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PUBLIC HEALTH

FACTORS THAT HAVE IMPACT ON NATURAL POPULATION CHANGE IN REPUBLIC OF NORTH MACEDONIA

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Key words: population, birth rate, mortality, natural change of population, North Macedonia.

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Abstract

The planning of public health programmes is directly related with the demographic characteristics and the population change has longterm impact on the health, health care and community interventions. The objective of this paper is to analyze the factors influencing the trend of population change in the Republic of North Macedonia. Material and methods: Data from the National Statistical Office and World Health Organization have been used. Literature review was conducted applying public health approach and descriptive method. Results: The natural population change in North Macedonia has negative trend in the last 10 years, the birth rate has declined, while the mortality is increasing. The biological factors and fertility rate have significantly influenced the birth rate, while the burden of chronic noncommunicable diseases, road injures, violence and COVID-19 are lead causes of mortality. Numerous factors indirectly affect the negative trend of population change such as the high rate of unemployment, poverty, socioeconomic and political context, migration and availability and quality of health care. Conclusion: A detailed analysis of the factors affecting the natural population change and an appropriate national response with the aim of reducing the negative trends is needed.

ЈАВНО ЗДРАВЈЕ

ФАКТОРИ КОИ ВЛИЈААТ НА ПРИРОДНОТО ДВИЖЕЊЕ НА НАСЕЛЕНИЕТО ВО РЕПУБЛИКА СЕВЕРНА МАКЕДОНИЈА

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Извадок

Планирањето на јавноздравствените програми е директно поврзано со демографските карактеристикии природното движење на населението и има долгорочно влијание врз здравјето,здравствената заштита и интервенциите во заедницата. Целта на овој труд е да се анализираат факторите кои влијаат на трендот на природното движење на населението во Република Северна Македонија. Материјал и методи: Користени се податоци од датабазата на Државниот завод за статистика и Светската здравствена организација, кои се статистички обработени и прикажани табеларно и графички. Извршен е преглед на литература, а применет е јавноздравствен пристап и метод на дескриптивна анализа. Резултати: Природното движење на населението во Македонија покажува негативен тренд во последните десет години, односно се намалува наталитетот додека морталитетот е во позитивна насока, со зголемен број на починати лица. Биолошките фактори и стапката на фертилитет значајно влијаат на намалување на наталитетот, а од друга страна оптовареноста со хроничните незаразни болести, сообраќајните несреќи, насилството и Ковид-19 се главните причини за зголемената смртност. Бројни индиректни фактори влијаат на негативниот тренд на природното движење на населението, како што се високата стапка на сиромаштија и невработеност, социоекономскиот и политички контекст, миграциите и пристапот и квалитетот на здравствена заштита. Заклучок: Потребна е детална анализа на факторите кои влијаат на природното движење на населенето и соодветен национален одговор со цел намалување на негативниот тренд.

Introduction

The natural population change in the Republic of North Macedonia (hereinafter referred to as Macedonia) stands as one of the most important components on which the dynamics and the population number depend.

The natural population change is a biological movement that pertains to reproduction, or better, the sustainability of the human race. It depends on the number of births, i.e. birth rate, and the number of deaths, or the mortality rate, and the natural increase is a result of their mutual relationship, i.e. the difference between the two.[1]

The birth rate represents the ratio between the number of live births and the average population number in the middle of the year for which the calculation is made, calculated per 1000 inhabitants[1].

The mortality rate represents the ratio of the number of people who died during the entire year (calendar year) and the average population number in the middle of the year, calculated per 1000 inhabitants, which means the rate shows how many people died on average per 1000 inhabitants

The natality depends on numerous factors such as biological, socio-economic, cultural and psychological.[2] At the global level, three types of birth rate can be distinguished: low birth rate up to 15‰ annual rate, medium from 16 to 25‰ and high above 25‰.[2] The birth rate in Macedonia exhibits a gradually decreasing trend over the years. The number of live births in 1994 stood at 31 421 children, while in 2021 it stood 18 790 children.

Mortality is influenced by numerous factors such as the age structure of the population, socioeconomic conditions, environmental conditions, level of health care and health services, the standard of living, whether or not there is warfare, disasters and others.[2] The mortality rate in Macedonia has been increasing constantly, in particular during the Covid-19 pandemic, when the mortality rate in 2020 was 12.4 deaths per 1000 inhabitants, or the total number of deaths was 25,755.1 In 2021 in Macedonia the mortality rate is 15.5 deaths per 1000 inhabitants or the number of deaths is 28 516 people.[1] The global mortality rate in 2020 stood at 8 dead people, and in 2021 it stood at 8.4 per 1000 inhabitants[3]

The natural increase in Macedonia stood at 15,772 in 1994, though it has been declining since 2019. In 2019, the natural increase stood at -601, in 2020, as a result of Covid-19, it stood at -6,724, and in 2021, the natural increase showed a negative trend of -9,868. Unlike recent years, the natural increase in 2010, which is only ten years ago, was +5 183.1.[1]

The purpose of this paper is to analyze the natural change in the population in Macedonia and to summarize the factors that contribute to the negative trend of the natural increase observed in recent years.

Materials and methods

Data on birth rate, mortality rate and natural increase in Macedonia from the MaxStat database of the State Statistics Office of the Republic of North Macedonia, the World Health Organization (WHO) Health for All databases and the European Health

Information Gateway were used, as well as the database and publications of the Institute for Health Metrics and Evaluation in Washington (Institute for Health Metrics and Evaluation-IHME).

A literature review was performed, and a public health approach and descriptive analysis method were applied. The data are statistically processed and presented in tables and charts.

Results

Natality

The natality in Macedonia exhibits a decreasing trend over the course of the last decade. The number of live births in 2010 was 24,296, and in 2020, it was 19,031 live births. According to the data of the State Statistics Office in 2021, 18,790 children were born in Macedonia, of which 18,648 were live births and 142 were stillborn. The number of live births is 2.0% lower compared to the year before.[1]

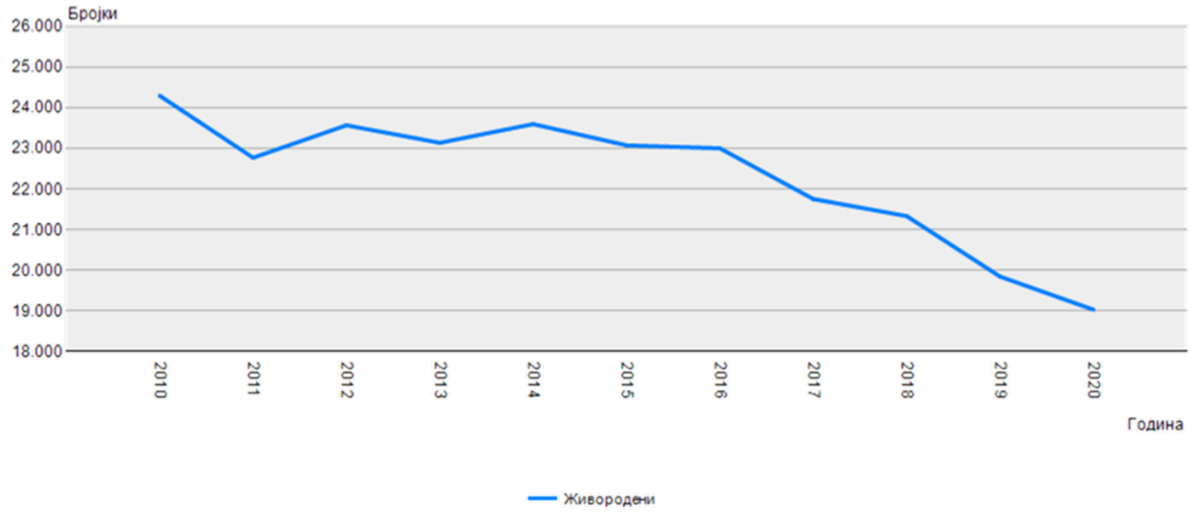
Looking at regions, the largest number of live births in 2021 were in the Skopje region, 7256, followed by the Polog region with 2762 live births. The lowest percentage of live births, 1173, was in the eastern region. In the Skopje region, the highest number of live births were in the municipality of Chair, 873, and the lowest in the municipality of Shuto Orizari, with 380 live births. For example, in 2005, the situation was different with a total of 22482 live births, of which 7282 were in the Skopje region, 3602 in the Polog region, 2213 in the southwest, and 1619 in the easter region.[1]

The birth rate in Macedonia in 2021 was the highest in the Skopje region, and the lowest in the eastern region (table 1)[1]

Table 1: Birth rate, mortality rate and natural increase in Macedonia in 2021, by region

2021	Birth rate	Mortality rate	Natural increase
Macedonia	10.2	15.5	-5.4
Vardar region	9.1	17.0	-8.0
Eastern region	7.8	17.9	-10.1
Southwestern region	9.4	14.8	-5.4
Southeastern region	8.6	16.7	-8.1
Pelagonian region	8.3	17.2	-8.9
Polog region	11.0	14.2	-3.2
Northeastern region	9.9	16.0	-6.1
Skopje region	12.0	14.4	-2.4

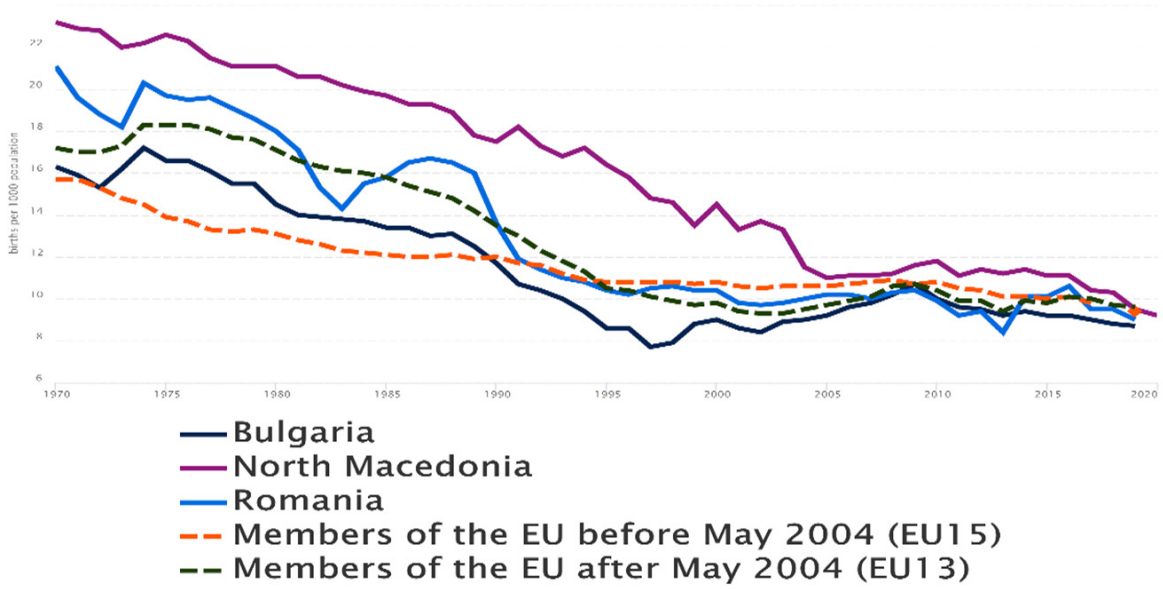
Source: State Statistics Office of the Republic of North Macedonia, 2022.[1]



Source: State Statistics Office of the Republic of North Macedonia, 2022[1]

Graph1: Number of live births (total number) in Macedonia in the period 2010 to **2020.**

We can see on graph 1 the natality linear movement in Macedonia in the period between 2010 to 2020 according to the data from the State Statistics Office. The trend line is in a slight decline, with the declining trend line more noticeable since 2018.[1]

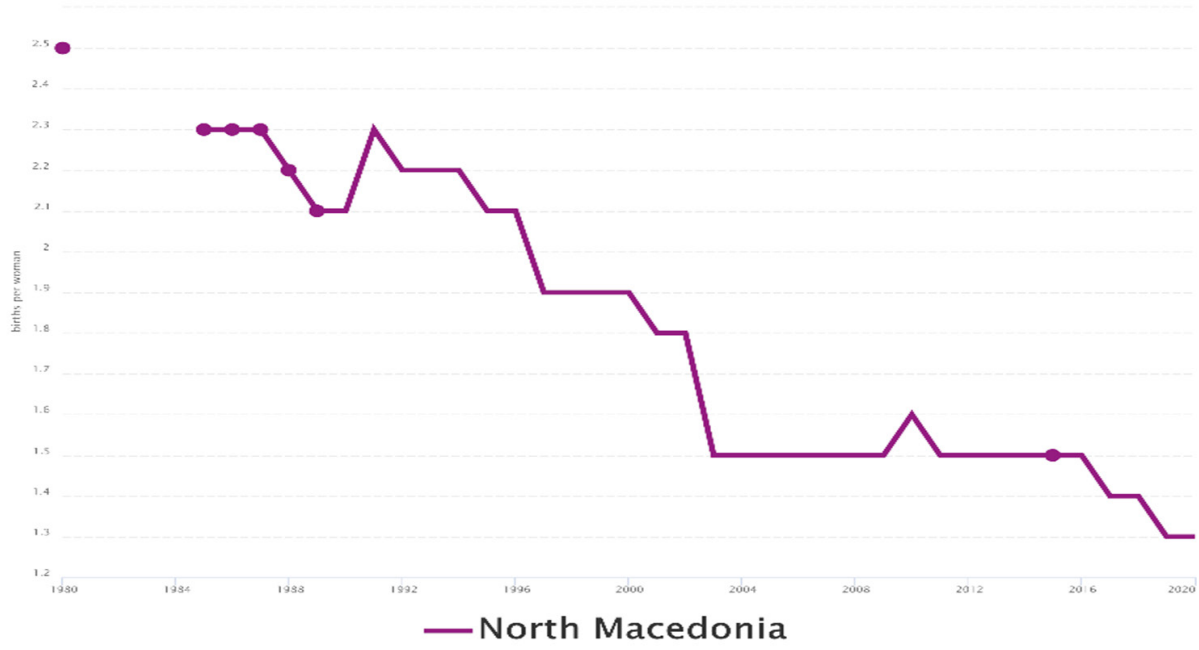


Source: European health information gateway,2022[4]

Graph 2: Birth rate, births per 1000 inhabitants in Macedonia, Bulgaria, Romania and the average of the member states of the European Union for the period between 1970 to 2020.

The rate of live births per 1000 inhabitants in Macedonia for 2020 stood at 9.2 and is in along the same lines as the member states of the European Union, where the rate stands at 9.6 (graph 2).[4]

-The fertility rate in Macedonia exhibits a constant negative trend and in 2020 it stood at 1.3 births per woman. (graph 3)[4]



Source: European health information gateway, 2022[4]

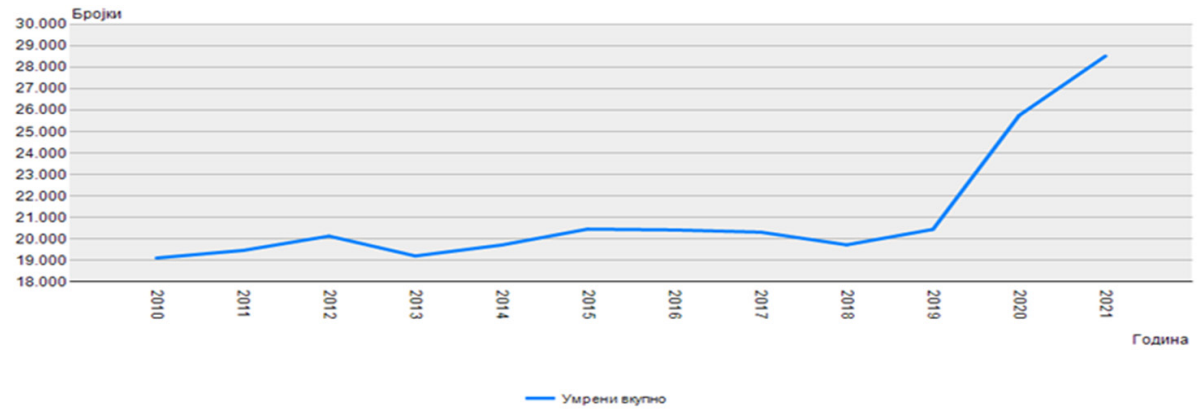
Graph 3: Graph 3 Fertility rate among women in Macedonia in the period between 1984 to 2020.

Mortality

In Macedonia, the mortality trend has been increasing in the last decade, reaching the highest point in 2020 due to the Covid-19 pandemic, when this number increased significantly. The number of deceased persons in 2010 was 19,113, and in 2020 that number reached 25 755 deceased persons. In 2021, the number of deceased persons was 10.7% higher than the year before and amounted to 28516 deceased persons. The average age of deceased men was 71.6 while the average age of decease women was 75.2 years. The highest number of deaths was in the Skopje region with 8715 deaths, while the lowest was in the Vardar region with 2 365 deaths.[1]

The mortality rate by region in Macedonia in 2021 stood the highest in the Eastern region, with the lowest in the Polog region (table number 1).[1]

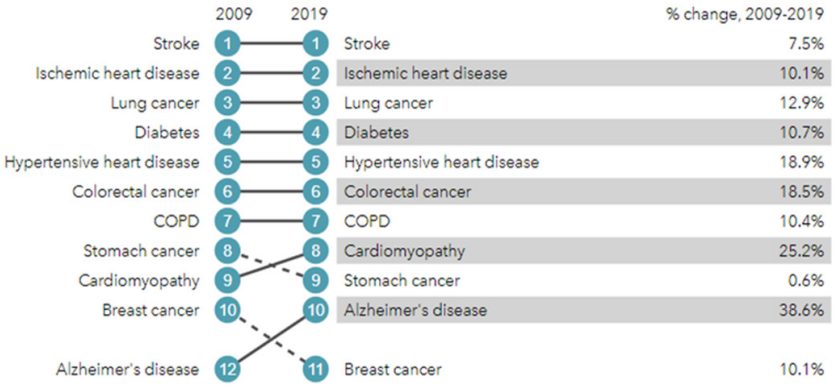
The trend between 2010 to 2019 shows a slight increase, while from 2019 onwards, the trend shows a sharp increase (graph 4).[1]



Source: State Statistics Office of the Republic of North Macedonia, 2022[1]

Graph 4: Number of deaths in Macedonia in the period between 2010 to 2021

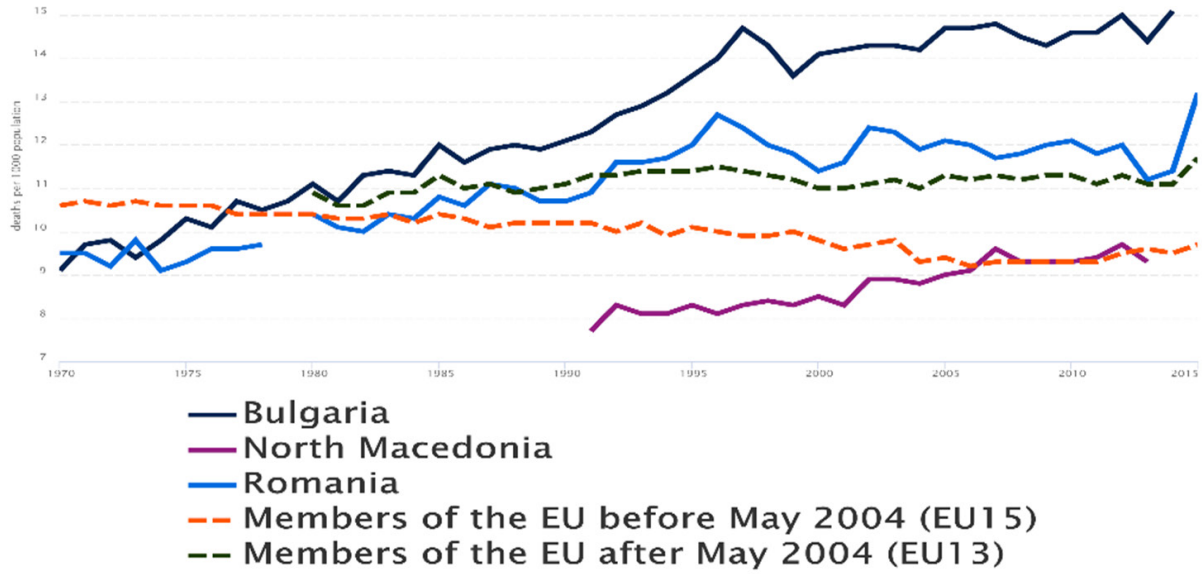
The leading causes of death in Macedonia in 2019 were stroke, ischemic heart disease and lung cancer, with their share remaining unchanged compared to 2009, showing a worsening trend. Diabetes and hypertensive heart disease were the next leading causes of death. Alzheimer's disease and breast cancer (graph 5) stood last as the causes of death)[5]



Source: IHME, 2019[5]

Graph 5: 10 leading causes of death in Macedonia in 2009 and in 2019

The death rate per 1000 inhabitants in Macedonia in 2015 was 9.3, compared to the members of the European Union where it was 11.7, and Bulgaria with 15.1 deaths per 1000 inhabitants (graph 6).[4]



Source: European health information gateway,2022[4]

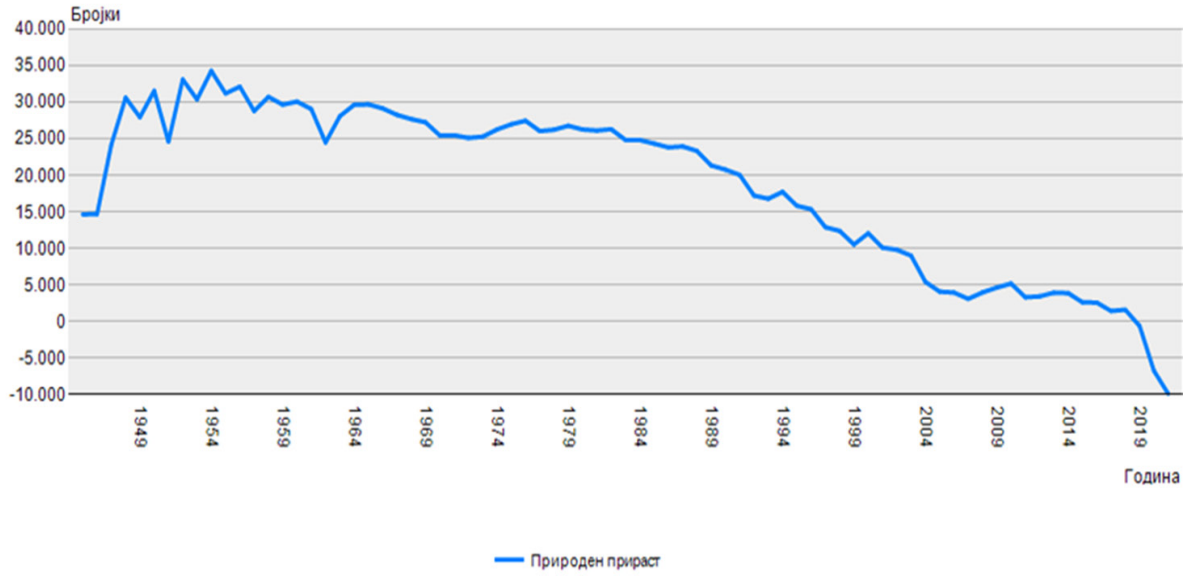
Graph 6: Mortality rate, deaths per 1000 inhabitants in Macedonia, Bulgaria, Romania and the average of the member states of the European Union, for the period between 1970 to 2015

Natural increase

The natural increase in Macedonia shows a negative trend. In 1949, the natural increase reached 27 917, while in 2021 it stood at -9 868. According to the data from the State Statistics Office in the second half of

2022, the natural increase was negative, amounting to -381, which shows the number of people by which the number of live births is lower than the number of deceased people (graph 6).[1]

The number of live births in the second quarter of 2022 compared to the same period of the previous year decreased by 6.5% and amounted to 4379 live births. The number of deceased persons in the first half of 2022 dropped by 33.4% compared to the same period of 2021, amounting to 4 760 deceased persons, of which 22 were infants.[1]



Source: State Statistics Office of the Republic of North Macedonia, 2022[1]
Graph 7: Trend of natural increase in Macedonia in the period 1949 to 2021

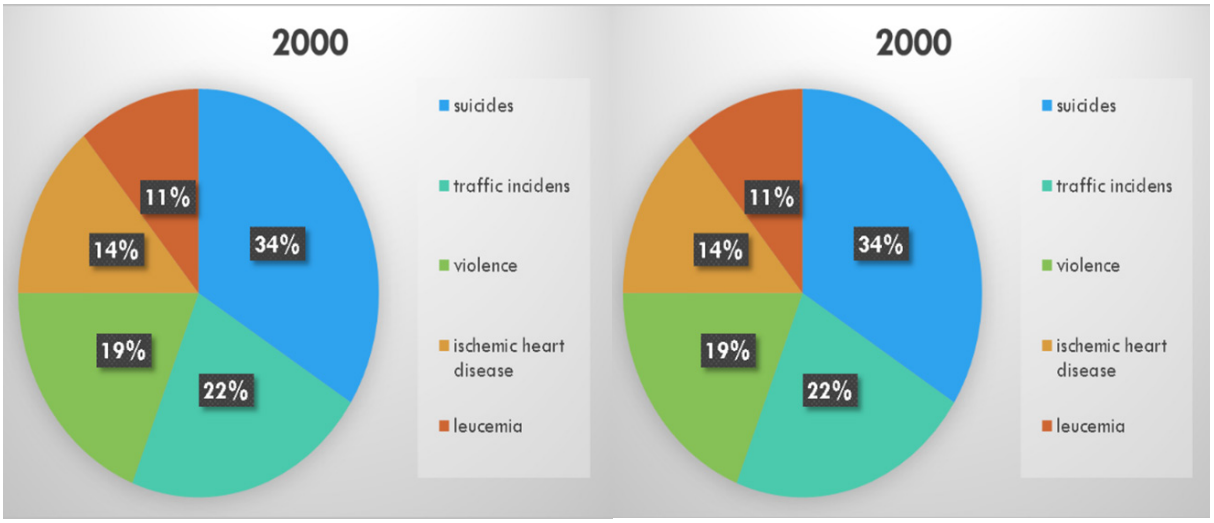
The rate of natural increase in Macedonia in 2021 is the highest in the Skopje region, and the lowest in the eastern region (table 1).[1]

Leading causes of death in Macedonia in the period between 2000 to 2020

Among young people aged 15 to 24 in Macedonia, traffic accidents and suicides were the leading cause of death with a share of the total mortality of 4.8% and 3.2% in 2000 and 2020 respectively.

Among the population aged 25-34 the leading cause of death was suicide in 2000, while in 2020, Covid-19 took the lead (chart 8).[6] In the age group from 35 to 54 the dominant cause of death in 2000 was ischemic heart disease with 42% of the total number of deaths, and in 2020 the dominant cause of death was Covid-19 with 51%.[6]

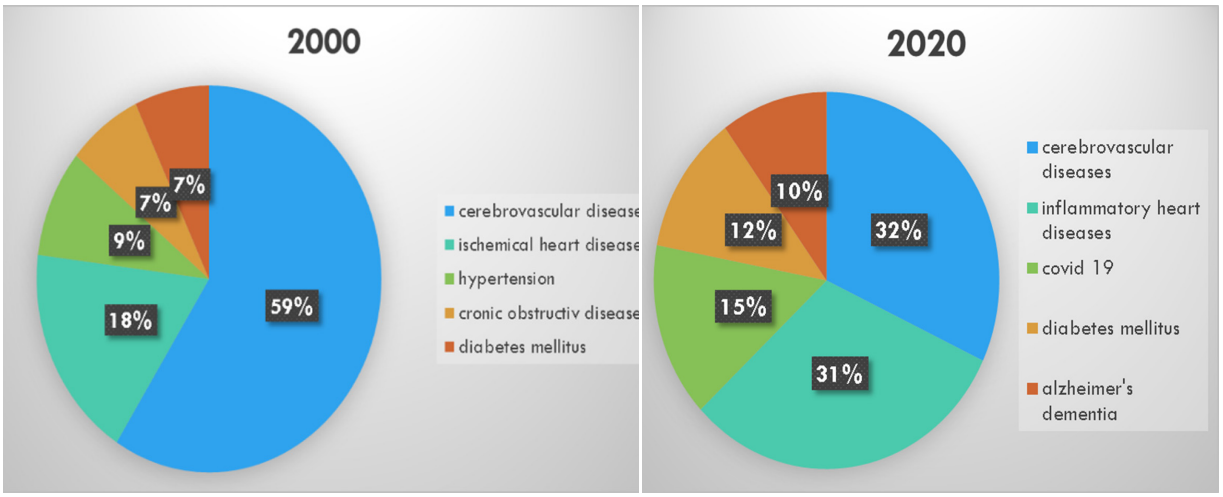
Similarly, in the age group from 55 to 74 years, Covid-19 was the leading cause of death in 2020 with a share of 15%, followed by cerebrovascular diseases with 14.1% of deaths and diabetes mellitus with 1.91%, while in 2000, the main causes were cerebrovascular diseases.[6]



Source: World Health Organisation, 2022[6]

Graph 8: Causes of death in the age group 25 to 34 years, in the period between 2000 to 2020 in Macedonia

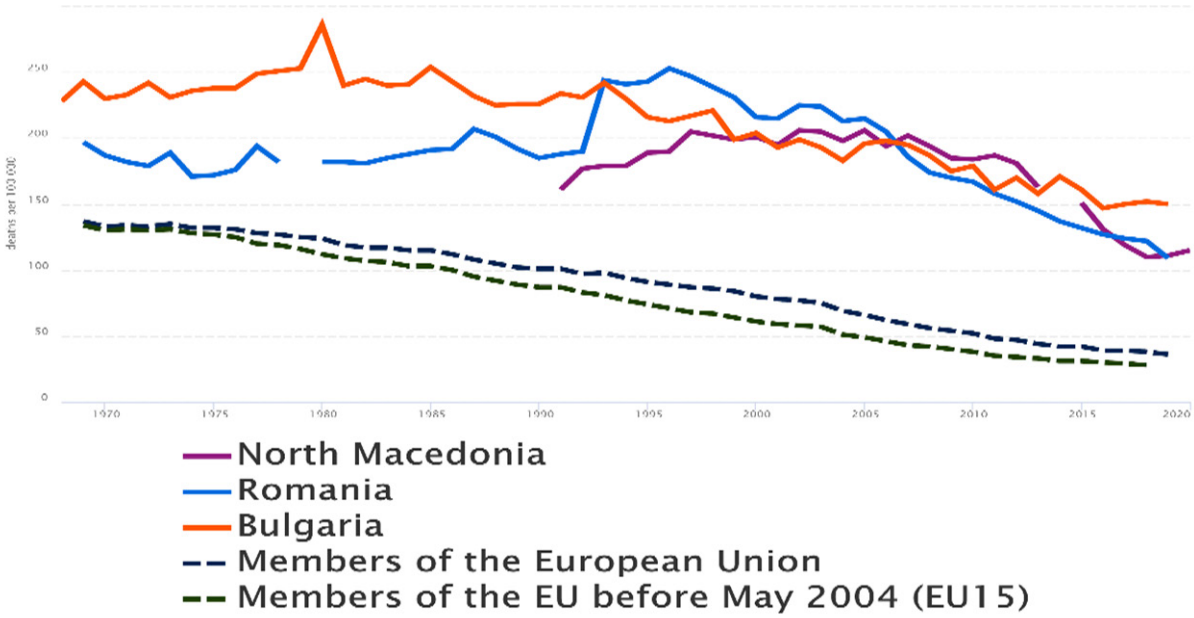
The most common causes of death among the age group over 75 in 2000 are cerebrovascular diseases with 59%, and in 2020, apart from cerebrovascular diseases, Covid -19 is also among the main causes of death, with a share of 31% of the total mortality (Graph 9).[6]



Source: World Health Organisation, 2022[6]

Graph 9: Causes of death in the age group over 75, between 2000 to 2020 in Macedonia

The death rate from cerebrovascular diseases per 100,000 inhabitants in Macedonia was 17.7 in 2020, which is much higher compared to the members of the European Union where the death rate is 13.3 (graph 10).[4]



Source: European health information gateway , 2022[4]

Graph 10: Trend of death rate per 100,000 inhabitants from cerebrovascular diseases in Macedonia, Bulgaria, Romania and the average of the member countries of the European Union in the period from 1970 to 2020

Discussion

Direct factors

The natality has been declining from 24 296 live births in 2010 to 19031 in 2020. Both globally, as well as in Macedonia, with the modernization of society and an increasing number of women in employment, unlike in the past, the number of children a woman gives birth to during her life is also decreasing. In 1950 the average number of children per woman was 5, while in 2020 the average was 2.5 children per woman. This is impacted by education, the economic development of the state, modernization and urbanization of society, the emancipation of women[7], s well as political freedom, which plays a role in the perceptions of the population regarding fertility.[8]

At the global level, according to the WHO, the top 10 causes of death have been selected, where the first place is taken by ischemic heart disease, second place is stroke, the third is chronic obstructive pulmonary disease, the 4th place is lower respiratory tract infections, the 5th place is neonatal conditions, 6 cancer of the trachea, bronchi and lungs, Alzheimer's disease is at the 7th place, followed by diarrheal diseases, and the last two places are taken by diabetes mellitus and kidney diseases.9

In developed countries, 55% of deaths or 55.4 million people died from the three most common groups of diseases, namely cardiovascular diseases (ischemic heart disease, stroke), respiratory diseases, chronic obstructive pulmonary disease, lower respiratory tract infections and neonatal conditions (asphyxia, birth trauma, neonatal sepsis and infections and complications at childbirth). Unlike developed countries, in countries with medium and low economic development, the first three causes of death are infectious diseases such as malaria, tuberculosis and HIV in-

fection.6,9 Diseases primarily of the cardiovascular and respiratory system, but also other infectious and non-infectious diseases have a major impact globally on high mortality in both developed and developing countries.[6]

Mortality rates among infants and children have significantly decreased both globally as well as in Macedonia, while the mortality rate among the elderly population is increasing. If we take into account the extended life span and the aging trend of the population, it is clear why the leading causes of mortality are chronic non-communicable diseases, and hence it can be seen that the age structure is a significant factor affecting mortality.[10]

The most important determinant of mortality is health care, as according to the literature, low quality of health services is the main driver of premature mortality from chronic non-communicable diseases and about 8.6 million deaths can be prevented by improving access and quality of healthcare.[11]

A detailed assessment of the national diseases and risk factors burden along the lines of strengthening health care and in particular, prevention, is the key to reducing the mortality of the population.

Indirect factors

Indirect factors also play a major role in the natural changein the population. The impact of social determinants on health can come from various aspects of life and environment, a consequence of some decisions made, government activities, or wars that can significantly change the demographic map of a country. Natural disasters (earthquakes, droughts, ice rinks, avalanches, floods, etc.) affect the natural population change.

The territory of Macedonia has such a geographical position that it is suitable for natural disasters, which can be directly or indirectly influenced by man. Throughout history, the most famous natural disasters on the territory of Macedonia are: the earthquake in Skopje in 1963 with 1100 victims and over 4000 injured, the earthquake in Valandovo in 1931 with 15-200 victims and hundreds of injured, the avalanche-landslide along the Radika river valley in 1956 with 52 casualties, torrential flood in Skopje 2016 with 23 casualties, landslide in Kavadarci in 1956 with 11 casualties, lightning strike in Berovo in 1996 with 9 casualties and around 50 injured, earthquake in Debar in 1967 with 6 casualties, torrential flood in Shipkovica in 2015 with 5 casualties, heat wave in July and August 2007, when dozens of people died either directly or indirectly as a result of it.[12]

Socioeconomic factors and political context

Wars, epidemics, crises, food production, technical breakdowns, accidents, health conditions, social conditions, poverty and hunger, material status, culture, ethics, ideological and psychological heritage, religious influences, territorial threats, and population policy affect the natural population change in Macedonia.

The poverty rate in Macedonia in 2020 was 23%, compared to 2019 when it was 17%, as a result of the Covid 19 crisis.[13]

The unemployment rate in Macedonia was 16.7% in 2020, and the number of unemployed was 159,623 people. The unemployment rate in 2019 was 17.3%.[4]

The main obstacles and problems in the provision of healthcare services in Macedonia are: poor availability of outpatient clinics and health facilities, women from rural areas do not have access to a gynecologist, a poor network of local health services, lack of appropriate valid health documentation for a large number of citizens and others.[14-16]

Biological or human factors

Physiological readiness, age, the desire to reproduce, infertility, hereditary traits, lactation and other biological factors influence the natural increase of the population.[17]

Government policies in some countries have a significant impact on population growth, such as the example of China where the government has banned the birth of a third child. Another significant factor is the emancipation of women, their position in society, education and the growing desire for a greater position in the working environment, which can lead to delayed birth.[17]

Urbanization on the other hand leads to an increase in the birth rate and a decrease in the death rate. People have better access to timely use of medical facilities in urban areas, which can reduce neonatal and infant mortality.[17.18]

Education is an important factor in population growth. Education is important for reducing the mortality rate, by educating people about the prevention of communicable and non-communicable diseases. An example is some diseases that in the past have killed millions of lives, but today they have been eradicated by properly educating people on how to protect and treat themselves. Spreading the literacy of mothers to protect themselves and their children has a particular impact, which reduces mortality and morbidity among pregnant women, nursing mothers, newborns and children.[18]

Among the important factors affecting mortality are the programs and activities undertaken in low and medium growth countries, such as support from developed countries for the delivery and availability of medicines, food and basic necessities of life for people, presentation of various immunization programs and campaigns, preservation of the environment, reduction of air pollution, tobacco control programs, presentation of the dangers of drugs and psychotropic substances.[17]

Through the improvement of economic growth, better education of the population, increase in per capita income, and improved health conditions, the life expectancy rate can be increased in both developed and developing countries. According to WHO, the average global life expectancy today is 73.4 years, while in 2000 it was 66.8 years.

Politics has an impact on the natural increase. Various political disputes and quarrels lead to wars and conflicts and thus population migration and increased mortality. The economic conditions in the countries further motivate people to move to countries with better conditions for a higher salary, the possibility of ad-

vancement, better health conditions, and better conditions for starting a business and its development.[17]

Conclusion

The study of the natural population change in Macedonia is an important topic in public health in order to plan health care and respond to the needs of the population. In Macedonia, there is a continuous downward trend in natality and an upward trend in mortality, which results in a negative natural increase. The most dominant factor that has influenced this situation in recent years has been the Covid-19 pandemic as a direct factor to an increase in mortality, but also as an indirect factor, by highlighting inequalities and poverty. This trend is expected to continue due to the aging of the population and the burden of chronic non-communicable diseases, injuries and violence as public health priorities that are not adequately addressed.

Hence the need for a detailed analysis of the factors that influence this negative trend of the natural population change, especially the indirect factors, as well as an appropriate national response.

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PUBLIC HEALTH

QUALITY OF LIFE IN PATIENTS WITH VITILIGO IN NORTH MACEDONIA

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Abstract

Vitiligo is an acquired depigmentation deficit with a high prevalence, ranging from 0.5% to 7.8%. The aim of the study was to measure the quality of life (QL) of patients with vitiligo, expressed through the Dermatological Quality of Life Index (DLQI). Materials and methods: This cross-sectional study was realized in a period of 1 year. Two questionnaires were used in the study. The first questionnaire contains data from the DLQI, designed for use in adults over 16 years of age, taken from the Cardiff University in the UK. The second questionnaire contains demographic and clinical characteristics of patients (age, gender, place of residence, marital status, education), activity, comorbid diseases and BMI, age at onset, site of onset of lesions, duration of disease, family history, type, activity, natural course, body mass index (BMI) and therapy. Results: Among 71 subjects included in the study, the total score of the DLQI ranged from 0 to 28 (from a maximum of 30 points), and the average was 11.70 ± 5.7. Female patients had greater QL impairment (total mean value of 8.03) than men (5.99); there was a statistically significant difference between both sexes (P = 0.019). The total score of QL in terms of symptoms related to the condition in the six domains strongly affected QL of 45.1% of patients. The QL was significantly worse in the studied group of 16-30 years (13.85 ± 5.3) compared to the population of 51-60 and over 60 years (6.75 ± 5.7, and 7.0 ± 2.3). As the age of patients advanced, the QL improved. Subjects with higher education had a higher score (14.41 ± 6.6; p=0.001). Conclusion: Female patients with vitiligo have impaired QL in comparison to male. With age, the QL in patients with vitiligo improves. Patients with a lower degree of education have a better QL.

ЈАВНО ЗДРАВЈЕ

КВАЛИТЕТ НА ЖИВОТ НА ПАЦИЕНТИ СО ВИТИЛИГО ВО СЕВЕРНА МАКЕДОНИЈА

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Извадок

Витилиго е стекнат дефицит на депигментација со висока преваленција, која се движи од 0,5% до 7,8%. Целта на студијата беше да се измери квалитетот на живот (КЖ) кај пациенти со витилиго, изразен преку Дерматолошкиот индекс на квалитет на животот (ДИКЖ). Материјали и методи: Оваа студија на пресек беше реализирана во временски интервал од 1 година. Во студијата беа користени два прашалника. Првиот прашалник содржи податоци од ДИКЖ, дизајниран за употреба кај возрасни лица, постари од 16 години, преземен од Универзитетот Кардиф во Велика Британија. Вториот прашалник содржи демографски и клинички карактеристики (возраст, пол, место на живеење, брачен статус, образование), активност, коморбидни заболувања и БМИ, возраст на почетокот, место на појава на лезии, времетраење на болеста, семејна историја, тип, активност, природен тек, БМИ и терапија. Резултати: Кај 71 испитаник вклучени во студијата, вкупниот скор за ДИКЖ се движеше во опсег од 0 до 28 (од максимални 30 поени), а просечно изнесуваше 11,7 ± 5,7. Женските пациенти имаа поголемо оштетување на КЖ (вкупна средна вредност од 8,03) од мажите (5,99); постои статистички значајна разлика помеѓу резултатите за двата пола (P = 0,019). Вкупниот скор за квалитетот на животот од аспект на симптомите поврзани со состојбата на кожата кај пациентите со витилиго, во шесте домени, силно го афектираа квалитет на животот на 45,1% од нив. Квалитетот на животот беше значајно полош кај испитуваната група од 16 до 30 години (13,85 ± 5,3) во споредба со популацијата од 51 до 60 и над 60 години (6,75 ± 5,7, и 7,0 ± 2,3) во поглед на дневните активности и слободни активности и тераписки третман. Со напредување на возраста на пациентите со витилиго, се подобрува квалитетот на животот. Испитаниците со повисоко образование имаа повисок ДИКЖ скор (14,41 ± 6,6; p = 0,001). Заклучок: Женските пациенти имаат полош КЖ во споредба со машките. Со возраста, КЖ кај пациенти со витилиго се подобрува. Пациентите со понизок степен на образование имаат подобар КЖ.

Introduction

Quality of life (QL) is defined by the WHO (World Health Organization) as the perception of individuals about their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns1.This definition reflects the view that quality of life is a multidimensional index that refers to a subjective evaluation that is embedded in a cultural, social and environmental context.[1]

Vitiligo is an acquired de-pigmentary disease characterized by white macules on the skin, mucous membranes and hair due to the selective destruction of melanocytes.[2]

According to the definition of Vitiligo European Working Group, vitiligo vulgaris is an acquired chronic pigmentation disorder characterized by white macules, often symmetrically distributed, which usually increase in size over time, corresponding to a significant loss of function of epidermal and sometimes hair follicle-melanocytes.[3] Following the classic morphology of vitiligo, the lesions are discrete, uniformly milky-white macules of round, oval, or irregular shape ranging in size from millimeters to many centimeters, surrounded by normal or hyperpigmented skin. The disease is asymptomatic, but in some cases itching or a burning sensation may occur. Although vitiligo does not cause direct physical impairment, it is commonly believed that it can produce an important psychosocial burden. Several authors report that patients with vitiligo suffer from poor body image, low self-esteem and that they experience a high level of disability from their skin disease.[3-6] Vitiligo patients feel distressed and stigmatized by their condition, especially in relation to social activities. It is also believed that exposing the body causes anxiety and embarrassment, and may have a negative effect on sexual relationships.

The aim of the study was to measure the quality of life (QL) of patients with vitiligo, expressed through the Dermatological Quality of Life Index (DLQI).

Materials and methods

This research was the first in North Macedonia that measured the quality of life inpatients with vitiligo. This cross-sectional study was conducted in a period of one year (2021) . Two questionnaires were used: the Dermatology Quality of Life Questionnaire from the Cardiff University, UK with consent obtained from Prof. Finlay *et al.*, translated in Macedonian language, and the second questionnaire which contained questions about demographic characteristics and disease activity.[3] All subjects/patients who met the selection criteria were included in the study. DLQI questionare includes 10 items about apatient's feelings and many aspects of the illness that occurred in the last 7 days. Questions include "vitiligo symptoms" (itching, pain, irritation), "feelings" (shame, anxiety and anger), "everyday activities" (shopping and activities in the home), "type of clothing", "social or leisure activities", "physical exercis-

es", "educational activities", "sexual activities", "interpersonal relations" (with husband/s, friends, relatives) and 'treatment opportunities'. Each item is scored on a scale from four points (3 = a lot, 2 = moderately, 1 = a little, 0 = not at all). The total score of DLQI was calculated by summing the score of each of the 10 questions assessed and interpreted: as no impairment of quality of life (0–1), minor damage (2–5), moderate damage (6–10), severe damage (11–20), or a serioussevere impairment (21–30). In the second questionnaire, the data was filled out by the researcher of the Department of dermatology in "Remedika" Private General Hospital after a clinical examination of the patient and includes data on age, sex, place of residence, education, marital status, Fitzpatrick skin type, comorbid diseases (hyperlipidemia, diabetes mellitus type 1, hyperthyroidism, hypothyroidism, pernicious anemia, alopecia areata, ophthalmic abnormalities), familial history of the disease, use of alcohol, cigarettes, BMI. Data related to vitiligo include age at onset, family history of vitiligo, therapeutic history (with or without therapy), type of vitiligo (non-segmental, segmental and unclassified), vitiligo activity (in years), the natural flow (stable, unstable and with regression) and percentage of occupation of body surface. The localization and type of the disease were diagnosed with standard physical examination and using Wood's light. The percentage of skin area involved was calculated using the rule of nine undertaken fromthe Vitiligo European Task Force (VETF).[4]

Statistical analysis

Data analysis was performed using the statistical programs Statistics 7.1 for Windows and SPSS Statistics 23.0. The quality of life in patients with vitiligo were analyzed with Dermatological Quality of Life Index, where by the internal consistency between the answers to the 10 questions was assessed by making Reliability Statistics - Cronbach's Alpha / Total score / Average score.

Results

A total of 71 patients with vitiligo were included in the study, of which 38 (53.5%) were male and 33 (46.5%) female patients. Demographic data and patient characteristics are presented in Table 1. Patients were aged 16 to 30 and 31 to 40 years, 27 (38%) and 23 (32.4%) patients, consequently. According to place of residence, majority of patients - 48 (67.6%) were from urban areas. Unmarried were 35 (49.3%) patients, the same number of patients were married, and one patient was a widow. Body mass index usually ranged from 25 to 29.9 kg/m^2, that is, most of the subjectswere overweight. Ten (12.7%) patients were obese, with values of the index higher than 30 kg/m^2. Forty patients (56.3%) declared themselves as active cigarette smokers. Among them, 6 patients (8.45 %) smoked more than 20 cigarettes per day. Subjects mostly consumed less than one glass of alcohol per week – 45 patients (63.4%).

Table 1. Characteristics of recruited patients

Patients' characteristics	n (%)
Gender	
Male	38 (53.5 %)
Female	33 (46.4 %)
Age/years	
16 – 30	27 (38 %)
31 – 40	23 (32.3 %)
41 – 50	11 (15.4 %)
51 – 60	4 (5.6 %)
> 60	6 (8.4 %)
Place of residence	
Village	23 (32.3 %)
Urban/city	48 (67.6 %)
Marital status	
Unmarried	35 (49.2 %)
Married	35 (49.2 %)
Widow	1 (1.4 %)
BMI kg/m^2	
18.6 – 24.9	28 (39.4 %)
25 –29.9	34 (47.8 %)
30 – 34.9	4 (5.6 %)
35 – 39.9	3 (4.2 %)
> 40	2 (2.8 %)
Smoking (cigarettes /daily)	
Never	31 (43.6 %)
1 – 5	13 (18.3 %)
6 – 10	12 (16.9 %)
11 – 20	9 (12.6 %)
> 20	6 (8.4 %)
Consuming alcohol	
consume less than one glass of alcohol per week	45 (63.38 %)
1 – 3 glass of alcohol	24 (33.80 %)
4 glass of alcohol	2 (2.82 %)

More than half of the subjects, 42 patients (59.1%), had a positive family history of vitiligo. Anamnestic data presented that the appearance of vitiligo was at the ages of 16 and 30, 21 patients (29.6%). In 19 patients (26.8%) the disease first appeared at the age between11 and 15 years. By the age of five, the disease was diagnosed in 11 patients (15.5%). Itching as a symptom of the disease appeared in 27 (38%)patients. Positive Kebner phenomenon, i.e., appearance of vitiligo in places of previous skin trauma was registered in 42 patients (59.15 %). In this study, patients had the most common 4 types of vitiligo: non-segmental, rofacial, mixed type, non-segmental focal, and segmental focal type, found in 15 patients (21.1%), 14 (19.7%), 13 (18.3%), and 10 (14.1%) patients, respectively. In more than half of the subjects, that is, in 41 (57.75%) patients the disease was stable, and did not spread over the last year.

The total score of DLQI ranged from 0 to 28 (out of a maximum of 30 points), and the average was11.70 ± 5.7 (Table 2).

Table 2. Mean DLQI scores of the sample according to different heading items and rates of answers

	mean ± SD	min–max	95 % CI
Symptoms and feelings	2.75 ± 1.4	0 – 6	1.2 – 1.7
Daily activities	2.51 ± 1.4	0 – 6	1.2 – 1.7
Leisure	2.13 ± 1.5	0 – 6	1.3 – 1.8
Work and school	1.14 ± 1.3	0 – 4	1.1 – 1.5
Personal relationship	2.04 ± 1.7	0 – 6	1.5 – 2.1
Treatment	1.15 ± 0.98	0 – 3	0.8 – 1.2
Total	11.70 ± 5.7	0 – 28	4.9 – 6.9

Table 3. DLQI score according to Hongbo *et al.*[5]

	n (%)
0–1 no effects on patients' lives	3 (4.22%)
2–5 small effects	6 (8.45%)
6–10 moderate	24 (33.8 %)
11–20 very large	32 (45.07 %)
21–30 extremely large	6 (8.45 %)

Discussion

Skin diseases affect different aspects of patients' lives and how successful treatment may improve patients' quality of life (QL). The number of publications on QL in dermatology has been constantly growing each year over the last 20 years.

The total DLQI in all subjects with vitiligo in our study was 11.70 ± 5.72. Among male subjects, the score was 10.34 + 5.7, and 13.27 + 5.4 in the group of female patients with vitiligo. The difference between both groups was 2.93, which was statistically significant. The significance was evident in performing daily activities. In the present study, the DLQI mean score was statistically higher in female patients than in male. The greater impairment of QL in females affected by vitiligo is under debate.

If we compare the research data published from 1996 to 2012, the mean scores of the DLQI for vitiligo across the world ranged from 1.82 to 15, and the overall mean was 8.2, indicating a moderate effect of the QL. In fact, some studies showed a higher DLQI mean score in female patients.[7-25]

Ongenae *et al*. noted that women were more embarrassed and self-conscious about the disease, more impaired in their daily routine and more influenced in their choice of clothing than men.[9,10,30,31] In our study, the age of the studied group of patients with vitiligo had a significant statistical impact on the quality of life. The quality of life was significantly worse in the study group of 16–30 years compared to the population of 51–60 and over 60 years in terms of symptoms, daily activities and leisure activities and treatment. With advancing age, the quality of life of vitiligo patients improved.

In the present study, the DLQI mean score was statistically higher in female patients than in male. The greater impairment of QL in females affected by vitiligo is under debate. In fact, some studies showed a higher DLQI mean score in female patients in a selected sample. In contrast, several authors pointed out the same impairment of QL between sexes. The mean scores of the DLQI across the world ranged from 1.82 to 15, and the overall mean was 8.2, indicating a moderate effect of the QL.

Identical results to ours were presented in the study by Budania *et al*., with an average score of 11.52, as well as in the study by Sahni *et al*., with an average score of 11.42, and Parsad with an average score of 10.70.[26-29]

Compared to other dermatological diseases, the QL in patients with vitiligo in our study was the same as in patients with psoriasis. In the literature, patients with psoriasis had more impaired disease-related quality of life than vitiligo and alopecia areata patients.[31-33] In a study performed by Ongenae *et al*., patients with vitiligo were compared to psoriasis patients. They found a mean DLQI score of vitiligo that was lower than the score obtained for psoriasis.

The QL in patients with vitiligo was significantly worse compared to melasma and significantly better compared to psoriasis.[33]

Conclusion

This research was the first in North Macedonia that measured the quality of life in patients with vitiligo. The

goal was to detect patients who were at risk of poor quality of life and to identify the variables that could predict this QL impairment. Also, this study aimed to provide an additional and significant boost in the development and improvement of quality standards in the support of vitiligo patients.

Patients in our study showed a moderate limitation of QL, comparable to that of other chronic skin diseases. Limitations of this study include a small study sample, as well as possible selection bias as participating patients were recruited from the Dermatology center in the "Remedika"General Hospital, Skopje N. Macedonia.

Further multi-centric studies are needed to validate the results. Females were shown to be more affected by vitiligo in all dimensions of the scale.

It should be emphasized that efforts of the management should focus on psychosocial and economic factors, especially in females, in addition to therapeutic efforts and hence better QL and treatment outcomes.

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PUBLIC HEALTH

ASSESING THE QUALITY OF LIFE IN INDIVIDUALS WITH MULTIPLE SCLEROSIS

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Abstract

Multiple sclerosis (MS) is linked with a wide range of physical, psychological, and societal challenges that significantly impact the quality of life (QoL) of those affected by the disease. This comprehensive study delved into the multifaceted aspects of MS, aiming to unravel the intricate relationships between disability, self-efficacy, acceptance of illness, and various dimensions of QoL. Material and methods: The study, encompassing 778 participants from diverse backgrounds, highlighted the nuanced experiences of individuals with MS, emphasizing the importance of understanding the unique challenges faced by different age groups and disease subtypes. The findings revealed profound connections between MS-related symptoms and psychological well-being, underscoring the necessity for tailored interventions. Notably, self-efficacy and acceptance of illness emerged as pivotal factors influencing QoL, providing crucial insights for healthcare providers and policymakers. Furthermore, this study underscored the importance of a holistic approach to MS management, integrating biomedical and psychosocial perspectives. The study's outcomes offer valuable direction for future research endeavors, advocating for longitudinal studies to capture the dynamic nature of QoL challenges, exploring patient perspectives through qualitative methods, and investigating the impact of socioeconomic factors on QoL outcomes. Additionally, the potential of telemedicine and digital interventions in providing continuous support and evidence-based counseling for individuals with chronic conditions is highlighted. By addressing these critical areas, future research endeavors can contribute to a more compassionate and empowering framework, enhancing the lives of those affected by MS and their families.

ЈАВНО ЗДРАВЈЕ

ПРОЦЕНКА НА КВАЛИТЕТОТ НА ЖИВОТОТ КАЈ ЛИЦАТА СО МУЛТИПНА СКЛЕРОЗА

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Клучни зборови: мултипна склероза, рехабилитација, квалитет на живот, функционално нарушување, активности од секојдневниот живот.

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Извадок

Мултипната склероза (МС) претставува комплексна мрежа на физички, психолошки и општествени предизвици кои значително влијаат врз квалитетот на животот на оние погодени од болеста. Ова сеопфатно истражување навлегува во повеќеслојните аспекти на МС, со цел да ги разоткрие сложените односи помеѓу попреченоста, самоефикасноста, прифаќањето на болеста и различните димензии на квалитетот на животот. Студијата, која опфаќа 778 учесници од различно потекло, ги истакна нијансираните искуства на лицата со МС, нагласувајќи ја важноста од разбирање на уникатните предизвици со кои се соочуваат различни возрасни групи и подтипови на болести. Наодите откриja длабоки врски помеѓу симптомите поврзани со МС и психолошката благосостојба, нагласувајќи ја потребата за приспособени интервенции, како и поврзаност на квалитетот на животот со полот и видот на МС. Имено, само-ефикасноста и прифаќањето на болеста се појавија како клучни фактори кои влијаат врз квалитетот на животот, обезбедувајќи клучни сознанија за здравствените професионалци. Ова истражување ја нагласува важноста на холистичкиот пристап кон менаџирањето на МС, интегрирајќи ги биомедицинските и психосоцијалните перспективи. Резултатите од истражувањето нудат вредни насоки за идните истражувачки напори, застапувајќи за лонгитудинални студии за да се долови динамичната природа на предизвиците на квалитетот на животот, истражување на перспективите на пациентите преку квалитативни методи и истражување на влијанието на социо-економските фактори врз резултатите од квалитетот на животот. Се истакнува потенцијалот на телемедицината и дигиталните интервенции за обезбедување континуирана поддршка и советување засновано на докази за лица со хронични состојби.

Introduction

MS is one of the most mysterious and disabling autoimmune diseases of the central nervous system affecting millions of people globally. This disease presents complex pathophysiological mysteries including immune system dysregulation that leads to demyelination and axonal damages resulting into diverse signs and symptoms such as muscle weakness and sensory disturbances, cognitive deficiencies and clinical manifestations, however, lies a profound and often overlooked aspect of the disease: the quality of Life (QoL).[1]

Quality of life (QoL) refers to the complete health of an individual as it extends beyond physical health incorporating mental health, social connections, and satisfaction with life. Every day is a challenge for people with MS whether apparent or not. Some visible problems include difficulties in movement and walking as well as chronic pains and exhaustion that greatly affect patients' daily functioning. However, some of the hidden challenges are more powerful and pose serious problems. They include psychological traumas of living with sickness, uncertainty regarding future disease evolution, and the sense of alienation associated with disability.[2]

Apart from restricting capacity for daily activities, these physical disabilities manifest themselves in impaired mobility and dexterity resulting into loss of independence and freedom. Impairment of cognitive skills such as minor memory lapses up to severe executive dysfunctions may lead to patients' reduced confidence and hinder their interaction with others. Moreover, such emotional disorders as depression and anxiety, observed in MS patients, produce chronic turmoil that has far-reaching effects on an individual's life including her/his interpersonal relations and overall sense of wellbeing.[3]

The inner battles are not the only determinants of quality of life in MS patients; moreover, society plays a critical part in what constitutes normality. The problems endured by people with MS usually become aggravated when coupled with stigmatization, inaccessibility of support systems and poor knowledge of the condition. Thus, the need arises for a sensitive analysis of the quality of life of persons with multiple sclerosis.[4]

This study aimed to obtain a thorough knowledge of the determinants of QoL in MS by meticulously analyzing the complex causal relationship among disease-specific factors, mental health, societal support, and the availability to medical care. The aim of this study was not only to bring to light problems encountered. In addition, it attempted to find ways that can be used in helping and providing support for MS patients. It will help in formulating an appropriate care strategy by knowing the particular areas in which people's lives are adversely affected. Furthermore, increasing awareness on the unseen disabilities that come

with MS could help create an understanding nation, which is sympathetic enough to help people living with this unrelenting illness.[5]

It is believed that multiple sclerosis involves an interaction between genetic factors and environmental factors, resulting in an immune inflammatory response within the central nervous system. Although consistent immunological abnormalities have been reported, not all components of the immune response in tissue damage and the extent to which these changes are a cause or consequence of myelin are yet to be fully understood. There is strong evidence for the genetic component of multiple sclerosis, while the influence of the environment is conditioned by variations in the incidence and prevalence of the disease across geographic regions. [6,7]

Currently, there is no cure for multiple sclerosis, but there is a wide range of treatment options that improve long-term outcomes for patients. Without treatment, the condition of patients gradually worsens over time. The goal of therapy in multiple sclerosis is to reduce relapses and improve and maintain functionality throughout a patient's life.[8]

Although neurological rehabilitation does not improve the underlying damage that continues to progress, it has a positive impact on many symptoms, disability, and many aspects of QoL. The neurological rehabilitation process should be continuous throughout the entire evolution of the disease, carried out in specialized centers, as well as in the community.

The aim of this study was to provide invaluable contributions to the medical profession in the development of better specificity and individualization for improving the quality of life of multiple sclerosis patients. The main goal of our study was to identify the gender-specific and subtype-specific variations in QoL of MS patients in order to create more precise interventions for promoting better health and QoL.

Materials and methods

Instrument and procedures

Expanded Disability Status Scale (EDSS) - Evaluation of neurological impairment in disabled multiple sclerosis subjects. This scale quantifies impairments in eight functional systems: Pathway: Pyramidal pathways - cortical tracts of cerebral motor cortex associated with large pyramidal neurons; cortico-spinal pathway - projection of the motor cortex into the cerebral column as T5-L2 - anterior horn cells. The segment of EDSS scale related to motor function was used in this study. Scores for the scale vary between 0 and 10, where score of 0 indicates a normal neurological examination, and score of 10 indicates death.

MSQOL-SF and MSQOL-29. - MSQOL survey was used to measure the standard of living of the study group. This is a multi-faceted instrument addressing general as well as specific issues regarding people with MS. This includes 18 items in

the generic dimension and touches on issues affecting people with MS involving their cognitive function, daily living, and social interactions among others. The MSQOL instrument encompasses twelve subscales that explore areas such as physical aspect, physical limitations, emotional health, pain, fatigue, social relations, cognitive and general health.

Patients were given separate sections of the scale for motor activity and handicap. Participants were informed about the general component of the MSQOL questionnaire plus different subscales. The survey was done respecting participant's feeling, comfort and anonymity. Respondents were asked to give their responses whenever they were willing to, under no pressure. We made our detailed analysis of their neurological status and quality of life based on the responses received.

This study was conducted worldwide by using an internet questionnaire, necessitated by the COVID-19 pandemic, which limited traditional data collection methods. Respondents from diverse continents, including Europe, Asia, and Africa (with a smaller representation), actively participated, with the majority of respondents from North America, specifically the United States and Canada.

Table 1. Age of participants

Age	*Participants*	%
10 - 20 years	**74**	**9**
20 - 30 years	**230**	**30**
30 - 40 years	**270**	**35**
40 - 50 years	**151**	**19**
50 - 60 years	**43**	**5**
60 - 70 years	**7**	**1**
70 - 80 years	***1***	***1***

Results

In our study, 778 respondents provided data on the age of onset of multiple sclerosis. The youngest participant was 10 years old, while the oldest was 80 years. On average, MS onset occurred at 33 years (SD = 10.84). The majority of respondents

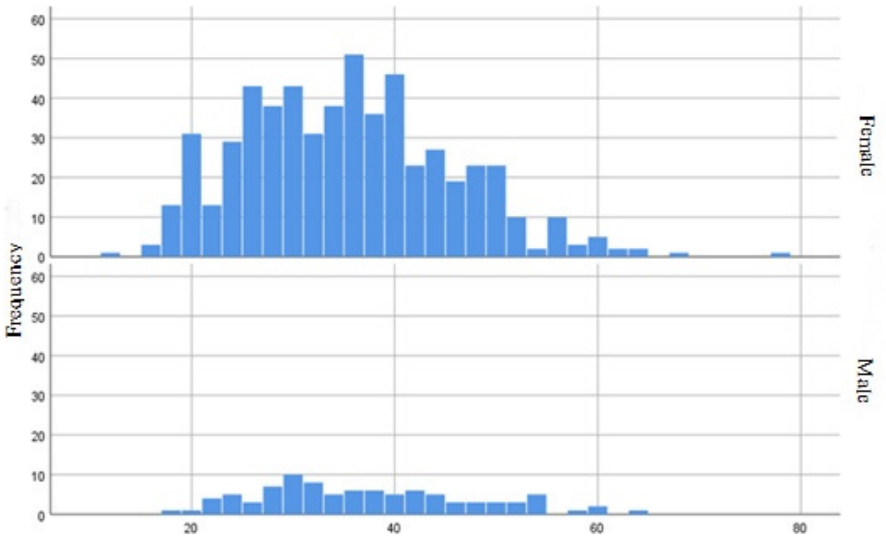

Fig. 1. Age of diagnosis of multiple sclerosis in men and women.

were aged between 30 and 40 years.

Figure 2 presents the correlation of the age of participants with the time of diagnosis of multiple sclerosis in men and women included in the study. The most common age of onset of multiple sclerosis was between 20 and 50 years among participants at the international level, while fewer participants were affected by the disease at around 70 years of age. In men, the mean age of developing multiple sclerosis was 36.73 years, while in women it was 34.84 years, with a standard deviation about 10 years for both genders.

Table 2. EDSS scale for the level of disability in participants.

No.	*Level of disability*	*f*	*%*
0.0	Normal neurological examination, without disability in any functional system, ambulatory patient without assistance from another person.	72	*10*
1,0	No disability, minimal signs of impairment in one functional system.	77	*10*
1,5	Without disability, minimal signs of impairment in more than one functional system.	68	*9*
2,0	Minimal disability in one functional system.	24	*3*
2,5	Mild disability in one functional system or minimal disability in two functional systems.	50	*6*
3,0	Moderate disability in one functional system or mild disability in three or four functional systems, without walking impairment.	22	*3*
3,5	Moderate disability in one functional system or more than one minimal disability in various functional systems, without walking impairment	31	*4*
4,0	Significant disability, independent for up to 12 hours a day. Able to walk up to 500 meters without assistance.	46	*6*
4,5	Significant disability, but independent for most of the day. Capable of working full-time, but with limitations in everyday activities or requiring minimal assistance from others. The person is able to walk without an assistive device for up to 300 meters.	39	*5*
5,0	Significant disability that impairs daily activities and ability to work. Able to walk without an assistive device for up to 200 meters.	50	*6*
5,5	Significant disability that excludes independent activities of daily living. The person is able to walk up to 100 meters without an assistive device	49	*6*

6,0	Significant disability that excludes independent activities of daily living. The person is able to walk up to 100 meters without an assistive device.	112	14
6,5	The person requires two mobility aids (cane, crutches, walker) to walk up to 20 meters without resting	38	5
7,0	The person is unable to walk more than 5 meters even with an assistive device. He/she is limited to a wheelchair but can operate it independently. The person spends 12 hours a day in a wheelchair.	31	4
7,5	The person is unable to take more than a few steps and is confined to a wheelchair, requiring assistance with transfers. He/she can independently operate the wheelchair but cannot operate a standard wheelchair (only motorized).	20	2
8,0	The person is bedridden and the wheelchair is operated with the assistance of another person. The person retains only a few self-care functions. Generally, there is effective use of the upper extremities.	24	3
8,5	The person is essentially confined to bed for most of the day. He/she has minimal use of his/her upper extremities and retain minimal independence in self-care.	9	1
9,0	The person is bedridden. He/she can communicate and eat.	8	1
9,5	The person is bedridden and entirely dependent on another person. He/she cannot effectively communicate or eat/swallow.	7	1
10,0	*Death due to multiple sclerosis during the study.*		

Table 2 illustrates the level of disability in 778 participants. Based on the results obtained, the largest number of participants had a disability level of 6.0, i.e. 112 participants, and the smallest number of participants had a disability level of 9.5, i.e., 7 participants, excluding the death case at level 10.0 (SD = 27.06).

The scale regarding disability level showed the mobility, everyday activities, use of assistive devices, and need for personal assistance and care for the participants. The scale itself with a level of 4.5 indicates that participants are completely independent and have a low level of disability. This study included 429 participants up to level 4.5 of the scale, i.e., these participants had a higher level of independence with a percentage of 55%.

The scale from 5.0 to 10.0 indicates a significant level of disability of participants, who require the use of assistive devices, assistance in daily activities, or the need for a personal assistant or caregiver. A total of 349 participants or 45% in our study responded to be at this level. SD between these divisions was 40.

Table 3. QoL among survey participants

	f	%
Terrible	26	*3*
Very dissatisfied	185	*24*
Neither satisfied nor dissatisfied	214	*28*
Satisfied	306	*40*
Enthusiastically satisfied	*41*	*5*

Table number 3 provides a detailed analysis of the descriptive method for assessing the quality of life among participants with multiple sclerosis. According to the data obtained, the majority of participants reported being satisfied with their quality of life, which corresponded to the numerical representation of the quality of life (7.8), while a small percentage of participants reported feeling terrible about their quality of life (3%), which

corresponded to the numerical representation of the quality of life (1.2). The standard deviation of the population sample was 106.59944, and the variance was 11363.44.

Table 4. T-test for mean QoL score between men and women

QoL	*N*	*Mean*	*SD*	*Std. error mean*
Men	100	5,54	2,129	*213*
Women	*590*	*6,29*	*2,125*	*088*

A t-test was employed to assess whether the mean quality of life score differed between men and women. The results presented in Table 4 indicate a lower mean score for men, with a significance level of p = 0.001, suggesting a significant difference in overall quality of life between the two genders.

Table 5. Mean score of quality of life among participants depending on the type of multiple sclerosis.

QoL	*Sum of squares*	*df*	*Mean square*	*F*	*P*
Between 2 groups	172,477	2	86,239	19,904	*0,000*
With 2 groups	2842,306	656	4,333		
Total	*3014,783*	*658*			

We employed an ANOVA test to examine whether mean scores in participants with different types of multiple sclerosis were similar or varied. The results revealed significant differences among participant groups (p = 0.000). As illustrated in the box plot, individuals with relapsing-remitting multiple sclerosis and clinically isolated syndrome exhibited a higher quality of life scores in comparison to those with primary progressive and secondary progressive types of multiple sclerosis.

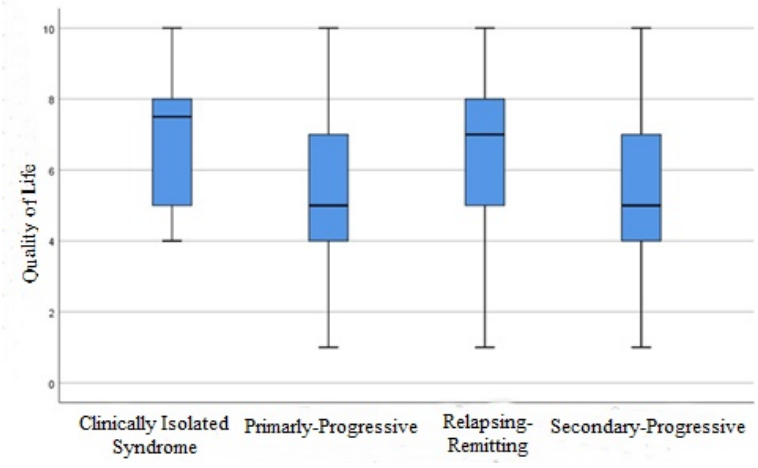

Fig. 2. Box plot for the mean score of quality of life among participants compared to the type of multiple sclerosis.

Discussion

MS is an intricate neurological disease which presents itself in varied forms, manifesting by several facets of problems and symptoms affecting different people in diverse ways. This study included a total of 778 participants, all representing different stories of lives with MS. This paper acknowledges the inherent variation in participants such as that they could have varying degrees of their symptoms and may also give very diverse responses to some questions. Participants frequently experience discomfort or unease when talking about some symptoms as a result of the heterogeneous character of MS. This particularly refers to probing questions that are highly intimate and touchy regarding the routine daily activities and wellness. As such, participants responses show changes in different questions, which signifies the complex nature of their experiences.

The diverse responses given by participants is a sign of the complexities of living with multiple sclerosis. Some participants are willing to disclose their problems but others could find it difficult and reveal less information. We are aware of these nuances as researchers, and hence, our data consist of more than numbers, but a mix of respondents' physical and emotional wellbeing. When evaluating the results, respondents' disparities should be tackled cautiously and taking into account their feelings. The fact that some of these differences have been observed does not undermine the validity of our findings. Instead, it adds to the knowledge of how multiple sclerosis is experienced differently by different individuals.

Multiple sclerosis tends to have a greater impact on quality of life than on its duration, and the expected lifespan of patients only decreases slightly. However, the probability of death among multiple sclerosis patients is more than four times higher than that of the general population.[9]

One study investigated the relationship between disability status, as measured by the Expanded Disability Status Scale (EDSS), and health-related quality of life (HRQOL) in MS patients. Surveys were sent to 7305 MS patients, with 3157 participating. Patients were categorized into three groups based on disability status. Interestingly, the study found a non-linear relationship between disability status and HRQOL. Specifically, the differences in HRQOL between different disability groups were not consistently proportional to the increase in EDSS score, challenging the assumption of the EDSS being interval scaled. This suggests that absolute EDSS scores might not be the most suitable outcome variable in MS studies.[10]

In one systematic review, a comprehensive analysis of clinical, sociodemographic, and psychosocial factors affecting QoL in adults with multiple sclerosis was undertaken. The study encompassed various risk factors such as disability, fatigue, depression, cognitive impairment, and unemployment, while identifying protective factors such as higher self-esteem, self-efficacy, resilience, and social support. Additionally, the review explored a range of psychological interventions including mindfulness, cognitive behavioral therapy, self-help groups, and self-management, all of which exhibited

positive effects on different aspects of QoL.[11]

In one research, the aim was to assess the level of adaptation to multiple sclerosis and health-related quality of life (HRQoL) in 137 patients. Various factors such as motor impairment, neurological disability, adaptation to illness, and HRQoL were analyzed. Correlations were discovered between motor impairment, neurological disability, adaptation to illness, and HRQoL. Lower-limb disability, fatigue, and mood disorders showed strong correlations with adaptation. Additionally, all symptoms, including lower-limb disability, fatigue, other MS-related problems, and mood disorders, were found to impact HRQoL significantly.

Comparatively, our study outcomes are in agreement with the findings presented in the previous research, emphasizing the significant impact of factors like lower-limb disability, fatigue, and mood disorders on adaptation to MS and HRQoL. In both studies, the importance of these specific symptoms on the overall well-being of individuals with MS has been highlighted. Additionally, while our study explored differences in HRQoL among different types of MS, the previously mentioned study delved into the relationships between adaptation, disability, and HRQoL, enriching the collective understanding of MS-related challenges and their effects on patients' lives.[12]

The combined insights from both studies emphasize the multidimensional nature of MS and showed the importance of tailored interventions that address specific symptoms, adaptation challenges, and varying types of MS, ultimately contributing to a comprehensive approach to enhancing the overall quality of life of individuals living with this condition.

One study described the unique challenges faced by pediatric-onset multiple sclerosis (POMS) patients, emphasizing the importance of a comprehensive disease management to optimize the quality of life of these individuals. Our study focused on adults with MS, while the mentioned study concentrated on POMS cases, particularly during adolescence. The shared emphasis was on holistic management, including disease-modifying therapies, nutritional considerations, exercise, and behavioral interventions.[13]

Our study, examining adults with MS, is an addition to the POMS study by extending the understanding of QoL challenges across different age groups affected by multiple sclerosis. While the focus in the POMS study was on younger patients, our study provided valuable insights into the experiences and QoL concerns of adults. By integrating these perspectives, a comprehensive understanding of the lifelong impact of MS on QoL emerges.

Considering the age factor in our participants, ranging across various stages of adulthood, the integration of findings illuminates the diverse experiences and challenges faced by individuals at different life stages. This comprehensive perspective enriches the understanding of QoL issues in the broader context of multiple sclerosis, guiding the development of tailored interventions and support systems that can help the unique needs of individuals across different age groups and disease onset stages.

Conclusion

Overall, this study has shed light on some crucial issues that determine the quality of life of people suffering from multiple sclerosis. We have found strong relationships of disability, fatigue, self-efficacy, as well of acceptance of illness with some aspects of the QoL. Findings have demonstrated interrelationships between biomedical and psychological factors, highlighting the necessity for an integrated approach to management of MS.

It is important that health care providers and policy makers understand how these factors affect QoL so as to develop tailored interventions for addressing multiple problems that MS patients face. Thus, by understanding that self-efficacy and acceptance of illness are crucial factors in boosting psychological well-being, interventions can fit the needs of people with MS, leading to a better quality of life.

Building on the insights gained from this study, future research in the field of MS should explore nuanced areas to further enhance our understanding and refine interventions:

- Longitudinal studies: Carry out longitudinal studies in order to monitor changes in the QoL and its key predictor factors through time, presenting a more complete picture of fluctuating nature of challenges associated with multiple sclerosis.
- Interventional research: Evaluation of the efficacy of tailored interventions like cognitive-behavioral therapy, mindfulness programs and peer support networks in enhancing self-efficacy, acceptance and overall QoL of individuals with multiple sclerosis.
- Incorporating patient perspectives: Employ exploratory/qualitative methods like interviewing and focus groups to understand the experiences of people living with MS.
- Exploring socioeconomic factors: Investigating how socio-economic factors such as access to healthcare, job opportunities, and social relations affect the QoL of people with MS will provide a broader perspective for interventions approach.
- Telemedicine and digital interventions: Investigate the effectiveness of telemedicine programs and digital health solutions offering continuous support, self-management of symptoms, and evidence based counseling or psychological treatment of chronic conditions.

Thus, the potential areas for future research may extend in order to provide better help to those suffering from MS so that we achieve a more open, encouraging and inspiring framework that supports such persons and their families.

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PUBLIC HEALTH

EFFECTIVENESS OF AN ONLINE PARENTING PROGRAM FOR CHILDHOOD ANXIETY IN NORTH MACEDONIA

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Abstract

Anxiety is considered a basic and adaptive emotion. However, anxiety problems are one of the most prevalent mental health problems, with multiple negative effects and a tendency to worsen with age. The high prevalence rates and their negative consequences accent the importance of developing timely and effective prevention strategies. The aim of the study was to evaluate the effectiveness of an online parenting program in reducing anxiety symptoms in young children in the Republic of North Macedonia. Materials and methods: A controlled randomized controlled study was conducted including parents of children aged 2-9 years old in North Macedonia. Eligible parents were assessed at baseline and post-intervention, using self-report questionnaires on sociodemographic characteristics and childhood anxiety (CBCL anxiety scale, CBCL-A; CBCL anxiety/depression scale, CBCL-AD). Parents were assigned to five group sessions of a parenting program, as the intervention group, or a structured group presentation, as a control group. Results: A total of 288 parents were included in the study. The findings showed significant reductions in childhood anxiety symptoms reported by parents in both the parenting program and the active control condition. However, between-group comparisons showed no significant differences between the two conditions. Conclusions: The study is the first to evaluate the effectiveness of an online group parenting program in reducing anxiety symptoms in young children in North Macedonia. The findings demonstrate that it is possible to achieve a significant change in child anxiety problems, using technology-assisted methods of intervention delivery in the country.

ЈАВНО ЗДРАВЈЕ

ЕФЕКТИВНОСТ НА ОНЛАЈН ПРОГРАМА ЗА РОДИТЕЛСТВО ВО НАМАЛУВАЊЕ НА АНКСИОЗНОСТ КАЈ ДЕЦА ВО СЕВЕРНА МАКЕДОНИЈА

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Извадок

Анксиозноста се смета за основна и адаптивна емоција. Но, анксиозните проблеми се едни од најзастапените ментално-здравствени проблеми, со негативно влијание врз функционирањето и со тенденција да се влошуваат со возраста. Високите стапки на застапеност и негативните последици ја истакнуваат потребата од развивање навремени и ефективни стратегии за превенција. Целта на студијата беше да ја процени ефективноста на онлајн програма за родителство во намалување на анксиозни симптоми кај мали деца во Република Северна Македонија. Материјали и методи: рандомизирана контролирана студија беше спроведена која вклучи родители на деца од 2-9-годишна возраст во Северна Македонија. Родителите беа проценети пред и по интервенцијата, користејќи прашалници за самопроценка во однос на социодемографските карактеристики и анксиозноста (CBCL скала за анксиозност, CBCL-A; CBCL скала за анксиозност/депресија, CBCL-AD) кај деца. Родителите беа рандомизирани во групна програма за родителство од пет сесии, како интервентна група, или еднократна презентација за родителство, како контролна група. Резултати: Вкупно 288 родители беа вклучени во студијата. Резултатите покажаа статистички значајни намалувања на анксиозните симптоми кај децата во програмата за родителство и во активната контролна група. Но, споредбата меѓу групите не покажа статистички значајни разлики. Заклучок: Студијата е прва која ја проценува ефективноста на онлајн програмата за родителство за намалување анксиозност кај мали деца во Северна Македонија. Резултатите ја демонстрираат можноста да се достигнат значајни подобрувања во анксиозни симптоми кај деца во државата, користејќи технолошко-поддржани методи на спроведување.

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Клучни зборови: родителство, анксиозност, деца, интернет, онлајн

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Introduction

Anxiety is considered a basic and adaptive emotion that is strongly influenced by the family environment[1]. Yet, anxiety problems are also known to emerge early in development, as early as in preschool-aged children[2]. They are considered one of the most prevalent mental health problems[3], with a tendency to worsen with age[1]. Child anxiety problems interfere with later academic, professional, family, and social functioning[4], and increase the risk for developing additional mental health problems[5]. Their high prevalence and negative consequences accent the importance of developing timely and effective prevention strategies[6]. However, there is a gap in the delivery of evidence-based prevention programs for mental health problems in children, which are especially scarce in low- and middle-income countries[7]. Evidence-based prevention programs for childhood anxiety in North Macedonia are currently unavailable.

A high priority is given to prevention research on childhood mental health problems, due to their high costs to society, families and individuals8. Research indicates that the family environment is essential in targeting child internalizing problems[9],[10]. Accordingly, parenting programs are shown as a viable prevention option through their impact on parenting practices and improving parent-child interactions, which may lead to changes in emotional and behavioral problems in children[6]. A recent meta-analysis, conducted by Yap *et al.*[11], examined the effects of parenting interventions for internalizing problems in children. Their results indicate that programs directed at parents are a beneficial prevention option with small yet significant effects. Overall small and significant effects have also been found in a similar earlier review of parent-child interventions for anxiety, indicating the importance of involving parents in preventive programs for children[12]. However, parenting programs can be a costly and culturally inappropriate prevention method in low-resource settings[13]. This calls for the development of accessible and affordable methods of delivery for parents in need[14].

The aim of the current study was to evaluate the effectiveness of an online parenting program in reducing anxiety in preschool and school-aged children in North Macedonia. It was hypothesized that compared to an active control, the parenting program would lead to significantly lower anxiety symptoms in children.

Materials and methods

Study design

A randomized controlled study was conducted in order to examine an online parenting program for parents of children aged 2-9 years old in North Macedonia. Parents were recruited through kindergartens, primary schools, leaflets, social media advertisements, and community referrals. Inclusion criteria required parents to be at least 18 years old, to live in the same household as the target child, and to report emotional and/or behavioral problems about their child. Once considered eligible through a telephone screening process, parents were sent a link to complete the baseline assessments,

which included self-report questionnaires on sociodemographic characteristics and childhood anxiety. Participants were randomly assigned to the parenting program or the active control condition, using an online software (www.randomizer.org). Upon the completion of the groups, parents were once again sent a link to complete the assessments.

Outcome measures

At baseline and posttreatment, parents were asked to share demographic and socioeconomic characteristics, including parent and child age and gender, number of children and adults living in the household, level of completed education, marital status, and employment status. Data was also collected on attendance rates.

Childhood anxiety was assessed using available subscales of the Child Behavior Checklist (CBCL[15,16]): the CBCL anxiety problems scale (CBCL-AP[17]) and the CBCL anxiety scale (CBCL-A[18]) for children aged 6-9, and the CBCL anxiety/depression scale (CBCL-AD1[5,16]) for children aged both 2-5 and 6-9. The scales are parent-rated with response options given on a 3-point range (0 = not true, 1= somewhat or sometimes true, 2 = very true or often true), where higher scores indicate higher severity of problems. The CBCL-AP assesses anxiety-specific problems in school-aged children, the CBCL-A assesses anxiety and functional somatic symptoms, while the CBCL-AD assesses anxiety with depressive symptoms. The scales are shown to discriminate between children with and without anxiety[19,20,21]. However, the internal consistency of the CBCL-AP scale was low (Cronbach's alpha= 0.50) for the current sample. Therefore, the CBCL-AP was not included in the analysis.

Parenting program

The parenting program represents an adapted version of an initiative by the World Health Organization, UNICEF, Clowns Without Borders, and several universities[22], aiming to reduce child maltreatment and improve child mental health wellbeing. The analyzed program consists of five group sessions delivered on a weekly basis, engaging parents in learning positive parenting skills and reinforcing positive behaviors in their children. It aims to build on the parent-child relationship, giving positive reinforcements, and learning positive discipline strategies. The content offers structured and facilitated activities, including illustrated comics presenting key positive parenting skills, group discussions on presented skills, homework assignments for practice, as well as simple stress management activities for parents. The covered skills include spending time with the child, praising and rewarding positive behaviors, setting rules and routines, as well as dealing with challenging behaviors. The program was administered using the internet platform Zoom.

Control condition

The parents allocated in the control group received a structured presentation, covering challenges of parenting and typical child development. The presentation was delivered in one 2-hour session, with contents including stages of development,

risk and protective factors, as well as some useful tips for parents to promote child well-being. An effort was made to avoid overlapping information that could make it similar to the parenting program. In order to avoid methodological limitations, research indicates that active or alternative control conditions may be more adequate, compared to waitlist conditions, in evaluating the effectiveness of technologically-assisted parenting interventions[11, 23].

Data analyses

Preliminary analyses were conducted to confirm the equivalence of the intervention and control groups at baseline on all sociodemographic variables using analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables. All data were analyzed using the principle of intention-to-treat, where all cases were included in the analysis. Pre/post assessment differences were analyzed using paired t-tests, comparing baseline and post-assessment scores for both participants in the parenting program and the active control condition. Differences between the parenting program and active control were examined using the univariate analysis of covariance (ANCOVA), with post-assessment scores as dependent variables and baseline data included as covariates.

Results

A total of 288 parents participated in the study, out of which 148 were allocated to the parenting program and 140 to the active control condition. The majority of participants in the total sample were women (95.1%), they were married and lived together with their partner (85.1%), had completed university (72.2%), and were employed (88.2%). The target children were mostly boys (59%) with an average age of 5.4 years (SD= 2.2). The preliminary analyses indicate that significantly more parents dropped out in the control condition at baseline, compared to the parenting program (χ^2 = 13.64, p= 0.000). Table 1 shows the sociodemographic characteristics of the sample in the parenting program and the active control.

Table 1. Sociodemographic characteristics of the sample in the parenting program and control condition

	Parenting program		Active control			
	M	*SD*	*M*	*SD*	*F*	*p*
Age						
Parent	36.82	4.76	37.16	4.82	0.36	0.548
Child	5.41	2.23	5.32	2.21	0.12	0.730
Household size						
Adults	2.40	0.89	2.38	0.87	0.04	0.846
Children	1.58	0.74	1.57	0.73	0.01	0.911

Childhood anxiety						
CBCL-AD (age 2-5)	50.39	10.09	50.32	11.27	0.00	0.972
CBCL-AD (age 6-9)	54.29	11.14	54.44	10.69	0.01	0.939
CBCL-A (age 6-9)	3.67	3.22	3.21	2.21	0.9	0.342
	N	*%*	*N*	*%*	*X2*	*p*
Parent gender						
Male	5	3.4	9	6.4	1.45	0.229
Female	143	96.6	131	93.6		
Child gender						
Male	87	58.8	83	59.3	0.01	0.931
Female	61	41.2	57	40.7		
Education level						
Completed elementary school	2	1.4				
Completed high school	5	3.4	5	3.6		
Some vocational school	1	0.7				
Completed vocational school	21	14.2	12	8.6	7.26	0.298
Some university			2	1.4		
Completed university	103	69.6	105	75.0		
Other	16	10.8	16	11.4		
Marital status						
Single	4	2.7	5	3.6		
In a relationship and living together	4	2.7	5	3.6		
In a relationship and not living together	1	0.7				
Married and living together	122	82.4	123	87.9	4.30	0.636
Married and not living together	1	0.7				
Separated or divorced	12	8.1				
Widowed	4	2.7				

In terms of effectiveness, the results show that there were significant reductions in childhood anxiety symptoms reported by parents in the parenting program, including on CBCL-AD for ages 2-5 (t= 3.92, p= 0.000), CBCL-AD for ages 6-9 (t= 5.99, p= 0.000), and CBCL-A for ages 6-9 (t= 3.15, p= 0.003). Moreover, significant reductions were also reported by parents in the active control group, including on CBCL-AD for ages 2-5 (t= 5.48, p= 0.000), CBCL-AD for ages 6-9 (t= 4.28, p= 0.000), and CBCL-A for ages 6-9 (t= 2.52, p= 0.016). However, the between-group comparisons showed no significant differences between the two conditions on all measures, including on CBCL-AD for ages 2-5 (F= 1.11, p= 0.293), CBCL-AD for ages 6-9 (F= 0.01, p= 0.919), and CBCL-A for ages 6-9 (F= 1.61, p= 0.208). Table 2 shows the within- and between-group differences from baseline to post-assessment.

Table 2. Within- and between-group comparisons of the parenting program and active control conditions

	Parenting program					Active control					
	Pre		Post			Pre		Post			
	M	*SD*	*M*	*SD*	*t*	*M*	*SD*	*M*	*SD*	*t*	*F*
CBCL-AD	50.54	10.21	45.67	8.53	3.92**	50.67	12.11	42.81	7.63	5.48**	1.11
CBCL-AD	54.11	11.125	47.58	9.46	5.99**	53.72	11.04	48.23	9.39	4.28**	0.01
CBCL-A	3.70	3.19	2.61	2.91	3.15*	3.00	2.22	2.13	1.89	2.52*	1.61

*p<0.01, **p<0.001

Discussion

The current study is the first to evaluate the effectiveness of an online parenting program in reducing anxiety symptoms in young children in North Macedonia. The results showed that both the parenting program and the active control group contributed to significantly lower anxiety symptoms in preschool and school-aged children at post-assessment. However, contrary to expectations, the parenting program did not show significantly greater reductions in anxiety compared to the active control condition.

Although the findings add to the evidence of the efficacy of online parenting programs for anxiety problems, the current study did not show the between-group differences as presented in similar studies. For example, Morgan *et al.*[24] conducted a randomized controlled trial with parents of children aged 3-6 years in evaluating the effectiveness of an internet-delivered group parenting program for preventing anxiety disorders. Their study showed that the intervention group had significantly greater improvements in childhood anxiety symptoms compared to a waitlist control group, with a small to moderate effect. A similar study testing the effectiveness of an internet-delivered positive parenting program, conducted by Sanders *et al.*[25] with parents of children aged 2-9 years with behavioral problems, showed significant improvements in the intervention group on emotional symptoms compared to an internet-use-as-usual control group.

Unlike the aforementioned studies, the present study incorporates an active control condition. As meta-analytic research shows that most studies on parenting interventions for child internalizing problems do not include an active control condition[11], it is recommended that more studies include an active control condition in their study designs to better demonstrate treatment effectiveness[11, 26]. An interesting finding of the current study was that significantly more parents dropped out from the control condition at baseline, which may reflect a greater interest and preference of parents for the parenting program.

The findings should also be interpreted with some limitations. Firstly, data was collected predominantly from mothers and with a very limited involvement of fathers. Secondly, since the majority of participants were employed and highly educated, parents of lower socioeconomic status were underrepresented in the

study. Thirdly, there may be cultural variations in the expression of problems and how measures were interpreted in the context of research, which could make it harder to detect differences27. Lastly, there may be confounding factors that contribute to improvements in both conditions, yet they were not assessed in the study. Nevertheless, the present study demonstrated that it was possible to achieve a significant change in child anxiety problems, using technology-assisted methods of intervention delivery in North Macedonia.

Conclusion

The present study evaluated the effectiveness of an online group parenting program in reducing anxiety symptoms in children aged 2-9 years in North Macedonia. The findings showed that parents in the intervention group reported significant improvements in child anxiety symptoms at post-assessment, yet no significant differences were found in the reduction of symptoms between the intervention and control group. Future research could explore additional variables that contribute to treatment effectiveness, include more fathers and parents of lower socioeconomic status as participants, as well as incorporate active control conditions in study designs.

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CLINICAL SCIENCE

INSULIN RESISTANCE AND METABOLIC SYNDROME IN HEPATITIS C VIRUS SERONEGATIVE HEROIN DEPENDENTS

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Abstract

Initial studies on impaired glucose-insulin homeostasis in heroin dependents have not defined the impact of concomitant hepatitis C infection (HCV), which has been strongly associated with the development of insulin resistance and metabolic syndrome (MS). The aim of our study was to evaluate the association of heroin dependence with glucose-insulin homeostasis disturbances and MS in heroin dependents with HCV seronegativity. Materials and methods: The study was prospective and cross-sectional, including 160 heroin dependents compared to a control group of 60 participants.MS was diagnosed using International Diabetes Federation criteria. The homeostatic model assessment for insulin resistance (HOMA-IR) and pancreatic β-cell function (HOMA-%B) were used for assessing insulin resistance and β-cell function of pancreas. Results: MS was detected in 9.32% of heroin addicts. Heroin dependents with MS compared to dependents without MS were older, had higher BMI, waist circumference and significantly higher systolic and diastolic blood pressure, increased triglycerides (F=8.233, df=2, p<0.001), apoB (F=8.154, df=2, p=0.001), and reduced HDL-C (F=25.926, df=2, p<0.001) and apoA-I (F=16.406, df=2, p<0.001), significantly increased inuslinemia (F=4.928, df=2, p<0.05), insulin resistance-HOMA-IR (F=4,928, df=2, p<0,05) and insignificantly increased pancreatic β-cell function (194.66 ±224.05) (F=2.461, df=2, p>0.05). Conclusions: Insulin resistance and MS, independent of HCV, was also registered in heroin dependence. Timely recognition will enable more successful treatment of comorbidities and illicit drug dependence.

КЛИНИЧКИ ИСТРАЖУВАЊА

ИНСУЛИНСКА РЕЗИСТЕНЦИЈА И МЕТАБОЛИЧЕН СИНДРОМ КАЈ ХЕПАТИТИС Ц ВИРУС СЕРОНЕГАТИВНИ ХЕРОИНСКИ ЗАВИСНИЦИ

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Клучни зборови: хероинска зависност, метаболичен синдром, инуслинска резистенција, HOMA-IR, HOMA-%B

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Извадок

Првичните студии за нарушена глукозно-инсулинска хомеостаза кај хероински зависници не го дефинираа и влијанието на хепатитис Ц инфекцијата (ХЦВ), која е силно поврзана со развој на инсулинска резистенција и метаболичен синдром (МС). Целта на нашата студија беше да ја процени поврзаноста на зависноста од хероин со нарушувањата во глукозно-инсулинската хомеостаза и МС кај хероински зависници кои се ХЦВ серонегативни. Материјали и методи: Студијата беше проспективна и пресечна, вклучувајќи 160 хероински зависници и контролна група од 60 испитаници. МС беше дијагностициран според критериумите на Меѓународната федерација за дијабетес. За проценка на инсулинската резистенција и функцијата на β-клетките на панкреасот беше користен хомеостатскиот модел за инсулинска резистенција (HOMA-IR) и функцијата на β-клетките на панкреасот (HOMA-%B). Резултати: МС беше детектиран кај 9,32% од хероинските зависници и тие во споредба со зависниците без МС беа постари, со повисок БМИ, обем на половината и значително повисок систолен и дијастолен крвен притисок, покачени триглицериди (F=8, 233, df=2, p<0,001), apoB (F=8,154, df=2, p=0,001), и намалени HDL-C (F=25,926, df=2, p<0,001) и apoA-I (F=16,406, df=2, p<0,001), со значително зголемена инсулинемија (F=4,928, df =2, p<0,05), инсулинска резистенција – HOMA-IR (F=4,928, df=2, p<0,05) и незначително зголемена функција на β-клетките на панкреасот (194,66 ±224,05) (F=2,461, df=2, p>0,05). Заклучок: Инсулинската резистенција и МС, независно од ХЦВ инфекција, се регистрира и кај хероинската зависност. Навременото препознавање ќе овозможи поуспешен третман на коморбидитетите и на болеста на зависноста од илегални дроги.

Introduction

The research interest in heroin dependence (HD) and associated complications in the last decades has been focused on studying the metabolic disturbances along with the infectious complications. During the '90s of the 20thcentury, the metabolic derangements in HD were investigated through the glucose metabolism which presented diabetic type 2 of glucose utilization, thus insulin resistance (IR) was speculated[1]; performing the hyperinsulinemic euglycemic glucose (HIEG) clamp technique as a golden standard for detecting IR was inapplicable for this population group due to their low compliance. Later, lipid metabolism disorders as hypertriglyceridemia[2] and low HDl-C3in HD were reported. At the beginning of the 21st century the presence of metabolic syndrome (MS) was shown in opioid dependents[4]. There were reports of cardiovascular complications[5], rheological disorders[6], reduced central arterial elasticity[7] in HD, and complications usually associated with MS in the general population. Among the most common comorbidities in HD was chronic hepatitis C virus infection, which was significantly associated with IR leading to type 2 diabetes mellitus[8] and MS[9]. So far, the reports that have analyzed the metabolic disturbances in HD have not assessed the influence of HCV infection on IR, lipid disorders and MS.

However, IR and MS have also been significantly associated with cognitive[10] and psychiatric disorders, especially depression11 as very common comorbidities in HD, which may have a particular impact on heroin dependents who report in detoxification or substitution programs and may affect their motivation for treatment.

The aim of our study was to evaluate the association of heroin dependence with glucose-insulin homeostasis disturbances and MS in heroin dependents with HCV seronegativity.

Materials and methods

The study had a prospective cross-sectional design and enrolled 160 opiate dependents and 60 healthy controls, all cigarette smokers, who previously signed written informed consent for participation in the study. The study was approved by the Ethics Committee of the Faculty of Medicine in Skopje. Blood samples and urine were taken at the moment of patients' admission to the University Clinic for Toxicology for introducing buprenorphine substitution therapy. Only patients who obeyed the recommendation for night and morning fasting before admission to the Clinic were analyzed. The inclusion criteria were: 1) heroin dependence lasting minimum one year (diagnosed according to International Classification of Diseases-Classification of Mental and Behavioral Disorders –Clinical Description and Diagnostic Guidelines, 11th revision (ICD 11), 2) reference BMI (18,5-24,9 mg/m2). Exclusion criteria were:1) use of psychostimulant substances in

the last 7 days, 2) history of obesity, 3) family history of diabetes, 4) history of hyperuricemia, 5) use of anti-inflammatory drugs in the last 7 days (NSAID, steroids, salicylates), 6) acute infectious or chronic disease, 7) use of antioxidants in the last 4 weeks, 8) HIV, hepatitis B or C infection seropositivity, 9) more than twofold increase in aminotransferase level over the upper reference range.

The following clinical and paraclinical investigations were performed: 1) anamnesis and physical examination, including unstandardized questionnaire adapted according to Addiction Severity Index, 5th edition, 2) standard biochemical and toxicological analysis, 3) C-peptide measurement (chemiluminescence immunoassay (immunology analyzer IMMULITE 2000), expressed in ng/ml), 4) Brinkman Index – a mathematical model for the estimation of cumulative index of smoking yield by multiplying number of smoked cigarettes per day and years of smoking12, 5) lipid status: triglycerides (TGl), high-density cholesterol (HDL-C), low density cholesterol (LDL-C) (enzymatic colorimetric test on an INTEGRA 400 autoanalyzer, Roche) and apolipoprotein A (ApoA-I) and apolipoprotein B (apoB) (immunoturbidimetric method, autoanalyzer INTEGRA 400, 6) IR was calculated using homeostatic models for assessment of IR (HOMA-IR) and beta cell function (HOMA-%B) by Mathews DR. This mathematical model uses values of fasting glycemia (mmol/l) and fasting insulinemia (μU/ml) to calculate IR (IR): HOMA-IR=(FPIxFPG) / 22.5 and beta cell function: HOMA-%B= (20 xFPI) x (FPG -3.5)13. Insulinemia was determined by MEIA (microparticle enzyme immunoassay) μU/ml, 7) Clinical criteria of International Diabetes Federation (IDF) for assessing MS were used14. Waist circumference was measured midway between rib arch and superior iliac spine on the same side at the end of normal expiration in a standing position. Waist circumference critical value for European males is ≥94 cm and for European females is ≥84 cm and plus the presence of any two of the following four factors: a) TGl ≥1.7 mmol/l or specific treatment for this lipid abnormality, b) HDL-C (m) ≤1.03 mmol/l and HDL-C (f) ≤ 1.29 mmol/l or specific treatment for this lipid abnormality, c) blood pressure ≥130/85 mmHg or treatment of previously diagnosed hypertension were measured by trained staff using standardized protocols), d) glycemia ≥5.6 mmol/l or previously diagnosed type 2 diabetes.

Statistical analysis

The results obtained are presented as mean±SD, frequencies and percentages. Continuous variables were compared using Student's t test and one-way analysis of variance (Tukey). Categorical variables were compared using the Chi-square test. The association of HOMA-IR with the independent variables (predictors) and the associated influence of the independent variables on HOMA-IR were assessed with the multiple regression analysis. P val-

ues less than 0.05 were considered to be statistically significant. Data were analyzed using the SPSS/Win program (version 25).

Results

The study enrolled 220 participants - 160 heroin dependents (HDs) and 60 controls. MS was registered in 9.32% of HD. Also, 17.1% of HDs who did not have MS defined by these criteria, had increased waist circumference. HDs were divided into two groups of subjects: subjects with MS according to the IDF criteria (HDM+) and subjects where the criteria for MS were not met (HDM-) (Table 1).

HDM+ compared to HDM- and the control group were significantly older (F=3.698, df=2, p<0.05), with higher BMI but in reference range (F=9.874,df=2, p<0.001), with larger mean waist circumference (F=22.548, df=2, p<0.001), higher mean systolic (F=7.923, df=2, p<0.001) and mean diastolic blood pressure (F=7.597, df=2, p=0.001), higher mean TGl (F=8.233, df=2, p<0.001). There were significantly lower mean HDL-C and insignificantly lower apoA-I in HDM+ compared to HDM-, but both groups showed significantly lower values of HDL-C(F=25.926, df=2, p<0.001) and apoA-I (F=16, 406, df=2, p<0.001) compared to the control group. However, there was significantly higher apoB (F=8.154, df=2, p=0.001) in HDM+ compared to HDM- group (Table 1).

Carbohydrate profile showed no significant difference in glycemia (F=1.497, df=2, p>0.005) as opposite to the higher values of insulin (F=4.667, df=2, p<0.05) and HOMA-IR (F=4.928, df=2, p<0.05) and in significantly higher HOMA-%B (F=2.461, df=2, p>0.05) and C-peptide (F=1.389, df=2, p>0.05) in HDM+ compared to HDM- group (Table 1).

There was no significant difference between HDM+ and HDM- group in heroin dependence duration (t=-0.140, DF=158, p>0.05), but HDM+ had higher Brinkman index (F=4.389, df=2, p<0.05). The difference in gender distribution between HDM+ and HDM- was insignificant ($\chi 2$=0.419, DF=1, p>0.05), but it was significant in comparison to controls ($\chi 2$=7.230, df=2, p<0.05). Males were predominant in HD group ($\chi 2$=11.267, df=1, p<0.05). Inhalation and intravenous route of drug administration showed a similar distribution in both HDM+ and HDM- groups ($\chi 2$=0.473, DF=1, p>0.05) (Table1).

Table 1. Mean values of the observed variables in heroin dependents with and without MS and controls

Variable	HDM (-) N =145	HDM(+) N= 15	Controls N=60
Age (years)	27.87± 5.78≠	31.27 ± 5.775*	29.89 ± 6.200
Gender (m/f)%	87.7% / 12.3%	93.3% / 6.7%	73.8% / 26.2% ^.≠
Route of drug administration (inh/I.V.)	49.3% / 50.7%	40% / 60%	/

BMI kg/m2	21.40 ± 1.721	23.20 ±2.10*	22.25 ±1.84^
Waist circumference (cm)	88.61±4.32	96.47 ±2.10	88.52 ±4.08
HDD (years)	5.04 ±4.26	5.20 ±4.52	/
Brinkman index	349.21 ±168.45	456.00± 239.21*	237.77±154.80
Systolic BP(mmHg)	102.19 ±11.49	115.67±17.51*	104.67±11.93^
Diastolic BP(mmHg)	67.50±7.59	76.33±11.25*	68.28± 8.16^
TGl (mmol/l)	1.51±1.012	2.32±0.79*	1.27± 0.34^
HDL-C (mmol/l)	1.15±0.26	0.98± 0.26*	1.46 ±0.36 ^≠
apoA-I(g/l)	1.26±0.20	1.18±0.23	1.60 ±0.28 ^≠
apoB(g/l)	0.63±0.21	0.87± 0.25*	0.81±0.17≠
Glucose (s) (mmol/l)	5.24±0.82	5.24± 0.94	5.0 ±0.66
Insulin (s)(μU/l)	8.98 ±15.37	16.15 ±16.67*	4.95 ±2.61^
C-peptide (ng/ml)	1.84 ± 1.17	3.38 ±3.14	1.63 ±0.56
HOMA-IR	2.17 ±4.10	4.03 ±4.58*	1.12 ±0.64^
HOMA-%B	138.11± 262.90	194.67 ± 224.05	64.90 ± 33.43

(HDM+)- heroin dependents with MS, (HDM-) – heroin dependents without MS, HDD- heroin dependence duration,

** significant difference between HDM+ and HDM-, ≠ significant difference between HDM- and control group, ^significant difference between HDM+ and control group*

When determining the predictors for MS in HD, the joint influence of predictor variables was tested: age, duration of heroin addiction, waist circumference, Brinkmann index, BMI, HOMA-IR, HOMA-B, TGl, HDL-C, diastolic and systolic blood pressure, glycemia and gender. The independent variables (duration of HD, Brinkman index, BMI, HOMA-%B, age, HDL-C, diastolic and systolic blood pressure, glycemia and gender) did not have a statistically significant influence as predictors for MS in the group of HD. Waist circumference is a variable with the greatest predictive value, where an increase of 1 cm in waist circumference increases the risk of metabolic syndrome by 3.12 (95%CI 1.41 – 6.89). The next significant risk factor is HOMA-IR since with each unit increase, the risk of MS increases by 1.5(95%CI 1.02 – 2.45). An increase in the concentration of TGl by 1 mmol/l under combined influence with other predictors increases the risk of occurrence of MS by 2.38 (95%CI 1.01 – 5.61). An increase in age by one year increases the risk by 1.2 (95%CI 0.86 -1.88) for the occurrence of MS, but this effect is not considered significant (p>0.05).

All independent variables together influenced on 74.8% of MS variability, while in 25.2% of MS variability was due to the influence of other factors (Table 2).

Table 2. Predictive parameters for MS in HD

Metabolic syndrome		p	OR	95% CI3a OR	
				Lower CI	Upper CI
Predictor	Waist circumference(cm)	0.005	3.125	1.416	6.899
	TGl(mmol/l)	0.046	2.386	1.015	5.610
	HDL-C(mmol/l)	0.809	0.578	0.007	49.444
	Glucose(s) (mmol/)l	0.163	0.278	0.046	1.675
	Systolic BP (mmHg)	0.987	1.002	0.815	1.231
	Diastolic BP(mmHg)	0.541	1.103	0.805	1.513
	Age (years)	0.226	1.274	0.861	1.884
	Duration of HD (years)	0.722	1.089	0.680	1.745
	HOMA – IR	0.043	1.821	1.018	3.259
	HOMA-%B	0.160	0.993	0.984	1.003
	Gender (m/f)	0.391	0.005	0.000	872.979
	BMI kg/m2	0.775	0.892	0.408	1.952
	Brinkman index	0.692	0.997	0.980	1.014
	Const	0.005	0.000		

Method: Enter:- ; -2 Log likelihood :27 500; Nagelkerke R2: 0.748, OR- odds ratio

Discussion

Our study found MS in HD who were seronegative for HCV infection and had BMI in reference range. It was detected in 9.32% of HD and was identified using the IDF criteria for clinical assessment of this syndrome. These are the first results in our country to address the issue of MS in HD who are serologically negative for HCV and HBV infection. Until now, the study of Mattoo *et al*. presented the occurrence of MS in alcohol and HD4 with significantly higher representation of MS (29.3%) compared to that in our study. This difference was a result of the inclusion of subjects with liver disease and diabetes, an older group of subjects (37.43 ±10.89 years) in a significantly smaller sample of observed subjects (41 patients). Also, a high prevalence of MS was registered in the group receiving methadone maintenance therapy who were older (46.1 ± 9 years) than our subjects[15]. In the study by Nebhinani N *et al*., the prevalence of MS in heroin dependence was 9.6%, which was very similar to the results obtained in our study[16]. However, a lower sensitivity of the IDF criteria in detecting MS in HD was reported, with prevalence of 5.1% compared to 20.3% prevalence by using the revised National Cholesterol Education Program Adult Treatment Panel III guidelines[17]. The prevalence of MS in the general population was significantly higher compared to our results, where 21.8%[18], 21%[19], 33.7%[20] and 22.6%[21] were registered, but older age groups were included and a larger number of respondents compared to our study subjects. In the study by Hildrum *et al*., MS de-

tected in line with the IDF criteria in a younger population group of Europeans aged 20-29 years was found in 9-11% of subjects, which was considered as a high prevalence for this age group, and corresponded to the prevalence of MS in our subjects[22]. MS is associated with an increased risk of cardiovascular diseases and events; has its own special significance in heroin dependence, considering the fact that cardiovascular diseases appear to be a more significant cause of morbidity and mortality compared to infectious diseases in this population group, i.e., cardiovascular events were on the third place as a cause of mortality (0.17%) in this population group and on the fourth place (9.4%) as a factor that contributed to the shortening of life during the evaluation using the "years of potential loss of life" method in HD[23].

There are many reports about the association of MS with IR24. In our study, glycemia was insignificantly higher in HDM+ in contrast to significantly increased insulinemia and HOMA-IR in HDM+ compared to MSD-, implying IR in HD. There is an increasing number of reports that have explained the complex mechanism of IR, some of them even including the effects of opioids, like influence on receptor levels, transport molecules, adipocyte hormones as well as influence on insulin-degradation enzymes. Desensitization of insulin signaling through μ-opioid receptors by enhancing serine 612 phosphorylation of the insulin receptor supstrate-1(IRS-1 Ser612), as well as other serine residues, resulted in dissociation of the insulin receptor from its main adapter signaling complexes and reduced activity[25]. The mechanism of chronic intermittent hypoxia[26] as a very common phenomenon in HD[27] also reduces GLUT4 (glucose transporter 4) activity, thus inducing IR in peripheral tissues[28]. The excess of free radicals and low concentration of antioxidants, which have already been observed in chronic heroin use[29], induced reduced GLUT4 activity, too[30]. Additionally, the low levels of adiponectin in heroin dependance[31] were associated with IR independently of body weight and adipose tissue[32].

Disturbed nutrition and its composition can affect glucose regulation primarily due to the zinc deficiency observed in HD, and the decrease in zinc concentrations was linear to duration of heroin use observed in a study in a 6-year period[33]. The insulin degrading enzyme, as a metalloprotease, contains zinc which is essential for the enzyme's catalytic activity. Zinc deficiency, in proportion to the duration of heroin dependance, would reduce the activity of the insulin-degrading enzyme during long-term heroin use and thus may cause reduced degradation of the hormone besides the desensitizing effect of heroin metabolites on insulin receptors and the induction of IR. Given the fact that C-peptide and insulin are produced in equimolar concentrations[34], this mechanism can be associated with our finding of significantly higher HOMA-IR with non-significantly higher basal values of C-peptide

and HOMA-%B in HDM+ compared to HDM- and the group of healthy subjects, implying a reduced insulin clearance as one of the mechanisms for sustained increased insulinemia with IR.

Inflammation and inflammatory mediators are one of the first observed key factors associated with IR and MS as a proinflammatory condition. Heroin and morphine, as an active metabolite of heroin, in immunomodulatory manner can affect IR by changing the levels of certain cytokines. These include morphine-stimulated elevation of interleukin (IL)-6 levels[35], thereby inducing IR through ubiquinone-mediated IRS-1 degradation. In one study, under the influence of heroin, concentrations of IL-10 that supported insulin sensitivity decreased[36]. Increased IL-6 and decreased IL-10 levels participate in the development of muscle and hepatic IR. These findings can be empirically supported when insulin response in HD was improved with salicylates administration[37].

The increased blood pressure is an important criterion in defining MS. The mean systolic and diastolic blood pressure in our subjects did not reach anticipated values for hypertension, but they were significantly higher in HDM+ compared to HDM-. This has also been reported by other authors[4,16,17,38]. The association of IR and MS was reported as a result of impaired renal sodium metabolism, renin-angiotensin-aldosterone, sympathetic nervous systems[39] and endothelial dysfunction[40].

In our study, HDM+ were significantly older and with higher BMI, waist circumference, higher TGl, decreased HDL-C, apoA-I, and increased apoB.

Several longitudinal studies have shown that patients with MS are at increased risk of cardiovascular complications regardless of their BMI[41,42]. Hence, BMI subphenotypes have been defined as metabolic-obese normal weight individuals (normal BMI, increased IR, increased central obesity and with all clinical parameters of MS, 3-28% of observed population), and metabolically healthy obese individuals who, despite a BMI over 30 kg/m^2, are insulin sensitive and not exposed to cardiovascular risk, represented by 11-28%. The representation of MS in HD in our study falls within the range of the group of metabolic-obese individuals with normal weight and monitoring of clinical parameters for MS should be the same as in the general population.

Dyslipidemia profile in HDM+ in this study was characterized by increased TGl, apoB, and decreased HDL-C and apoA-I concentrations. Increased TGl with decreased HDL-C have been described in studies investigating MS in HD[4,16,17,38]. At the same time, increased TGl are among the most common registered disorders in MS in this population group, but the association with HCV infection was not investigated[17,38,43]. Studies that report the effect of heroin on biochemical parameters associate this phenomenon with morphine direct effect of decreased li-

polytic activity in adipocytes, which gradually reaches a level of tolerance[44]. From a clinical point of view, an important mechanism that induces an increase in the concentration of TGl are episodes of hypoxia, common in heroin use[27], which increases the level of TGl by reducing its clearance[45].

A significant reduction in HDL-C concentrations has been described in several studies46. Wilcheck *et al*. explained the low HDL-C as result of the liver lesion in their group of dependents[3]. Maccari *et al*. observed decreased levels of HDL-C in HD with normal BMI, which is in agreement with our results. However, they did not define the prevalence of HCV infection, but only the correlation with ALT, which in their case was negative[2]. In contrast, our results in HDs were with no pathological findings on abdominal ultrasound, seronegative findings for HCV infection and no more than twofold elevated aminotransferases. The decreased level of adiponectin, noted also in HD[31], was significantly associated with the occurrence of the combination of lipid disorders of the type of hypertriglyceridemia with a decrease in HDL-C, independent of intra-abdominal obesity and insulin resistance[32]. Hypoadiponectinemia also correlates with an increased hepatic lipase activity increasing the catabolism of HDL-C and apoA-I[47]. Of course, cigarette smoking and alcohol are significant mechanisms that participate in less than 50% of the variation of HDL-C values in the general population and in the population of HD, in addition to TGl, cholesterol and IR[48]. Considering the protective functions of apoA-I and HDL-C, several controlled epidemiological studies have confirmed the existence of a significant inverse association between HDL-C and its major lipoprotein ApoA-I with a high cardiovascular risk and atherosclerosis. In our study, HDM+ had significantly higher levels of apoB compared to HDM- and these levels were insignificantly higher compared to the index value in the control group. The apoB was considered as the most significant marker of the atherogenic potential in the body and strongly correlated with the ultrasonographic finding of atherosclerotic changes of blood vessels and the occurrence of MS in the general population. The presented apolipoprotein levels in HDM+ group could be partially explained by the significantly increased cumulative index of cigarette smoking, Brinkman index, i.e, decreased apoA-I with increased apoB profile was associated with cigarette smoking[48].

Identifying HD with IR and MS may serve as a criterion for recommending the type of substitution program (methadone or buprenorphine) taking into consideration the reports where patients on buprenorphine substitution program presented better metabolic profile compared to methadone[43].

Conclusion

Heroin dependence does not exclude the association of opioid use with IR and MS, independently of BMI and

HCV infection. Timely recognition of IR and MS and treatment of HD can increase the success in reducing comorbid complications, can help in recommending the type of substitution therapy, thereby indirectly contributing to more successful dependents' rehabilitation and better quality of life.

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ORAL HEALTH

DETERMINATION OF ULTRASRUCTURAL CHANGES IN THE ENAMEL OF PRIMARY TEETH IN STARTING PHASES OF EARLY CHILDHOOD CARIES, WITH AND WITHOUT LOCAL FLUORIDE THERAPY

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Key words: primary teeth, enamel, remineralization, fluoride, Scanning Electronic Microscope.

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Abstract

Early childhood caries is often found under the name connected with the manner of feeding nutrition of children such as “Baby bottle Syndrome” or “Baby bottle caries”. The aim of the study was to determine ultrastructural changes in the enamel of primary teeth in starting phases of early childhood caries, with and without local fluoride therapy, because it has of great influence in the preventive aspect of the disease. The investigation was done on laboratory tests on tree groups extracted primary teeth: one of 20 healthy mandibular incisors, as control group and two more groups of primary tested teeth: 10 maxillary incisors with initial lesion and 10 maxillary incisors with superficial form. The all dental samples were observed with Scanning Electron Microscope (SEM) and we made comparative analyzes in ultrastructural changes of enamel between untreated and treated teeth, and control group teeth. After that, we have analysis with SEM photo attachments. In some dental samples with initial lesion after local treatmant we managed to get almost healthy enamel, i.e. complete remineralization process. Once again, we have confirmation of one of the many benefits of fluoride in dentistry which is long been known.

ОРАЛНО ЗДРАВЈЕ

ДЕТЕРМИНИРАЊЕ НА УЛТРАСТРУКТУРНИТЕ ПРОМЕНИ ВО ЕМАЈЛОТ НА МЛЕЧНИ ЗАБИ ВО ПОЧЕТНИ ФАЗИ НА КАРИЕС НА РАНО ДЕТСТВО, СО И БЕЗ ЛОКАЛНА ФЛУОРИДНА ТЕРАПИЈА

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Цитирање: Кокочева –Ивановска О. Детерминирање на ултраструктурните промени во емајлот на млечни заби во почетни фази на кариес на рано детство, со и без локална флуоридна терапија. Арх Ј Здравје 2023;15(2) 60:69.

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Клучни зборови: млечни заби, емајл, реминерализација, флуориди, скенинг електронски микроскоп

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Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Кариесот на раното детство се среќава под имиња поврзани со начинот на исхраната кај децата како “Синдром или Кариес предизвикан од исхрана со шише”. Целта на оваа студија беше да ги утврдиме ултраструктурните промени во емајлот на млечни заби во почетните фази на кариес на рано детство со или без локална флуоридна терапија, со големо влијание од превентивен аспект, за ова заболување. Во лабораториското испитување вклучивме три групи на екстрахирани млечни заби: една со 20 здрави млечни мандибуларни инцизиви, како контролна група и две испитувани групи млечни заби: 10 максиларни инцизиви со иницијална лезии и 10 максиларни инцизиви со суперфицијална лезии. Кај сите примероци на заби со Скенинг Електронски Микроскоп (СЕМ) вршевме компаративна анализа помеѓу ултраструктурните промени на нетретираните и третираните заби со локален флуориден третмани и контролната група здрави заби. Резултатите покажаа дека кај некои забни примероци со иницијална лезии, добивме скоро здрав емајл, со речиси комплетна реминерализација, како резултат од реминерализирачкото дејство на локалниата флуоридна терапија. Така уште еднаш се потврди еден од многуте претходно познати бенефити на флуоридите во детската стоматологија.

Introduction

Early Childhood Caries (ECC)[1] actually present one or few decayed lesions (cavitated or noncavitated), missing or filled tooth surfaceon primary teeth inchildren[2]. ECC was often associated with the feeding and nutrition of children[3,4] and named as "Baby bottle Syndrome" or Baby bottle caries". Sugary liquid drinks (milk and juices) for longer period of time, with the presence of bacteria such as Streptococcus mutans, present very high risk[5,6].

ECC appears very early in babies from 6 months, it progress rapidly[7] and often affects all four upper incisors.[8] In the initial phase, ECC is presented like white demineralized enamel which quickly advances to decay around the gingival margin[9] Carious lesions are spread on the labial or lingual surfaces of the teeth, or on both sides. The decayed tooth is with yellow or brown cavitated area.[1,2,9]

The children disease is with multifactorial etiology and microbial investigations show presence of Streptococcus Mutans and Lactobacillus[5,6]. Mother's poor oral hygiene habit, dietary habit and activity which increase the possibility of saliva contact between mother and child are often mentioned as possibility of transmission risk S. Mutans in children aged 3-5 years old. Children with ECC have higher risk for developing caries in permanent dentition[9], they regularly visit emergency services, have restricted feeding activities and poor oral health.

In the Republic of Macedonia, this type of caries is widely spread in pre-school children. In the central area of the City of Skopje, children 18 to 42 months old, have 17, 9% of notified caries presence, which, according to the criteria of the World Health Organization, is estimated as high prevalence.[10] In the developed countries as a result of effective and well timed implementation of the primary preventive measures, the Early Childhood Caries has relatively low prevalence of 3 %. In the undeveloped countries, because of lack of information on the adequate way of feeding and no solid oral hygiene[5, 7] the prevalence of the Early Childhood Caries is up to 45%.

Clinical survey of Early Childhood Caries showed that this type of caries goes through several phases in its development[10]. Starting phase of development is the initial lesion (white spot lesion) and superficial form at the early childhood caries[11, 12].

Dental caries is a dynamic group of complex physical-chemical processes on the tooth surface that occur in vivo, with alternating periods of demineralization and remineralization and numerous inter reaction processes leading to imbalance and loss of minerals[11]. Enamel demineralization is the process of dissolving calcium and phosphate ions from hydroxylapatite crystal, which then pass into the plaque and saliva. Initially, caries affects the hydroxyl apatite crystals and the hydroxyapatite demineralization process takes place.[12,13] The early stage is the initial lesion, known as macula alba or white spots, which is reversible process[14]. At this stage the caries has not completely penetrated the enamel border. At the moment when it breaks, it spreads along it and then cavitation occurs due to cracking of

the enamel surface[12] and formed caries lesion (superficial form). Beneath the surface of the initial caries lesion or white spot there is a part with lost minerals just below the intact surface of the enamel. That part with fewer minerals is capable of a reversible remineralization process[14]. With remineralization, hydroxyl apatite increase and if fluoride is present in the medium, fluoride apathies will be formed[13]. Remineralization is the treatment for active initial unvaccinated carious lesion, allowing process reversibility or at least stopping progression to cavitation. From a preventive dentist practice, early detection (initial lesion) is of particular importance, because at this stage the caries process can be completely stopped or reversed[15] (biological repair). But once the cavitation in the enamel has taken place, the caries process can be chronized[13] and to stop the further progradation

The aim of the research is to determine ultra-structural changes in the enamel substance in the starting phases of local fluoride therapy, because it has great influence in the preventive aspect of the disease.

Materials and methods

Clinical research

Taking into account the fact that the initial stages of early childhood caries, have an acute course and occur immediately after the eruption of teeth, in the clinical research, we included children of different sexes, aged 1.5 up to 3.5 years at the Clinic for Pediatric and Preventive Dentistry in Skopje, North Macedonia. We have made selection 117 children, with a fully formed primary denture, in which by standard clinical examination we diagnosed early childhood caries in the early stages: initial lesion-white spot (macula alba) and superficial lesion.

Laboratory research

The research was performed on the group of children with a fully formed primary denture, and it is formed two basic groups:

- 60 children treated with local fluoride treatment
- 57 children followed, but did not undergo local fluoride treatment

From 57 children all of these, 31 children were diagnosed with an initial lesion, and 26 of them had a superficial lesion of the maxillary primary incisors.

Out of the same 57 children, after we ascertained the advanced physiological resorption in the observed teeth, we selected 10 of them with initial lesionss and 10 with a superficial lesion of ECC, extracted one maxillary incisior.

Thus, in order to carry out further laboratory tests, we formed two groups of untreated samples:

I. Examined group of teeth:

- 10 extracted maxillary incisions with initial lesion-white spot (macula alba), and
- 10 extracted maxillary incisiors with a superficial form of circulatory caries.

II. Tooth control group:

- 20 extracted healthy mandibular incisiors

The above 60 children, covered with local fluoride therapy with p-p amino fluoride (once a week), were selected with equal attendance at the two initial stages of ECC, i.e.:

- 30 children with initial white spot lesion
- 30 children with superficial lesion

After completing the six-month local fluoride treatment, in further laboratory tests, we included:

III Examined group of treated samples with local fluoride therapy:

- 10 extracted maxillary incisions with initial lesion-white spot (macula alba), and
- 10 extracted maxillary incisions with a superficial lesion of ECC

The extracted teeth were kept in pure alcohol (96%) and before the analysis, the teeth were dehydrated and covered by a thin layer of gold on the surface, with cathode dispersion technique. Investigation was made with the scanning electronic microscope (JSM 5300, SEM, JEOL, USA), and this procedure took place at the Institute for biomedical research of the Faculty of Medicine in Nis, Serbia. The enamel surface was observed and analyzed.

Results

1. SEM evaluation of ultra-structural enamel changes in untreated specimens of primary health incisors

- Ultrasound of healthy enamel tooth substance from the dental control group -mandibular primary incisors).

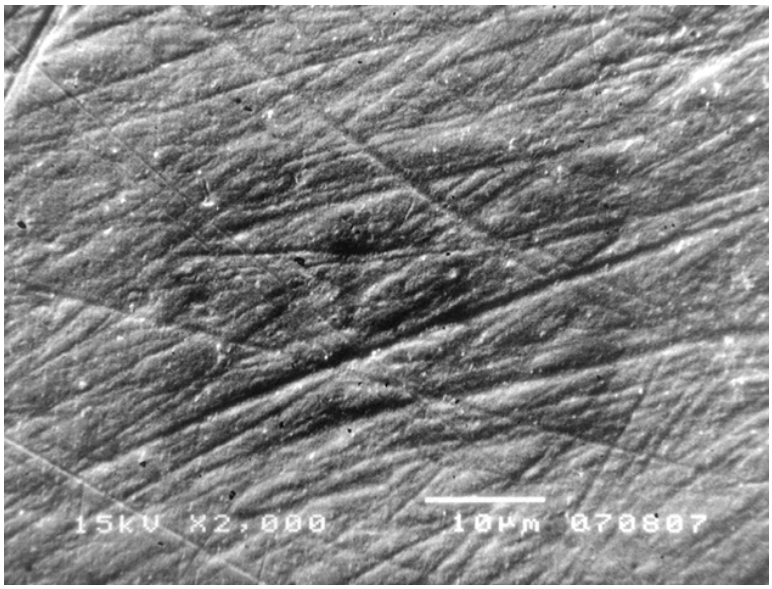

Figure. 1 Longitudinal section of a healthy enamel

On Fig. 1 is presented the longitudinal section ofthe outer surface of a healthy enamel. It is homogeneous, flat, with a less tooth brush traces wavy appearance (magnification 2000 times). The transverse lines seen on the surface are visible traces of mechanical tooth brushing.

- Ultrasound changes in the untreated initial lesion (maxilarry primary incisors)

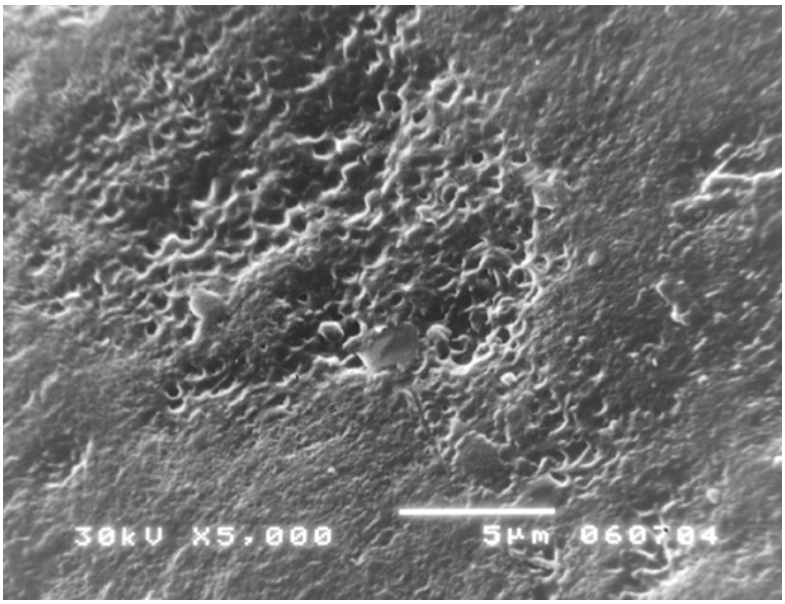

Figure. 2 Initial lesion of maxillary incisor

Fig. 2 shows an island of initial demineralization in the initial lesion and around it is retained and enamel cuticle of a healthy enamel (magnification 5000 times)

2. SEM evaluation in enamel ultrastructure of initial lesion after topical fluoride treatment

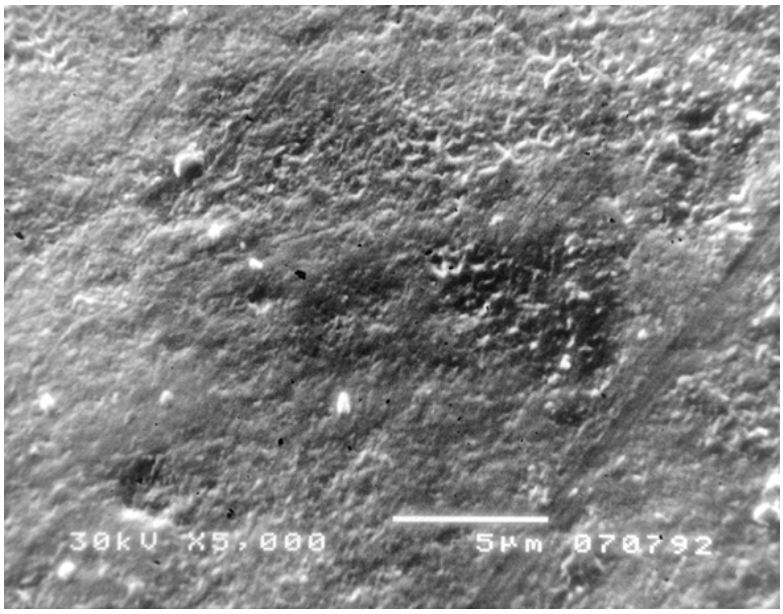

Figure. 3 Treated inicial lesion of maxillary incisor

On Fig.3 can be seen the advanced, almost complete remineralization of the initial lesion (white spot), where the enamel residue is similar to the surface of the healthy enamel (magnifying 5000 times respectively).

- Ultrastructural changes of the untreated superficial lesion (maxillary primary incisors)

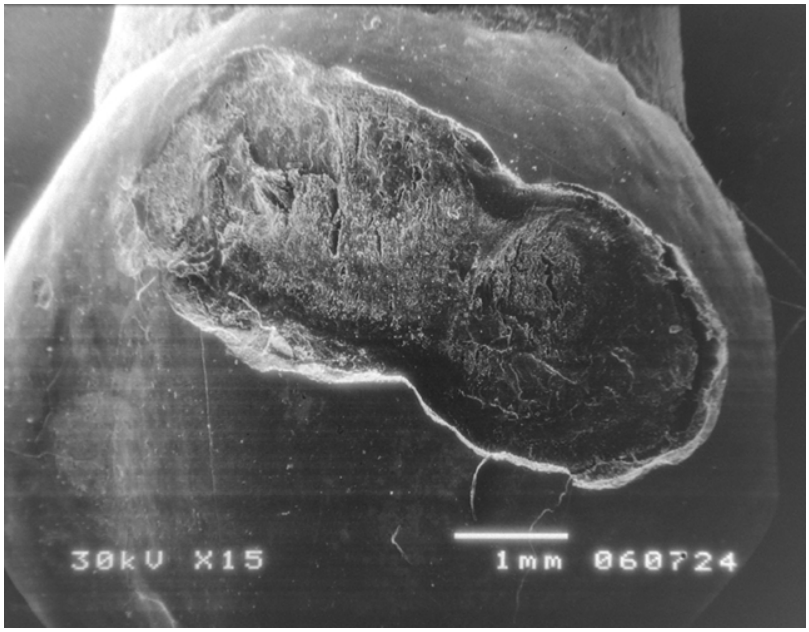

Figure. 4 Typical example of circulatory caries of maxillary incisor

On Fig.4 with a slight increase (75O times) is shown by a typical example of circulatory caries, limited by a healthy surrounding enamel.

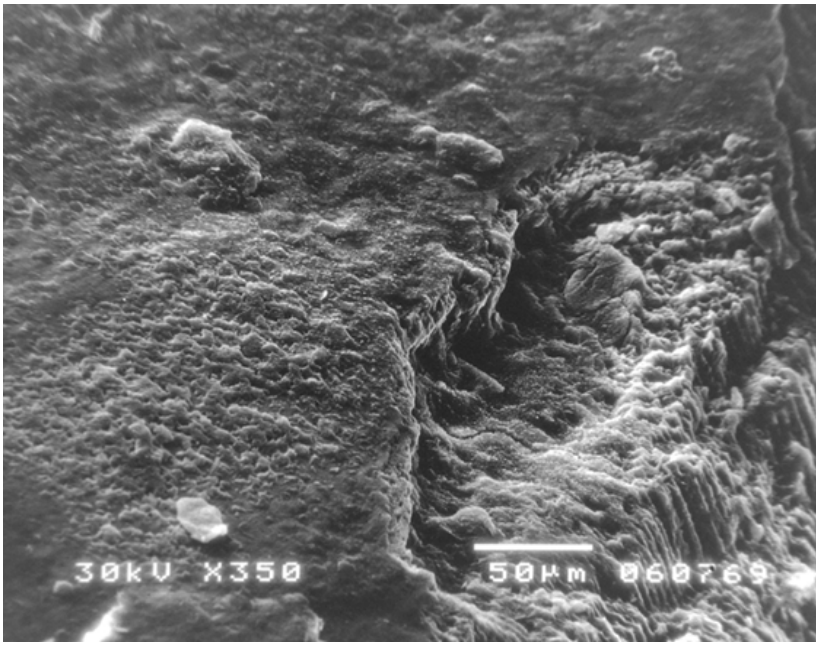

Figure. 5 Superficial lesion penetration at several levesl

Figure 5 shows an interesting photo showing part of a healthy enamel cuticle and the penetration of a caries lesion on several levels with the loss of prismatic ridges (magnifying 350 times respectively).

3. Ultrastructural changes of treated teeth with topical fluoride treatment (maxillary incisiors) with superficial lesion

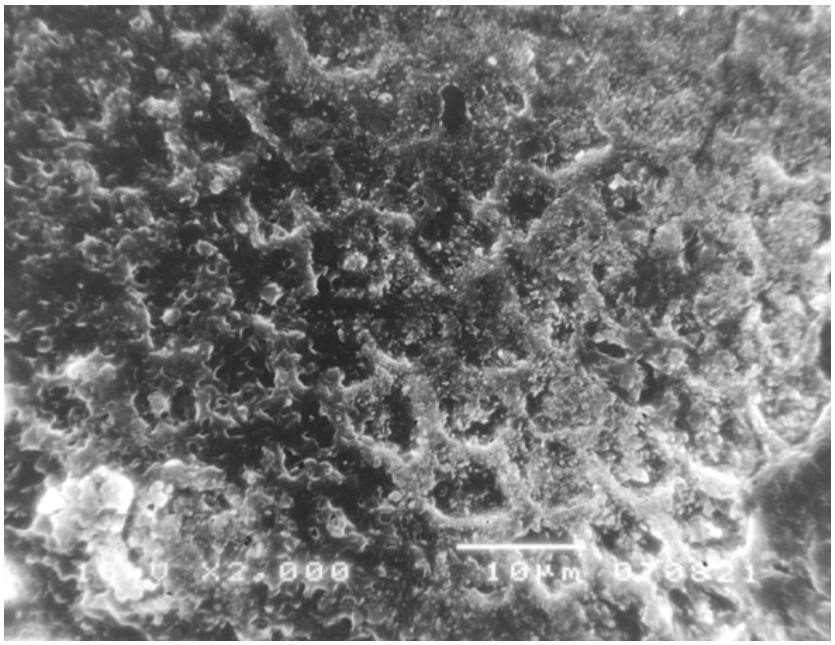

Figure. 6 Treated superficial lesion of maxillary incisor

In Fig. 6 the black fields on the left side are a complete destruction of the enamel prisms with wide interprismatic spaces, and on the right side is a filling, i.e. stopping of this destructive process. (magnifying 5000 times respectively).

Discussion

Enamel is made of hydroxyl apatite crystals arranged in prisms which extend from the dentin-enamel junction to the surface11. Macroscopically crystals are packed tightly with inter crystalline spaces filled with water and organic material15. ECC appears very early in babies from 6 months, it progress rapidly, and often affects all four upper incisors. If the deposits accumulate over a longer period of time on the tooth surfaces, we do not have oral hygiene or the presence of fluorides, demineralization processes will dominate, which leads to cracking of the surface layer of the enamel and the initial lesion (white spot) at the level of the enamel, and then progresses in width and depth through the dentin. So the chances of a white spot being demineralized,[12] or how long it will remain subclinical before programming into a clinically visible carious lesion, will depend on a number of factors, including the fact that caries is a multicellular[9] disease. How successful remineralization will be, depends on the predominant, protective, or pathogenic factors[14, 16].

The question arises when it is best and most effective for the dentist to begin local fluoride therapy. Considering the fact that the enamel surface of the newly erupted enamel is not yet fully mineralized, and the teeth are most sensitive to cariogenic nicks in the first few months of eruption, local treatment should begin at age of two years, when most of the deciduous teeth are present and have already erupted[17]. There are various local fluoride agents in various forms: toothpastes, rinsing agents, solutions, gels, jellies, varnishes, etc. However, it is necessary to emphasize that the frequency of the preparation should be directly

related to the patient's risk of caries, and the choice of fluoride preparation should be the choice of the dentist.The application of the primary preventive measures can successfully prevent the Early Childhood Caries, and parents and the dentists, have the important role in that process, too.[18,19], Avoiding food high in sugar, leaving baby bottle at 12-18 month of age, dental screening, counseling and preventive procedures are some of the measures and policies for EEC10,[17]. Best professional preventive method a dentist can use is local fluoride therapy[20], when tooth surface is periodically varnished with fluoride solution[17]. Best composition, concentrate of fluor and capacity for penetration in dental enamel are still investigate[18]. Fidya et all.[21]studied the difference in penetration of Nano-NaF compared to ordinary NaF solution, and found that Nano-solution application can increase the levels of fluoride (0.1289%) and fluorapatite (20.35%) more than NaF application. Both fluoride solutions proved their influence for enamel endurance toward caries.

Diagnosing the disease in the early phase of clinical evolution – white spot lesion is very important, and the implementation of the primary preventive measures can achieve the biological reparation of the lesion and prevent the carious lesion extending and complications.[2, 16,, 22, 23]. Unfortunately in most cases, the Early Childhood Caries findings are in the advanced phase, and the dentist usually can't manage the consequences[2].

Conclusions

From the overall SEM analysis of the evaluation of the ultrastructural changes of the enamel dental substance in untreated and treated dental specimens with local fluoride therapy, it is concluded:

- The appearance of ultrastructural changes in the enamel is correlated with the loss of minerals in the tooth substance
- The initial lesion is followed by demineralization and retraction of the prismatic ridges, destruction of the crystals and alteration of their arrangement in the prisms, expansion of the interprismatic spaces between the prisms and a multitude of dark spaces that are more pronounced in a deeper initial lesion.
- In the treated teeth with local fluoride treatment the interprismatic spaces are narrowed, the prismatic ridges are repaired and the surface of the enamel is leveled

We can also conclude that consumption of fluoride supplements, varnishes and fluoride tooth pastes must be provided. The application of the primary preventive measures can successfully prevent the Early Childhood Caries, and parents and the dentists, have the important role in that process. Best professional preventive method a dentist can use is local fluoride treatment, when tooth surface is periodically varnished with fluoride solution. All above can help in creation of the strategy for successful prevention of these disease.

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ORAL HEALTH

NUTRITIONAL HABITS AS RISK FACTORS FOR DENTAL CARIES IN CHILDREN FROM RURAL AND URBAN AREAS IN SKOPJE

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Abstract

Proper nutrition is a long-term investment in one's own health. Oral health as an integral part of general health is in bidirectional relationship with diet and nutrition. Globalization and urbanization have led to nutrition transition from a traditional agriculturally-based diet to consumption of processed foods that are high in sugar. Children have been particularly affected by this change. The aim of this study was to investigate the association between specific nutritional and hygiene habits and the development of caries in children from urban and rural areas. The study was conducted in December 2019 and comprised children aged 6 years. A survey was made and children's dental status was tested. The results obtained showed a higher percentage of healthy deciduous (50%) and permanent (35%) teeth in children from rural areas than in children from urban area. Both groups had similar habits in terms of cariogenic and cariostatic food intake, but there were differences in children's hygiene habits.

ОРАЛНО ЗДРАВЈЕ

НУТРИТИВНИТЕ НАВИКИ КАКО РИЗИК ФАКТОР ЗА ПОЈАВА НА ДЕНТАЛЕН КАРИЕС КАЈ ДЕЦА ОД РУРАЛНА И УРБАНА СРЕДИНА ВО СКОПЈЕ

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Клучни зборови: дентален кариес, исхрана, орално здравје, деца

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Извадок

Правилната исхрана е долготрајна инвестиција во сопственото здравје. Оралното здравје како нераскинлив дел од целокупното здравје е во директна двострана корелација со исхраната. Глобализацијата и урбанизацијата доведоа до една нутритивна транзиција, кога од традиционална исхрана со свежи земјоделски производи се премина на процесирана исхрана богата со шеќери, промена од која посебно се засегнати децата. Целта на оваа студија беше да се испита поврзаноста помеѓу специфични нутритивни и хигиенски навики и појавата на кариес кај деца од урбана и рурална средина. Истражувањето беше направено во декември 2019 година кај деца на возраст од 6 години,на кои им беше направено анкетирање и утврдување на денталниот статус. Според нашата студија, поголем беше процентот на здрави млечни(50%) и трајни (35%)заби кај децата од селска средина отколку кај градските деца. И кај двете групи имаше слични навики во однос на внес на кариогена и кариостатска храна, но постојат разлики во хигиенските навики.

Introduction

Proper nutrition is a long-term investment in one's own health. Oral health as an integral part of general health is in bidirectional correlation with diet and nutrition. Sufficient intake and availability to relevant nutrients are of key significance for the growth, development, and repair of oral tissues and healthy dentition[1] hence, a lack of certain nutrients might result in developmental anomalies of the craniofacial system, and on the other hand, increased intake of other nutrients can lead to onset of dental caries as the most common oral disease. In case of poor oral health, teeth absence or a feeling of pain and discomfort due to dental or oral diseases, there is a reduced masticatory ability. This can lead to consumption of inadequate food, that in the long term might cause certain diseases and conditions in the body such as obesity, hypertension, diabetes or cardiovascular diseases. Oral diseases are still the most common non-communicable diseases globally[2,3] and pose an important public health problem because of their prevalence, their impact on individuals and society, and they also result in high treatment costs.[4] In spite of the enormous improvements in prevention and treatment of oral diseases in the last decades, problems still persist causing pain, fear, anxiety, functional limitations (with poor attendance and performance of children in school) as well as social handicap due to tooth loss.[5] In addition to negative influences on quality of life, treatment of dental caries is a health system burden consuming about 10% of health-care budgets in industrialized countries; dental caries is the fourth most expensive disease to be treated in the world.[2,3,6] It has been estimated that in 2010 a total of 442 billion dollars were spent globally for dental caries treatment.[7] Dental caries is a lifelong progressive and cumulative disease, hence, low levels of caries in childhood is something we should pay attention to[8] in order to reduce caries rate and associated costs. The causal relationship between fermentable carbohydrates and caries was for the first time reported in the scientific literature in the 50s of the last century.[9] The relationship between caries and carbohydrates is well known: dental hard tissues are demineralized under the influence of acidic by-products produced by bacteria in biofilm (dental plaque) during the fermentation process of carbohydrates[10], with a rapid reduction of pH in the saliva below 5.5 in tooth biofilm. This low pH has impact on the balance of microbes in the biofilm by increasing the proportion of acidogenic types of bacteria, thus intensifying tooth demineralization.[11] Over the last decades, globalization and urbanization, especially in the countries with low and middle income, have brought to a kind of nutrition transition from a traditional agriculturally-based diet to consumption of processed foods that are high in sugar. This change has particularly affected children.[12,13,14] According to the information note about sugar and dental carries released by WHO in

2017, economic growth is characterized by nutrition transition to a diet with a high proportion of free sugars and fats in the total daily energy intake. [7]

The aim of this study was to examine socio-behavioral risk factors for onset of caries, i.e., to analyze the relationship between specific nutritional and hygiene habits and prevalence of caries in children from urban and rural areas in Skopje.

Materials and methods

The study was conducted in December 2019, in primary preventive and dental care center within the public health institution Health Center Skopje. It included 60 children, born in 2013, at the age of 6 years, of both sexes and of any nationality, who were divided into two groups according to the place of residence – 30 children from urban and 30 children from rural areas. A detailed dental examination was made by a licensed dentist, and Gnatus dental chair, dental reflector, dental mirror, probe, buster and personal protective equipment were used. Data were obtained and retrieved in line with the WHO 2017 form. After the examination, a survey among children's parents was made by distributing a questionnaire containing demographic data, data on the type of diet/nutrition and on oral cavity hygiene. For the purposes of this study, a simple statistical analysis of data was made.

Results

The study included 16 boys and 14 girls who lived and attended school in rural areas, and 16 girls and 14 boys from urban area. The percentage was the same (79.3%, i.e., 23 children) in both groups of children who preferred white bread over black or corn bread. Regarding the answer to the question *Do you eat sweets often, rarely or never*, fourteen of children (46%) from rural areas chose *often*, and a larger percentage (53.3%, i.e.,16 children) opted for *rarely*. Contrary to this, 18 city children (60%) answered they often ate sweets and cakes. However, 12 children (40%) from rural areas more often drank sugar-sweetened beverages than those from urban area (26.7%, i.e., 8 children). Four of the city children said they never drank sugar-sweetened beverages (13.3%) (Figure 1).

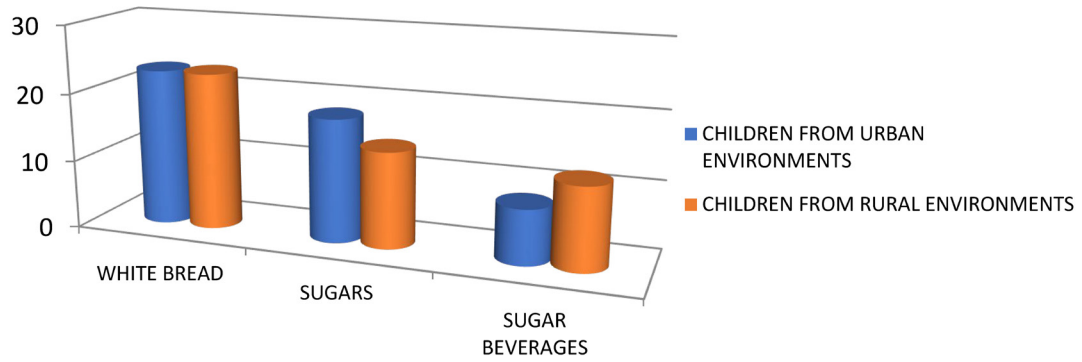

Figure. 1 Consumption of food with a cariogenic effect

Children from urban area in our study consumed more often milk as a food with cariostatic effect (19 children, i.e., 63.3%) than children from rural areas: 15 children (50%) from rural area often consumed milk; 40% (12 children) answered they drank milk rare and three of them (10%) never drank milk. Both children from rural and urban areas often ate fruit and vegetables, whereas children from rural areas more often ate meat, fish and eggs, but there was no significant percentage difference (Figure 2).

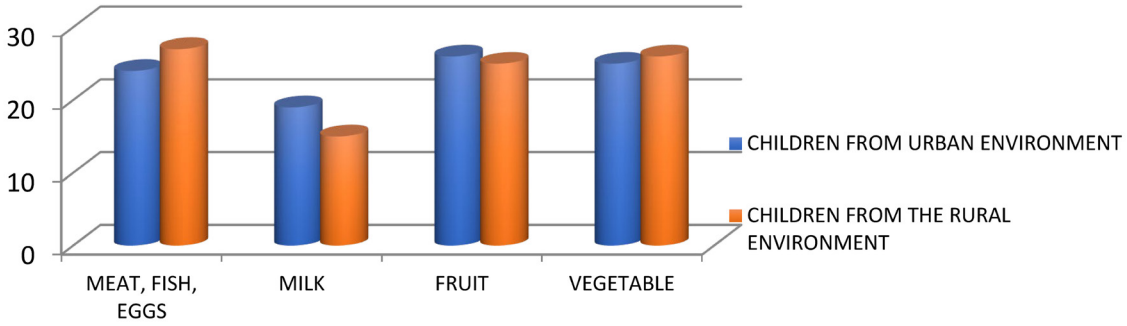

Figure. 2 Consumption of food with a cariostatic effect

In both groups, all 60 children (100%) had toothbrush, but 26 of city children (86.7%) used it on a regular basis. The percentage of children from rural areas that were regularly brushing their teeth was smaller (76.7%, i.e., 23 children). A higher percentage of rural children (40%, i.e., 12 children) were brushing their teeth for 2-3 minutes compared to majority of city children (17 children or 56.7%/) who were brushing their teeth for less than 1 minute. All 30 children (100%) from urban area used fluoride toothpaste, but there was four of them who used dental floss and water for mouthwash as basic tools for maintaining oral hygiene. In the group of children from urban area there was no child who ever used dental floss or water for mouthwash for routine oral hygiene (Table 1).

Table 1. Hygienic habits

	Toothbrush		Washes the teeth			Duration			Uses		
	Yes	No	Regularly	Occasionally	Never	<1min	1 min	2-3 min	Fluoride toothpaste	Dental floss	Water for mouthwash
Urban area	30 100%	/	26 (86.7%)	4 (13.3%)	/	5 (16.7%)	17 56.7%	8 26.7%	30 100%		
Rural area	30 (100%)	/	23 (76.7%)	7 (23.3%)	/	5 (16.7%)	13 (43.3%)	12 (40%)	26 (86.7%)	2 (6.7%)	2 (6.7%)

In the end, an analysis of the dental status was performed and it comprised 120 first permanent molars and 60 first deciduous teeth from each group of children. The following results were obtained: in city children, 95 of the first permanent molars were unerupted (77.5%), only 3.3% (4 permanent first molars) had caries, 7.5%, i.e., nine were healthy, twelve (10%) were teeth with resin composites and sealants, and only 3(2.5%) were molars with filled tooth surfaces but no caries. In the group of rural children, 64 of the first permanent molars were unerupted (53.3%), 35% (42 permanent first molars) were healthy, 5% (6 molars) had caries, 5.83%, i.e., seven were with resin composites and sealants, and only one (0.83%) had filled tooth surfaces. The analysis of the first deciduous teeth showed that in city children 24 of deciduous teeth (40%) were with dental caries, 35% (21) were healthy teeth, 21.6% or 13 of the deciduous teeth had fillings, one tooth was extracted (1.66%) and the same percentage was found regarding resin composites. In rural children, there was a higher percentage of carious first deciduous molars (45%, i.e., 27 deciduous teeth), but also there was a higher percentage of healthy first deciduous molars (50%, i.e., 30 deciduous teeth); there were no teeth with resin composites and adhesives, only 1 deciduous tooth (1.66%) was extracted and only two (3.22%) had filled tooth surfaces (Table 2). When comparing the percentage of healthy and carious teeth in rural and urban children, the percentage of healthy teeth in the primary dentition was higher in children from rural areas (50%in rural children versus 35% in children from urban area). The difference in the percentage of carious deciduous teeth existed (45% in rural children versus 40% in urban children) but it was smaller and insignificant.

Table 2. Dental status of first permanent molars and first deciduous molars

	State of first permanent molars - total 120					State of first deciduous molars (54.74) -total 60				
	caries	healthy	unerupted	resin composites	fillings	caries	healthy	extracted	resin composites	fillings
Urban area	4 (3.3%)	9 (7.5%)	93 (77.5%)	12 (10%)	3 (2.5%)	24 (40%)	21 (35%)	1 (1.66%)	1 (1.66%)	13 (21.66%)
Rural area	6 (5%)	42 (35%)	64 (53.3%)	7 (5.83%)	1 (0.83%)	27 (45%)	30 (50%)	1 (1.66%)	/	2 (3.33%)

Discussion

Donald L. Chi in 2019 has stated that nowadays knowledge about the role of excess intake of sugars (defined as free sugars or added sugars to the food, other than those found in the structure of grains, vegetables, fruits and milk) has been widely accepted as a factor for occurrence of

dental caries, but also of other systemic health problems such as obesity, diabetes and cardiovascular diseases.[5,9,15,16,17] The most cariogenic sugar is sucrose, a disaccharide consisting of its monosaccharides glucose and fructose, and which presence causes dental plaque with smaller amount of calcium, inorganic phosphates and fluorides, ions necessary for enamel remineralization. In 2015, WHO released a new guideline on sugars intake in adults and children with a strong recommendation for reduced intake of free sugars that has to be less than 10% of total energy intake, and with an additional recommendation for further reduction of the carbohydrates intake to less than 5% of total energy intake.[5] Education conducted by dental teams regarding consumption of 100% fruit juices should be consistent with the manual of the American Academy of Pediatricians.[18] According to this manual, children under the age of one year, should not be given juices unless medically indicated.

Foods such as milk and dairy products, apples, cranberries, tea and high-fiber foods have been considered to have cariostatic effects, i.e., they inhibit the development of caries, but further investigations are necessary in order to confirm this statement (Moynihan P.)[19,20] This effect is due to their composition rich in fibers, water, protective factors such as polyphenolic compounds, calcium, but also due to mechanical stimulation of secretion of greater amount of saliva.[21,22,23] Lactose is considered to have a smaller cariogenic effect because its fermentation produces a smaller reduction in Ph in the saliva.[24] The caries disease process is a multifactorial and dynamic process conducted in the biofilm with active participation of free sugars via the phases of demineralization and remineralization of dental hard tissues.[13] The process of demineralization happens during prolonged presence of carbohydrates in the mouth resulting from a poor oral hygiene. Therefore, we have also examined hygienic habits as a risk factor that would influence on the presence or absence of caries in the oral cavity in 6-year-old children.

Conclusion

The results obtained in this study showed that the percentage of healthy deciduous (50% or 30 teeth) and permanent (35% or 42 teeth) teeth was higher in children from rural areas in comparison with 9 of healthy permanent first molars (7%) and twenty-one (35%) healthy first deciduous molars in children from urban area. Both groups presented with similar habits in terms of intake of cariogenic and cariostatic food, but there were differences in the hygiene habits. Hygiene habits had a larger impact on onset of caries than nutritional habits, however, further investigations are necessary that would comprise a larger group of examinees along with a more detailed analysis regarding frequency and total daily intake of carbohydrates.

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CASE REPORT

FINAL HEIGHT IN A BOY WITH ACHONDROPLASIA TREATED WITH GROWTH HORMONE- CASE REPORT

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Abstract

Achondroplasia is the most common genetic form of skeletal dysplasia in humans. It is characterized by short stature and skeletal disproportion. Patients with this condition have comorbidities, such as cardiovascular problems, spinal cord problems, hearing and dental problems as well as psychological issues. We report final height of 147 cm in a 17-year-old boy treated with growth hormone, however without improvement in body proportions. Surgical therapy for limb lengthening had been proposed, which the patient refused. At this age he developed hypertension and was referred to a cardiologist, nephrologist, as well as to an orthopedic surgeon and psychologist. Recently, a new treatment with vosoritide has been introduced, promising better height outcome, but uncertain phenotype improvement. Multidisciplinary approach is recommended for these patients and close monitoring during childhood, adolescence and adulthood. Genetic counseling is also advised.

ПРИКАЗ НА СЛУЧАЈ

КОНЕЧНА ВИСИНА КАЈ МОМЧЕ СО АХОНДРОПЛАЗИЈА ТРЕТИРАНО СО ХОРМОН ЗА РАСТ – ПРИКАЗ НА СЛУЧАЈ

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Клучни зборови: ахондроплазија, терапија со хормон за раст, висина

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Извадок

Ахондроплазијата е најчеста генетска форма на скелетна дисплазија кај луѓето. Се карактеризира со низок раст и скелетна диспропорција. Пациентите со оваа состојба имаат коморбидитети, како што се кардиоваскуларни, проблеми со ,рбетниот мозок, со слухот и забите, како и психолошки проблеми. Утврдивме конечна висина од 147 cm кај 17-годишно момче третирано со хормон за раст, но без подобрување во пропорциите на телото. Предложена е хируршка терапија за издолжување на екстремитетите, која беше одбиена од страна на пациентот. На истата возраст кај пациентот се појавила хипертензија и бил упатен на кардиолог, нефролог, како и на ортопед и психолог. Неодамна, воведен е нов третман со восоритид, кој ветува подобри резултати во однос на висината, но со ограничени резултати за фенотипска презентација. За овие пациенти се препорачува мултидисциплинарен пристап и внимателно следење во периодот на детството, адолесценцијата и зрелоста. Кај нив се предлага и генетско советување.

Introduction

Severe growth retardation occurs in most skeletal chondrodysplasias. Among these bone disorders, achondroplasia is the most common genetic form in humans and it features short-limb dwarfism, macrocephaly with a prominent forehead, and a mid-face hypoplasia1. Patients with achondroplasia have comorbid conditions and complications ranging from infancy to adulthood. It has been reported that mortality may be higher related to heart disease, although most of them have normal or near normal life expectancy[2,3].

Growth hormone (GH) is an important factor for growth and differentiation of chondrocytes. Trials with GH treatment in achondroplasia have been reported for a long time in different countries[4-7]. Yet, a worldwide consensus has not been reached. The patient must satisfy selection criteria, such as young age, current body height, physical characteristics, MRI-CT examinations[8].

Following our publication in 2016[9], we decided to report the outcome and final height of this patient with achondroplasia.

Case report

As a reminder, our patient was diagnosed prenatally in the 7th month of gestation. The mother's pregnancy was uneventful and regularly controlled. The parents were of average height (mother 163 cm, father 172 cm). At birth, he had all clinical stigmata of the disorder. Genetic testing revealed a mutation of C 1138 G>A in the gene FGFR3 in a heterozygous constellation. Growth hormone treatment was initiated at the age of three years and four months, at a dose of 0.06 mg/kg, and adjusted accordingly to body weight in the following years. IgF1 was monitored regularly as well as glycaemia and thyroid hormones. His growth was on the 3rd percentile of the growth curve until the age of 13 years, when it started to decline. Growth hormone was discontinued at the age of 15 years, and bone age was 16 years. His height was 145 cm and weight 66 kg. The body disproportion did not improve during the growth hormone treatment.

The parents and patient were informed of the possibility of orthopedic treatment (Ilisarov procedure), which the patient refused.

At the age of 17 years, the final height was 147 cm and weight 66.5 kg (Picture 1 and 2). He complained on hypertension that had occurred on several occasions (150/100...140/95 mmHg). His blood tests were normal, but the ECG and ultrasonography of the heart revealed hypertrophy of the left ventricle. Treatment was initiated with beta blockers and antihypertensive medication suggested by a cardiologist. The clinical examination for eventual kidney disease showed no signs of pathological abnormalities. An orthopedic specialist performed CT examination of the spinal cord which was negative for compression due to foramen magnum stenosis. A cranial MRI, to identify possible ventricular enlargement, is also planned. The parents also complained that he had psychological issues although his peers were treating him well. A recommendation was given to consult a psychologist.

Discussion

The average adult height in achondroplasia in the Caucasian population is between 112 and 136 cm (mean 124 cm) for women and 118 and 145 (mean 132) for men[10]. A consensus for growth hormone treatment has not been reached everywhere. For instance, in Japan, GH treatment is included in their Clinical Practice Guidelines for Achondroplasia[8]. However, the first European consensus on principles of management of achondroplasia does not recommend GH treatment[10], although it allows patient and family to make a decision about limb lengthening.

Our patient grew an additional 2 cm following discontinuation of treatment. He did not experience a pubertal growth spurt which is typical for these patients. Pubertal sexual development was normal. GH treatment improved his height, but not the physical features of the skeletal dysplasia. Our patient's young age at initiation of treatment prevented height deficit from accumulating. The proposed surgical limb lengthening which could offer the possibility of a more proportionate adult stature, was not accepted byour patient. This decision is multifactorial and should include different specialists (physicians, surgeons, physiotherapists, and occupational therapist). This should be a shared decision with the family and the patient[10]. Patients with achondroplasia tend to have comorbidities, such as foramen magnum stenosis, ventricular enlargement, spinal canal stenosis, kyphosis, obstructive sleep apnea and respiratory symptoms, hearing loss, and cardiovascular issues[8].

Other patients with achondroplasia have also been treated with GH at our Department, but with unsatisfactory results probably due to older age or other factors. Mutations of the FGFR3 gene result in suppression of chondrocyte differentiation and proliferation, leading to impaired endochondral ossification and all clinical symptoms.

Recently, a new treatment has been introduced, a biological analogue of endogenous c-type natriuretic peptide which blocks the FGFR3 signal and is a potent stimulator of endotracheal ossification[11]. Clinical trials have shown improvement of growth, however there is limited data on clinical features improvement.

Conclusion

GH treatment in our patient improved the final height, however without results regardingskeletal disproportion. Surgical limb lengthening was refused by our patient. Hopefully, new medications will overcome these obstacles. At present, the focus is on adequate diagnosis prenatally and at birth, lifelong support and management, avoiding and treating complications that come with this condition, multidisciplinary approach and continuous monitoring throughout childhood, adolescence and adulthood. Future genetic counseling of the family is also advised.

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