%
Non-progressive spermatozoa (60 minutes) n (%) ≤ 8% >8%	 184 (90.64) 17 (8.37)	
Immotile spermatozoa (60 minutes) (mean ± SD) (min – max)	(43.1 ± 17.2) (9 – 97)	
Immotile spermatozoa (60 minutes) n (%) ≤ 60% >60%	 86 (42.36) 115 (56.65)	
Progressive spermatozoa (120 minutes) (mean ± SD) (min – max)	(47.9 ± 17.3) (2 – 87)	≥ 32%
Progressive spermatozoa (120 minutes) n (%) ≥ 32% <32%	 102 (50.25) 100 (49.26)	
Non-progressive spermatozoa (120 minutes) (mean ± SD) (min – max)	(6.8 ± 3.2) (1 – 30)	≤ 8%
Non-progressive spermatozoa (120 minutes) n (%) ≤ 8% >8%	 188 (92.61) 13 (6.4)	

Immotile spermatozoa(120 minutes) (mean ± SD) (min – max)	(44.3 ± 17.4) (11 – 100)	
Immotile spermatozoa(120 minutes) n (%) ≤ 60% >60%	86 (42.36) 115 (56.65)	
Sperm vitality (mean ± SD) (min – max)	(65.6 ± 14.9) (0 – 100)	
Sperm vitalityn (%) ≤58% >58%	14 (6.89) 188 (92.61)	

Table 5. Basic differential morphological analysis of spermatozoa

Basic differential morphological forms of spermatozoa	
	n (%)
Normal spermatozoa n (%) (WHO-5 reference values) ≥4 <96	130 (64.04) 73 (35.96)
Deviant spermatozoa n (%) <96 ≥4	134 (65.51) 69 (33.99)
Head deviations n (%) <30 ≥30	184 (90.64) 19 (9.36)
Midpiece deviations n (%) <30 ≥30	169 (83.26) 34 (16.74)
Tail deviations n (%) <30 ≥30	174 (85.71) 29 (14.29)
Cytoplasmic residue n (%) <30 ≥30	189 (93.10) 14 (6.90)
Combined deviationsn (%) <40 ≥40	168 (82.76) 35 (17.24%)

Morphological analysis showed presence of 6.9% of morphologically normal spermatozoa in the ejaculates. The results of the differential morphological analysis of spermatozoa found 130 (64%) ejaculates with normal shape of spermatozoa. In the remaining 73 (35.96%) ejaculates, the presence of deviations in the heads, midpiece and tails of the spermatozoa was observed, as well as cytoplasmatic residue. Analysis of the sperm

head showed presence of this deviation in 19 (9.36%) ejaculates, analysis of the midpiece showed presence of this deviation in 34 (16.74%)ejaculates, while analysis of the tails of the spermatozoa showed deviation in 29 (14.29%) ejaculates. Presence of cytoplasmic residue in spermatozoa was noticed in14 (6.90%) ejaculates.Combined sperm abnormalities were observed in 35 (17.24%) ejaculates (Table 5).

Table 6. Semen quality in young men in North Macedonia

Total number of respondents N (203)	Age (years)	Volume (ml)	Sperm concentration (million/ml)	Total sperm concentration (million)	Progressive spermatozoa (million/ml)	Morphology (%)
Mean (SD)	24.3 (4.2)	3.45 (1.5)	62.4 (39.2)	211.2 (173.2)	38.4 (52.8)	6.9 (3.6)
Median	24	3	62	207	37.1	7.2

Discussion

Evaluation of the parameters of the spermogram is one of the best indicators of male reproductive health15. A large number of studies from different countries worldwide point to a declining trend in semen quality; therefore,an early screening of young men for semen quality can contribute to preserving and improving fertility[3].

We conducted this study in order to gain insight into the fertilecapacity of young men in North Macedonia and to compare the obtained results with the latest reference values of the World Health Organization, as well as with other studies on this topic in the world.

Our study comprised young healthy men aged 18-32, because many studies suggest that spermatogenesis in men at this age is at its highest level [4,5]. Volume of the semen fluid was within normal reference values, according to WHO guidelines,3.45 ± 1.5ml (mean ±SD), as it was in the study of Mendiolaet *al.*, Jorgensen et al. and Rao et *al* [1,8,11].

The values for sperm concentration in 1 milliliter of ejaculate were 62.4 ± 39.2 x10(6) /ml (mean ± SD), which is in accordance with the WHO reference values, ≥15 x10(6) /ml. The total sperm concentration in the ejaculate was 211.2 ± 173.2 x10(6) (mean ± SD), >39 x10(6). Similar values for sperm concentration per milliliter of ejaculate and total sperm concentration were reported in the studies by Jiang et al. and Hallinget *al.*[16,21].

Most studies report assessing sperm motility over a single time interval. In our study, we assessed sperm motility at two-time intervals. The first time interval, group A - 60 minutes after ejaculation, showed 48.6 ± 18.1% for progressive spermatozoa and 6.5 ± 3.4% for non-progressive spermatozoa. At the second time interval, group B - 120 minutes after ejaculation, results for progressive spermatozoa were 47.9 ± 17.3% and for non-progressive spermatozoa 6.8 ± 3.2%. There was no statistically significant difference between the two

time intervals (group A and group B) when interpreting sperm motility, t=0.4028; p=0.6873; p>0.005. The obtained values for sperm motility were within the WHO reference values. Similar values for sperm motility were shown in the study by Li et *al.*[7]. Sperm viability tests showed values within the WHO reference values, ≥58. The values were 65.6 ± 14.9%. Sperm morphology analysis detected presence of 6.9% of morphologically normal spermatozoa, which is within the WHO reference values, according to Kruger's strict criteria. In 130 ejaculates, normal morphological forms of spermatozoa were found, with the presence of >4% of morphologically normal forms of spermatozoa, while in 73 ejaculates deviant morphological forms of spermatozoa were found, ≥96%. Guzick et *al*. in their study noticed presence of morphologically normal forms of spermatozoa higher than 12% in fertile men[18]. Assessing morphologicallydeviant forms, we found that sperm head deviations, >30%, were noted in 19 ejaculates, sperm midpiece deviations, >30%, were noted in 34 ejaculates, sperm flagellum deviations, >30%, in 29 ejaculates, while presence of sperm cytoplasmic residue, >30%, was noted in 14 ejaculates. The presence of combined deviations, >40%, was found in 35 ejaculates. For 20 years, sperm morphology assessment has been described by some authors as a good indicator of male fertility[19]. Data from our study show higher values of sperm motility and concentration, and lower value of sperm morphology compared to the study of Dobrinov et al., conductedon young men from Bulgaria[20]. Our findings about the quality of the ejaculate in young men were similar to those presented inthe study of Halling J et *al.*[21], done with young men in the Faroe Islands. The resultsof our study for sperm volume and sperm concentration were also similar to the results in the study performed by Paasch et al.,which referred to young men in Germany[22]. A higher value for sperm concentration was shown in the study by Cok et *al.*[23], which involved a population of young men in Turkye, as well as in the study made by Li et *al.* which comprised young men in China[17].

Conclusion

The results presented in this study have given a realistic picture for the quality of the ejaculate in young, healthy men from our region. These results are characteristic for the young male population with the same or similar conditions in lifestyle, work, diet and tradition typical for the Republic of North Macedonia.

These initial results allow us to compare them with those obtained in other countries in the world, so we can conclude that the quality of ejaculate in young men in North Macedonia is within the WHO reference values, and also our results are similar to those from Germany, Turkey, Bulgaria, Faroe Islands.

These results will be supplemented with data in the next few years, in order to establish reference values for the parameters of the spermogram of the young male population in North Macedonia.

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CASE REPORT

AVASCULAR NECROSIS OF THE FEMORAL HEAD IN PATIENT WITH LYME DISEASE AND DEVIC'S OPTIC NEURITIS

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Abstract

Avascular necrosis of the femoral head is a condition that leads to the collapse of the femoral head, which eventually ends in osteonecrosis of the hip head and the need for a total hip replacement. It affects patients of both sexes between 20-55 years of age. The pathogenetic cause is a progressive reduction of blood circulation which leads to destruction of the femoral head. Most often the causes are corticosteroid therapy, alcoholism, smoking, trauma, etc. Decompression of the femoral head accompanied by application of mesenchymal stem cells to the necrotic zone is a promising regenerative method of treatment. We present a case of a 20-year-old patient who was diagnosed with avascular necrosis of the femoral head of the left hip, due to a high dosage of corticosteroid therapy, with Lyme disease and Devic's optic neuritis. Corticosteroid- induced avascular necrosis of the femoral head most commonly affects the femoral head, but other skeletal parts are not excluded. Majority of patients complain of pain with an insidious onset, which exacerbates with physical activity, and tends to worse with time. Early diagnosis and treatment arecrucial. Despite some controversy regarding the treatment of avascular necrosis of the femoral head with stem cells, the general outcomes of using stem cells appear to be positive in terms of efficacy and safety

ПРИКАЗ НА СЛУЧАЈ

АВАСКУЛАРНА НЕКРОЗА НА ГЛАВАТА НА БУТНАТА КОСКА КАЈ ПАЦИЕНТ СО ЛАЈМСКА БОЛЕСТ И ДЕВИКОВ ОПТИЧКИ НЕВРИТИС

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Клучни зборови: аваскуларна некроза, глава на бутна коска, матични клетки

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Печатарски права: ©2023 Вилијам Велковски, Илир Шабани, Виктор Камнар, Антонио Гавриловски, Теодора Тодорова, Милена Богојевска-Доксевска, Даница Поповска, Ериета Николиќ-Димитрова. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираат оригиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Аваскуларната некроза на главата на бутната коска е состојба која доведува до колапс на феморалната глава, што на крајот завршува со остеонекроза на главата на колкот и потреба од алоартропластика на колкот. Оваа состојба ги афектира пациентите од двата пола на возраст од 20 до 55 години. Патогенетската причина е прогресивно намалување на циркулацијата на крвта што доведува до уништување на феморалната глава. Најчесто причините се примена на кортикостероидна терапија, алкохолизам, пушење, траума итн. Декомпресија на главата на бутната коска придружена со апликација на мезенхимални матични клетки во некротичната зона е ветувачки регенеративен метод на лекување. Прикажуваме случај на 20-годишна пациентка кај која беше дијагностицирана аваскуларна некроза на главата на бутната коска од левиот колк поради примена на високи дози кортикостероидна терапија, со Лајмска болест и Девиков оптички невритис. Аваскуларната некроза индуцирана од примена на високи дози кортикостероиди најчето ја афектираглавата на бутната коска, но не се исклучуваат и останатите делови од скелетот. Повеќето од пациентите се жалат на болка со подмолен почеток, која се влошува со физичка активност и со текот на времето станува поинтензивна. Раната дијагноза и третман се од клучно значење. И покрај некои контроверзии во врска со третманот на аваскуларна некроза на главата на бутната коска со матични клетки, резултатите од користењето на матични клетки се чини дека се позитивни во однос на ефикасноста и безбедноста.

Introduction

Avascular necrosis of the femoral head (AVN) is a condition that leads to collapse of the femoral head, which eventually ends in osteonecrosis of the hip head and the need for a total hip prosthesis. This is a condition that affects patients of both sexes between 20-60 years of age. The pathogenetic cause is a progressive reduction of blood circulation which leads to destruction of the femoral head.[1-4] The etiological causes are multifactorial.[5] Most often the causes are corticosteroid therapy, alcoholism, smoking, trauma, etc. The symptomatology and radiological findings depend on the degree of damage to the femoral head, classified according to the Ficatclassification.[6] The main symptoms are pain and limited internal rotation of the hip. The exact assessment of the degree of damage is determined by magnetic resonance imaging.

There are several types of surgical methods in the treatment of AVN, from decompression of the hip head, osteotomy, bone graft and finally total hip replacement surgery.

Decompression of the femoral head accompanied by application of mesenchymal stem cells to the necrotic zone is a promising regenerative method of treatment.[7] Stem cells are obtained by harvestingbone marrow aspirate from the iliac bone. Satisfactory clinical and radiographic results have been reported in patients classified after Ficat I and II classification in 75% of cases and more than 40% in patients classified as Ficat stage III. The mechanism refers to the increased proliferation of cells in the process of construction and remodeling of the decompressed necrotic zone. Biological efficiency is determined by the activity of cytokines and growth factors (beta growth factor, interleukin [8], stromal cellular alpha factor and vascular endothelial growth factor), which act as mediators in the regeneration of the bone matrix and allow its further remodeling. All this results in slowing down the process of chondral degeneration, subchondral sclerosis and definite arthrosis of the hip joint which is treated exclusively with alloarthroplasty, a total hip replacement.[8]

The procedure is a simple, bloodless, short-term method with unknown complications. Patients can tolerate stress and return to daily activities and functional life early.[9]

Case report

We present a case of a 20-year-old female patient treated at the University Clinic for Neurology due to an acute demyelinating process, transverse myelitis. Positive Borrelia IgM titer and positive Western-Blot test were obtained during hospitalization.The patient was treated with a high dosage of corticosteroids. After the hospital treatment, rehabilitation was performed for 4 weeks, followed by improvement of sensitivity, stability when walking, control of urination. She was referred to the University Clinic for Infectious Diseases where after a diagnostic lumbar puncture she was hospitalized for further examination and treatment.

The patient presented to the University Clinic for Orthopedic diseases for examination due to pain in the left inguinal region, the left hip, which radiated along the left leg, for a period longer than 6 months.Limited and painful hip flexion as well as external rotation were followed up for clinical examination. According to the VAS scale, the patient rated the degree of pain with a score of 8, and the value for the Harris Hip Score was 44. Pelvic X-rays and magnetic resonance imaging were performed in support of avascular necrosis of the femoral head of the left hip, according to the Ficat classificationstageIII. After the clinical and paraclinical examinations, an indication was set for surgical treatment. Decompression and application of mesenchymal stem cells, which were taken from the bone marrow of the iliac bone, was performed. They were processed by centrifugation and separation using the Artrex Angel system. The patient was introduced to spinal anesthesia and placed on an extension chair. 180 ml of bone marrow were aspirated using a 6 cm long trocar needle 1.5 mm in diameter placed in the anterolateral part of the iliac crest. It was transferred to a plastic container with anticoagulant and further preparation in a centrifuge followed to separate the stem cells from the blood elements. The prepared device was implanted through a trocar directly into the decompressed necrotic segment as well as intraarticularly in the hip joint. Quality cytometry was performed to control the quality, the total number of nuclear cells and their viability. The patient was verticalized on the first postoperative day with a note not to weight bear the operated leg, and on the third day she was discharged from the hospital. Afterthe hospital treatment, physical rehabilitation was performedfor four weeks, so at the control examination after the rehabilitation, the patient did not complain of pain, the movements were neat and painless, and the Harris Hip Score was 51 points. The next control examination of the patient was atthe third month after surgery. A native pelvic x-ray showed an increase in bone density in the duct from the surgically made tunnel to the change as well as an increaseinbone density in the necrotic zone. The Harris Hip score was 67 points. The patient was advised to move without crutches and to continue strengthening the muscles above the knees.

Six months after surgery, an MRI of the pelvis with both hipswas performed. A bone defect wasstill present at the proximal end of the head of the left femur from the previous decompression with initial chondromalacia of the ipsilateral femoral head and slightly reduced acetabular joint space, but without the presence of an osteochondral lesion. The Harris hip score was 78 points, whichindicated a good clinical outcome.

On the control examination 19 months after surgery, the patient wasstill limping, but had no pain and she returnedto everyday activities just like before the condition.

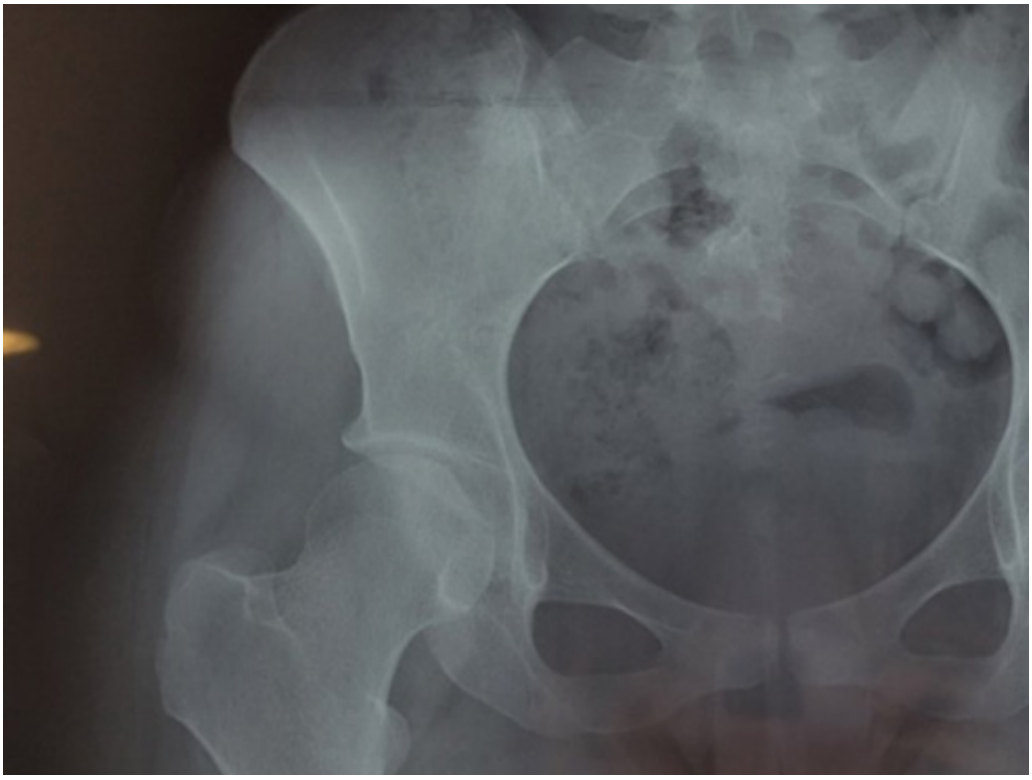

Fig. 1 Preoperative X ray of the pelvis, showing AVN of the femoral head of the left hip, according to Ficat classification stage3

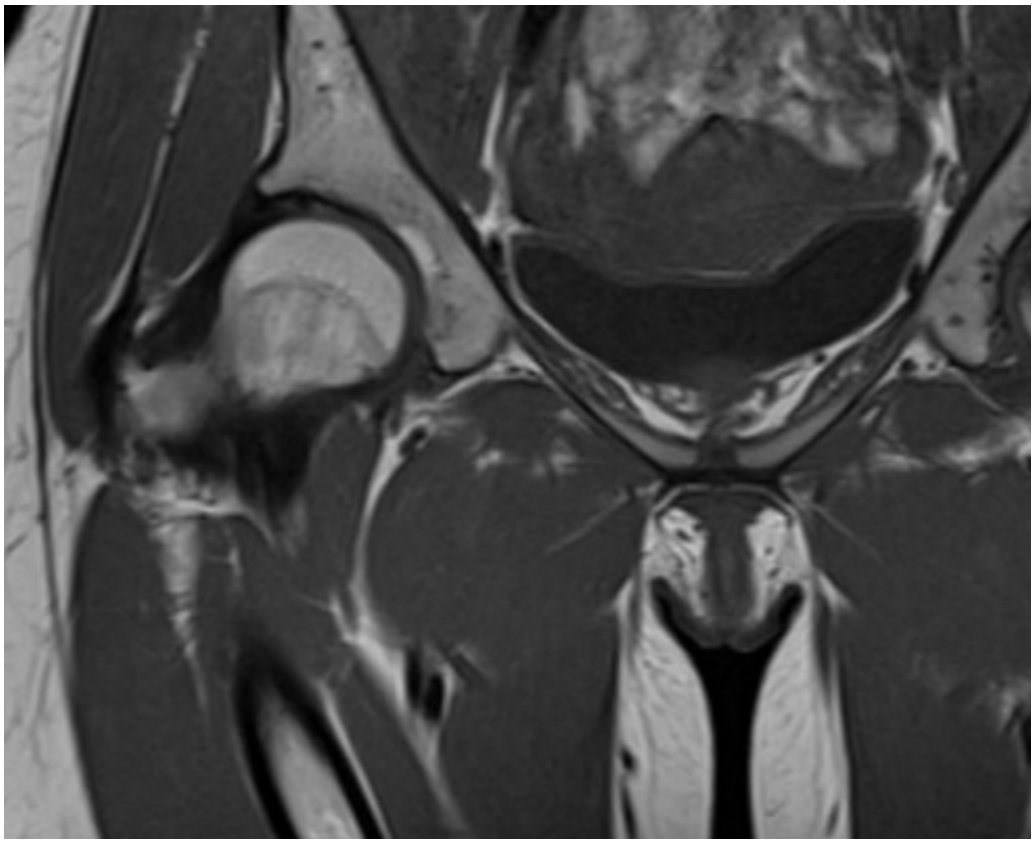

Fig. 2 Preoperative MRI of the pelvis - coronal view

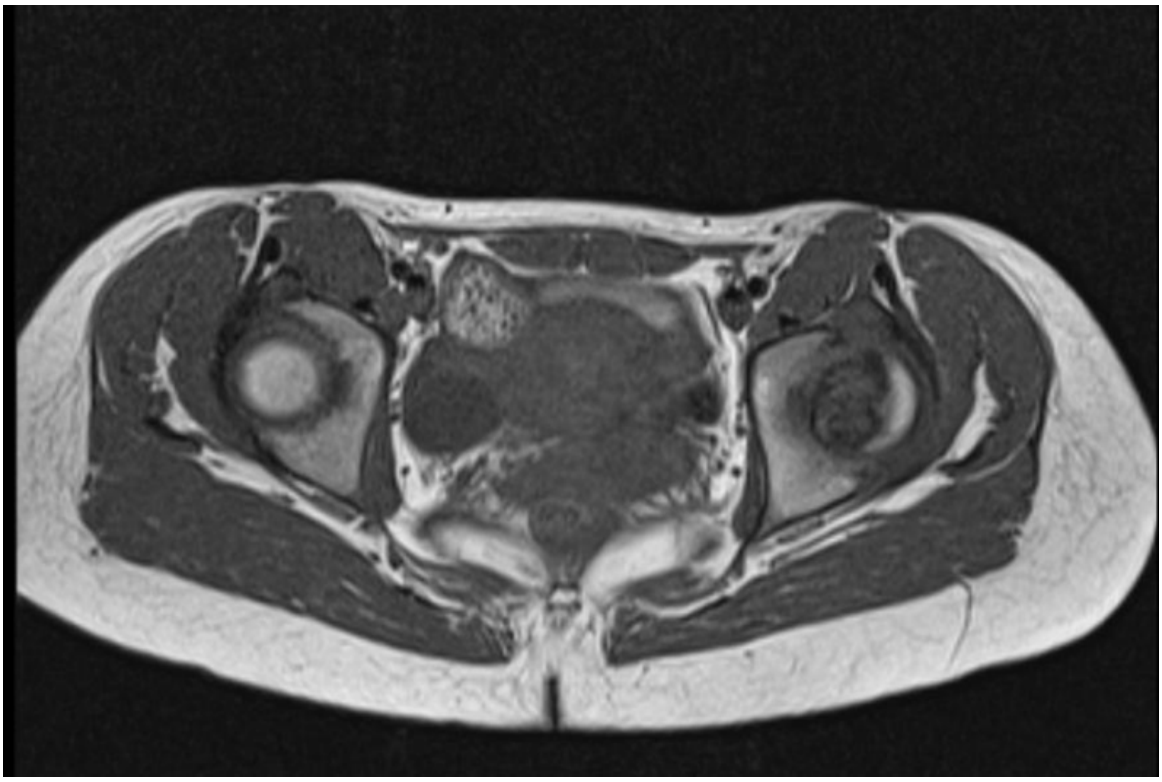

Fig. 3 Preoperative MRI of the pelvis - transverse view

Fig. 4 Control X-ray 19 months after surgery

Discussion

Corticosteroid-induced avascular necrosis of the femoral head most commonly affects the femoral head, but other skeletal parts are not excluded.[10,11] Majority of patients complain of pain with an insidious onset, which exacerbates with physical activity, and tends to worse with time. Early diagnosis and treatment are crucial, because treatment modalities in advanced diseases are limited and most of the patients who suffer from this condition are young people and physically active.

The prevalence of corticosteroid-induced avascular necrosis of the femoral head varies between 3-38% and mainly depends on the dosage and route of administration of the drug.[10]

The pathophysiological mechanisms till now have not been fully understood; they include different theories such as fat embolisation, intravascular coagulation, hypertrophy of the fat cell and osteocyte apoptosis, with a common pathway to compromise the vascularization of the bone and the bone marrow, leading to ischemic event and subsequent ischemic necrosis of the bone tissue and finally collapse of the bone.[12] Recently, a new theory for corticosteroid-induced osteocyte apoptosis has been suggested as an another pathogenetic mechanism of avascular necrosis of the femoral head, as apoptotic osteocytes were found in a specimen of the femoral head during total hip arthroplasty in a patient who had a medical history of corticosteroid usage.[13,14] These findings are not detected in patients who have avascular necrosis of the femoral head with previous history of trauma or alcohol abuse. These osteocytes tend to accumulate in the bone and lead to disruption of the osteocyte-lacunar-canalicular system, as well asin the vascular space and in the end the result is collapse of the femoral head.[15]

As a classical surgical treatment, core decompression itself usually is effective for small necrotic lesions, but the combination of core decompression with application of bone marrow aspirate concentrate is associated with improved radiological signs and clinical outcomes.[16,17]

A large number of transgenic MCS for specific functions have been studied and stem cell technology is rapidly evolving. It is very important to highlight the need of further genetic studies for genetic safety of transgenes and stem cell subpopulations. The strong expression of some specific factors may affect other normal tissues and the effect of small molecule drugs on the differentiation of the stem cells and proliferation has been confirmed. Small molecule drugs seem to be convenient for stem cell pretreatment and may be a research direction for stem cell pretreatment for avascular necrosis of the femoral head in the future.[18]

The major concern regarding treatment with stem cells is their safety. Flushing, fever, mild headache are the complications reported in a few studies.[19- 21] It has also been reported in a few studies that transplantation of embryonic stem cells may lead to teratoma formation. Immune rejection and genetic modification can also limit the clinical use of transplanted stem cells for osteonecrosis of the femoral head. [21,22]

The results obtained in this study have shown that after the application

of stem cells in the necrotic zone of the femoral head and after intraarticular application, good functional results have been achieved. Radiographically confirmed good bone regeneration was achieved and the progression of necrosis to a higher degree was prevented.

Conclusion

The treatment of avascular necrosis of the femoral head through a minimally invasive tunneling and decompression technique and the simultaneous application of autologous mesenchymal stem cells obtained by processing bone marrow taken from the iliac crest gives rapid and biologically effective results as well as good functional results. Despite some controversy regarding the treatment of avascular necrosis of the femoral head with stem cells, the general outcomes of using stem cells appear to be positive in terms of efficacy and safety. The future perspectives are in qualitative and quantitative characterization of cellular therapies.

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ORAL HEALTH

NON-SYNDROMIC MULTIPLE TEETH IMPACTION - CASE REPORT

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Key words: tooth eruption, impacted teeth, first permanent molar, second permanent molars, Schwartz removable appliance.

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Abstract

Tooth eruption is a continuous process by which developing teeth move through the soft tissue, oral epithelium, jaw bones and overlying mucosa, to emerge in the oral cavity, contact the teeth of the opposing dental arch, and enable teeth functional position in mastication. Abnormal tissue interactions during tooth development may be potentially revealed as ectopic tooth development, ectopic eruption or tooth impaction. In human dentition, permanent tooth impaction is relatively common. Impaction of the first permanent molar is an uncommon condition and few cases are reported in the literature. It is essential to diagnose and treat the impacted permanent molars as early as possible because treatment at a later stage is usually more complicated due to the tendency of malocclusion to increase with time. We report a case with impaction of the maxillary first permanent molar and impaction of all, maxillary and mandibular permanent second molars. This condition compromise masticatory function. Unilateral mastication also compromises the function of temporomandibular joint. The aim of this case-report was to present orthodontic treatment with Schwartz removable appliance in a patient with maxillary left-side impaction of the second premolar, first molar and second molar. The goal of the first phase was positioning the maxillary first molar into the dental arch with good bone and periodontal support. The surgical intervention, operculectomy, was done and the orthodontic treatment started by traction of the first molar with elastic ligature attached from the bonded bracket to the mobile appliance. One month later the tooth movement was obvious.

ОРАЛНО ЗДРАВЈЕ

ИМПАКЦИЈА НА ПОВЕЌЕ ЗАБИ БЕЗ ПРИСУСТВО НА СИНДРОМ - ПРИКАЗ НА СЛУЧАЈ

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Цитирање: Србиноска Д, Трпевска В, Мијоска А. Импакција на повеќе заби без присуство на синдром - приказ на случај. Арх Ј Здравје 2023;15(1) 134:144.

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Клучни зборови: ерупција на заб, импактирани заби, прв траен молар, втори трајни молари, подвижен апарат според Шварц.

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Печатарски права: ©2023 Даниела Србиноска, Весна Трпевска, Анета Мијоска.. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираат оригиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Ерупцијата на забите е континуиран процес со кој забите во развој се движат низ мекото ткиво, оралниот епител, коските на вилиците и слузницата што ги покрива, за да излезат во усната шуплина, да дојдат во контакт со забите од спротивниот забен лак и да ја овозможат функционалната положба на забите при џвакање. Абнормалните ткивни интеракции за време на развојот на забите потенцијално може да се откријат како ектопичен развој на забите, ектопична ерупција или импакција на забите. Кај човечкото забало, импакција на траен заб е релативно честа појава. Импакција на првиот траен молар е невообичаена појава и само неколку случаи се пријавени во литературата. Импактирани трајни катници неопходно е да се дијагностицираат во рана фаза и да се третираат што е можно порано, бидејќи третманот во подоцнежната фаза е обично покомплициран поради тенденцијата да се зголеми можноста за развој на дентална малоклузија со текот на времето. Во овој приказ на случај станува збор за импакција на првиот максиларен траен молар и импакција на сите, максиларните и мандибуларните трајни втори молари. Оваа состојба ја оневозможува џвакалната функција на пациентот. Едностраната мастикација исто така влијае негативно и на темпоромандибуларниот зглоб. Целта на овој приказ на случај беше да се претстави ортодонски третман со мобилен апарат според Шварц кај пациент со едностран максиларна импакција на лев втор премолар, првиот молар и вториот молар. Целта на првата фаза беше позиционирање на максиларниот прв молар во забниот лак со добра коскена и пародонтална подршка. Беше направена хируршка интервенција, оперкулектомија, и ортодонскиот третман започна со влечење на првиот молар на кој беше поставен стандарден брекет со еластична лигатура прикачена на мобилниот апарат. Еден месец подоцна движењето на забот беше очигледно.

Introduction

Tooth eruption is a continuous process by which developing teeth move through the soft tissue, oral epithelium, jaw bones and overlying mucosa, to emerge in the oral cavity, contact the teeth of the opposing dental arch, and enable teeth functional position in mastication. Humans are diphyodonts, which means we have two sets of teeth during lifetime. The first set, the primary teeth, also called deciduous teeth, or baby teeth, start erupting at around six months of age. The primary teeth fall out and are replaced by second set, permanent teeth about six years of age. The tooth eruption occurs in three phases, pre-eruptive, eruptive and post-eruptive phase. The teeth eruption driving force is still unknown but is thought to be due to a combination of a few factors, which include signals originating from the dental follicle, root formation and elongation, which could drive the tooth in order to acquire space within the jaw and an occlusal force, aiding in eruption[1]. Tooth development results from a complicated multistep interaction between the oral epithelium and the underlying mesenchymal tissue. Abnormal tissue interactions during tooth development may potentially result in ectopic tooth development and eruption. Tooth eruption occurs as a tooth moves from the developmental position to the functional position. It is a complex process that can be influenced by a number of general factors like genetics, nutrition, preterm birth, hormonal factors, various systemic diseases and some local factors[2]. Delayed eruption or impaction of permanent teeth is one of the severe problems that can occur during the mixed dentition period. An impacted tooth is one that fails to erupt into the dental arch within the expected time. The permanent teeth impaction usually occurs in the downward order of third molars, maxillary canine, mandibular premolars, mandibular canine, maxillary premolars, maxillary central incisors, and mandibular second molars[3]. These conditions can occur in any permanent tooth, but the incidence of delayed eruption of the permanent first molars, especially maxillary permanent first molars, is very low. Permanent first molars, known as the “key teeth” in occlusion, are very important as guide to the correct position of the teeth in the dental arch. The eruption of the first and second permanent molars is especially significant for the coordination of facial growth, and for providing sufficient occlusal support for undisturbed mastication. There are many studies of impaction in the literature but only a few cases involving impacted permanent first molars. The impaction of permanent first and second molars is uncommon, with prevalence rates of 0.08% for the second maxillary molar and less than 0.01% for the first maxillary molar. Although, the impaction of mandibular second molars, given that its incidence is 0.03 to 0.21%, is a rare complication in tooth eruption. It has been detected more often in the unilateral form than in the bilateral one and is

more common in the mandible than in the maxilla. Several systemic and local factors are related to the cause of this anomaly. Impaction may result from local causes, such as malocclusion disturbances of the primary dentition, the position of the neighbouring teeth, supernumerary teeth, cysts, and odontoma[4-6]. Tooth retention has been attributed to an alteration of the dental follicle, which is unable to initiate the metabolic processes leading to bone resorption and eruption[7]. Roots develop completely even when the tooth cannot erupt because root formation seems to be unrelated to the eruption process. Retention may be related to ankylosis, which is probably due to a localised alteration of the periodontal ligament, but it has not yet been determined whether impairment of the eruptive mechanism occurs before or after ankylosis. Based on Winter's classification systems, impacted molars can be classified as vertical, distoangular, mesioangular, or horizontal in position according to tooth angulation. The occlusal plane can be used as a reference to check the depth of the impacted molars[8]. 2D and 3D radiographs are more than necessary for diagnosis and treatment planning of impacted teeth. Cases with impaction of more than one tooth are indication for CBCT[9]. Multiple impacted teeth are rare condition and usually present in some syndromes. Multiple impacted teeth with no obvious aetiology is rare dental anomaly. In literature, few reports are related to multiple impacted teeth with no known aetiology[10].Complexity of the treatment varies widely, so management is a big challenge and needs a multidisciplinary specialist approach. Treatment of impacted permanent molar consist of its surgical exposure and removal of any possible barrier[11]. Orthodontic treatment is necessary in the event of abnormal positioning of the tooth, malocclusion, lack of space in the dental arch, or if spontaneous eruption is not expected. Orthodontic correction or prosthetic replacement of the missing tooth are often required. It is essential to diagnose and treat the impacted permanent molars as early as possible because treatment at a later stage is usually more complicated due to the tendency of malocclusion to increase with time and decrease the ability of remaining dentition to adjust[12]. We report a very rare case with multiple teeth impaction where there was impaction of the maxillary first permanent molar, impaction of both maxillary second premolars and impaction of all, maxillary and mandibular permanent second molars. This condition compromise masticatory function. Unilateral mastication also compromise temporomandibular joint (TMJ).

The aim of this case-report was to present orthodontic treatment by Schwartz removable appliance in a patient with maxillary left-side impaction of the second premolar, first molar and second molar. Due to the low prevalence of impaction of the first and second permanent molars, there is a lack of uniformity in the management of these impact-

ed teeth, and published reports are mostly based on case reports with mesially inclined molars. In general, treatment options depend on the age of the patient as one of the key factors, severity of impaction, bone anatomy and position of vital structures, the amount of space available, oral health, type of malocclusion, patient motivation and opinion, as well as patient-related circumstances (finances). Cooperation between different specialties (orthodontists, oral surgeons and paediatric dentists), provides the best, individual results for each patient.

Case report

Treatment objectives

The primary objectives in our treatment were:

- to create anchorage for the orthodontic traction and incorporation of the impacted first molar into the dental arch with good bone and periodontal support;
- to regain slightly more space for the impacted second premolar;
- to position the maxillary and mandibular second molars into the dental arch, and
- to provide functional position to all impacted teeth.

The other objectives were to establish a good occlusion, to obtain an optimal overbite-overjet relationship and to provide long-term retention, to enhance the health of the periodontium, and most importantly to provide bilateral mastication.

Treatment diagnosis

A 12-year-old girl with a late mixed dentition was brought to our Clinic for orthodontic treatment one year ago. The chief complaint was the presence of problems during mastication on the left side due to delayed eruption of the posterior teeth. The patient had no complain of pain, no signs of infection and had a good oral hygiene. Clinical examination revealed normodivergent face and presence of good facial balance in all proportions. Intraoral clinical examination revealed maxillary, unilateral, left-side absence in the oral cavity of the permanent second premolar, first molar and second molar and right-side absence in the oral cavity of the second premolar and second molar. Furthermore, the right and left mandibular second molars were also absent. The mandibular midline was shifted due to hypodontia of the mandibular central incisor. There was a space deficiency for teeth alignment. The patient revealed a limited mouth opening, microstomia. The occlusal examination noted a right-side Angle Class II, OJ was 3 mm and OB 5 mm. There was anterior deep bite and crossbite of the right permanent first molar and primary first molar (Fig. 1 a, b, c, d, e).

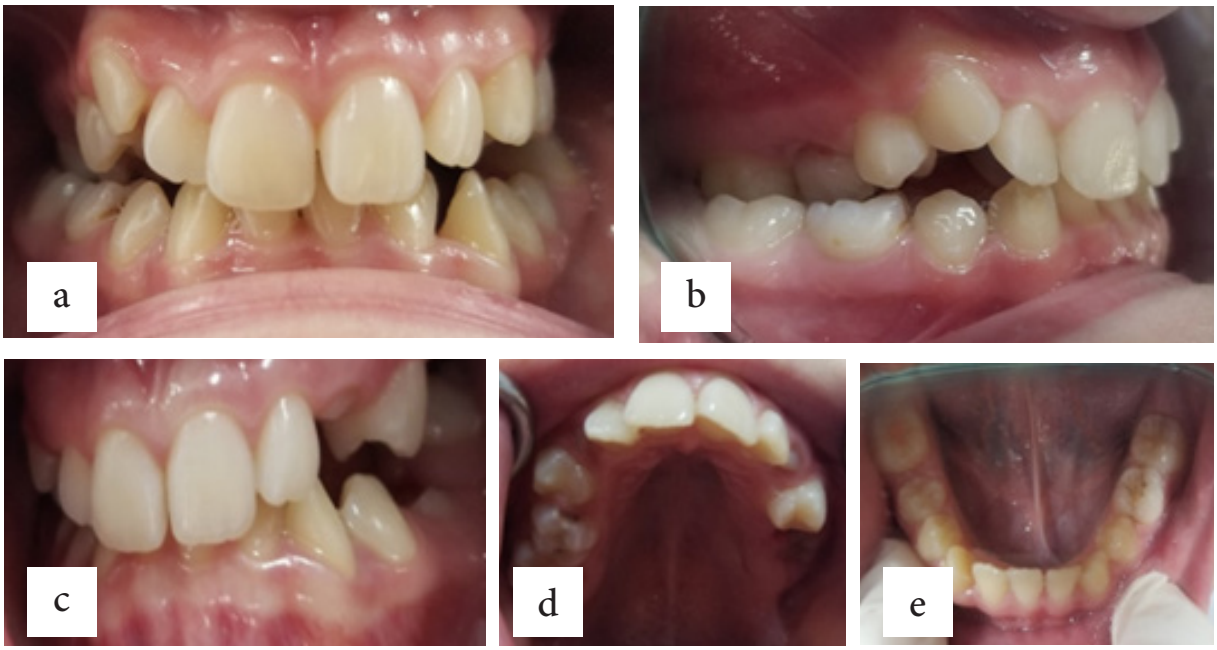

Figure 1. Intraoral clinical examination of a 12-year-old patient: a) Frontal view in occlusion and shifted mandibular midline, b) Cross bite of the right permanent first molar and primary first molar, and right-side Angle Class II, c) Left-side view, d) Upper occlusal view of the maxilla with left-side absence of permanent second premolar, first molar and second molar, e) hypodontia of the left mandibular permanent central incisor.

The panoramic radiograph revealed that all teeth were present (excluding the third molars and mandibular left central incisor). Hypodontia of the left mandibular central incisor was obvious. The left-side maxillary permanent second premolar, first molar and second molar were impacted. Furthermore, there was impaction and transposition of the right-side maxillary second premolar and impaction of all, maxillary and mandibular second molars and therefore, delayed teeth eruption to the dental arch. The panoramic radiograph revealed that the left-side second premolar and first molar posture were mesioangular and the position of the right-side second premolar was almost horizontal (Fig. 2).

Figure 2. Panoramic radiograph of a 12-year-old patient before treatment

A CBCT was prescribed at this stage due to the impaction of many teeth. The CBCT showed areas with partial absence of alveolar bone and periodontal ligament on labial side of the left-side maxillary and mandibular first molars. Extrusion of the left mandibular first molar was notable due to absence of its antagonist and unilateral mastication (Fig. 3 a, b).

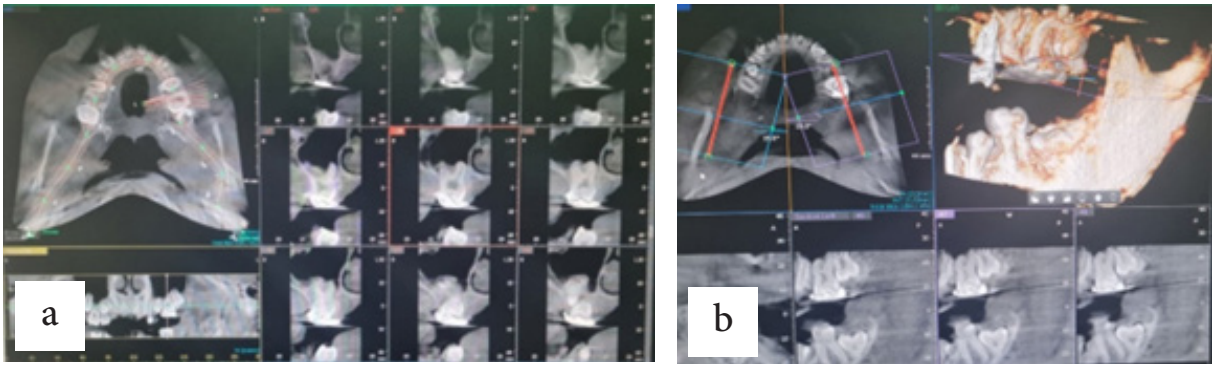

Figure 3. CBCT radiograph of a 12-year-old patient before treatment: a) Occlusal view of upper dental arch and labial view of partial absence of alveolar bone and periodontal ligament of the left-side maxillary and mandibular first molar, b) Notable extrusion of the left mandibular first molar due to absence of antagonist (maxillary first molar) and unilateral mastication.

Treatment plan

In the presented case we used Schwartz removable appliance for the traction of the left upper first molar and expansion of the maxilla and mandibula. Based on the patient's symptoms, extraoral and intraoral examination, as well as on panoramic radiograph and CBCT analysis, our treatment plan included:

- consultation with an oral surgeon about operculectomy of the impacted left-side maxillary first molar;
- intervention, surgical removal of the mucosa tissue of the occlusal surface of the first permanent maxillary molar was done and then we monitored/observed the impacted tooth until the spontaneous eruption occurred;
- in our case eruption did not occur, and hence we assisted the eruption of the impacted teeth by orthodontic traction.

The initial therapy had started with wearing mobile appliance one year ago. A standard molar bracket was bonded three days after operculectomy, so we started positioning the tooth in the dental arch (Fig. 4 a, b).

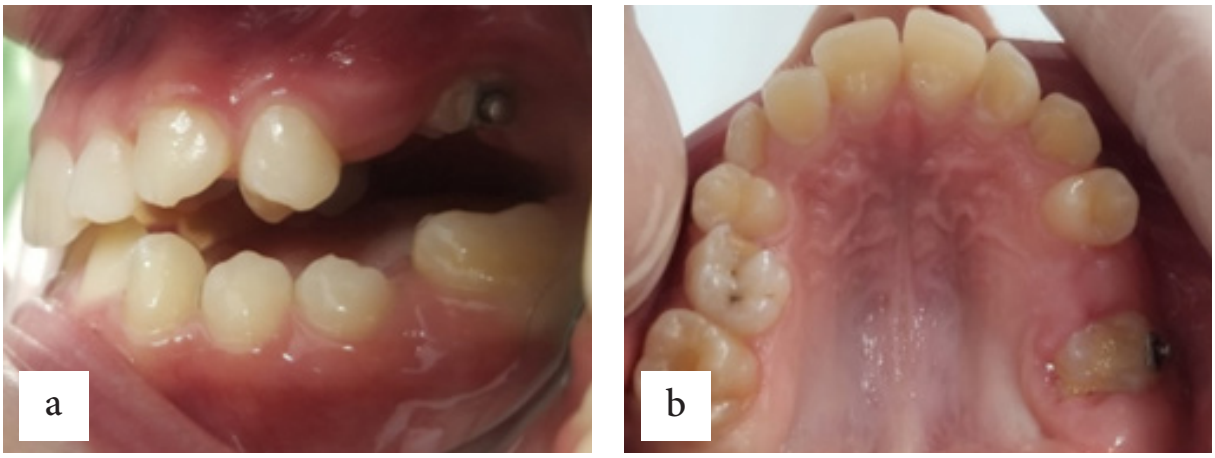

Figure 4. a) Standard molar bracket bonded three days after operculectomy b) Occlusal view

The traction of the first molar was with elastic ligature attached to the mobile appliance. Furthermore, the orthodontic treatment in mandibula as in maxilla continued by their expansion (Fig. 5 a, b, c, d).

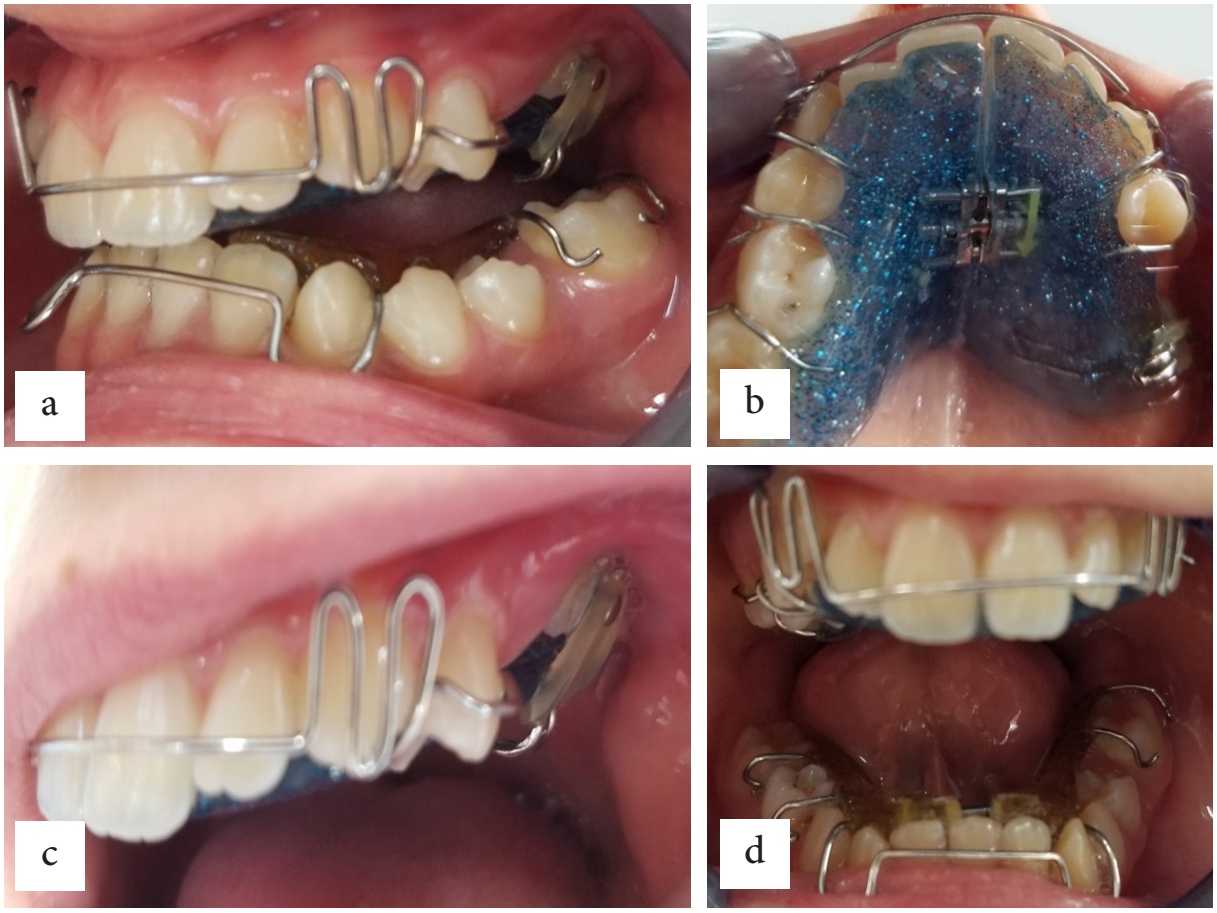

Figure 5. a) Removable Schwartz appliance with expansion screw in maxilla and mandibula, b) Occlusal view of maxillary appliance, c) Traction of the first molar with elastic ligature attached to the mobile appliance, d) Expansion of the mandibula by turning the screw.

One month later, the tooth movement was obvious, the upper first molar emerged from the gingiva and reached a more occlusal position by traction. The molar was further extruded. At 10-month follow-up, the extrusion of the left maxillary molar continued, remained vital and responded normally to mobility and sensitivity with a good width of attached gingiva.

Discussion

Tooth eruption is the axial movement of the tooth from its position in the bone to its final functional occlusion in the oral cavity and it is often used to indicate the moment of emergence of the tooth into the oral cavity[13]. The normal eruption of deciduous and permanent teeth into the oral cavity occurs over a broad chronologic age range. It can be influenced also by racial, ethnic, sexual and individual factors[14]. There are numerous eruptions regulating

molecules having similar and overlapping functions, which ensures that even the absence of a single factor does not interrupt the event of eruption. EGF, EGF-R, CSF-1, CSF-1R, IL-1, IL-1R, c-Fos, NFB, MCP-1, TGF-b1, PTHrP, Cbfa-1, OPG, RANK/RANK L are the major tooth eruption molecules. Majority of the eruption molecules reside in the dental follicle with few in the Stellate reticulum[15]. Some genetic disorders may be responsible for abnormalities in the eruption. Significant deviations from accepted norms of eruption sequence are often observed in clinical practice. Premature eruption has been noted but delayed tooth eruption is the most commonly encountered[16]. In normal eruption scenario, permanent teeth erupt eventually and replace their primary predecessors. However, some teeth fail to erupt. Most of these unerupted teeth are deviated or angulated aberrantly and eventually lose their potential to erupt and are referred to as impacted teeth. Epidemiological studies have reported dental impactions to affect 25 to 50% of human population[14]. Impaction of teeth can result from biomechanical impediments, crowding and malpositioning of adjacent teeth, previous dento-alveolar trauma, insufficient maxillofacial skeletal development, thickened mucosal and osseous tissues, eruption disturbances, indirect effects of cysts or neoplasms[17]. Impaction of a single tooth is a commonly observed clinical finding but impaction of multiple teeth is uncommon. Therefore, only a few cases of non-syndrome multiple impacted teeth were reported in literature[18-21]. In those studies, the predominant explanation was that some physical barrier led to impaction and non-eruption of teeth[22]. Multiple teeth impaction is often associated with multiple syndromes such as Cleidocranial dysplasia, Gardner's syndrome, Yunis-Varon syndrome, Gorlin-Sedano syndrome[23]. It is also common in endocrine disorders such as hypothyroidism, hypopituitarism, hypoparathyroidism. Metabolic disorders like vitamin D deficiency are also associated with impacted teeth. Our patient was with multiple teeth impaction, but no features of any disorder or syndrome were diagnosed. Further investigation and medical history of the patient showed no signs of metabolic disorders like vitamin D deficiency. Impacted teeth are those which are prevented from eruption by some physical barrier in their path of eruption. In our case, it seems that there was no local factor leading to multiple impactions of the permanent teeth. The oral soft tissues in our case were unremarkable and histopathological evaluations of gingivae were normal. The clinical and radiographic examinations of our case revealed relatively normal jaws and teeth. Delayed or arrested eruption was probably caused by lacking of eruptive force due to either general, neurogenic or mucosal and bone disorder. This was a case of primary failure of tooth eruption with no other systemic involvement. Candidate genes for primary failure of eruption would be the molecules that function solely

in the pre-eruptive phase and are expressed in cells of the dental follicle and surrounding structures. Hence, it is likely that genes like CSF-1, NFB, and c-fos are the genes responsible for the eruption defect and hypodontia[24]. Duration and results of treatment in less frequent cases of multiple impactions are a major concern when compared to more frequent single impaction cases. Multidisciplinary approach would be the appropriate choice as treatment involves aesthetics, functional, and oral health problems. In case of unerupted teeth, orthodontic extrusions should be attempted[25]. Obtaining stable results along with enhanced aesthetics, oral health, and the most important function, mastication, are the objective of our treatment.

Conclusion

The appearance of simultaneous multiple impactions of permanent teeth can be observed in both sexes with a healthy systemic condition, without any symptoms of any syndrome. These non-syndromic cases of multiple impactions are very rare. Impaction of the maxillary first molar and maxillary and mandibular second permanent molars does not occur frequently. Therefore, it is important to make an early diagnosis in order to start treatment at an optimal time, since masticatory function is compromised as in the reported case. The decision on how to manage orthodontic treatment is individual and based on more general factors such as age, psychological profile of the child, position of the affected teeth, financial situation. These patients require a multidisciplinary approach to guide "eruption" of the teeth. The listed reasons show that the treatment of more impacted teeth in children is a real challenge, as is the particular case.

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