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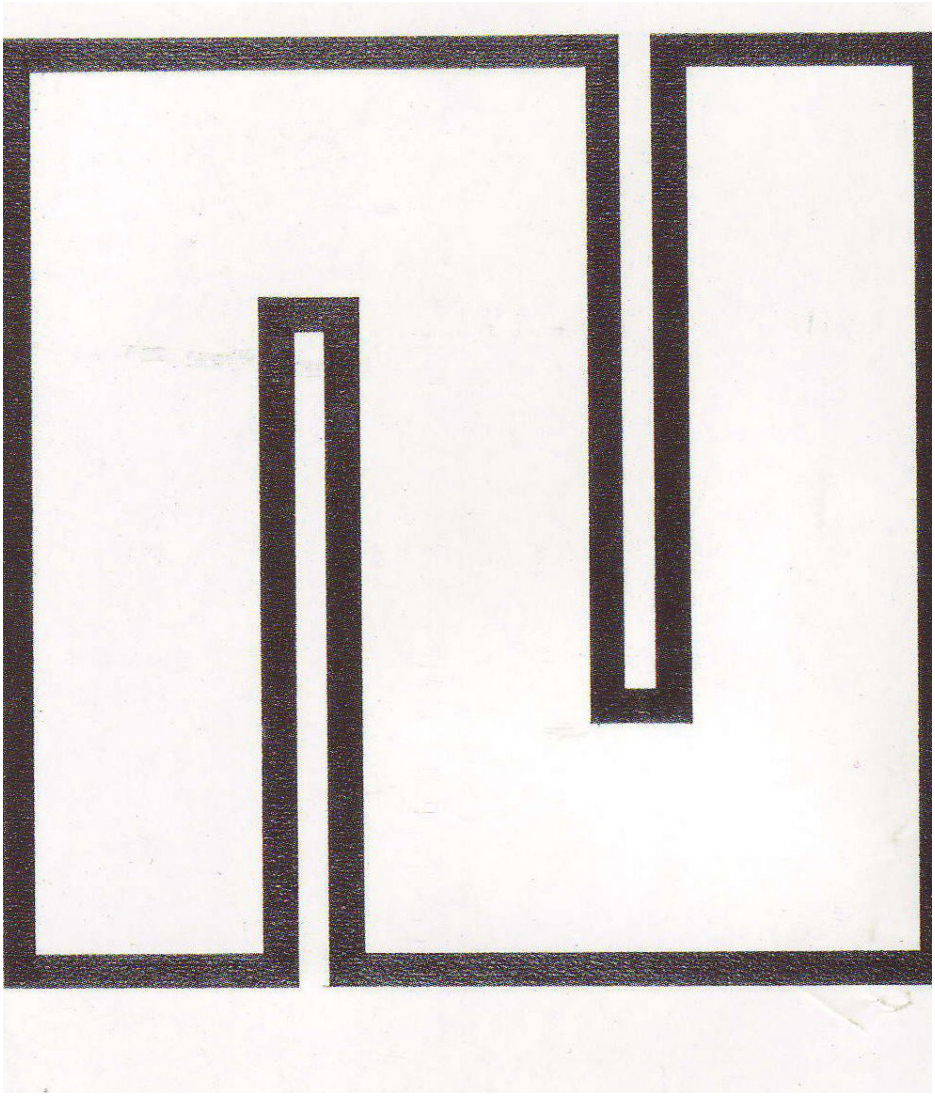

Julije Knifer, Meandar, 10-23 XI.78. Zg, 1978.
drawing, pencil on paper
MLU-4838

Josip Juraj Strossmayer University of Osijek
Faculty of Medicine

[100 YEARS SINCE THE BIRTH OF JULIJE KNIFER]
Julije Knifer (23 April 1924, Osijek – 7 December 2004, Paris)

After completing elementary and high school education, he went to study at the Academy of Fine Arts in Zagreb, majoring in painting which he completed in Zagreb in 1956 in the class of Prof. Đuro Tiljak. He was one of the co-founders and a member of the Gorgona Group (from 1959 to 1966), and also a member of the New Tendencies movement.

Along with painting, he did illustration and graphic arts. The motif of the meander is a leitmotif in Knifer's painting, in which he introduced minimalistic, but artistically significant changes in the same formula (variations were in the colors: blue, gold and gray, from the late 1960s to the early 1970s).

In the late 1950s, he started to implement Cubist principles which eventually led him to extreme reductionism, there were fewer details taken from reality and they became less recognizable, whilst his color palette became significantly muted.

He created his first meanders in the late 1950s and the beginning of the 1960s as an expression of extreme reductionism, a presentation of an anti-painting try, but also a manifestation of contemplativeness. From the beginning of the 1970s, he transferred the meander motif onto much larger formats, or to be more precise, he painted them on the exterior and interior walls. He actively participated in the New Tendencies exhibitions (in 1963, 1969 and 1973), at the São Paulo Art Biennial (1973) and in Venice (1976), while in 2001 he represented Croatia at the Venice Biennale. Zvonko Maković, our distinguished art historian and retired professor at the Faculty of Humanities and Social Sciences in Zagreb, took interest in Knifer's artwork, and it was his suggestion that Knifer represents Croatia at the Venice Biennale. In the collection of the Museum of Fine Arts (MLU), in Collection of Paintings of the Second Half of the 20th Century and the Collection of Drawings and Graphics of the Second Half of the 20th Century (both collections are managed by Valentina Radoš, a museum advisor) there are 17 Knifer's artworks in total (Info MLU).

"Truly, the meanders are an exceptional case, an excess within the history of modern painting and it is exactly because of the way they are, they represent a final affirmation of the individual fight, proof of the achievement of exceptionally individual art. The paradox repeated even in Knifer's case, which was first studied by Mondrian: distancing from every excessive outburst of subjectivity, in the pursuit of the biggest objectivity possible, one arrives unexpectedly, but completely understandable to manifestation of subjective identity, necessary in the adventure of art. Few people have, using extremely concise resources, elevated such valued vertical: not only in the uniqueness of the symbol with which he identified or elaboration of the plastic problems he carried out but most of all due to the interior spiritual dimension of his painting, Knifer is a remarkable figure of the European art scene, enduring more than the last two decades. At the beginning of that period, Knifer made his pioneer breakthroughs, and during that time he experienced critical and art-historical verification, whilst towards the end of that period the art remained a challenging problem. Seemingly weird, we are still not familiar with Knifer's artwork in its entirety; a large majority of his work, which was made in Germany and stayed there until this day, was never exhibited near us. So, there is an opportunity to continue, as in the case of Knifer's meanders, a repeated situation: the meanders will always remain the same, but the projection of those who will think about them in the future will certainly change as the spirit of time changes."

(Ješa Denegri, Julije Knifer, retrospective catalog Julije Knifer, Bez kompromisa [Uncompromising], 2014, officially published: Ješa Denegri, "Julije Knifer", in: Julije Knifer, catalog, Gallery of Fine Arts in Osijek, November December 1984, pages 3–9)

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Contents

SEEMEDJ SOUTHEASTERN EUROPEAN MEDICAL JOURNAL

Dear colleagues, dear friends,

There have been some changes in the Southeastern European Medical Journal (SEEMEDJ). Professor Ines Drenjančević, MD, PhD, who established the journal and invested significant effort into its development, has decided to step down as Editor-in-Chief. She will continue her work as a member of the editorial board. We are immensely grateful for Professor Drenjančević's contributions to SEEMEDJ from 2017 to 2023.

The role of Editor-in-Chief has been taken over by Dunja Degmečić, who, along with members of the editorial team—Maja Miškulin, Aleksandar Kibel, Antonio Kokot, Jasenka Wagner Kostadinović, Hrvoje Brkić, Anđela Grgić, Marija Raguž, and Kristina Kralik—will continue the development of our journal.

The editorial team is pleased to present the new Volume 7, Number 2, 2023 issue of the Southeastern European Medical Journal (SEEMEDJ). This issue includes articles from various specialties in medicine, such as cardiology, internal medicine, pediatrics, psychiatry, addictions, public health, health studies, and an article on the history of medicine. The themes of the articles are truly intriguing and interesting.

It is also important to highlight the artwork on the cover page of this issue. It features a pencil drawing on paper by Julije Knifer, titled "Meandar," 10-23 XI.78 Zg, 1978, from the fund of the Museum of Fine Arts in Osijek (MLU – 4838).

On behalf of the editorial board and myself, I warmly greet our readers and invite them to join us in publishing their own scientific work with the Southeastern European Medical Journal (SEEMEDJ). Together, let us continue to illuminate the path ahead, guided by the spirit of inquiry, compassion, and progress in the ever-intriguing field of medicine.

Sincerely,

Dunja Degmečić
Editor-in-Chief

Original article

Sex-Related Differences in Characteristics and Therapy of Heart Failure Patients

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Abstract

Aim: To determine the differences in comorbidities, therapy and echocardiographic measures among patients hospitalized for heart failure relative to gender.

Methods: The study included patients hospitalized for heart failure at the Department of Cardiovascular Diseases of the Clinical Hospital Center Osijek in the period from 1 January 2020 to 30 March 2021.

Results: There were 200 patients included in the study, of which 100 (50%) were male and 100 (50%) were female. Female patients were older, while male patients more frequently had a history of coronary artery disease. Men had a higher dose of loop diuretic on admission to the hospital. No significant difference was found in the representation of beta blockers and ACE inhibitors in therapy with regard to gender. On the other hand, men more frequently used MRA, sacubitril/valsartan and antiplatelet medication at hospital admission. Male patients had a larger left ventricular end-diastolic diameter, left ventricular end-systolic diameter and a lower left ventricular ejection fraction (EF). Regarding the type of heart failure according to EF, 72% of men had HFrEF, 20% HFmrEF and 8% HFpEF. In women, 47% had HFrEF, 33% HFmrEF and 20% HFpEF. During hospitalization due to heart failure, 22 patients died, an equal number of men and women.

Conclusion: This research confirmed the differences in risk factors and pathophysiology of heart failure between males and females. Medicine is progressing towards an individual approach to each patient, so further research will be needed to find the best therapy for both male and female patients

(Dragila Ž*, Gvozdanović L, Marušić R, Maričić L. Sex-Related Differences in Characteristics and Therapy of Heart Failure Patients. SEEMEDJ 2023; 7(2); 1-10)

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KEYWORDS: very low birth weight, comorbidity, cerebral intraventricular hemorrhage, necrotizing enterocolitis

Introduction

Heart failure (HF) is a clinical syndrome that includes symptoms and signs that arise due to structural and/or functional heart disorders. The most common cause is systolic (with or without diastolic) myocardial dysfunction. Other factors contributing to the development of HF include pathology of the heart valves and pericardium, heart rhythm and conduction disorders. According to the 2021 guidelines of the European Society of Cardiology with regard to ejection fraction (EF), HF is divided into: HF with reduced EF (HFrEF) (< 40%), mildly reduced EF (HFmrEF) (40–49%) and preserved EF (HFpEF) (≥ 50%) (1). It is believed that the prevalence of HF in the world is about 64.3 million. In developed countries, about 1–2% of the population is diagnosed with HF. About half of patients have preserved EF, and it is believed that this percentage is increasing (2).

Gender differences in patients with HF exist in disease distribution, outcome and risk factors that lead to HF. Women have a lower incidence of HF than men in all age groups, except those older than 74 years. However, women still make up half of HF patients in terms of disease prevalence because women have higher life expectancy. In addition, a smaller percentage of women undergo hospitalization for HF, but those who go on to be hospitalized, are hospitalized in more advanced stages of HF (3). Although the prognosis of HF is poor in both sexes, it is known that mortality is higher in men (4). The pathophysiology of HF differs in men and women. In men, the occurrence of HF is more common as a result of direct injury to the myocardium during ischemia, leading to focal fibrosis at the site of the injury and eccentric hypertrophy, i.e. dilation of the ventricles and ultimately reduced EF. On the other hand, HFpEF is more common in women, which is the result of chronic inflammation as part of comorbidities such as obesity, hypertension and diabetes mellitus, which leads to myocardial remodeling and interstitial fibrosis (5).

Although the number of patients with HF is equal with regard to gender, most studies do not emphasize the differences in the etiology, pathophysiology and treatment of HF in men and women. The aim of this study was to examine the differences in comorbidities, therapy and echocardiographic measurements of patients hospitalized for HF with regard to gender.

Patients and methods

Study design

The research was designed as a cross-sectional study with historical data at the Department of Cardiovascular Diseases of the Clinical Hospital Center Osijek. The research was approved by the Ethics Committee of the Osijek Faculty of Medicine of the Josip Juraj Strossmayer University of Osijek (CLASS: 602-04/20-08/07; REG. NO.: 2158-61-07-20-183).

Patients

The study included patients hospitalized for heart failure at the Department of Cardiovascular Diseases of the Clinical Hospital Center Osijek in the period from 1 January 2020 to 30 March 2021, when the target number of 200 subjects was reached. The exclusive criterion was patients with myocardial infarction and active malignant disease. During hospitalization due to heart failure, 22 patients died and therefore data on therapy at discharge were available for 178 patients.

Methods

Data on patients were collected by searching the hospital information system. The patients' age, gender, comorbidities (hypertension, diabetes mellitus, chronic obstructive pulmonary disease, aortic stenosis and atrial fibrillation), vital signs on arrival (systolic and diastolic arterial pressure, blood oxygen saturation and heart rate) and the number of prior hospitalizations were recorded. It was recorded if the patient had a beta blocker, angiotensin-converting enzyme (ACE) inhibitor, sacubitril/valsartan, mineralocorticoid receptor antagonist (MRA), loop diuretic, calcium channel blocker, antiplatelet and anticoagulant therapy at admission as well as at discharge. In laboratory findings at admission, the values of

leukocytes, neutrophils, lymphocytes, erythrocytes, red blood cell distribution width (RDW), hemoglobin, thrombocytes, glucose, creatinine, urate, C-reactive protein (CRP), albumin, N-terminal proB type natriuretic peptide (NT-proBNP), sodium and potassium

were monitored. During hospitalization, all patients underwent echocardiography, where data on left ventricular EF, left atrium diameter, left ventricular diameter in diastole and systole as well as tricuspid annular plane systolic excursion (TAPSE) were recorded. Patients were divided into two groups based on gender (male and female).

Statistical analysis

Categorical data were presented in absolute and relative frequencies. Differences in categorical variables were tested with the χ2-test. The normality of the distribution of numerical variables was tested with the Shapiro-Wilk test. Numerical data will be described by the arithmetic mean and standard deviation in the case of distributions that follow the normal and in other cases by the median and the limits of the interquartile range. Differences in numerical variables between two independent groups were tested with the Student's t-test in the case of distributions that follow the normal and in other cases by the Mann-Whitney U test. All P values are two-sided. The significance level was set at Alpha = 0.05. The statistical program MedCalc Statistical Software version 19.1.7.(MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020) was used for statistical analysis

Results

There were 200 patients included in the study, of which 100 (50%) were male and 100 (50%) were female. The median age was 76 years, interquartile range (73–79 years). Regarding age, female patients were older than male patients (median 79 years vs. 72 years, P < 0.001, Mann-Whitney U test). The most common comorbidity was hypertension (172 patients, 86%), followed by atrial fibrillation (120 patients, 60%) and coronary artery disease (80 patients, 40%). Diabetes mellitus was present in 68 (34%) patients. A significantly higher incidence of coronary artery disease was observed in male patients (51% of men vs. 29% of women, P =0.002, χ2 test) (Table 1).

At hospital admission, most patients had in therapy a beta blocker (140 patients, 70%), an ACE inhibitor (119 patients, 59.5%) and a loop diuretic (121 patients, 60.5%). Male patients had a higher dose of loop diuretic at hospital admission (median 80 mg in men versus 40 mg in women, P < 0.001, Mann-Whitney U test). No significant difference was found in the representation of beta blockers and ACE inhibitors in therapy with regard to gender. On the other hand, male patients more frequently used MRA (39% of men and 23% of women, P = 0.01, χ2 test), sacubitril/valsartan (20% of men and 4% of women, P < 0.001, χ2 test) and

Table 1. Sex-related differences in comorbidities of heart failure patients

		Male N (%)	Female N (%)	*P*˚	Total N (%)
Comorbidity	Hypertension	90 (52.3)	82 (47.7)	0.1	172 (86)
	Diabetes mellitus	39 (57.4)	29 (42.6)	0.14	68 (34)
	CAD	51 (63.7)	29 (36.2)	**0.002**	80 (40)
	Aortic stenosis	22 (48.9)	23 (51.1)	0.87	45 (22.5)
	Atrial fibrillation	61 (50.8)	59 (49.2)	0.77	120 (60)
	COPD	18 (62.1)	11 (37.9)	0.16	29 (14.5)
First hospitalization		53 (47.7)	58 (52.3)	0.48	111 (55.5)
Total		100 (50)	100 (50)		200 (100)

CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease

Table 2. Sex-related differences in therapy on admission of heart failure patients

		Male N (%)	Female N (%)	*P**	Total N (%)
Therapy on admission	Beta blockers	73 (52.1)	67 (47.9)	0.36	140 (70)
	ACE inhibitors	61 (51.3)	58 (48.7)	0.67	119 (59.5)
	MRA	39 (62.9)	23 (37.1)	**0.01**	62 (31)
	Sacubitril / valsartan	20 (83.3)	4 (16.7)	**<0.001**	24 (12)
	Loop diuretic	60 (49.6)	61 (50.4)	0.89	121 (60.5)
	SGLT2 inhibitor	2 (50)	2 (50)	>0.99	4 (2)
	Other diuretics†	22 (53.7)	19 (46.3)	0.6	41 (20.5)
	CCB	20 (47.6)	22 (52.4)	0.73	42 (21)
	Antithrombotic	36 (66.7)	18 (33.3)	**0.004**	54 (27)
	Anticoagulant	38 (50)	38 (50)	>0.99	76 (38)
Total		100 (50)	100 (50)		200 (100)

MRA = mineralocorticoid receptor antagonist; SGLT2 = sodium-glucose cotransporter-2; CCB = calcium channel blockers

* $\chi 2$ test

† torasemide, indapamide, hydrochlorothiazide

antiplatelet drugs (36% of men and 18% of women, P = 0.004, $\chi 2$ test) at admission to the hospital (Table 2). During hospitalization due to heart failure, 22 patients died, an equal number of men and women.

At discharge from the hospital, 161 (80.5%) patients had a beta blocker, 117 (65.7%) an ACE inhibitor and 168 (94.4%) loop diuretic. No significant gender difference was found in the prescribed beta blockers. ACE inhibitors were more often prescribed to female patients (49% of men and 68% of women, P = 0.003, $\chi 2$ test), while male patients were more often prescribed sacubitril/valsartan (35% of men and 11% of women, P < 0.001, $\chi 2$ test) (Table 3).

Table 3. Sex-related differences in therapy on discharge of heart failure patients

		Male N (%)	**Female N (%)**	***P****	**Total N (%)**
Therapy on discharge	Beta blockers	80 (49.7)	81 (50.3)	0.77	161 (80.5)
	ACE inhibitors	49 (41.9)	68 (58.1)	**0.003**	117 (65.7)
	MRA	67 (54.5)	56 (45.5)	0.08	123 (69.1)
	Sacubitril / valsartan	35 (76.1)	11 (23.9)	**<0.001**	46 (25.8)
	Loop diuretic	83 (49.4)	85 (50.6)	0.52	168 (94.4)
	SGLT2 inhibitor	5 (83.3)	1 (16.7)	0.1	6 (3.4)
	Other diuretics†	10 (52.6)	9 (47.4)	0.81	19 (10.7)
	CCB	12 (37.5)	20 (62.5)	0.12	32 (18)
	Antithrombotic	26 (53.1)	23 (46.9)	0.62	49 (27.5)
	Anticoagulant	61 (52.1)	56 (47.9)	0.43	117 (65.7)
Total		100 (50)	100 (50)		200 (100)

MRA = mineralocorticoid receptor antagonist; SGLT2 = sodium-glucose cotransporter-2; CCB = calcium channel blockers

* $\chi 2$ test

† torasemide, indapamide, hydrochlorothiazide

Table 4. Sex-related differences in laboratory measurements of heart failure patients

	Male median (IQR)	Female median (IQR)	*P**	Total median (IQR)
Age (years)	72 (62.5 – 81)	79 (69.5 – 84)	**<0.001**	76 (73 – 79)
Loop diuretic dose (mg)	80 (40 – 125)	40 (40 – 80)	**<0.001**	80 (40 – 80)
Heart rate (/min)‡	102 (29)	100 (31)	0.58†	101 (30)
Systolic blood pressure (mmHg)‡	130 (25)	133 (29)	0.37†	132 (27)
Diastolic blood pressure (mmHg)	80 (70 – 90)	79 (67 – 89)	0.16	80 (78 – 80)
Blood oxygen saturation (%)	96 (92 – 97)	93 (89 – 96)	**0.002**	95 (94 – 95)
Leukocytes ($x10^9$/L)	8.6 (6.6 – 11.8)	8.7 (7.1 – 11.7)	0.61	8.7 (8.3 – 9.4)
Neutrophils (%)	73 (67 – 79)	73 (66 – 81)	0.93	73 (72 – 74)
Lymphocytes (%)	16 (10 – 22)	16 (11 – 23)	0.95	16 (15 – 18)
Erythrocytes ($x10^{12}$/L)	4.6 (4.1 – 5.1)	4.2 (3.8 – 4.6)	**<0.001**	4.4 (4.2 – 4.5)
RDW (%)	14.6 (13.8 – 16.5)	15 (13.8 – 16.4)	0.59	14.9 (14.5 – 15.3)
Hemoglobin (g/L)	138 (120 – 150)	120 (107 – 132)	**<0.001**	127 (123 – 129)
Thrombocytes ($x10^9$/L)	191 (149 – 247)	224 (184 – 275)	**0.008**	210 (196 – 225)
Glucose (mmol/L)	7.1 (6.2 – 9.1)	8.1 (6.5 – 11)	**0.04**	7.8 (7.2 – 8.1)
Urea (mmol/L)	9.2 (7.1 – 14.4)	9.5 (7.5 – 13.9)	0.86	9.5 (9 – 10.5)
Creatinine (μmol/L)	118 (93.5 – 148)	101 (79 – 133)	**0.02**	110.5 (104 – 118)
C reactive protein (mg/L)	9.8 (5.7 – 23.5)	11.1 (5.1 – 22.2)	0.91	10.9 (9.1 – 12.9)
Urate (μmol/L)	512 (432 – 646)	466 (355 – 634)	0.06	489 (458 – 542)
Albumin (g/L)	36 (33 – 39)	36 (32 – 39)	0.76	36 (35 – 37)
Sodium (mmol/L)	139 (136 – 141)	139 (137 – 141)	0.48	139 (139 – 140)
Potassium (mmol/L)‡	4.3 (0.6)	4.2 (0.6)	0.5†	4.2 (0.6)
NT-proBNP (pg/L)	5,569 (2,362 – 12,134)	6,780 (2,724 – 12,477)	0.31	6,352 (5,211 – 7,565

IQR = interquartile range; RDW = red blood cell distribution width; NT-proBNP = N-terminal probrain natriuretic peptide

* Mann-Whitney U test

† Student's t-test

‡ expressed as arithmetic mean (standard deviation)

The arithmetic value (standard deviation) of systolic arterial pressure was 132 mmHg (27), and median diastolic arterial pressure was 80 mmHg (interquartile range 78–80 mmHg). No significant difference was found regarding gender. Male patients had significantly higher blood oxygen saturation (96% vs. 93%, P = 0.002, Mann-Whitney U test). Regarding laboratory findings, male patients had significantly more erythrocytes (4.6 vs. 4.2x1012/L, P < 0.001, Mann-Whitney U test),

Table 5. Sex-related differences in echocardiographic measurements of heart failure patients

	Male median (IQR)	Female median (IQR)	*P**	Total median (IQR)
LA (mm)	50 (45 – 53)	47 (44 – 52)	**0.04**	48 (47 – 50)
LVEDD (mm)‡	58.1 (8.7)	50.8 (9.6)	**<0.001**†	54.4 (9.8)
LVESD (mm)‡	47.7 (9.2)	39.9 (10.1)	**<0.001**†	43.8 (10.4)
EF (%)	33 (25 – 40)	40 (33 – 50)	**<0.001**	35 (34 – 38)
TAPSE (mm)	16 (14 – 20)	18 (14 – 21)	0.26	17 (15 – 18)

LA = left atrial diameter; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; EF = ejection fraction; TAPSE = tricuspid annular plane systolic excursion

* Mann-Whitney U test

† Student's t-test

hemoglobin (138 vs. 120 g/L, P < 0.001, Mann-Whitney U test) and creatinine (118 vs. 101 µmol/L, P = 0.02, Mann-Whitney U test), as well as significantly lower thrombocytes (191 vs. 224x109/L, P = 0.008, Mann-Whitney U test) and glucose (7.1 vs. 8.1 mmol/L, P = 0.04, Mann-Whitney U test) (Table 4). Regarding the echocardiographic measurements, male patients had a larger left atrial diameter (50 vs. 47 mm, P = 0.04, Mann-Whitney U test), left ventricular end-diastolic diameter (58.1 vs. 50.8 mm, P < 0.001, Student's t-test), left ventricular end-systolic diameter (47.7 vs. 39.9 mm, P < 0.001, Student's t-test) and lower left ventricular ejection fraction (33 vs. 40%, P < 0.001, Mann-Whitney U test). The function of the right ventricle was preserved with no difference regarding gender (Table 5). Regarding the type of HF according to EF, 72% of men had HfrEF, 20% HFmrEF and 8% HFpEF. In women, 47% had HFrEF, 33% HFmrEF and 20% HFpEF.

Discussion

In this study, differences in comorbidities, therapy and echocardiographic measurements of patients hospitalized for HF were examined with regard to gender. Regarding comorbidities, no significant difference was found, except for coronary artery disease, which was more common in men. Men were more often prescribed MRA, sacubitril/valsartan, an antiaggregation drug as well as higher doses of loop diuretic, while women were more often prescribed an ACE inhibitor at discharge which is in line with the previous results considering that more men have HFrEF than women. Significant differences in biochemical variables between men and women corresponded with expected sex-related variations. No significant difference was found in survival during hospitalization with regard to gender.

In this study, women were older than men, had a higher EF and less often had ischemic cardiomyopathy or coronary artery disease underlying HF, which is in line with previous studies on the typical presentations of women with HF (6–8). The main difference in the etiology of HF is the greater presence of ischemic heart disease in men, which leads to the activation of certain pathophysiological mechanisms and affects middle-aged men more often. Direct injury of myocytes by ischemia or myocarditis leads to inflammation that will end in eccentric hypertrophy (9). On the other hand, HFpEF is a slowly progressive disease in which no initial event that causes myocardial injury can be found but is a consequence of a long-term chronic pro-inflammatory condition in the setting of different comorbidities (2). This explains the greater proportion of men in patients with HFrEF and the greater proportion of women in patients with HFpEF. Furthermore, the protective role of the female gender and estrogen in certain remodeling patterns and further progression to HF is known. With aging, the protective role of estrogen is lost, which explains the similar incidence of HF in patients in advanced age groups, regardless of gender. In the study by Hall et al. early menopause and nulliparity have been found to increase the risk of developing HF, especially HFpEF (10). In our

study, no difference was found in the presence of hypertension and diabetes mellitus with regard to gender. Although it is known that women with HF more often have comorbidities (such as hypertension and diabetes mellitus), it is important to emphasize that the risk of developing HF in patients with the aforementioned comorbidities varies depending on gender. Namely, in the Framingham heart study, it was found that men with diabetes mellitus have twice the frequency of HF, while women have five times more (11). In a meta-analysis that included more than 12 million patients, the relative risk for developing HF in women with diabetes mellitus type 2 was 1.95 (95% CI 1.70–2.22), while in men it was 1.74 (95% CI 1.55–1.95) (12). Previous research has shown that women had more severe symptoms, more pronounced signs of congestion and a lower quality of life, and despite this, a similar number of hospitalizations due to heart failure (8). NT-proBNP values in our study do not correlate with the level of symptoms, which is in line with other research (13). No significant difference was found in the value of NT-proBNP depending on gender. In our study, the number of men and women treated with loop diuretic was equal, but men had a significantly higher dose. Given that it is known that women appear in advanced stages of HF, unlike men, it is possible that they did not show up on time for control examinations where there was an opportunity to increase the dose.

Guideline-directed medical therapy for HF according to the 2021 guidelines of the European Society of Cardiology is equal regardless of gender (1, 14, 15). Recently, studies have been conducted that show the shortcomings of this uniform approach to treatment, given that there are differences in pharmacokinetics and pharmacodynamics depending on gender, influencing the choice and the dose of the medication (16). Similarly, in previous studies, it was shown that women are not appropriately treated with guideline-directed medical therapy. Fonarow et al. studied gender differences in a total of 48,612 patients from the OPTIMIZE-HF registry and found that significantly fewer women had an ACE inhibitor, beta blocker and MRA in therapy while significantly more women had a loop diuretic (17). In our research, no significant difference was found in the prescribed ACE inhibitor and beta blocker at admission, depending on gender, which represents progress compared to previous research. Significantly more men had MRA on therapy at admission, which is likely a reflection of the higher proportion of HFrEF in men. At discharge from the hospital, significantly more men were prescribed sacubitril/valsartan than women. Studies on the use of sacubitril/valsartan in patients with HFmrEF and HFpEF did not find a significant reduction in heart failure hospitalizations and mortality (18). However, looking at women and men separately, women with HFpEF and HFmrEF benefited more from sacubitril/valsartan in reducing HF hospitalizations than men (19) which leaves room for further studies and emphasizes the need for an individual approach to the treatment of HF. In our study, only a minority of patients were treated with sodium-glucose cotransporter-2 (SGLT2) inhibitors because it was conducted before the results of the EMPULSE trial were published (20, 21).

Differences in echocardiographic measurements between women and men are a reflection of different pathophysiological mechanisms of the origin and progression of HF. Myocardial remodeling in men leads to left ventricular dilatation and fibrosis. On the other hand, women experience concentric hypertrophy and a decrease in the volume of the left ventricle (6, 22). In our study, women had a smaller diameter of the left atrium and a smaller diameter of the left ventricle in systole and diastole. On the other hand, they had higher TAPSE (tricuspid annular plane systolic excursion), i.e. better right ventricular function and left ventricular EF, which is in line with other studies. Women have a higher ejection fraction and TAPSE, which follow diastolic dysfunction and HFpEF, while in men the above measures are lower as a reflection of biventricular systolic dysfunction (23). Sex-related variations in echocardiographic measurements should be noted as confounding factors.

The research was conducted as a cross-sectional study, which is the main limitation of

this research. The therapy was observed at the time of admission and discharge of the patient, but the doses of drugs (except loop diuretic) were not recorded, which makes it impossible to draw more detailed conclusions regarding the differences in the therapy of men and women with HF. Furthermore, the BMI of the patients was not recorded, i.e. the presence of obesity as one of the important risk factors for the development of HF.

Heart failure is a heterogeneous clinical syndrome. Considering the existence of differences in pathophysiological processes between men and women, it is to be expected that there are also differences in risk factors and pathophysiology of HF, which was confirmed in this and other studies. Despite this, women are underrepresented in research on HF therapy. Medicine is progressing towards an individual approach to each patient, so further research will be needed to emphasize these differences and to find the best therapy for both men and women

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Spolno uvjetovane razlike u obilježjima i terapiji srčanih bolesnika

Sažetak

Cilj: Odrediti razlike u komorbiditetima, terapiji i ehokardiografskim mjerenjima među pacijentima hospitaliziranima zbog zatajenja srca u odnosu na spol.

Metode: Studija je uključila pacijente hospitalizirane zbog zatajenja srca na Odjelu za kardiovaskularne bolesti Kliničkog bolničkog centra Osijek u razdoblju od 1. siječnja 2020. do 30. ožujka 2021. godine.

Rezultati: U studiju je bilo uključeno 200 pacijenata, od kojih je 100 (50 %) bilo muškaraca i 100 (50 %) žena. Ženske pacijentice bile su starije, dok su muškarci češće imali povijest koronarne arterijske bolesti. Muškarci su na prijemu u bolnicu primali višu dozu diuretika Henleove petlje. Nije pronađena značajna razlika u zastupljenosti beta blokatora i ACE inhibitora u terapiji s obzirom na spol. S druge strane, muškarci su češće koristili MRA, sakubitril/valsartan i antitrombocitne lijekove pri prijemu u bolnicu. Muški pacijenti imali su veći krajnji dijastolički promjer lijeve klijetke, krajnji sistolički promjer lijeve klijetke i nižu ejekcijsku frakciju (EF) lijeve klijetke. S obzirom na tip zatajenja srca prema EF-u, 72 % muškaraca je imalo HFrEF, 20 % HFmrEF, i 8 % HFpEF. Kod žena, 47 % ih je imalo HFrEF, 33 % HFmrEF i 20 % HFpEF. Tijekom hospitalizacije zbog zatajenja srca, umrla su 22 pacijenta, jednak broj muškaraca i žena.

Zaključak: Ovo istraživanje potvrdilo je razlike u rizičnim čimbenicima i patofiziologiji zatajenja srca između muškaraca i žena. Medicina napreduje prema individualnom pristupu svakom pacijentu, stoga će biti potrebna daljnja istraživanja kako bi se pronašla najbolja terapija za muškarce i žene.

Original article

Neurodevelopmental Outcomes of Very Low Birth Weight Preterm Infants in The Regional Pediatric Clinic

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Abstract

Aim: To examine the incidence and etiology of neurodevelopmental outcomes in very low birth weight preterm infants, maternal and perinatal risk factors, comorbidities, and clinical presentation and compare with newborns of the same gestational age who did not develop a neurodevelopmental disorder.
Methods: The research was conducted at the Pediatric Clinic in KBC (Clinical Hospital Center) Osijek. All newborns born from 1 January 2018 to 31 December 2019 with birth weight < 1,500 g and gestational age < 37 weeks are included in the research. The data were collected by reviewing medical records and the hospital's IT system.
Results: In the observed period, 120 children with birth weight < 1,500 g and gestational age < 37 weeks were born. Maternal and perinatal risk factors for premature birth include autoimmune diseases of the mother, infections during pregnancy and birth complications. Early complications that accompany the selected group are RDS, ROP, NEC, IVH, sepsis, congenital heart defects and glucose metabolism disorder. Slowed motor, cognitive and speech development are mostly influenced by low body weight, higher degree of IVH, lower AS in the first minute and the presence of NEC. Significant risk factors for death are gestational age < 25 weeks, body weight < 800 g, infections in pregnancy and autoimmune diseases of the mother.
Conclusion: The neurodevelopmental outcome of very low birth weight preterm infants depends on a combination of comorbidities, as well as maternal, perinatal and neonatal risk factors.

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KEYWORDS: very low birth weight, comorbidity, cerebral intraventricular hemorrhage, necrotizing enterocolitis

Introduction

Definition

Very low birth weight (VLBW) infants refer to infants born before 37 weeks of gestation with a birth weight of less than 1,500 g. VLBW infants are more prone to develop morbidities throughout life, including cerebral palsy (CP), cognitive delays, psychomotor delay, blindness, deafness and other chronic diseases. The incidence of VLBW varies globally, with approximately 11.5% in underdeveloped countries and 9.3% in middle to high-income countries. In Croatia in 2021, out of 36,991 births, 2,500 were preterm and 13% of preterm births were VLBW infants (1).

The etiology of preterm births is multifactorial, with 50% being unknown, and the other half being attributed to factors such as maternal disease, age, obstetric and placental complications, fetal anomalies, etc. (2).

Short-term complications of prematurity

Due to their physiological and anatomical characteristics and functional immaturity, preterm infants are at higher risk of both short-term and long-term complications. The most common short-term complications include respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), early-onset sepsis, intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL).

Neurodevelopmental complications

Neurodevelopmental disorders can be divided into low-risk (speech, communication, behavior and learning disorders) and high-risk groups (mental retardation, epilepsy, CP). Research indicates that 30–60% of VLBW children show neurological deficits, with 10–15% developing CP. CP is a group of non-progressive movement and posture disorders caused by damage to the immature brain. The world's prevalence ranges from 2.0 to 2.8 per 1,000 live births. In Croatia, in 2022, there were 24,698 individuals with CP and other paralytic syndromes. The incidence of CP has increased by over 20%, which is linked to improved survival of VLBW infants, representing 35% of CP cases (2, 3).

Diagnosis

The diagnosis of neuromotor deviations involves clinical examination, radiological diagnostic methods, evoked potentials, psychological and speech therapist evaluations and others.

Brain ultrasound (US) has become the gold standard in diagnosing perinatal brain damage, offering high predictive value for neurodevelopmental deviations. The outcome depends on the location, size and type of lesion.

Common findings include IVH and PVL. The incidence of periventricular-intraventricular hemorrhage is inversely proportional to gestational age, with an overall incidence of 15 to 40%, and for VLBW infants, it is 25%. Another US-significant finding is PVL: a symmetric infarction of white matter, i.e. hypoxic-ischemic damage in the border zones of vascular supply. The incidence ranges from 4 to 7% with long-term consequences in 35–90% of cases (4).

Treatment

A multidisciplinary approach is the preferred therapy adapted to the individual based on the clinical presentation and therapeutic possibilities (5). The goal is to re-establish the function of damaged areas of the central nervous system based on brain neuroplasticity (6). The most common are Bobath, Vojta, medical gymnastics, baby handling, sensory integration and supportive pharmacotherapy for CP.

Participants and methods

All live-born infants born in the period from 1 January 2018 to 31 December 2019, at the Department of Pediatrics, Clinical Hospital Center Osijek, were included in the study. A total of 120 infants of both genders were enrolled. The inclusion criteria for participants were birth weight < 1,500 g and gestational age < 37 weeks. Exclusion criteria were infants with birth weight > 1,500 g, gestational age > 37 weeks, as well as

newborns who received palliative care immediately after birth.

Data were collected by reviewing the medical documentation and the hospital information system. The collected information included perinatal, neonatal and postnatal risk factors, comorbidities, information about the child's condition, laboratory characteristics in the first 72 hours of life, parameters of mechanical ventilation, the occurrence of neurodevelopmental abnormalities at the age of three and treatment options.

Results

In the observed period, at the Clinical Hospital Center Osijek, 3,754 children were born, of which 120 were VLBW preterm infants, constituting an incidence of 3.19%. The study involved 110 mothers and 120 preterm infants. Early perinatal characteristics of preterm infants are presented in Table 1.

Table 1. Early perinatal characteristics of preterm infants with a birth weight below 1,500 g (n = 120)

	Number of infants	Median (IQR)	Minimum - Maximum
Gestational age (weeks)	120	28+6 (25+3 to 31+2)	22–36
Birth weight (g)	120	1,066 (763–1,347.8)	400–1,499
Length (cm)	120	36 (32–39)	22–43
Apgar 1'	120	6 (3–9.8)	0–10
Apgar 5'	120	8 (6–10)	1–10

n – number, IQR – interquartile range, g – gram, cm – centimeter, Apgar 1' and 5' – Apgar at 1 minute and 5 minutes

Table 2. Interventions and procedures during the stay of preterm infants with birth weight below 1,500 g (n = 120)

	Number of kids	Median (IQR)	Minimum – maximum
Incubator (days)	120	24 (11–40)	1–109
O2 (days)	120	22 (8.3–40.8)	1–115
Infusion (days)	115	11 (6–24)	1–90
Phototherapy (hours)	118	10 (0–22.5)	0–60
Non-invasive support [n = 88 (73.3%)]			
Duration of non-invasive support (days)	88	11 (5–23)	1–51
Invasive support [n = 54 (45%)]			
Duration of invasive support (days)	54	6.5 (2–15)	1–66
Additional oxygenation (days)	90	19 (12–25)	4–45
Maximum % of oxygen during additional oxygenation	90	30 (30–30)	20–40
Total oxygenation (days)	119	26 (12–46)	0–126

O2 – oxygen, n – number, IQR – interquartile range

All preterm infants required care in an incubator for a period ranging from 1 to 109 days, with a median of 24 days. Oxygenation was necessary for all infants, and they received oxygen for 1 to 115 days, with a median of 22 days. Infusion with glucose-electrolyte support was provided for a period ranging from 1 to 90 days, with a median of 11 days. Due to the occurrence of

hyperbilirubinemia, 118 (98.3%) preterm infants received phototherapy for a duration of up to 60 hours, with a median of 10 hours. Mechanical ventilation was used as a means of respiratory support for most participants: 88 (73.3%) received non-invasive respiratory support for a duration of 1 to 51 days, and 54 (45%) received invasive support for a duration of 1 to 66 days (Table 2)

Out of early complications, RDS was present in 96 (80%) preterm infants, 65 infants had IVH: 10 with 1st degree, 32 with 2nd degree, 20 with 3rd degree, 3 with 4th degree and 20 with 5th (leukomalacia). ROP was present in 44 (36.7%) preterm infants, most commonly found in Zone 2. NEC occurred in 31 (25.8%) preterm infants, and 5 (4.2%) preterm infants did not survive. Most cases were grade 1A. Early sepsis was present in 48 (40%) preterm infants, while late sepsis occurred in 40 (33.3%). Isolated bacterial cultures included MRSA, Streptococcus/Enterococcus and Pseudomonas/E. coli/Morganella. Among neurological abnormalities, CP was present in 5 (4.2%) preterm infants, seizures in 15 (12.5%) preterm infants, and high neuro-risk children constituted 12 (10%) cases.

Eleven (9.9%) mothers had gynecological diseases. Hematological disorders were present in 8 (7.5%) mothers, of whom 7 out of 8 had anemia. Autoimmune diseases were recorded in 38 (34.4%) mothers, infections during pregnancy in 37 (33.6%) of them, and six (5.4%) mothers had other diseases. Fatal outcomes occurred in 30 (25%) preterm infants, mostly with extremely low birth weight and gestation, with a median weight of 613 g and low Apgar scores (AS) at 1 and 5 minutes. The median time to death was 3 days.

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Table 3. Characteristics of premature infants with fatal outcomes compared to survivors

	Survived (n = 90)	**Died (n = 30)**	*P*
Birth weight (grams) [Median (IQR)]	1,199.5 (915–1,427)	613 (504.3–807.3)	**<0.001‡**
Apgar 1' [Median (IQR)]	8 (5–10)	3 (2–5)	**<0.001‡**
Apgar 5' [Median (IQR)]	9 (7–10)	5 (2–7)	**<0.001‡**
Number of days until death [Median (IQR)]	-	2 (1–8)	-
Corticosteroids [n(%)]	61 (68)	17 (57)	0.27*
Surfactant [n(%)]	50 (56)	7 (23)	**0.04***
Mechanical ventilation [n(%)]			
Invasive	43 (48)	11 (37)	0.29*
Non-invasive	85 (94)	3 (10)	**<0.001***
Chromosomal abnormalities [n(%)]	8 (9)	5 (17)	0.31*
Mothers' infections [n(%)]	32 (36)	15 (50)	0.16*
Mothers' autoimmune disease [n(%)]	24 (27)	10 (33)	0.49*
Brain US (n=12) [n(%)]			
I degree of IVH			
II degree of IVH	13 (16)	1 / 12	**0.001‡**
III degree of IVH	33 (41)	4 / 12	
IV degree of IVH	14 (17)	4 / 12	
IV degree of IVH	0	3 / 12	
V degree (leukomalacia)	21 (26)	0	

Apgar 1', 5' – Apgar sum at 1 minute and 5 minutes, US – ultrasound, g – grams, n – number, IQR – interquartile range *Chi-square test; ‡Fisher's exact test; ǂMann-Whitney U test

Seventeen (57%) of them received corticosteroid therapy, and 11 (37%) were on invasive mechanical ventilation. Chromosomal abnormalities were noted in 5 (17%) cases, mother's infection in 15 (50%) and autoimmune disease in 10 (33%) cases. Four out of twelve preterm infants had grade II or III IVH (Table 3).

There are no significant differences in neurodevelopmental outcomes and comorbidities in preterm infants with a birth weight below 1,500 g concerning maternal diseases during pregnancy (Table 4)

Table 4. Neurodevelopmental outcomes and comorbidities in preterm infants with a birth weight below 1,500 g concerning maternal diseases during pregnancy

	Number (%)			*P*
Motoric development	**Delayed**	**Average**		
Infection in pregnancy	10 (40)	20 (32)		0.49*
Mothers' autoimmune disease	5 (20)	18 (29)		0.39*
Number of drugs in pregnancy				
One	3 (15)	6 (11.3)		0.92†
Two	3 (15)	9 (17)		
Two or more	14 (70)	38 (71.7)		
Corticosteroids	16 (64)	42 (48)		0.80*
Antibiotics	9 (36)	34 (54)		0.16*
Speech	**Delayed**	**Average**	**Does not speak**	
Infection in pregnancy	12 (44)	17 (30)	1 / 2	0.32†
Mothers' autoimmune disease	7 (26)	14 (25)	1 / 2	0.68†
Number of drugs in pregnancy				
One	3 (13)	5 (10.4)	1 / 2	0.53†
Two	3 (13)	9 (18.8)	0	
Two or more	17 (73.9)	34 (70.8)	1 / 2	
Corticosteroids	6 (22)	15 (26)	1 / 2	0.60†
Antibiotics	11 (41)	31 (54)	1 / 2	0.67†
Convulsions/ epilepsy	**No**	**Yes**		
Infection in pregnancy	40 (38)	7 (47)		0.53*
Mothers' autoimmune disease	31 (29)	3 (20)		0.55*
Number of drugs in pregnancy				
One	11 (12.6)	1 (7.7)		0.91†
Two	18 (20.7)	2 (15.4)		
Two or more	58 (66.7)	10 (76.9)		
Corticosteroids	68 (65)	10 (67)		>0.99†
Antibiotics	55 (52)	7 (47)		0.79†
Cognitive development	**Delayed**	**Average**		
Infection in pregnancy	11 (44)	19 (31)		0.32*
Mothers' autoimmune disease	5 (20)	17 (28)		0.59*
Number of drugs in pregnancy				
One	2 (9.5)	7 (13.5)	9 (12.3)	0.92†
Two	3 (14.3)	9 (17.3)	12 (16.4)	
Two or more	16 (76.2)	36 (69.2)	52 (71.2)	
Corticosteroids	19 (76)	39 (64)		0.32*
Antibiotics	10 (40)	33 (54)		0.34†

*χ^2 test; †Fisher's exact test

Delayed motor development is seen in infants with lower birth weight (P = 0.03), lower AS at the first minute (P = 0.04) and a significantly higher incidence of NEC (P = 0.02). Delayed speech is significantly associated with lower birth weight (P = 0.03) and the presence of NEC (P = 0.04). Seizures are significantly more common in preterm infants with NEC (P = 0.001) and a higher degree of IVH (P = 0.008).

Table 5. Neurodevelopmental outcomes and comorbidities in preterm infants with birth weight below 1,500 g in relation to perinatal risk factors

	Number (%) of infants			*P*
Motor development	**Delayed**	**Average**		
Birth weight (grams) [Median (IQR)]	1,024 (780–1,308)	1,229 (1,037–1,481)		**0.03‡**
Apgar 1' [Median (IQR)]	6 (4–9)	9 (5–10)		**0.04‡**
Apgar 5' [Median (IQR)]	8 (7–10)	9 (8–10)		0.07‡
Early sepsis	10 / 10	27 (87)		0.56†
Late-onset sepsis	14 / 14	22 (96)		>0.99†
NEC	11 (48)	12 (21)		**0.02***
Jaundice	5 (20)	24 (38)		0.09*
Brain US [n(%)]				
I degree of IVH	1 (4.8)	11 (19)		0.33†
II degree of IVH	9 (42.9)	23 (39.7)		
III degree of IVH	3 (14.3)	11 (19)		
V degree (leukomalacia)	8 (38.1)	13 (22.4)		
Speech	**Delayed**	**Average**	**Does not speak**	
Birth weight (grams) [Median (IQR)]	1,070 (760–1,241)	1,217 (985–1,491)	1,340 (882–1,130)	**0.03§**
Apgar 1' [Median (IQR)]	7 (5–9)	9 (5–10)	9 (7–10)	0.06§
Apgar 5' [Median (IQR)]	8 (7–10)	9 (7–10)	10 (10–10)	0.22§
Early sepsis	10 / 12	26 (93)	0	0.57*
Late-onset sepsis	17 / 17	18 (95)	0	>0.99*
NEC	12 (46)	11 (20)	0	**0.04†**
Jaundice	8 (30)	20 (35)	0	0.74†
Brain US [n(%)]				
I degree of IVH				
II degree of IVH	2 (9.1)	10 (18.5)	0	0.19†
III degree of IVH	8 (36.4)	22 (40.7)	1 / 2	
IV degree of IVH	2 (9.1)	12 (22.2)	0	
V degree (leukomalacia)	10 (45.5)	10 (18.5)	1 / 2	
Convulsions/ epilepsy	**No**	**Yes**		
Birth weight (grams) [Median (IQR)]	1,106 (780–1,368)	825 (660–1,024)		0.07‡
Apgar 1' [Median (IQR)]	7 (3–10)	6 (–8)		0.70‡
Apgar 5' [Median (IQR)]	8 (6–10)	8 (6–9)		0.46‡
Early sepsis	42 (91)	6 / 6		>0.99†
Late-onset sepsis	35 (97)	5 / 5		>0.99†
NEC	21 (26)	10 / 14 (71)		**0.001†**
Jaundice	29 (28)	2 / 15 (13)		0.35†
Brain US [n(%)]				
I degree of IVH	14 (17.3)	0		**0.03†**
II degree of IVH	34 (42)	3 (25)		
III degree of IVH	14 (17.3)	4 (33.3)		
IV degree of IVH	1 (1.2)	2 (16.7)		
V degree (leukomalacia)	18 (22.2)	3 (25)		
Cognitive development	**Delayed**	**Average**		
Birth weight (grams) [Median (IQR)]	1,070 (770–1,234)	1,230 (1,001–1,491)		**0.004‡**
Apgar 1' [Median (IQR)]	7 (5–10)	9 (5–10)		0.21‡
Apgar 5' [Median (IQR)]	8 (7–10)	9 (7–10)		0.80‡
Early sepsis	9 / 9	27 (87)		0.56†
Late-onset sepsis	14 / 14	21 (96)		>0.99†
NEC	11 (50)	12 (20)		**0.008†**
Jaundice	4 (16)	24 (39)		**0.04†**
Brain US [n(%)]				
I degree of IVH	3 (13.6)	9 (16.1)		**0.008†**
II degree of IVH	5 (22.7)	26 (46.4)		
III degree of IVH	2 (9.1)	12 (21.4)		
V degree (leukomalacia)	12 (54.5)	9 (16.1)		

Apgar 1', 5' – Apgar score at 1 minute and 5 minutes, NEC – necrotizing enterocolitis, US – ultrasound, g – grams, n – number, IQR – interquartile range *Chi-square test; †Fisher's exact test; ‡Mann-Whitney U test; §Kruskal-Wallis test

Table 6. Retinopathy, bronchopulmonary dysplasia, occurrence of bronchitis, visual impairments and gastrointestinal diseases in preterm infants with birth weight below 1,500 g in relation to perinatal risk factors

ROP	**No**	**Yes**	***P***
Birth weight (grams) [Median (IQR)]	1,229 (875–1,443)	1,099 (803–1,270)	**0.02‡**
Apgar 1' [Median (IQR)]	8 (4–10)	7 (5–10)	0.65‡
Apgar 5' [Median (IQR)]	9 (7–10)	9 (7–10)	0.80‡
Mechanical ventilation [n(%)]			
invasive	22 (44)	29 (66)	**0.03**†
non-invasive	41 (82)	44 (100)	**0.003**†
Early sepsis	19 (86)	19 (95)	0.61†
Late-onset sepsis	16 (94)	23 (100)	0.43†
NEC	14 (29)	16 (39)	0.33*
BPD	**No**	**Yes**	
Birth weight (grams) [Median (IQR)]	490	846 (64–1,029)	-
Apgar 1' [Median (IQR)]	6	6 (3–10)	-
Apgar 5' [Median (IQR)]	8	8 (7–10)	-
Mechanical ventilation [n(%)]			
invasive	0	17 (81)	0.23†
non-invasive	0	21 (100)	0.05†
Early sepsis	1 / 1	6 / 6	-
Late-onset sepsis	0	14 / 14	-
NEC	0	11 / 18 (61)	-
Bronchitis	**No**	**Yes**	
Birth weight (grams) [Median (IQR)]	1,058 (720–1,375)	1,098 (848–1,247)	0.98‡
Apgar 1' [Median (IQR)]	6 (3–9)	9 (6–10)	**0.03**‡
Apgar 5' [Median (IQR)]	8 (6–10)	9 (7–10)	0.07‡
Mechanical ventilation [n(%)]			
invasive	0	17 (81)	0.23†
non-invasive	0	21 (100)	0.05†
Early sepsis	1 / 1	6 / 6	**-**
Late-onset sepsis	0	14 / 14	-
NEC	0	11 / 18 (61)	-
Feeding difficulty	**No**	**Yes**	
Birth weight (grams) [Median (IQR)]	1,084 (780–1,356)	716 (602–1,171)	0.09‡
Apgar 1' [Median (IQR)]	6 (3–9)	7 (5–10)	0.55‡
Apgar 5' [Median (IQR)]	8 (6–10)	8 (8–10)	0.48‡
Mechanical ventilation [n(%)]			
invasive	48 (42)	6 / 6	**0.007†**
non-invasive	82 (72)	6 / 6	0.19†
Early sepsis	46 (92)	2 / 2	>0.99†
Late-onset sepsis	34 (97)	6 / 6	>0.99†
NEC	28 (31)	3 / 6	0.38†

GI diseases	**Celiac disease**	**Hernia**	**Anomalies**	
Birth weight (grams) [Median (IQR)]	1,262 (895–1,497)	1,075 (745–1,281)	834 (596–1,379)	0.33§
Apgar 1' [Median (IQR)]	9 (5–10)	8 (–9)	7 (4–10)	0.55§
Apgar 5' [Median (IQR)]	9 (8–10)	9 (6–9)	8 (6–10)	0.67§
Mechanical ventilation [n(%)]				
invasive	2 / 4	4 / 6	2 / 4	>0.99†
non-invasive	4 / 6	6 / 6	2 / 4	0.13†
Early sepsis	1 / 2	0	**1 / 3**	>0.99†
Late-onset sepsis	1 / 1	3 / 3	2 / 2	-
NEC	1 / 4	4 / 6	2 / 4	0.79†

ROP – retinopathy of prematurity, Apgar 1', 5' – Apgar score at 1 minute and 5 minutes, NEC – necrotizing enterocolitis, US – ultrasound, BPD – bronchopulmonary dysplasia, GI diseases – gastrointestinal diseases, g – grams, n – number, IQR – interquartile range *Chi-square test; †Fisher's exact test; ‡Mann-Whitney U test; §Kruskal-Wallis test

Delayed cognitive development is significantly more associated with lower birth weight (P = 0.004), a higher incidence of NEC (P = 0.008), less frequent jaundice (P = 0.04) and a higher incidence of leukomalacia (P = 0.008) (Table 21). ROP is more frequent in preterm infants with lower birth weight (P = 0.02), and in those who underwent either invasive (P = 0.03) or non-invasive (P = 0.003) mechanical ventilation. Feeding difficulties are significantly more present in preterm infants who were on invasive mechanical ventilation (P = 0.003) (Tables 5 and 6).

Discussion

During the observed period, 3,754 children were born, of which 120 were born with a birth weight of less than 1,500 g and a gestational age of less than 37 weeks. Their incidence rate is 3.19%, which is lower than the global prevalence, ranging between 5 to 7% (7, 8). The lower value in this study is attributed to better prenatal care, consistent with the average preterm birth rate in Croatia (9). A total of 30 infants died before reaching the age of three, with the final number of 90 (55.55% boys and 44.45% girls). The data that boys are more likely to be born prematurely are supported by numerous other studies (7, 10). In our study, the median maternal age was 31 years.

Mothers' diseases did not show statistically significant differences in children with normal or pathological neurodevelopmental outcomes but certainly influenced preterm birth, especially autoimmune diseases that were found in 34% of mothers. This is also confirmed by other studies (11). Infections during pregnancy were reported in 37 mothers.

Early perinatal characteristics were explored. The AS at the first minute had a median of 6 with a range from 0 to 10, and at the fifth minute, the median was 8 with a range from 1 to 10. AS values at 5 and 10 minutes did not prove statistically significant in our research, indicating that a combination of multiple risk factors is needed to assess the outcome.

All children spent a certain period in the incubator. The median number of days in the incubator was 24. More than one-third of preterm infants, 36.7% of participants, developed ROP, which is in line with the global prevalence of ROP in VLBW children but lower than the expected prevalence of ROP in Croatia, which is 56.5% (12). The most affected zone was Zone II, correlating with a 2016 study where 56.5% of involvement was in Zone II. Statistically significant risk factors for ROP development were low birth weight and the frequency of invasive and non-invasive ventilation. Additionally, infants on invasive ventilation more often developed feeding difficulties.

NEC occurred in 25.8% of preterm infants, most commonly at Stage 1A. A meta-analysis from 2020 presented data showing that NEC in VLBW infants occurs in the range of 2 to 13%, significantly lower than in our study (13).

A statistically significant finding is IVH, which occurs twice as often in our study than in others (4, 14). IVH increases the risk of permanent psychomotor deviation and reduces the survival of newborns. The pathogenesis of IVH is influenced by low AS, hypoxia, hypercapnia, infections, RDS and many others. The most common finding is Grade II IVH, which is associated with milder neurodevelopmental deviations, and PVL as the most severe degree associated with CP. Forty-five to 85% of VLBW infants with a high grade of IVH develop severe cognitive deficits, and 75% of them require specialized forms of education (15).

Despite the development of neonatal care, sepsis remains a common cause of neonatal morbidity and mortality (16). Our study showed that a statistically significant number of respondents had overcome sepsis, with early-onset sepsis occurring at a higher ratio than late-onset sepsis.

The mortality rate was 25% among newborns, with a median weight of 613 g, AS of 3 at the first minute and 5 at the fifth minute. The median number of days until death was 3 days, indicating progressive deterioration in these patients. Many of them received corticosteroids, surfactants and invasive mechanical ventilation.

Additionally, a statistically significant proportion of children had mothers with infections or autoimmune disorders. In comparison to survivors, they were more likely to be preterm, have lower birth weights, higher degrees of IVH, and received less surfactant or were less on non-invasive mechanical ventilation.

CP incidence was 4.2%, which is similar to A. Pascal's study that was conducted from 2006 to 2018, with a prevalence of 6.5%.

The development of motor, cognitive and speech functions directly correlates with the degree of IVH. Children with the highest degree of IVH achieved the weakest results in motor development. Slower motor development was associated with lower birth weight, lower AS at the first minute and the presence of NEC. Slower speech development was significantly associated with lower birth weight and the presence of NEC. Cognitive development was most influenced by the occurrence of NEC, a higher frequency of leukomalacia, lower birth weight and a lower frequency of jaundice. Seizures were significantly more common in preterm infants with NEC and a higher degree of cerebral hemorrhage.

Regarding the association between maternal diseases during pregnancy and neurodevelopmental outcomes, there were no statistically significant differences. However, preterm infants born by mothers with infections during pregnancy more frequently developed delayed motor and speech development. Similarly, preterm infants whose mothers took more than 2 prescribed drugs during pregnancy more often exhibited delayed motor development, while preterm infants whose mothers took antibiotics during pregnancy more frequently experienced delayed speech development.

Conclusion

Based on the conducted research and collected data, the following conclusions are drawn:

1. The incidence of preterm births with LBW below 1,500 g is 3.19%, which is within the lower European range.

2. The development of motor, cognitive and speech functions is directly related to the degree of IVH. Children with the highest degree of IVH achieve the weakest results. Slower motor development significantly more often occurs in children with a birth weight below 1,000 g, lower AS in the first minute and the presence of NEC. Cognitive development is significantly influenced by lower birth weight, higher degree of IVH with the occurrence of convulsive seizures, the presence of PVL and NEC.

3. The mortality rate occurs in 1/4 of VLBW preterm infants, and it is most common in infants with extremely short gestation below 25 weeks, and birth weight below 800 g, with pregnancy infections and maternal autoimmune diseases being significant risk factors for mortality.

4. Neurodevelopmental outcomes of VLBW preterm infants depend on a combination of various risk factors, including maternal diseases before pregnancy, complications during pregnancy, as well as different comorbidities and complications that occur sooner or later in the development of preterm infants with birth weight less than 1,500 g.

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Critical revision of the article for important intellectual content: SP
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Final approval of the article: SP
Guarantor of the study: IJ, SP
Provision of study materials or patients: SP
Statistical expertise: KK

Neurorazvojni ishodi nedonoščadi vrlo male rodne mase u regionalnoj pedijatrijskoj klinici

Cilj: Ispitati učestalost i etiologiju neuroloških ishoda u nedonoščadi s vrlo niskom porođajnom težinom, čimbenike rizika kod majke i tijekom perinatalnog perioda, komorbiditete i kliničku sliku i usporediti s novorođenčadi iste gestacijske dobi koja nisu razvila neurološki poremećaj.

Metode: Istraživanje je provedeno na Klinici za pedijatriju KBC-a Osijek. U istraživanje su uključena sva novorođenčad rođena u razdoblju od 1. 1. 2018. do 31. 12. 2019. godine s porođajnom težinom manjom od 1 500 g i gestacijskom dobi kraćom od 37 tjedana. Podaci su prikupljeni pregledom medicinske dokumentacije i bolničkoga informatičkog sustava.

Rezultati: U promatranom razdoblju rođeno je 120 djece s porođajnom težinom manjom od 1 500 g i gestacijskom dobi kraćom od 37 tjedana. Čimbenici rizika za prijevremeni porod kod majki i tijekom perinatalnog perioda uključuju autoimune bolesti majke, infekcije tijekom trudnoće i komplikacije pri porodu. Rane komplikacije koje prate odabranu skupinu su RDS, ROP, NEC, IVH, sepsa, kongenitalne srčane mane i poremećaj metabolizma glukoze. Usporeni motorički, kognitivni i govorni razvoj najviše su pod utjecajem male porođajne težine, višeg stupnja IVH-a, nižeg apgar indeksa u prvoj minuti i prisutnosti NEC-a. Značajni čimbenici rizika za smrt su gestacijska dob manja od 25 tjedana, porođajna težina manja od 800 g, infekcije u trudnoći i autoimune bolesti majke.

Zaključak: Neurološki ishod nedonoščadi s vrlo malom porođajnom težinom ovisi o kombinaciji komorbiditeta, majčinskih, perinatalnih i neonatalnih čimbenika rizika.

Review article

The Correlation between Iron Level and Schizophrenia: A Literature Review

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Abstract

Schizophrenia is a complex psychiatric condition that, if not adequately treated, can affect functional limitations. The exact etiopathogenesis of schizophrenia remains unknown. Research suggests an interaction between many factors, including genetic susceptibility, environment and psychological processes. Specific authors describe the association of a valuable mineral in the human body, iron, with pathophysiological mechanisms and related etiological factors in the development of the severe mental illness of schizophrenia.

Iron has important roles in the human body and affects various physiological processes. Some studies have shown a connection between the dysregulation of iron levels and the development of different mental disorders, including schizophrenia. Abnormal levels of iron in a specific region of the brain have been observed in people with schizophrenia. Iron levels may contribute to the pathogenesis of schizophrenia in combination with other genetic, environmental and dietary factors. Iron can also contribute to the better cognitive functioning of a patient with schizophrenia, and due to frequent malnutrition and undernourishment in this group of patients, it is crucial to take into account the need for routine hematological examinations and the determination of essential nutritional deficiencies.

Finally, our goals were to systematically review the literature published in the last two decades using PubMed, Web of Science, Scopus and Google Scholar. We described the clinical aspects and etiological factors of schizophrenia. We determined whether schizophrenia can be associated with iron concentration disorders to recognize and identify potential patients with iron deficiency and treat them promptly in daily clinical practice.

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KEYWORDS: iron, schizophrenia, anemia, oxidative stress

Introduction

Schizophrenia is a highly intricate and demanding psychiatric condition that affects a substantial proportion of individuals on a global level, about 1% of the worldwide population (1). The categorization of this condition entails the classification of different subtypes, which are based on the predominant symptoms. According to the current 10th revision of the International Classification of Diseases (ICD-10), we can differentiate paranoid, hebephrenic, catatonic and simplex forms of schizophrenia. If we are unable to categorize it into these subtypes, we are left with the possibility of other types of schizophrenia, as well as undifferentiated and unspecified types of schizophrenia (2, 3).

The etiology of schizophrenia is unknown, although empirical research suggests that there may be interactions among multiple factors, such as genetic susceptibility, environmental factors and psychological factors (4). Many considerable studies regard the involvement of iron in the pathophysiological mechanisms and etiological factors associated with schizophrenia, but some of them are inconsistent (5).

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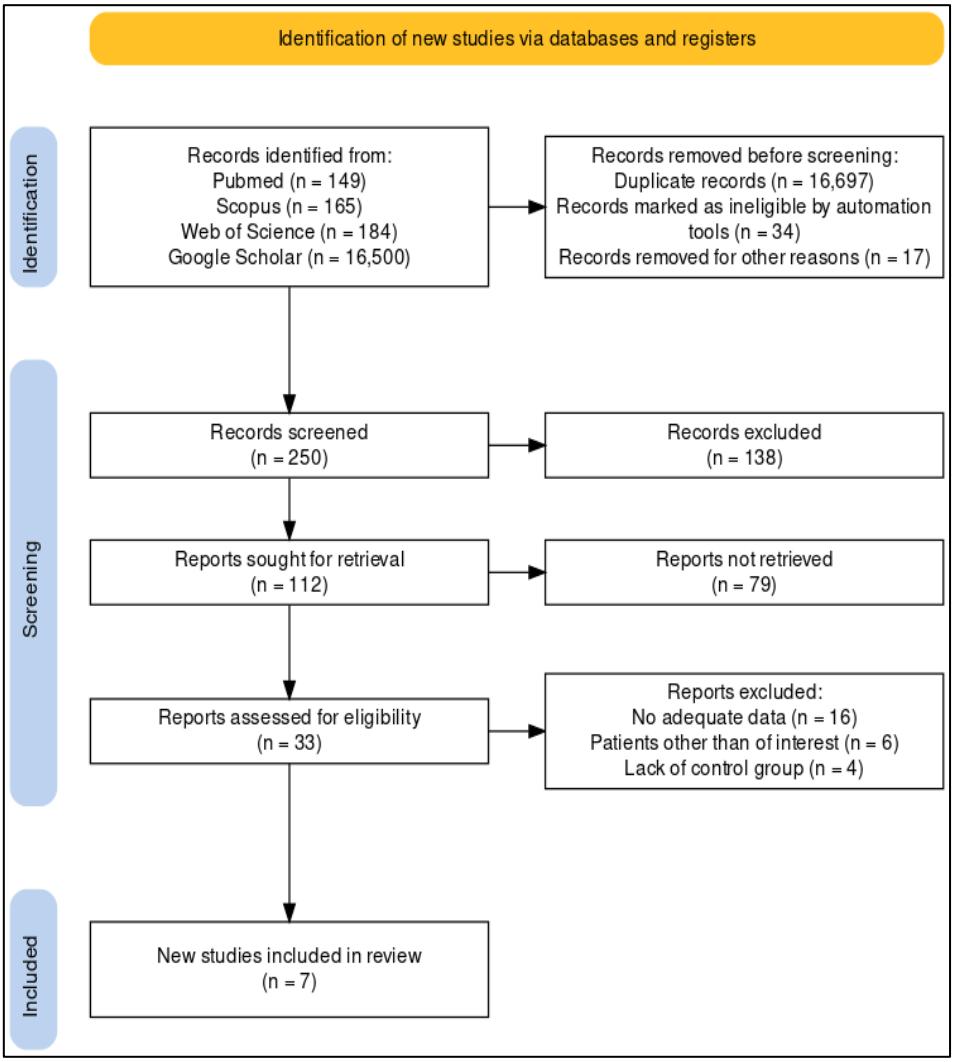

Figure 1 Flow diagram of the literature search process

Iron is an essential mineral in the human body; it is essential in many physiological processes, such as digestion, the production of enzymes, the growth of various human cells and the modulation of immunity. Iron is involved in synthesizing neurotransmitters and improves brain function by maintaining neuroplasticity (6). The existing study evidence reveals that people with schizophrenia have aberrant iron levels in specific brain regions when compared to people who do not have this disorder. This finding points to a possible link between iron dysregulation and the development of schizophrenia (7). Moreover, several studies have provided evidence suggesting that the provision of iron supplements may have the potential to improve cognitive functioning in individuals who have been diagnosed with schizophrenia (5)..

Table 1. Comparison of different studies about iron level, ferritin, hemoglobin and anemia in patients with schizophrenia

Author, year and country of study		Number of subjects				Serum iron level (µg/dl)		Ferritin (ng/ml)		Hemoglobin (g/dl)		Anemia (N)		Conclusion
		N	M	W	ALL	M	W	M	W	M	W	M	W	
Cao et al. 2019. China	S	105	44	61	211	131		X	X	X	X	X	X	There was a higher concentration of iron in the schizophrenia group.
	C	106	38	68		116		X	X	X	X	X	X	
Santa Cruz et al. 2020. Brazil	S	11	8	3	22	63.2		X	X	X	X	X	X	There was a higher concentration of iron in the schizophrenia group than in the healthy control group, but a small sample.
	C	11	8	3		42.1		X	X	X	X	X	X	
Liu et al. 2015. China	S	114	76	38	228	low(≤86)=21		X	X	X	X	21		Lower concentrations of iron and anemia are associated with an increased risk of schizophrenia.
	C	114	76	38		low(≤86)=7		X	X	X	X	7		
Chen et al. 2017. China	S	165	66	99	779	86.5		X	X	X	X	X	X	There was a lower concentration of iron in the schizophrenia group, but there were more men in the control group than women.
	C	614	518	96		108.3		X	X	X	X	X	X	
Memić-Serdarevic et all. 2020. Bosnia and Herzegovina	S	58	X	X	89	X	X	X	X	140.2		X	X	There is a lower concentration of hemoglobin in the schizophrenia group, and the control group made patients with bipolar disorder.
	C	31	X	X		X	X	X	X	146.8		X	X	
Ayyildiz et all. Turkey 2017.	S	518	384	134	609	X	X	X	X	142		X	X	Lower concentration of hemoglobin in the schizophrenia group.
	C	91	59	32		X	X	X	X	149		X	X	
Orum et al. 2018. Turkey	S	67	51	16	286	X	X	49.7		X	X	X	X	Lower ferritin in the schizophrenia group.
	C	219	127	92		X	X	50.3		X	X	X	X	

C = control group, S = schizophrenia, N = number, M = men, W = women, x = no data.

This review was conducted with the intention of not only providing a comprehensive analysis of the clinical symptoms and etiology of schizophrenia but also studying the probable relationship between schizophrenia and disruptions in iron levels. The primary goal of this review is to identify disorders in iron concentration and their association with schizophrenia. It could help to find disturbances in iron metabolism in schizophrenia patients in routine clinical practice with the possibility of more successful treatment

Methods of literature search

We exhaustively examined the literature published earlier using PubMed, Web of Science, Scopus and Google Scholar to identify articles published within the last two decades, from 2000 to the present. We oriented our search efforts towards meta-analyses, systematic reviews, randomized controlled trials and landmark studies that have previously addressed comparable subjects connected with iron levels and schizophrenia; see the flow diagram of the literature search process in Figure 1.

The first identification included the search strategy: (schizophrenia OR psychosis) AND (iron), and we got 16,814 results. Before screening, we removed duplicate records (n=16,697). Most of them were citations, illegible (n=34), and some of them were not in English or Croatian (n=17). We screened 250 records and excluded 138. We sought 112 records for retrieval but did not successfully retrieve 79 of them. For eligibility, we assessed 33 records, but some of them were excluded because some of them did not have adequate data (n=16), patients with other diagnoses but not schizophrenia (n=6), and a control group (n=4). We summarized our results in Table 1.

Classification of schizophrenia

The currently valid classifications that define and classify the differences in this clinical entity are the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the tenth revision of the International Classification of Diseases (ICD-10) and the upcoming eleventh revision of the International Classification of Diseases (ICD-11) (8, 9) (Table 2).

There are specific differences between these classifications in terms of schizophrenia.

According to the DSM-5, the patient must have exhibited a minimum of two (or more) of the symptoms to satisfy the diagnostic criteria for schizophrenia. These symptoms include delusions, hallucinations, negative symptoms, disorganized speech and catatonic postures. The presence of delusions, hallucinations or disorganized speech is a minimum requirement. The presence of ongoing symptoms of the disorder must endure for a minimum of six months. During this time, the patient must manifest active symptoms for at least one month (or shorter if effectively treated), resulting in significant functional limitations in social, occupational and other domains. There must not be other psychiatric, medical or substance abuse disorders that could explain the symptoms. When a child has a history of autism spectrum disorder or a childhood-onset communication disorder, the diagnosis of schizophrenia is only made if prominent delusions or hallucinations have been present for at least one month and only if they are effectively treated (10). Paranoid, disorganized, catatonic, undifferentiated and residual type are the five sub-classifications of schizophrenia that were included in the past DSM classifications, but they are not in the DSM-5. This sub-classification has been eliminated in DSM-5 due to its inadequate diagnostic stability, low reliability and poor validity (2, 11).

Schizophrenia is defined in ICD-10 in the block of disorders F20–F29, together with schizotypal and delusional disorders. This block includes schizophrenia (F20), schizotypal disorder (F21), persistent delusional disorders (F22), acute and transient psychotic disorders (F23) and induced delusional disorder (F24). Despite their controversial nature between delusional and affective disorders, schizoaffective disorders (F25) have been retained here..

Table 2. Comparison between current classification systems of schizophrenia

Difference	DSM-5	ICD-10	ICD-11
Chapter in...	Schizophrenia is within the schizophrenia spectrum and other psychotic disorders.	Schizophrenia is together with schizotypal and delusional disorders.	Schizophrenia is with other primary psychiatric disorders.
DFi	Not highlighted	Highlighted	Not highlighted
Du	At least six months	At least one month	At least one month
Function...	Work, relationships and self-care are below premorbid levels	Not included	Not included
Subtypes	Without	Paranoid, hebephrenic, catatonic, simplex, undifferentiated post-schizophrenic depression residual, other, non-specific	Without
Specific symptoms	Delusions, hallucinations Disorganised speech Psychomotor impairment Affective, negative, cognitive	Without	Positive, negative, affective, psychomotor, cognitive, aggressive
Cognit...	Specific symptom	Not included	Specific symptom
Course	The first episode or multiple episodes, continuous or unspecified. Currently in acute episode, partial remission, complete remission.	Continuous or episodic with a progressive deficit or with a stable deficit. Remittent, with incomplete or with complete remission. Other, with uncertain course or with a very short observation period.	First episode, multiple episodes, continuous, other, or unspecific. Currently symptomatic, in partial, in complete remission or unspecified.

Other nonorganic psychotic disorders (F28) and unspecified nonorganic psychosis (F29) are included in this category (12). According to the ICD-10, schizophrenia is defined by specific abnormalities in perception and thinking, as well as improper or reduced emotional responses. While clear thinking and intellectual capacity are typically preserved, specific cognitive impairments may manifest as time passes. Possible manifestations of schizophrenia include a continuous course, an episodic course with a growing or persistent deficiency, or one or more episodes with remission (13). It is advised not to get the diagnosis of schizophrenia when there are noticeable manic or depressed symptoms unless it becomes clear that the signs of schizophrenia precede the emotional disturbance. Schizophrenia should not be diagnosed in cases of evident brain illness, intoxication or drug withdrawal. When comparable symptoms occur alongside epilepsy or another neurological disorder, they should be classified as F06.2. However, if psychoactive substances induce these disorders, they should be categorized as F10-F19 (14). The ICD-10 classification of schizophrenia includes the following subtypes: paranoid schizophrenia (F20.0), hebephrenic schizophrenia (F20.1), catatonic schizophrenia (F20.2), undifferentiated schizophrenia (F20.3), post-schizophrenic depression (F20.4), residual schizophrenia (F20.5), simple schizophrenia (F20.6), other schizophrenia (F20.8) and unspecified schizophrenia (F20.9) (15).

Stable delusions, auditory hallucinations and perceptual disturbances characterize paranoid schizophrenia. Affect, volition, speech and catatonia disturbances are absent or mild (16).

Affective changes, fleeting delusions and hallucinations, irresponsible behavior and mannerisms characterize hebephrenic schizophrenia: poor disposition, disorganized thought and incoherent speech. People tend to isolate themselves. Rapid "negative" symptoms, such as affect flattening and loss of volition, typically worsen the prognosis. It is generally diagnosed in adolescents or young adults (17).

Hyperkinesis, stupor or automatic obedience are psychomotor disturbances that distinguish catatonic schizophrenia and negativism predominates. Extended periods can be spent in limited postures. Violent excitement may characterize the condition. Catatonia may be present along with oneiroid dreams and vivid scenic hallucinations (18).

Undifferentiated schizophrenia can be defined as psychotic conditions that meet the general diagnostic criteria for schizophrenia but do not fit any of the subtypes in F20.0-F20.2 or exhibit symptoms of multiple subtypes with no clear predominance (2).

Long-lasting post-schizophrenic depression is possible following schizophrenic episodes. While some "positive" or "negative" symptoms of schizophrenia may continue, they do not predominate in the clinical presentation. The state of post-schizophrenic depression increases the risk of suicide (14, 19).

Residual schizophrenia is a chronic stage of schizophrenia that is characterized by progressive "negative" symptoms. These symptoms include psychomotor slowdown, decreased activity, dulled affect, inactivity, lack of initiative, impaired speech and poor nonverbal communication (such as facial expression, eye contact and voice modulation) (20).

Simplex schizophrenia is a subtype of schizophrenia characterized by a gradual development of unusual behavior, an inability to meet social expectations and diminished performance with residual symptoms, such as affective blunting and loss of motivation, occurring without the presence of psychotic symptoms (21).

If the symptoms do not fit into one of the specified subtypes of schizophrenia, we can diagnose it as other schizophrenia or unspecified schizophrenia (14).

In ICD-11, schizophrenia is classified as a primary psychotic disorder that is characterized by persistent or recurring hallucinations, delusions or disordered thinking or behavior. First-rank symptoms are not prioritized, and the duration of psychotic disorders is a minimum of one month. There are no functionality criteria or specified subtypes. Symptom specifiers include positive symptoms, negative symptoms, affective symptoms, aggressive symptoms and cognitive impairments (2). Schizophrenia is diagnosed when specific symptoms accompany a noticeable deterioration in social, academic or occupational functioning. In addition, a severity specifier was added to ICD-11 to denote the degree of severity associated with the disorder. The degree of functional impairment and the quantity and severity of symptoms determine the severity specifier. The specifier comprises three severity levels: mild, moderate and severe. The specifier provides a more thorough and meaningful representation of the condition's severity degree and guides treatment decisions (8).

Etiology and pathophysiology of schizophrenia

Schizophrenia covers a wide range of mental disorders characterized by distortions in reality perception, affect and behavior. Although the precise etiology of this disease remains unclear, empirical research shows that it is a multifactor phenomenon that occurs under several psychological, biological and environmental factors. Several psychological factors, such as stress, trauma and addiction, are associated with initiating schizophrenia or exacerbating its symptoms (22).

Numerous studies of genetic factors have provided evidence to suggest that people with a family background associated with schizophrenia are more likely to develop psychotic disorders. Nevertheless, the etiology of schizophrenia is not only ascribed to genetic

and psychological causes. The effects of the environment can also exert a substantial impact (16). There have been several environmental factors found to include prenatal exposure to viruses, bacterial or parasitic infections, complications during pregnancy or childbirth, exposure to stress or trauma and abuse of various psychoactive substances (4).

The pathophysiological mechanisms underlying schizophrenia involve alterations in neuronal connectivity within the brain, resulting in disturbances in perception, cognition and behavior (23). The onset of schizophrenia is shaped by a complex interaction of multiple factors that ultimately affect the structure and function of the brain, as well as other clinical symptoms. Previously, different clinical presentations of schizophrenia were categorized into subtypes according to earlier classifications like ICD-10. Nevertheless, this classification has been discarded in the present DSM-5 and forthcoming ICD-11 (8).

Scientific research has investigated the impact of malnutrition as a possible causative element in the onset of schizophrenia. Several studies have provided evidence suggesting a higher prevalence of insufficient levels of some essential nutrients, such as vitamin D, B6, B8 and B12, omega-3 fatty acids, zinc, magnesium, calcium and iron, among individuals diagnosed with schizophrenia (5, 24). They are associated with the weight of the clinical presentation and the quality of life of the sick. Ensuring adequate consumption of vital nutrients is an integral part of treating individuals with schizophrenia (25).

Various studies have provided evidence of the important role of iron in brain functions and its potential impact on the onset of mental disorders such as schizophrenia. While specific studies characterize iron deficiency as a contributing factor to the development of schizophrenia, others propose that iron contributes to oxidative stress, resulting in harm to neurons and the progression of the disease (6). Further investigations are required to fully understand the role of iron in the onset and development of schizophrenia, given the difficult interplay among genetic factors and environmental effects. This will facilitate the development of extra efficacious preventive and healing tactics for this complicated mental disease (5).

The role of iron in the etiopathogenesis of schizophrenia

Iron is essential for many biological processes in the human body. Most iron in the human body is bound to proteins such as hemoglobin, myoglobin and various enzymes. In the body, iron is stored in the liver with ferritin and hemosiderin. Protein transferrin permits the transport of plasma iron. When it reaches the tissue, the transferrin forms a complex with a specific receptor (26). Iron is crucial in many intracellular processes, such as DNA replication, enzyme activity, mitochondrial function and neurotransmitter regulation. When the quantity of iron consumed fails to satisfy physiological requirements, the body will mobilize its iron reserves (27). The iron required to mature red and white blood cells is diminished under such conditions. As a result, inadequate cytokine synthesis, hypochromatic microcytic anemia and insufficient lymphocyte maturation may ensue. These conditions also deteriorate immune systems or processes implicated in inflammatory diseases that could harm brain functioning (28).

Iron is essential for developing and operating the central nervous system, particularly in synthesizing mood-regulating, behavior-improving and cognition-enhancing neurotransmitters (e.g. serotonin and dopamine). Iron facilitates myelin formation and maintenance, improving neural communication's effectiveness. Iron is also crucial for energy production in brain cells and for regulating oxidative stress (6). Oxidative stress arises from a discrepancy between the organism's capacity to eliminate reactive oxygen species (ROS) and its production capacity (29). Iron can cause oxidative stress by making more reactive oxygen species (ROS). This is done through the Fenton reaction, which creates highly reactive hydroxyl radicals that can induce pathological conditions and harm cellular

constituents such as proteins, lipids and DNA. Iron can be distributed throughout many human body compartments, such as intracellularly or within the extracellular space. Insufficient iron in the brain can lead to notable alterations in both structure and function, potentially giving rise to various neurological and psychiatric disorders (30). Figure 2 shows the pathophysiological mechanism of iron accumulation and its influence on the development of schizophrenia.

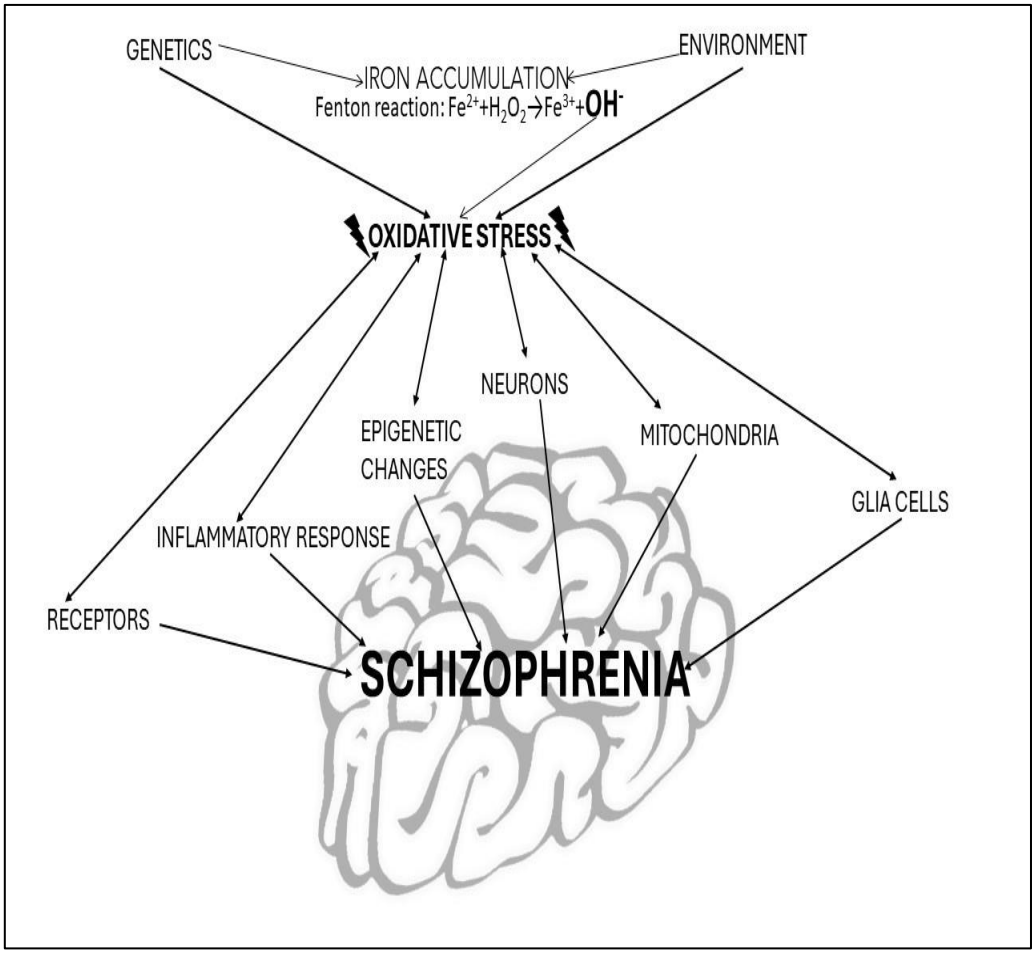

Figure 2. The influence of iron accumulation on oxidative stress and its impact on the development of schizophrenia

Studies showed a potential correlation between iron levels and the initiation and progression of schizophrenia. Insufficient iron levels throughout critical periods of brain development may be associated with incorrect synaptogenesis and, consequently, inadequate communication among neurons. Numerous studies prove the connection between disturbed iron levels in the brain or other spaces in the human body and numerous physiological processes, such as inflammation, oxidative stress and malfunctioning of mitochondria (6). As we explore the mechanisms underlying the causes of schizophrenia, it becomes clear that our understanding of this complicated mental disorder has been significantly improved. It is now evident that insufficient iron levels play a more substantial role in the development and progression of schizophrenia than we previously believed. These studies deepen our understanding of the complexities of this intricate psychiatric condition (31). Additional research is necessary to fully understand the role of iron in the development of schizophrenia. However, based on the existing research,

maintaining optimal iron levels might lower the chances of having this complex mental disease.

Discussion

The impact of iron deficiency on the development of schizophrenia has been examined by multiple researchers, giving inconclusive findings (see Table 1).

Some studies have concluded that a higher level of iron is associated with the onset of schizophrenia, indicating the possible harmful role of iron in stimulating oxidative stress. The study by Cao et al. 2019 showed lower serum iron levels in a healthy population compared to patients with schizophrenia (31). Brazilian research by Santa Cruz et al. from 2020 also observed higher serum iron levels in patients compared to a healthy control group. However, this study's small sample was noticeable, with only 22 subjects in the affected and control groups (32).

On the other hand, some studies found that low iron levels are associated with schizophrenia. In the 2015 study by Liu et al., lower serum iron levels were observed in patients with schizophrenia, leading to the conclusion of possible poorer nutrition in these patients and the role of iron deficiency in the inadequate production of neurotransmitters important for mental functions (33).

The Chen et al. study, conducted in 2017 with 779 subjects, showed lower serum iron levels in patients with schizophrenia. However, more men in the control group had higher iron levels physiologically (34).

In the study from Bosnia and Herzegovina, from 2020, Memic-Serdarevic et al. compared hemoglobin levels in patients with schizophrenia with a control group who had bipolar affective disorder and concluded that hemoglobin levels were lower in patients with schizophrenia, which may speak in favor of poorer malnutrition in patients with schizophrenia who have significantly impaired cognitive and social functions and consequently a more inferior quality of life compared to patients with bipolar affective disorder (35).

A 2017 Turkish study by Ayyildiz et al. also confirmed lower hemoglobin levels in applications with schizophrenia compared to a healthy control group (36), and the Turkish study by Orum et al. from 2018 showed lower ferritin levels in patients with schizophrenia (37).

The relationship between oxidative stress and iron levels has been identified as significantly associated with the etiology and development of schizophrenia (38). Oxidative stress is characterized by disequilibrium between generating reactive oxygen species and the organism's capacity to counteract their harmful effects, resulting in cellular and tissue damage (39). Research has revealed that individuals diagnosed with schizophrenia frequently exhibit elevated levels of oxidative stress within their cerebral regions, thereby potentially instigating neuronal impairment and detriment to other components of the brain (40).

Iron is a vital mineral involved in numerous physiological processes within the human body, encompassing the synthesis of erythrocytes and facilitating cerebral oxygen transportation. Nevertheless, scholarly investigations have revealed a correlation between individuals diagnosed with schizophrenia and disordered iron levels in their bloodstream. This phenomenon has been linked to oxidative stress and subsequent impairment of cerebral cells (6).

The precise correlation between iron, oxidative stress and schizophrenia remains incompletely comprehended; however, it is evident that these variables play a significant role in the onset and advancement of the disorder (38). More research is needed to understand better how iron and oxidative stress affect schizophrenia and to come up with more effective treatments that target these essential factors.

Conclusion

Several controlled studies have been conducted to analyze the hematological status and iron levels of patients diagnosed with schizophrenia. Nevertheless, the methodologies, sample sizes, inclusion criteria, reference values, gender distribution and other variables lack standardization. Hence, the

findings remain inconclusive, as specific authors assert a robust correlation between iron levels and the onset of schizophrenia, while others hold a contrasting viewpoint.

Based on a comprehensive review of several studies and a subsequent detailed analysis of the data, we can conclude that iron has a significant impact on the pathogenesis of schizophrenia. Iron is an essential element that plays a vital role in a multitude of biological processes, and its lack is related to the emergence of various mental disorders, including schizophrenia. However, there are also dubious conclusions about the harmfulness of elevated iron levels and the development of oxidative stress. It is essential to point out that the deficiency itself or high iron levels cannot cause schizophrenia. Probably, disturbances in the amount of iron can contribute to the pathogenesis of schizophrenia as a combination of genetic, environmental and nutritional factors.

Potential benefits of including routine hematological examinations in people diagnosed with schizophrenia include the identification of essential dietary deficiencies and the mitigation of systemic manifestations associated with malnutrition, which is more common in people with schizophrenia than in the general population. Further research is needed to gain a more detailed understanding of the association between the role of iron in the pathogenesis of schizophrenia as well as its possible implications for therapeutic and prevention options.

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Povezanost razine željeza i shizofrenije: Pregled literature

Shizofrenija je složeno psihijatrijsko stanje koje, ako se ne liječi na odgovarajući način, može dovesti do funkcionalnih ograničenja. Točna etiopatogeneza shizofrenije još uvijek je nepoznata. Istraživanja upućuju na interakciju između mnogih čimbenika, uključujući genetsku osjetljivost, okoliš i psihološke procese. Pojedini autori opisuju povezanost željeza, kao vrijednoga minerala u ljudskom tijelu, s patofiziološkim mehanizmima i povezanim etiološkim čimbenicima u razvoju teške mentalne bolesti - shizofrenije.

Željezo ima važne uloge u ljudskom tijelu i utječe na različite fiziološke procese. Neke su studije pokazale povezanost između disregulacije razina željeza i razvoja različitih mentalnih poremećaja, uključujući shizofreniju. Abnormalne razine željeza u specifičnoj regiji mozga zapažene su kod osoba sa shizofrenijom. Razine željeza mogu doprinijeti patogenezi shizofrenije u kombinaciji s drugim genetskim, okolišnim i prehrambenim čimbenicima. Željezo također može doprinijeti boljoj kognitivnoj funkciji pacijenata sa shizofrenijom, te je zbog česte pothranjenosti i malnutricije kod te skupine pacijenata važno uzeti u obzir potrebu za rutinskim hematološkim pregledima i određivanjem osnovnih prehrambenih nedostataka.

Na kraju, naš je cilj bio sustavno pregledati literaturu o ovoj temi objavljenu u posljednja dva desetljeća koristeći PubMed i Google Scholar. Opisali smo kliničke aspekte i etiološke čimbenike shizofrenije. Odredili smo može li se shizofrenija povezati s poremećajima koncentracije željeza kako bismo prepoznali i identificirali potencijalne pacijente s nedostatkom željeza te ih pravovremeno liječili u svakodnevnoj kliničkoj praksi.

Review article

Primary Hypertension in Children and Adolescents: Risk Factors and Vascular Damage

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Abstract

The incidence of primary hypertension is on the rise in the pediatric population, with an approximate prevalence ranging from 3% to 5%. The most significant risk factors for the onset and development of primary hypertension are well-known, and some of them are preventable, including increased salt consumption and obesity. Connected with metabolic risk factors, elevated blood pressure in childhood is carried into adulthood. Primary hypertension is associated with attenuated vascular responses to various physiological stimuli in both peripheral microcirculation and systemic macrocirculation in adults and children. Endothelial dysfunction is one of the most important features of arterial hypertension, together with an increased level of oxidative stress – both determinants significantly contribute to all the pathophysiological changes observed in hypertension. Systemic arterial hypertension has emerged as a prevalent cardiovascular risk factor associated with substantial morbidity and mortality. Hence, the timely identification of individuals with elevated blood pressure and early-life blood pressure management could serve as a crucial strategy to mitigate the risk of cardiovascular disease and mortality in adulthood.

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KEYWORDS: children, blood pressure, primary hypertension, vasculature, oxidative stress

Epidemiology, definition and classification of arterial hypertension in children and adolescents

Arterial hypertension is considered one of the most significant medical and public health problems in Western societies and the main, potentially reversible, cause of cardiovascular (CV) diseases. While juvenile arterial hypertension is less prevalent than in adults, the incidence of hypertension in children and adolescents has markedly risen in recent decades, partly attributed to the increasing prevalence of childhood obesity [1]. It should be pointed out that the rate of hypertension in children and adolescents is also determined by the definition used, which has changed over time and generally varies globally [2]. Approximately 3–5% of children and adolescents experience hypertension, while 10–14% exhibit elevated blood pressure (BP) levels, referred to as high normal BP [1, 3]. Therefore, hypertension represents one of the most common chronic diseases in adolescence [2]. Although it is multifactorially caused, among the most significant risk factors for hypertension are excessive salt intake and the epidemic of obesity among children. Given that primary hypertension already in childhood is often associated with subclinical target organ damage, it is not considered a simple hemodynamic problem, but the first stage in the development of cardiovascular diseases [4]. There is evidence indicating that hypertension in children may arise from a combination of genetic, environmental and biological factors. Children with elevated blood pressure have been observed to be at risk of developing hypertension in adulthood [5, 6], and evidence suggests that hypertension in adulthood has its origins in childhood [7].

The initial guidelines for blood pressure management in this age group were issued in 1977 [8]. Prior to that, there was no standardized definition of hypertension in the pediatric population, and blood pressure measurement was not routinely conducted in asymptomatic children and adolescents. While the association between blood pressure levels and cardiovascular disease is firmly established in adults, it is not clearly defined in children and adolescents. The development of cardiovascular complications in this age group is the outcome of the interplay between various risk factors and age. Consequently, the definition of reference values in the pediatric population is based on the percentile distribution of blood pressure values. According to the most recent guidelines from 2023 by the European Society of Hypertension (ESH) and the International Society of Hypertension (ISH), it is advised to characterize hypertension based on percentile distribution [9]. In children, hypertension is defined as systolic and/or diastolic arterial pressure values equal to or exceeding the 95th percentile for age, sex and body height, as measured in three distinct assessments.

Table 1. Classification of arterial hypertension in the pediatric population refers to the 2023 ESH and ISH guidelines

	0–15 years SBP and/or DBP percentile	16 years and older SBP and/or DBP values (mmHg)
Normal	<90th	<130/85
High-normal	≥90th to <95th percentile	130-139/85-89
Hypertension	≥95th percentile	≥140/90
Stage 1 hypertension	95th percentile to the 99th percentile and 5 mmHg	140-159/90-99
Stage 2 hypertension	>99th percentile plus 5 mmHg	160-179/100-109

Values < 90th percentile are considered normal BP and values from 90th to 95th percentile are high normal pressure. Hypertension stage 1 is considered to be systolic and/or diastolic pressure values ≥ 95th to 99th percentile + 5 mmHg, and stage 2 > 99th percentile +5 mmHg. According to the same guidelines [9], hypertension in adolescents aged ≥ 16 years is classified as in adults; systolic and/or diastolic pressure values < 130/85 mmHg are considered normotension, values 130–139/85–90 mmHg are considered high normal pressure and values ≥ 140/90 mmHg hypertension (Table 1).

The most important modifiable risk factors for arterial hypertension in childhood

Excessive salt intake

Elevated salt consumption is widely acknowledged as a key contributor to increased BP and arterial hypertension [10, 11], with associations with various cardiovascular disease outcomes [12, 13]. Consequently, excessive salt intake is recognized as the primary preventable factor contributing to morbidity and mortality [14]. The link between excessive salt intake and elevated BP/arterial hypertension has been established in the pediatric population as well [3, 15, 16], and this is significant because essential hypertension during childhood is connected with the onset of arterial hypertension in adulthood [17].

According to the World Health Organization guidelines, the recommended daily intake of sodium for adults is 2 g/day (approximately 5 g of salt), whereas recommended values for children should be further reduced proportionally to energy requirements [18]. However, a large number of conducted studies indicate that in almost most countries of the world, the daily salt intake is significantly higher than recommended, ranging between 6 and 12 g of salt per day [19, 20]. The alarming results of the research conducted on the adult population in Croatia in 2008 (Croatian Action on Salt and Health (CRASH)) showed that the average daily salt intake in our population was 11.6 g, which is more than twice the recommended values of the World Health Organization [21]. Encouraged by this research, the Croatian Institute of Public Health and the Ministry of Health presented a strategic plan intending to reduce daily salt intake by 4% every year [22], and data from 2019 showed that the average daily salt intake in Croatia decreased by 1 .6 g of salt in the last 12 years [23].

Elevated salt intake is recognized as a firmly established risk factor for the onset of arterial hypertension, irrespective of body weight, gender and age. However, the precise etiopathogenetic mechanisms underlying the development of arterial hypertension and its connection to excessive salt consumption remain incompletely understood. A recent study by Bigazziet et al. [24] revealed that genetic polymorphisms, previously linked to salt-sensitive hypertension in adults, influence BP values and sodium excretion in the adolescent population. This suggests the potential for impairment in the physiological systems for sodium control from an early age. Traditionally, the primary association between sodium and arterial hypertension was believed to involve an elevation in extracellular volume due to the osmotic impact of sodium, particularly in salt-sensitive individuals. However, this mechanism came under scrutiny with the realization that sodium can be more efficiently stored in the body in a non-osmolar form [25]. Recent hypotheses suggest that salt could influence BP through varied and intricate mechanisms. An overabundance of salt intake might induce alterations in the physiological systems responsible for regulating the functions of the heart, circulatory system and/or kidneys. In individuals with hypertension, particularly those who are obese, there is increased activity in the sympathetic nervous system [26]. This autonomic alteration is evident even in pediatric populations, as higher sympathetic modulation and lower parasympathetic modulation have been observed in hypertensive children [27] and adolescents [28]. Sympathetic nervous system activation has dual effects: it enhances sodium reabsorption in the proximal tubule and stimulates the local renin-angiotensin-aldosterone system (RAAS). The latter, in turn, amplifies distal sodium reabsorption and sympathetic activity through angiotensin II.

Moreover, the development of sodium-sensitive arterial hypertension appears to be influenced by a combination of genetic, hormonal and neuroendocrine factors [29].

Suckling et al. proposed that the consumption of high-sodium food results in a temporary elevation of plasma sodium concentration, potentially exerting toxic effects on the vascular system [30]. The plasma sodium concentration can influence blood pressure by altering the "stiffness" of endothelial cells. Elevated "stiffness" in endothelial cells may reduce the activity of endothelial nitric oxide synthase (eNOS), increase vascular resistance and contribute to elevated blood pressure. This condition might subsequently prompt microvascular remodeling and a systemic proinflammatory state, leading to microvascular endothelial inflammation, anatomical remodeling and functional abnormalities [15].

Excessive salt consumption presents a significant public health challenge in the pediatric population, with numerous studies establishing a link between high salt intake and elevated BP values [31, 32]. Recent meta-analyses have demonstrated an association between sodium intake and BP levels in children and adolescents. A compilation of eighteen studies examining sodium intake and BP demonstrated that each additional gram of daily sodium intake was correlated with a rise of 0.8 mmHg in systolic BP and 0.7 mmHg in diastolic BP. This association was more pronounced among overweight children and children with low potassium intake [16]. Supporting the notion that high salt intake contributes to elevated BP in children, a meta-analysis conducted a few years ago, encompassing 10 studies in children and adolescents, showed that reducing salt intake resulted in a decrease in BP (1.17 mmHg reduction in systolic BP and 1.29 mmHg reduction in diastolic BP). This provides robust evidence for the importance of limiting dietary salt intake in the early years of life [33]. In our previous study, we demonstrated that the estimated daily salt intake was 7.09 [5.25–9.59] g/day for children with normal BP and 10.7 [4.0–14.7] g/day for children with essential arterial hypertension. These findings underscore that, overall, children are consuming significantly more salt than the recommended values, particularly those with hypertension. Additionally, we validated the relationship between daily salt consumption, BP and body weight in the pediatric population [34]. Given the continuity of BP from childhood to adulthood, these findings suggest that reducing sodium intake during childhood and adolescence may contribute to lower BP and help prevent the development of hypertension later in life.

Overweight children and obesity

Another important modifiable factor that significantly affects the BP value at the individual and population level is obesity. In recent decades, in addition to the increase in arterial hypertension, there has also been a significant increase in the frequency of obesity in children and adolescents, and it is becoming one of the leading public health and medical problems. An alarming number of overweight and obese children has been recorded in all European countries, and it is estimated that more than 340 million children and adolescents aged 5 to 19 years are overweight or obese [35]. It is predicted that by 2025 there will be two billion overweight and obese people in the world. Unfortunately, Croatia also follows global negative trends and ranks high in fifth place with other countries in the Mediterranean region of Europe [36]. Our national study EHUH (Epidemiology of Hypertension in Croatia) showed that almost 70% of individuals whose body mass index (BMI) is greater than 30 kg/m2 also have arterial hypertension [37], while the studies conducted on children from second and third grade of elementary school showed that obesity is the main risk factor for the development of arterial hypertension already at that age. The results of the European initiative to monitor obesity in children (2018–2022) show a worrying proportion of children with excess body weight and obesity. Overall, almost every third child in the European region (29%) is overweight and obese, and in Croatia, 34.9% of children are overweight or obese [38].

According to the guidelines of the Pediatric Endocrinology Society [39], standardized BMI centile curves are used to assess the obesity degree in children and adolescents older than two years. BMI is obtained by dividing body mass in kilograms by the square of height in meters. Individual is considered overweight with BMI > 85th centile, and obese with BMI > 95th centile for age and sex according to revised centile curves [40].

Numerous studies indicate the connection between obesity and hypertension in children and emphasize the increased prevalence of hypertension in children with excessive body weight, indicating obesity is one of the main risk factors for the development of arterial hypertension in children [1]. In addition to arterial hypertension, childhood obesity is associated with an increased risk of developing numerous other health problems such as dyslipidemia, type 2 diabetes and left ventricular hypertrophy, all of which increase the risk of CV disease in adulthood [41]. The above is proof of the necessity of prevention and treatment of obesity in children.

Obesity in children is the result of a complex interaction of genetic, environmental, behavioral and socioeconomic factors [42], and unhealthy diet, lack of physical activity and insufficient sleep are increasingly present risk factors. Early recognition of obesity and the application of prevention measures are key to combating this problem. These include promoting a balanced diet, regular physical activity, reduction of sedentary lifestyle and education about healthy lifestyles. It is important to point out that the fight against childhood obesity requires a comprehensive approach at the global, national and individual level in order to create an environment that encourages healthy lifestyle habits [43].

Numerous potential pathophysiological pathways elucidate the link between obesity and increased BP as well as hypertension. Central to these pathways is the principle tied to dysfunctional adipocytes and the neurohormonal activation of the sympathetic nervous system. It is crucial to highlight that adipocytes function not solely as fat storage units but also as active endocrinological organs. The presence of excessive body weight and obesity is characterized by an augmented mass of adipose tissue, encompassing adipocytes, macrophages, fibroblasts and other cells [44]. Adipose tissue releases a variety of hormones and cytokines, referred to as adipokines, with increased secretion in the state of obesity. An imbalance arises when pro-inflammatory adipokines (such as leptin and resistin) predominate over anti-inflammatory adipokines (like adiponectin), resulting in dysfunctional adipose tissue and a persistent inflammatory condition. Several of these adipokines contribute to increased activity in the sympathetic nervous system, and research on humans has demonstrated that a leptin deficiency is linked to reduced sympathetic nervous system activity [45].

Activation of the sympathetic nervous system can impact various organs, with a noticeable preference for affecting the renal vasculature in cases of obesity. An elevation in BMI correlates with an increased secretion of noradrenaline [46]. In addition to its direct vasoconstrictive effects, increased sympathetic nervous system activity contributes to elevated BP and hypertension by enhancing the activity of the renin-angiotensin-aldosterone system. RAAS activity directly raises BP through angiotensin II-mediated vasoconstriction and indirectly through angiotensin II- and aldosterone-mediated salt and water reabsorption. As adipose tissue increases, RAAS activity intensifies, given that adipocytes also release RAAS hormones and mineralocorticoid stimulating factors [47]. Furthermore, obesity is linked to inflammation, as evidenced by macrophage infiltration in adipose tissue, and an elevated level of free fatty acids. Dyslipidemia, often present in obesity, is characterized by elevated LDL-cholesterol and triglycerides and low HDL-cholesterol. Elevated cholesterol is a known complex risk factor for CV diseases, contributing to increased BP and hypertension. Apart from inducing atherosclerosis, elevated LDL-cholesterol prompts chronic inflammation, activates the sympathetic nervous system and

enhances the activity of the RAAS system. [84]. Finally, obesity leads to complete metabolic dysfunction, which leads to impaired endothelial and vascular function and hypertension as a clinically recognizable outcome [48].

Hypertension, oxidative stress and vascular (dys)function

Primary hypertension in children is not harmless and can cause significant target organ damage, which is sometimes registered already at the time of diagnosis. Although CV disease is very rare in childhood, target organ damage represents a significant risk for developing CV events in adulthood. Over the past two decades, non-invasive markers have emerged and been employed to rate the progression of atherosclerosis and vascular dysfunction in the pediatric population. The non-invasive assessment of vascular structures and functions, utilizing tools like ultrasound and laser Doppler devices, has the potential to enhance screening programs for primary prevention in childhood. Additionally, incorporating vascular biomarkers as surrogates for CV risk in childhood could further improve these efforts [49].

Elevated BP in childhood and adolescence was found to be associated with increased carotid intima-media thickness, increased left ventricular mass and arterial stiffness [50]. Using laser Doppler flowmetry it has been shown that skin microvascular reactivity was significantly reduced in hypertensive subjects compared to normotensive controls [51]. Endothelial dysfunction plays a prominent role in the development of atherosclerosis and hypertension, and impaired endothelium reactivity is considered an initial sign of functional atherosclerotic changes [52–54]. When hypertension is present, the diminished availability of nitric oxide (NO) is partially offset by the activation of alternative pathways. This includes the production and release of endothelium-derived hyperpolarizing factor (EDHF), which plays a role in sustaining endothelium-dependent vasodilation [55]. Additionally, the intricate interplay between NO and endothelin (ET-1) may play a role in the progression of endothelial dysfunction in hypertension. Even with normal circulating levels of ET-1, individuals with hypertension exhibit increased vasoconstrictor activity of the peptide in the peripheral circulation, accompanied by a decrease in NO availability [56]. At the vascular level, by binding to its specific receptors mainly localized in smooth muscle cells, ET-1 stimulates vascular contraction and hypertrophy [57]. In addition to smooth muscle cells, ET-1 also binds to a large number of its receptors on endothelial cells and mediates the release of NO, thereby inhibiting vasoconstriction and cell proliferation. When endothelial dysfunction is evident, the activation of receptors on endothelial cells fails to enhance vasodilation mediated by NO, and the vasoconstrictive impact of ET-1 is increased [57]. This occurrence is further triggered by the diminished inhibitory influence of NO on the production and activity of ET-1 [55]. The overall disturbed equilibrium between these two systems can result in increased vasoconstrictive and proliferative activity of endothelin-1.

The most commonly used non-invasive technique for endothelial dysfunction detection in conduit arteries is flow-mediated dilation (FMD). A reduced FMD holds the potential to anticipate and detect risk factors for cardiovascular events, even in individuals without apparent symptoms [53]. In addition to the attenuated microvascular reactivity, arterial hypertension is also associated with reduced endothelium-dependent function of conduit artery circulation [58]. Brachial artery FMD was significantly weakened in children and adolescents with CV risk factors, including hypertension [59]. Because the number of studies on childhood microvascular and macrovascular function in primary hypertension is limited, the exact mechanisms of endothelial dysfunction are still not fully understood. However, what is well known is the early onset of atherosclerosis already in childhood, which is influenced by numerous risk factors, among them hypertension [60], suggesting that finding a reliable diagnostic tool for assessing early vascular changes is of great importance for

understanding the pathophysiological development of the disease.

Furthermore, since the increased level of oxidative stress is an important event in the development of vascular function disorders, it is necessary to evaluate its role in this function. A growing body of evidence suggests that oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) and nitric oxide, plays a pivotal role in the development of hypertension [61]. Excessive production of harmful ROS, surpassing the cellular antioxidant capacity, results in pathogenic oxidative stress [62]. In clinical settings, markers of systemic inflammation and oxidative stress are employed to establish a connection between vascular damage and endothelial dysfunction. While limited clinical studies have explored the role of oxidative stress in children with primary hypertension, the findings from these studies indicate a strong association between oxidative stress and primary hypertension, irrespective of BMI. Moreover, this association correlates with the severity of hypertension, target organ damage and other metabolic and immunologic abnormalities. In their study, Warolin and colleagues have found an elevated iso-prostane urinary excretion in obese children and adolescents, that is connected with visceral obesity regardless of BMI and BP [63]. Furthermore, a study in which normotensive and hypertensive age-matched and sex-matched children were compared demonstrated that hypertensive children had significantly increased levels of symmetrical and asymmetrical dimethylarginine in serum [64]. Turi et al. demonstrated significant alterations in oxidative stress biomarkers associated with the severity of hypertension in hypertensive children, such as glutathione depletion in red cells, when compared to age- and BMI-matched normotensive controls [65]. The correlation between the level of oxidative stress and higher blood pressure values was also observed in prepubertal children [66]. Studies on untreated primary hypertension in children revealed disrupted markers of oxidative stress, including increased thiobarbituric acid reactive substances, decreased glutathione and increased glutathione peroxidase activity [67].

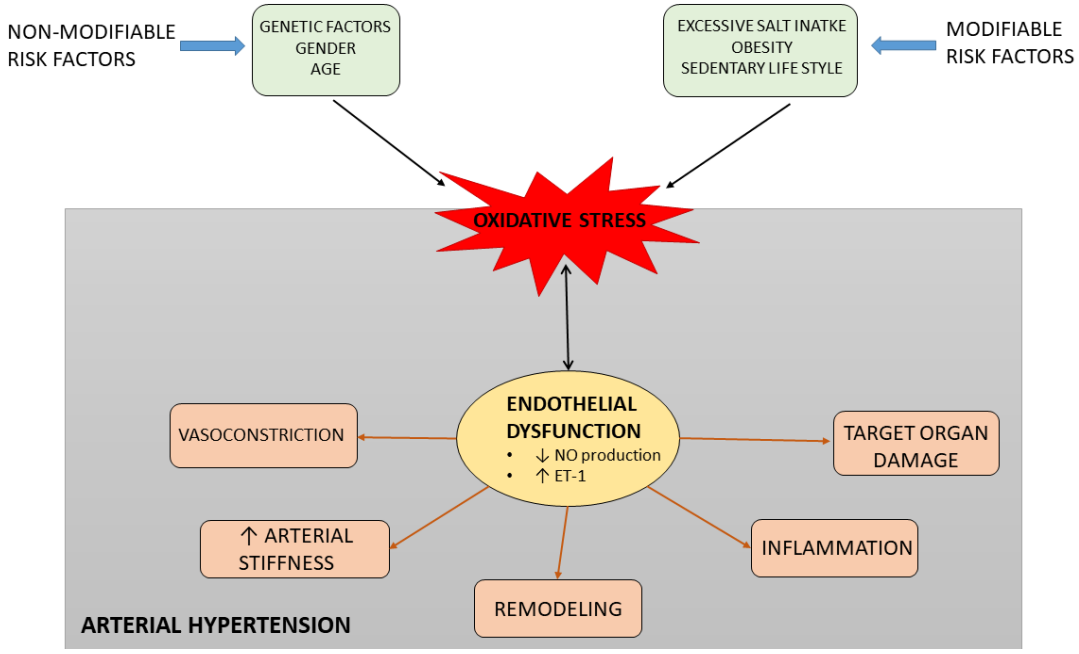

Figure 1. Risk factors for the development of endothelial dysfunction and arterial hypertension

Furthermore, serum thiobarbituric acid reactive substances were linked with left ventricular hypertrophy and concentric remodeling. Additionally, various oxidative stress biomarkers showed correlations with inflammatory activity, albumin excretion and systolic BP [67]. Despite abundant evidence supporting the role of oxidative stress in hypertension development and the potential preventive measures of antioxidant therapy, unresolved aspects regarding clinical translation remain.

Conclusion

Hypertension in children and adolescents has a significant impact on the quality of life in adulthood due to the increased cardiovascular risk since arterial hypertension is one of the main risk factors for the development of morbidity and mortality in the world. It has become a public health problem due to the increase in the prevalence of hypertension, primarily due to the childhood obesity epidemic. Arterial hypertension is associated with impaired NO balance, increased oxidative stress and vascular endothelial dysfunction, which further leads to various organ damage (Figure 1). Therefore, early prevention already in childhood – reducing salt intake and a balanced and healthy diet, as well as appropriate physical activity is of utmost importance for reducing the overall cardiovascular risk

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Competing interests. None to declare.

List of abbreviations:

BMI – body mass index
BP – blood pressure
CRASH – Croatian Action on Salt and Health
CV – cardiovascular
EHUH – Epidemiology of Hypertension in Croatia
eNOS – endothelial nitric oxide synthase
ESH – European Society of Hypertension
EDHF – endothelium-derived hyperpolarizing factor
ET-1 – endothelin 1
FMD – flow-mediated dilation
ISH – International Society of Hypertension
NO – nitric oxide
RAAS – local renin-angiotensin-aldosterone system
ROS – reactive oxygen species

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Primarna hipertenzija u djece i adolescenata: čimbenici rizika i vaskularno oštećenje

Učestalost primarne hipertenzije u porastu je u pedijatrijskoj populaciji, s približnom prevalencijom od 3 do 5 %. Najznačajniji čimbenici rizika za nastanak i razvoj primarne hipertenzije dobro su poznati, a neke je od njih moguće spriječiti, uključujući povećanu konzumaciju soli i pretilost. Povezano s metaboličkim čimbenicima rizika, povišen krvni tlak u djetinjstvu prenosi se u odraslu dob. Primarna hipertenzija povezana je s oslabljenim vaskularnim odgovorima na različite fiziološke podražaje u perifernoj mikrocirkulaciji i sistemskoj makrocirkulaciji kod odraslih i djece. Disfunkcija endotela jedna je od najvažnijih značajki arterijske hipertenzije, zajedno s povećanom razinom oksidativnog stresa - oba čimbenika značajno doprinose svim patofiziološkim promjenama koje se opažaju kod hipertenzije. Sistemska arterijska hipertenzija postala je raširen kardiovaskularni čimbenik rizika povezan sa značajnim morbiditetom i smrtnošću. Stoga bi pravovremena identifikacija osoba s povišenim krvnim tlakom i upravljanje krvnim tlakom u ranom životu moglo poslužiti kao ključna strategija za smanjenje rizika od kardiovaskularnih bolesti i smrtnosti u odrasloj dobi.

Original article

Factors Associated with the Quality of Life of the Nurses

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Abstract

Aim of the study: Research aim was to investigate the quality of life of the nurses and to determine sociodemographic factors associated with lower quality of life.

Methods: A convenience sample of 100 nurses from different medical institutions in Croatia was used. An anonymous on-line questionnaire containing sociodemographic questions was administered. Quality of life was measured using Short Form-36 (SF-36).

Results: Lower general health was associated with the older age of nurses and those working only morning shifts. Lower vitality and mental health were associated with working only morning shifts. Other investigated factors showed no association with the quality of life of the nurses.

Conclusion: The quality of life of the nurses is lower than the quality of life of the general population in Croatia, in domains related to the role limitations due to physical health, bodily pain, vitality and social functioning. Factors influencing the quality of life of the nurses are inconsistent with literature data and require further research.

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Introduction

Quality of life (QOL) is a concept referring to a general well-being of an individual, with regards to their goals, expectations, standards and living conditions. World Health Organization defines quality of life as one's perception of one's position in life in the context of the culture and value systems in which one lives (1). Health-related quality of life refers to the functioning and well-being within physical, mental and social dimensions of life (2). Many factors affect the quality of life of nurses and other health-care workers: age, gender, employment, profession, education, income, social support, marital status, work experience, position, department, shifts, workload (3–5), but the data are not consistent.

Nursing is one of four stressful professions in the world (6). Research has shown that healthcare professionals have lower QOL than other public sector personnel (5, 7) or general population (8, 9). Furthermore, nurses reported lower QOL than other health-care professionals, such as doctors and auxiliary personnel (7,8,10). QOL is an important tool for understanding the mental and physical health conditions of workers (11). For example, low physical domain of QOL was associated with lower working ability of emergency medicine employees (12). Lower QOL was also associated with high level of burnout and occupational stress in nurses (3, 8, 13). Furthermore, QOL can influence work efficiency, work quality, organizational commitment and job satisfaction in nurses (3).

The hypothesis of the research was that nurses have lower quality of life than general Croatian population and that sociodemographic factors are associated with the quality of life of the nurses. In the scope of continuous shortage of nursing professionals, data regarding the quality of life of the nurses and the factors associated with it could be valuable not only to the nurses but to the employers and a health-care system, since the nurses make the largest group of healthcare professionals in all countries (14) and management culture can improve the quality of life of the nurses (15). The research aim was to investigate the quality of life of nurses and to determine sociodemographic factors associated with lower quality of life of nurses.

Material and methods

Research was conducted in Croatia in the April 2019 by using an online survey. Ethical Committee of the School of Medicine at University of Zagreb approved the research (Classification: 602-04/19-119/1; Number: 380-59-10703-19-6661). A convenience sample of 100 nurses from different medical institutions was used. The survey was anonymous and nurses interested in participating in the study were invited to fulfill a questionnaire online. The questionnaire was distributed via social networks and was limited to only one participation by using Google Forms. The questionnaire consisted of sociodemographic questions related to age, sex, education level, marital status, work place, working schedule, total length of service and the length of service in shifts. Quality of life was measured by using Short Form-36 (SF-36), which measures quality of life in eight domains: general health (GH), social functioning (SF), bodily pain (BP), mental health (MH), vitality (VT), role limitations due to emotional problems (RE), role limitations due to physical health (RP) and physical function (PF) (16). This self-reporting instrument is the most widely used scale for assessing the quality of life. It contains 36 items and the results are scored from 0 to 100 where higher scores present better quality of life. The SF-36 version in Croatian language was validated for Croatian population and it was found reliable (17).

Statistical analyses

The Kolgomorov-Smirnov test was used to test the data distribution normality. Descriptive statistics were applied. Comparison of numerical variables was done using the Mann-Whitney U test and the Kruskal-Wallis test. The statistical significance level was set at $p<0.05$. The statistical package Statistica for Windows 2010 (version 10.0, StatSoft Inc., Tulsa, OK, USA) was used.

Results

Characteristics of the participants

The median age of the participants was 33.5 years (interquartile range 28.5–39.5), 79 (79%) were females. Educational level was as follows: 53% had finished secondary education, 34% were bachelors of nursing and 13% were masters of nursing. Working in the emergency departments was reported by 50% of the participants, while the other 50% worked outside emergency departments. The reported working shifts were as follows: working only morning shift was reported by 21% of participants; working in two day shifts (morning/afternoon) was reported by 30% of the nurses and 49% of the nurses reported working in three shifts including night shifts. Length of service in shifts was as follows: 41% of the participants reported working in shifts up to 5 years, 47% of the participants reported working in shifts for 6 to 15 years and 12% of the participants reported working in shifts longer than 15 years. Total length of service was as follows: 19% of the nurses reported working up to 5 years, 40% of the nurses reported working from 6 to 15 years, 24% of the nurses reported working from 16 to 25 years and 17% of the nurses reported working longer than 25 years in total. As for marital status, 12% were single, 63% were married, 9% were divorced, 16% were in a relationship and there were no widow(er)s (Table 1).

Table 1. Quality of life of nurses

QOL domains	Median	Interquartile range
PF	80.0	42.5–93.7
RP	50.0	6.25–100.0
RE	100.0	33.0–100.0
VT	50.0	40.0–60.0
MH	64.0	48.0–76.0
SF	62.0	50.0–75.0
BP	59.5	45.0–77.0
GH	55.0	45.0–75.0

Quality of life

The results of the quality of life are divided in eight domains and presented in Table 1. Factors found to be associated with lower QOL domains were older age group and working only morning shifts. Gender, work place, length of service in shifts, total length of service, educational level and marital status were not associated with difference in QOL domains. The oldest age group of the nurses had significantly lower scores in the QOL domain related to the general health. Nurses working only morning shifts had significantly lower scores in the QOL domains related to vitality, mental health and general health (Table 2).

Table 2. Sociodemographic factors associated with the quality of life of nurses

Sociodemographic factors	QOL domains							
	PF	RP	RE	VT	MH	SF	BP	GH
Gender	p=0.766*	p=0.877*	p=0.545*	p=0.763*	p=0.310*	p=0.431*	p=0.641*	p=0.696*
Age group	p=0.089†	p=0.617†	p=0.863†	p=0.395†	p=0.147†	p=0.818†	p=0.165†	**p=0.032†**
Work place	p=0.482*	p=0.934*	p=0.779*	p=0.320*	p=0.663*	p=0.666*	p=0.669*	p=0.782*
Type of work shifts	p=0.260†	p=0.159†	p=0.659†	**p=0.009†**	**p=0.032†**	p=0.379†	p=0.435†	**p=0.044†**
Length of service	p=0.212†	p=0.861†	p=0.674†	p=0.549†	p=0.080†	p=0.368†	p=0.383†	p=0.988†
Length of service in shifts	p=0.940†	p=0.839†	p=0.897†	p=0.410†	p=0.156†	p=0.470†	p=0.761†	p=0.691†
Educational level	p=0.147†	p=0.177†	p=0.061†	p=0.180†	p=0.724†	p=0.764†	p=0.521†	p=0.694†
Marital status	p=0.718*	p=0.456*	p=0.874*	p=0.799*	p=0.550*	p=0.843*	p=0.736*	p=0.073*

*Mann-Whitney U test; † Kruskal-Wallis test

Discussion

The study investigated the QOL of the nurses and sociodemographic factors that might be associated with it. Comparison of the results with the Croatian general population norms for SF-36 (17) showed nurses to have lower QOL of life in the following domains: RP, BP, VT and SF. The obtained results were higher than the Croatian general population scores for the following domains: PF, RE and MH, whereas they were similar for GH domain. Other QOL studies also found nurses to have lower QOL than general population of the country (7, 9, 10). Nurses in Italy had significantly lower QOL scores compared to Italian general population in the following domains: GH, VT, SF, RP, BP (9). Moreover, the nurses in Greece had lower QOL scores than the Greek general population (7).

Results from this study across five QOL domains (GH, RP, BP, VT, PF) were lower than the QOL scores obtained in 2019 for Italian nurses working night shifts (9) even though our sample included nurses working all kinds of shifts. The MH and SF domains were similar, while RE was higher in our study. Lower QOL domain scores indicated poorer physical health of nurses from Croatia than those in Italy. A study of Iranian nurses from 2022 showed better results than our study results for several domains: RP, BP, GH, VT; lower results for SF, RE, MH, and similar result for PF, also indicating that nurses from Croatia had poorer physical health than their colleges in Iran during the COVID-19 pandemic (6).

This study showed poorer general health to be associated with older age and working only morning shifts, while sex, work place, total length of service, length of service in shifts, educational level and marital status showed no association with general health. The Italian study obtained the opposite results, showing poorer general health in nurses working night shifts, those having longer length of service and in female nurses (9). Lower general health scores in the oldest age group of nurses are in congruence with the general fact that the quality of life decreases with age, and similar results were obtained for Croatian general population (17).

Lower vitality was associated with working only morning shifts in this study, while other factors showed no association with this domain. On the contrary, the Italian study showed that lower vitality was associated with the total years of service and the female gender (9). Poorer mental health was associated with working only morning shifts. Another study of Croatian clinical nurses found no association between the psychological health domain and shift work, gender or work experience (14), while the Italian study found lower mental health to be associated with female gender (9). The Lebanese study also found female nurses and those with lower education level to have lower psychological domain of the QOL (13). This study found no association between the investigated sociodemographic factors and physical function. Another study of Croatian clinical nurses also found no association between physical health domain and shift work, gender or work experience, but found association between physical health domain and lower education level (14), while the Italian study found association between physical function and female gender, longer length of service, longer service in shifts, longer time spent working in the same unit and older age (9). The Lebanese study also found female nurses, older nurses and those with longer length of service to have lower physical domain of the QOL (13). Role limitations due to physical health was not associated with the investigated sociodemographic factors in this study, while the Italian study found association with female gender (9). Bodily pain was not associated with the investigated sociodemographic factors, whereas the Italian study found association with marital status, gender, number of children, length of service, length of service in shifts, length of work in the same unit and age (9). Role limitations due to emotional problems was not associated with the investigated sociodemographic factors, while the Italian study found association with longer length of service in the same unit (9). Social functioning was not associated with the investigated sociodemographic factors. Another

study of Croatian clinical nurses found no association between the social interaction domain and shift work, gender or work experience, but found association between the social interaction domain and older age and being single (14), while the Italian study found association between social functioning and female gender, length of shift work and length of work in the same unit (9). The Lebanese study found the social relationship domain of the QOL to be lower in females, nurses working night shifts and those with longer length of service (13).

Literature data, including this study, indicate that factors influencing the quality of life of nurses are inconsistent and differ across the countries. Although gender was not associated with any of the QOL domains in this study, other studies found lower quality of life of female nurses (3, 6, 9, 13). A study of Chinese surgical nurses showed association between lower QOL and female sex, younger age, frequent night shifts and professional titles, which is contrary to our results, and found no association with length of service, education level, marital status and ethnicity, which is similar to our results (3). A study of Iranian nurses found association between lower QOL and female gender, being single, lower income, which is contrary to our results, and found no association with education level, which is similar to this study (6). A study of Italian nurses working night shifts found lower QOL to be related to female gender and longer commuting (9). Lebanese study of the QOL of nurses found lower education level, female gender, length of service, shift work and older age to be associated with lower QOL, while marital status and monthly income showed no association with the QOL (13). QOL was associated with age, marital status, education, work experience, position, department, shifts and employment status in Iranian nurses (4).

Several studies reported negative effects of shift work and night shifts on health (18). Shift work is the main characteristic of nursing and was found to be associated with sleep, digestive and cardiovascular disorders (14) and also with compassion fatigue and burnout (19). Shift work may worsen the quality of life (3,9), but this study did not confirm these results. The highest scores of the QOL in this study reported nurses that work in day shifts (morning/afternoon), and the worst scores of QOL reported nurses working only morning shifts. Nurses that work both day and night shifts had better QOL scores than nurses working only morning shifts. The reason for different results in different studies may reflect the work dynamics at different positions or departments. For example, nurses in Croatia working night shifts in prehospital emergency medical service may get several hours of sleep during the shift if there are no new patients to attend throughout the shift, while in some other departments during the whole night shift there is no opportunity to rest.

In this study, as well as in others, age was associated with lower quality of life (4, 13). Other factors that may influence the QOL of nurses and that should be investigated in the future include those related to working during COVID-19. Some studies already found COVID-19 anxiety to be associated with lower QOL of nurses (6).

Female nurses comprised the most of the study sample, which is representative of the nursing profession, given that it is considered to be a female profession (19). Other studies that we compared our results with also had their study samples mostly consisting of female nurses (3, 6, 7, 9, 13, 14, 19).

Most of the reference studies of the QOL of nurses used the same SF-363,5-11, while others used other available QOL instruments (4, 13, 14, 19). Therefore, data from this study are mostly comparable within the aspect of methodology.

Limitations of the study

This study has several limitations that need to be addressed. A convenience sample was used, which can cause selection bias and limit the potential to generalize the results. The cross-sectional study type cannot prove causality between the investigated variables. The use of self-reported questionnaires could be associated with the social desirability bias and the study sample was relatively small so it may not be representative of Croatian nurses. The use of an online survey probably implies

younger population of nurses that are more familiar with the use of internet, which is supported by relatively young median age of the participants. Further research should also use conventional channels for the collection of the study sample in addition to the online survey methods, which could enable participation of all age groups of nurses. Moreover, the reference scores for Croatian general population are from 2006 (17) and those might have changed over the years.

In conclusion, the quality of life of nurses is lower than the quality of life of general population in Croatia, in domains related to the role limitations due to physical health, bodily pain, vitality and social functioning. Data regarding factors influencing the quality of life of the nurses are inconsistent with literature data and require further investigation. Further research needs to be directed toward broadening the spectrum of investigated factors that may influence the quality of life of nurses and determining causality between them, possibly on the greater sample of nurses from different health-care departments. Changes in quality of life before, during and after the COVID-19 pandemic should also be evaluated since nurses and other health-care professionals carry the heaviest burden of the COVID-19 pandemic.

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Čimbenici povezani s kvalitetom života medicinskih sestara

Cilj istraživanja: Cilj istraživanja bio je ispitati kvalitetu života medicinskih sestara i utvrditi sociodemografske čimbenike povezane s nižom kvalitetom života.

Metode: Korišten je prigodni uzorak od 100 medicinskih sestara iz različitih medicinskih ustanova u Hrvatskoj. Proveden je anonimni on-line upitnik koji je sadržavao sociodemografska pitanja. Kvaliteta života mjerena je pomoću Upitnika za procjenu zdravstvenog stanja - 36 (SF-36, od engl. Short form - 36).

Rezultati: Lošije opće zdravlje povezano je sa starijom dobi medicinskih sestara i radom samo u jutarnjim smjenama. Niža vitalnost i mentalno zdravlje povezani su s radom samo u jutarnjim smjenama. Ostali ispitivani čimbenici nisu pokazali povezanost s kvalitetom života medicinskih sestara.

Zaključak: Kvaliteta života medicinskih sestara niža je od kvalitete života opće populacije u Hrvatskoj, u domenama koje se odnose na ograničenja uloga zbog tjelesnog zdravlja, bol, vitalnost i socijalno funkcioniranje. Čimbenici koji utječu na kvalitetu života medicinskih sestara nisu u skladu s podacima iz literature i zahtijevaju daljnja istraživanja.

Original article

Knowledge of Students in Health and Non-Health Studies about Diabetes Mellitus Type 1

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Abstract

The aim of the research: The aim of this research paper is to examine and compare the knowledge of students in health and non-health studies about diabetes mellitus type 1. Namely, the research examined whether the respondents are sufficiently educated about the disease itself, treatment and preventive measures of diabetes type 1. Their knowledge was examined with regards to their age, gender and the type of studies they attend.

Respondents and methods: The research was conducted as a cross-sectional study. 101 respondents participated in the research. An anonymous online questionnaire was used as a measuring instrument, which was created for the purpose of this research. The research was conducted in July and August 2022.

Results: Most respondents have good knowledge about diabetes mellitus, which is evident in the correct answers to the questions in the survey questionnaire. Statistically, significant differences were found in the students' knowledge with regards to their age, gender and type of study. Respondents who participate in health studies have a higher level of knowledge than respondents who do not participate in health studies. Female respondents have a higher level of knowledge than male respondents. Older respondents also have greater knowledge about the disease itself.

Conclusion: Students who study health studies show a higher level of knowledge than students of other studies. Most of the respondents were well educated about type 1 diabetes mellitus. Diabetes is one of the biggest public health problems nowadays, and measures of prevention and education of the population should be implemented as much as possible in kindergartens, primary and secondary schools, colleges, hospitals, and the health system.

(Kolačko Š, Kokot A, Čuljak N, Predović J, Hrvačić M, Luetić F, Bašković M. Knowledge of Students in Health and Non-Health Studies about Diabetes Mellitus Type 1. SEEMEDJ 2023; 7(2); 57-65)

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KEYWORDS: diabetes mellitus; students; type 1 diabetes

Introduction

Diabetes mellitus is a chronic metabolic disease caused by the interaction of hereditary and environmental factors that negatively affect the work of the pancreas, which then completely or partially stops producing the hormone insulin or insulin resistance occurs in the human body (1). As a result, hyperglycemia occurs, a condition of elevated blood glucose levels that can cause diabetic complications (2). Almost 50% of patients suffering from this disease will develop a serious complication during their lifetime (3, 4, 5). Some will lose their sight and others will develop end-stage kidney disease. The best control of the disease is achieved by applying appropriate therapy (6, 7, 8). The disease is widespread throughout the world and is considered to be a significant public health problem. The age limit of people suffering from diabetes is getting lower every year due to a fast and stressful lifestyle, lack of physical activity and consumption of unhealthy food (2). In addition to the aforementioned factors and genetic predisposition, there are other causes of the increase in the frequency of diabetes, one of which is the increase in life expectancy, which results in a greater proportion of elderly people in the population (9). It is extremely important to provide quality care for the sick, as well as to educate the sick and healthy population about diabetes (10, 11). The aim of this research was to examine the knowledge of health and non-health studies students about the disease type 1 diabetes, and to examine the differences in the knowledge of students regarding their age, gender and the type of study they are attending.

Respondents and methods

Structure of the study

For the purpose of this research, a cross-sectional study was conducted.

Respondents

Respondents in the research were health and non-health undergraduate students. The health study included students of the first year of undergraduate nursing studies at the Faculty of Dental Medicine and Health, Pregrada, Josip Juraj Strossmayer University of Osijek. The non-health study included undergraduate students of the Faculty of Economics and Business, University of Zagreb. In the period from 1 July to 31 August 2022, the students filled out an online questionnaire anonymously via the link that had been sent to them. The limitations of the study are the relatively small number of respondents, which opens up opportunities for further research work with a larger number of respondents who do not attend any health studies.

Methods

The survey was conducted via a Google form, which was sent to a closed group that the students used to share information. An anonymous survey questionnaire, created for the purpose of this research, was used as a measuring instrument. Participation in the research was voluntary and anonymous. By filling out the questionnaire, the respondents also gave their consent to participate in the research. The questionnaire consisted of 16 questions to which multiple answers were offered. Out of the total of 16 questions, the first four related to general information about the respondents and the study they were attending, while the other 12 questions related to testing the knowledge about type 1 diabetes prevention measures.

Statistical methods

Categorical data were presented by absolute and relative frequencies. The Chi-square test was used to analyze the differences between proportions. All P values were two-sided. The level of significance was set at Alpha of 0.05. The statistical analysis was performed using the IBM SPSS 23.0 Statistics for Windows (IBM, United States of America).

Results

One hundred and one subjects participated in this research, 40 (39.6%) of which were male and 61 (60.4%) were female. In the conducted

research, there were 36 (35.6%) respondents aged 18–25, 41 (40.6%) respondents aged 26–35, 17 (16.8%) respondents aged 36–45 and seven (6.9%) respondents aged 46–55. Eighty (79.2%) respondents stated that they live in the city and 41 (40.6%) of respondents answered that they were studying in a health study. When asked how type 1 diabetes is treated, 10 (9.9%) respondents answered with oral hypoglycemic agents, 69 (68.3%) respondents answered with insulin, while 22 (21.8%) respondents answered with a combination of insulin and oral hypoglycemic agents (p <0.001). When asked what the most frequent symptoms of type 1 diabetes are, more than 80% of respondents answered that these are frequent urination and thirst (Table 1).

Table 1: Answers to the question "The most common symptoms of type 1 diabetes mellitus are:"

	N	%
Frequent urination	83	82.18
Thirst	86	85.15
Sudden weight loss	72	71.28
Weakness	50	49.5
Blurred vision	46	45.5
Nausea and vomiting	30	30

Table 2: Answers to the question "How many basic types of diabetes mellitus are there?"

			2 types	3 types	4 types	χ2	p
Are you studying in health studies?	Yes	N	33	6	2	1,241	0.538
		%	80.5	14.6	4.9		
	No	N	44	14	2		
		%	73.3	23.3	3.3		

Table 3: Answers to the question "What is glycated hemoglobin HbA1c?"

			Three-month average of blood values	Blood sugar value measured on an empty stomach	Blood sugar value after eating	χ2	p
Are you studying health studies?	Yes	N	32	7	2	5,308	0.07
		%	78	17.1	4.9		
	No	N	36	12	12		
		%	60	20	20		

To the question that referred to the examination of the differences in the respondents' knowledge about the basic types of diabetes regarding the type of study, 80.5% of the respondents who attend health studies answered that there were two types of the disease, in contrast to 73.3% of respondents who do not attend health studies. Comparing the answers to the question about the basic types of diabetes in relation to the study participants, no statistically significant difference was found (Table 2).

Comparing the answers to the question about glycated hemoglobin HbA1c in relation to the study, the respondents studying in health studies have better knowledge about glycated hemoglobin (Table 3).

Comparing the answers to the question about the reference values of glycated hemoglobin regarding the type of study, it was noticed that the respondents studying in health studies have better knowledge about the reference values of glycated hemoglobin (Table 4).

Table 4: Answers to the question "What are the reference values of glycated hemoglobin HbA1c?"

			Below 4.5%	Below 6%	Below 8%	below 10%	χ2	p
Are you studying in health studies?	Yes	N	5	22	10	4	3,706	0.295
		%	12.2	53.7	24.4	9.8		
	No	N	12	22	15	11		
		%	20	36.7	25	18.3		

Comparing the answers to the question about the recommended values of glucose in the blood regarding the sex of the respondents, a statistically significant difference was observed.

It was observed that female respondents have better knowledge about recommended blood glucose values compared to male respondents (Table 5).

Table 5: Answers to the question "The recommended fasting blood glucose value is:"

			4-6mmol/L	5-7mmol/L	6-8mmol/L	χ2	p
Sex	male	N	26	5	9	7,207	0.027
		%	65	12.5	22.5		
	female	N	53	4	4		
		%	86.9	6,6	6,6		

Table 6: Answers to the question "The most dangerous complication of diabetes mellitus type 1 is:"

			Hypoglycemia	Diabetic ketoacidosis	Hyperglycemia	χ2	p
Age	18–40	N	11	22	7	11,357	0.003
		%	27.5	55	17.5		
	40–55	N	6	52	3		
		%	9.8	85.2	4.9		

By examining the differences in the respondents' knowledge about the most dangerous complication of type 1 diabetes regarding the age of the respondents, a statistically significant difference was observed. It was noticed that respondents aged 40–55 have better knowledge about the most dangerous complication of type 1 diabetes compared to respondents aged 18–40 (Table 6).

Discussion

The obtained results of the research confirmed that respondents who study in health studies are better acquainted with diseases than those who do not. Similar results were observed in a study conducted at the Ziauddin University in Karachi, Pakistan by Shadma, Tabind and Hemna. In the mentioned research, the knowledge of medical students about type 1 diabetes was compared. The average overall knowledge of medical students in the study was determined, while the students at clinical level of the study had better knowledge compared to those at pre-clinical levels. Similar results were observed among Pakistani nurses (12, 13).

In response to the question about the types of diabetes, the obtained results show that more respondents who do not participate in health studies answered this question incorrectly. This problem of ignorance regarding the disease itself could be solved by more frequent education of health personnel, hospitalized patients, patients in day hospitals, clinics and health centers (14, 15, 16).

Answers to questions about blood glucose values were compared with the gender of the subjects. It was noticed that more female than male respondents answered correctly. As previously stated, hypoglycemic events are associated with adverse effects on cognitive function and are linked to 4–10% of deaths associated with type 1 diabetes, so it is extremely important that patients, their families and others involved in treatment know the values of hypoglycemia in order to react in a timely manner (17).

The results obtained in the research we conducted in Zagreb show that respondents who participate in health studies have better knowledge about the HbA1c screening than respondents who do not participate in health studies. It is extremely important for the population to know what this test is. It is one of the first things a patient should do if they start to feel some of the symptoms of diabetes, such as frequent urination, thirst and fatigue (18, 19, 20).

When asked what the reference values of HbA1c are in relation to the type of study, respondents studying in health studies showed better knowledge – twenty-two (53.7%) respondents studying in health studies answered correctly, i.e. that the reference values are below 6%, while twenty-two of them (36.7%) who are not participating in health studies answered the same. The importance of reducing glycated hemoglobin is best demonstrated by the fact that lowering glycated hemoglobin by 1% reduces total mortality by 21%, i.e. mortality from microvascular complications of diabetes by 37% and from myocardial infarction by 14% (21, 22, 23).

The American Diabetes Association (ADA) defines the education for people with diabetes as a process of acquiring knowledge, skills and competences, the long-term goal of which is to train participants for adequate self-care of diabetes (24, 25).

It is believed that proper diet, education and physical activity can greatly reduce the probability of diabetes and many other diseases. Similar results to our study were observed in a study at the Ziauddin University in Karachi, Pakistan conducted by Shadma, Tabind and Hemna. A total of 366 subjects participated in the mentioned research, 145 of which (39.6%) were from a preclinical level and 221 (60.4%) from a clinical level of subjects. As an answer to the question related to disease prevention, 89% of the clinical group knew that diabetes can be prevented and the same number of students (89%) believed that there is a role of exercise in prevention, while almost half of the preclinical students (49%) had no idea about prevention and almost the same number of students (44%) did not know about the role of exercise in disease prevention ($p<0.001$). On the other hand, research conducted in America showed that

only 31% of non-diabetic health workers were aware of the role of exercise in prevention, which indicates ignorance about the key role of exercise in disease prevention (26, 27, 28).

The increasing prevalence of diabetes requires targeted screening to detect diabetes and prediabetes in at-risk groups. This is the basis for early measures to prevent diabetes in these groups and to delay the progression of diabetes (29).

Conclusion

The respondents who are students in health studies show better knowledge about diabetes type 1 than the respondents who do not study in health studies, as shown by the results: 80.5% of respondents who participate in health studies correctly answered the question about the basic types of diabetes type 1, while fewer respondents, 73 of them (3%) who are not studying in health studies answered the question correctly. There is a significant difference in the knowledge of all respondents involved in the research according to age and gender, with female respondents and elderly respondents showing a higher level of knowledge about type 1 diabetes.

Most of the respondents who were involved in the conducted research were well educated about the disease and treatment of type 1 diabetes. Research shows that education about available resources, adherence to given recommendations and regular use of prescribed therapy are extremely important for patients.

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Disclosure

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Competing interests. None to declare.

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Analysis and interpretation of data: KŠ, KA, ČN, PJ, HM, BM
Conception and design: KŠ, KA, ČN, PJ, HM
Critical revision of the article for important intellectual content: KŠ, KA, ČN, PJ, HM, BM
Drafting of the article: KŠ, KA, ČN, PJ, HM, BM
Final approval of the article: KŠ, KA, ČN, PJ, HM, BM
Guarantor of the study: KŠ, KA, ČN, PJ, HM
Provision of study materials or patients: KŠ, KA, ČN, PJ, HM
Statistical expertise: KŠ, KA, ČN, PJ, HM, BM

Znanje studenata zdravstvenih i ne-zdravstvenih studija o dijabetesu melitusu tipa 1

Cilj istraživanja: Cilj ovoga istraživačkog rada je ispitati i usporediti znanje studenata zdravstvenih i nezdravstvenih studija o dijabetesu melitusu tipa 1. Istraživano je jesu li ispitanici dovoljno educirani o samoj bolesti, liječenju i preventivnim mjerama dijabetesa tipa 1. Njihovo znanje ispitano je s obzirom na dob, spol i vrstu studija koje pohađaju.

Ispitanici i metode: Istraživanje je provedeno kao presječna studija. U istraživanju je sudjelovao 101 ispitanik. Kao mjerni instrument korišten je anonimni on-line upitnik, koji je kreiran za potrebe ovog istraživanja. Istraživanje je provedeno u srpnju i kolovozu 2022. godine.

Rezultati: Većina ispitanika ima dobro znanje o dijabetesu melitusu, što je vidljivo iz točnih odgovora na pitanja u anketnom upitniku. Statistički značajne razlike utvrđene su u znanju studenata s obzirom na dob, spol i vrstu studija. Ispitanici koji pohađaju zdravstvene studije imaju višu razinu znanja od ispitanika koji ne studiraju na zdravstvenim studijima. Ženski ispitanici imaju višu razinu znanja od muških ispitanika. Stariji ispitanici također imaju veće znanje o samoj bolesti.

Zaključak: Studenti koji studiraju na zdravstvenim studijima pokazuju višu razinu znanja od studenata drugih studija. Većina ispitanika bila je dobro educirana o dijabetesu melitusu tipa 1. Dijabetes je jedan od najvećih javnozdravstvenih problema danas, te bi mjere prevencije i edukacije stanovništva trebale biti što je moguće više implementirane u vrtiće, osnovne i srednje škole, fakultete, bolnice i zdravstveni sustav.

Review article

Enlightenment and Freemasonry in the Life and Work of the Physician Joannis Baptistae Lalangue

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Abstract

Data on the educational and Freemasonry activities of Doctor Joannis Baptistae Lalangue have been relatively modestly represented in the scientific literature until now. Based on recent research, we have come to the realizations that give us a new context for the life and work of Lalangue, especially from the aspect of his social activity. All of the above had very significant repercussions on his entire public health work and especially on his journalistic and publishing work. John the Baptist Lalangue was a successful physician. During his medical studies in Vienna, he was recognized by Baron van Swieten, the first name in medicine of the Habsburg Monarchy. Recent knowledge speaks of his very notable Enlightenment and Freemasonry work, which largely determined his life and work. Lalangue has created a truly impressive literary work, which is closely related to his active Enlightenment and public Masonry engagement. The mentioned progressive Enlightenment engagement is also responsible for the fact that thanks to Lalangue, we already had printed medical original professional literature in the Croatian language in the second half of the 18th century. This directly changed the conditions in society, primarily in the field of public health, for the better, not only in Croatia but also throughout the Habsburg Monarchy.

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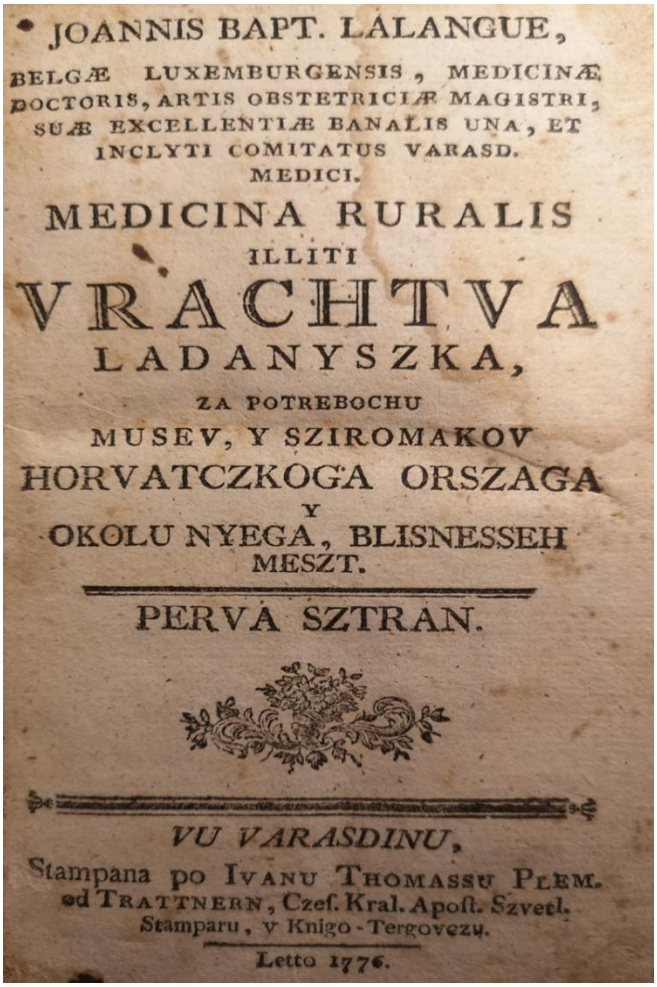
KEYWORDS: John the Baptist Lalangue, history of medicine, Enlightenment, Freemasonry

Introduction

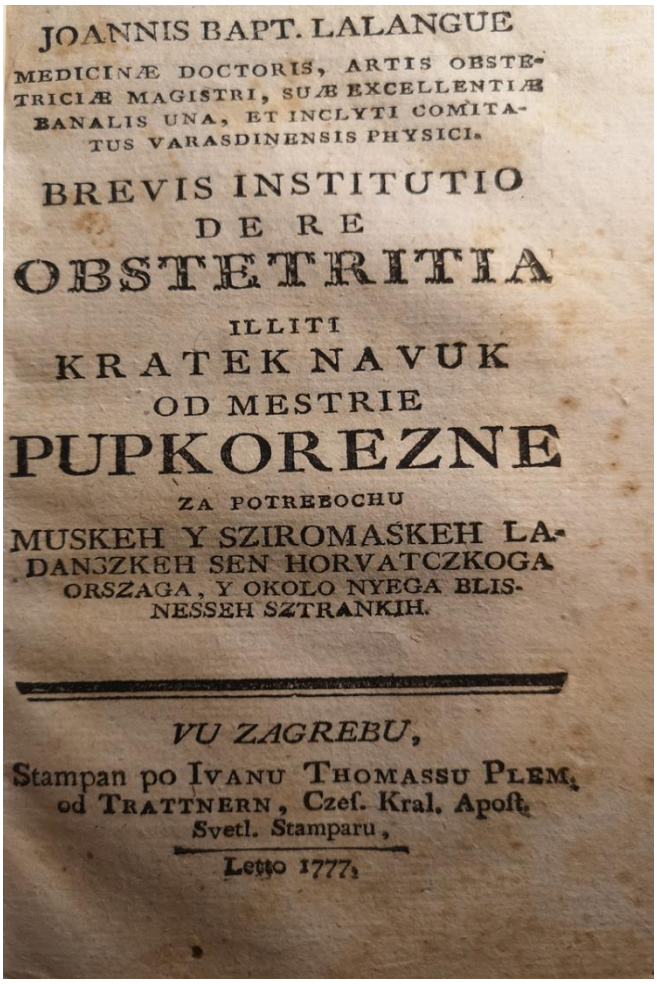
New information about John the Baptist Lalangue provides a very valuable insight into the social, economic, socio-economic and public health life of the 18th century in the Habsburg Monarchy. There is no doubt that the information about the overall Enlightenment and Freemasonry life and work of the distinguished and famous Doctor Joannis Baptistae Lalangue has so far been very poorly processed and represented in the scientific literature. On the trail of recent research, we acquired significant knowledge from which we obtained a lot of new data that complement previous research and represent the basis for further progress. It is precisely on the aforementioned foundations that we arrive at very reliable information, based on which a new account of the life and work of Doctor Lalangue is presented. The aforementioned recent knowledge certainly complements and rounds off numerous aspects of his social, public health and especially publishing and journalistic activities. Based on the aforementioned recent research, we have come to very significant discoveries that expand our knowledge about the truly peculiar and exceptional life of Doctor Lalangue. Doctor Lalangue himself undoubtedly left a very significant mark in the field of medicine, medical publishing, public health, Enlightenment and Freemasonry in the second half of the 18th century in the territory of Croatia and the entire Habsburg Monarchy. Although he has been unfairly neglected for many years, Lalangue has been getting his well-deserved valorization lately. Nowadays, John the Baptist Lalangue – Joannis Baptiste Lalangue (Matton, Luxembourg, 27 April 1743 – Varaždin, Croatia, 20 May 1799) is considered the founder of the original professional medical literature in the Croatian language. Lalangue published his first medical professional printed original book in the Croatian language in 1776, titled Medicina ruralis iliti Vrachtva ladanyszka, za potrebochu musev, y sziromakov Horvatczkoga orszaga y okolu nyega, blisnesseh meszt, Trattner, Varaždin (Picture 1). His debut contains the most common diseases of that time, following the medical knowledge of the second half of the XVIII century (1-8).


JOANNIS BAPT. LALANGUE,
BELGÆ LUXEMBURGENSIS, MEDICINÆ DOCTORIS, ARTIS OBSTETRICIÆ MAGISTRI, SUÆ EXCELLENTIÆ BANALIS UNA, ET INCLYTI COMITATUS VARASD. MEDICI.
MEDICINA RURALIS
ILLITI
VRACHTVA
LADANYSZKA,
ZA POTREBOCHU
MUSEV, Y SZIROMAKOV
HORVATCZKOGA ORSZAGA
Y
OKOLU NYEGA, BLISNESSEH
MESZT.
PERVA SZTRAN.
VU VARASDINU,
Stampana po Ivanu Thomassu Plem. od Trattnern, Czes. Kral. Apost. Szvetl. Stamparu, v Knigo-Tergovczu.
Letto 1776.

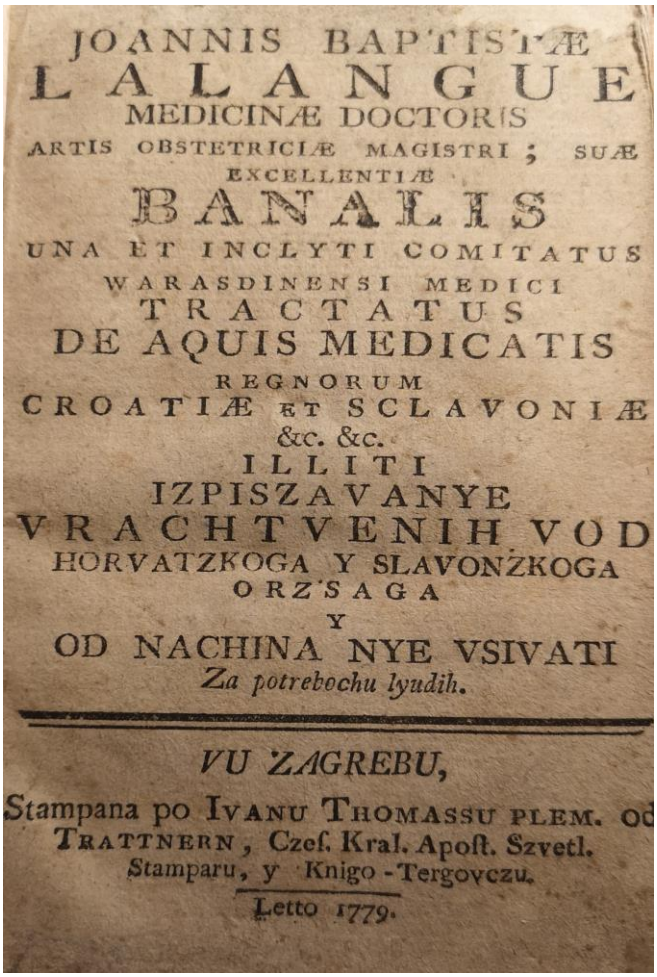
Picture 1 Cover of Lalangue's first book from 1776.

As early as 1777, Lalangue published his first Croatian midwifery book Brevis institutio de re obstetritia iliti Kratek navuk od mestrie pupkorezne za potrebuchu muskeh y sziromaskeh ladanskeh sen horvatszkoga orszaga y okolo nyega blisnesseh sztrankih, Trattner, Zagreb (Picture 2).

In 1779, Lalangue published his Croatian balneological debut, a book Tractatus de aquis medicati regnorum Croatiae et Slavoniae etc. iliti Izpiszavanye vrachtvenih vod Horvatzkoga y Slavonskoga orszaga y od nachina nye vsivati za potrebochu lyudih, Trattner, Zagreb (Picture 3) (1–8).


JOANNIS BAPT. LALANGUE
MEDICINÆ DOCTORIS, ARTIS OBSTETRICIÆ MAGISTRI, SUÆ EXCELLENTIÆ BANALIS UNA, ET INCLYTI COMITATUS VARASDINENSIS PHYSICI.
BREVIS INSTITUTIO DE RE OBSTETRITIA
ILLITI
KRATEK NAVUK OD MESTRIE PUPKOREZNE
ZA POTREBOCHU
MUSKEH Y SZIROMASKEH LADANJZKEH SEN HORVATCZKOGA ORSZAGA, Y OKOLO NYEGA BLISNESSEH SZTRANKIH.
VU ZAGREBU,
Stampan po IVANU THOMASSU PLEM. od TRATTNERN, Czes. Kral. Apost. Svetl. Stamparu,
Letto 1777.

Picture 2 Cover of Lalangue's second book from 1777.


JOANNIS BAPTISTÆ LALANGUE
MEDICINÆ DOCTORIS
ARTIS OBSTETRICIÆ MAGISTRI; SUÆ EXCELLENTIÆ
BANALIS
UNA ET INCLYTI COMITATUS WARASDINENSI MEDICI
TRACTATUS DE AQUIS MEDICATIS REGNORUM CROATIÆ ET SCLAVONIÆ &c. &c.
ILLITI
IZPISZAVANYE VRACHTVENIH VOD HORVATZKOGA Y SLAVONZKOGA ORZ'SAGA Y OD NACHINA NYE VSIVATI
Za potrebochu lyudih.
VU ZAGREBU,
Stampana po IVANU THOMASSU PLEM. od TRATTNERN, Czes. Kral. Apost. Szvetl. Stamparu, y Knigo-Tergovczu.
Letto 1779.

Picture 3 Cover of Lalangue's third book from 1779

The Enlightenment spirit of John the Baptist Lalangue

Due to his qualities, he was noticed during his medical studies in Vienna by the baron and the first name of imperial medicine – Gerard van Swieten, who then became his mentor (9–14).

To understand the Enlightenment aspirations in the second half of the 18th century and the role outside the influence of Swieten, it is important to mention the famous physician Anton de Haen (The Hague, The Netherlands, 8 December 1704 – Vienna, Austria, 5 September 1776) (14). De Haen studied medicine in Leiden under the auspice of Herman Boerhaave and at the invitation of his mentor van Swieten, he came to the University of Vienna in 1754.

Following the example of Leiden he established a large clinical center that was leading at that time in Europe (9, 10). Lalangue was fortunate to be in close contact with van Swieten and De Haen as leaders of these positive Enlightenment efforts of the second half of the 18th century and also to be a student and collaborator of many great medical thoughts of his time laying the solid foundations of the new systems and contributing to the improvement of public health conditions of the population throughout the Monarchy (1, 2, 5). Another professor of Lalangue at the Medical School in Vienna, Baron Heinrich Johann Nepomuk von Crantz (2, 3, 15) (Roodt, Luxembourg, 25 November 1722 – 18 January 1799, Judenburg, Styria, Austria) should be mentioned, as well as his magnificent work for the Habsburg Monarchy (Gesundbrunnen der Österreichischen Monarchie, Wien, 1777) (6, 15). It is their native country Luxembourg that is the link between the greatest minds of the second

half of the 18th century. Therefore, the reputation as well as the influence that Lalangue himself enjoyed as a medical student and as a young doctor is completely understandable. It is worth mentioning the important publishing work of Prof. Crantz, which highlights the pioneering grandiose publishing endeavor in the field of balneology, healing springs and mineral waters of the Habsburg Monarchy from 1775 (6). Lalangue also played a very important role in the work of Crantz by collecting samples of healing springs and mineral waters, which was of great use to him in publishing his book on Croatian and Hungarian spa and healing waters (this is the Croatian and Hungarian balneological debut, the author of which is Lalangue), which is very important for the study of balneology in this Croatian area (1, 2, 5, 16).

In 1782 Slovenians in Ljubljana received the first midwifery textbook in the Slovenian language by Dr Anton Makovic (Kostanjevica na Krki, 1750 – Idrija, Slovenia, 1803): Prashania, inu odgovori zhes vshegarstv, five years after Lalangue published the first midwifery textbook in Croatian (2). Makovic wrote his first Slovenian midwifery textbook (1782), modeled on the 1774 obstetric work and the 1775 midwifery textbook written by Viennese medical professor Raphael Johann Steidele (Innsbruck, Austria, 20 February 1737 – Vienna, Austria, 10 September 1823) (2). Like Lalangue's, Steidele's textbook of midwifery was printed at Trattner's printing house in Vienna (2, 17–21).

Lalangue and Croatian Freemasonry activities

Lalangue's Freemasonry activity most likely began already during his studies at the Faculty of Medicine in Vienna. His mentor, van Swieten, was a very influential Freemason and Lalangue himself very early came under the aforementioned influence of Freemasonry and Enlightenment. We do not yet have enough information about the involvement of Lalangue as a Freemason and further research is certainly ahead of us, which will help shed light on that period of his life and work. The best evidence that supports these facts comes from research, which shows that Lalangue joined the work of the Freemason's Lodge in Glina very soon after arriving in Croatia. John the Baptist Lalangue was an active participant in the European Enlightenment in the second half of the 18th century in the context of Freemasonry. For the sake of quality analysis, we must also be acquainted with several historical facts about Freemasonry or Masonry. Freemasonry appeared on the world stage at the beginning of the 18th century. The first Croatian Masonic Lodge was founded in 1754 in Glina (2, 22). Lalangue was already engaged in Masonic circles during his medical studies in Vienna. Lalangue's Luxembourg descent certainly helped him rise to the very top of the medical profession in the second half of the 18th century. This is evidenced by historical sources which confirm that many great men of medical thought of Lalangue's time, at the same time leaders of Enlightenment aspirations, were also of Luxembourgish descent. Most of them, like Lalangue, were Freemasons. Freemasonry in Lalangue's time had a very positive impact on all segments of society, including public health (2, 22). Numerous greats, the most important intellectuals of the Lalangue era from the ranks of Freemasons, should be commended for all the far-reaching strides they have made in almost all areas of social action. The positive effects of this free-thinking work, which began in the second half of the 18th century, are felt to this day (2, 13, 22, 23). With Lalangue's arrival, Croatia and the Croats got the most prominent educator in the field of public health. Lalangue left an indelible mark in all areas in which he was engaged and which were of interest to him, with the primary goal of improving the living conditions of Croatian people (2, 13, 22, 23). John the Baptist Lalangue joined the Croatian Freemasons and their lodge in Glina (L 'Amitié de Guerre – War Friendship) where he was admitted on 18 November 1771. This information is the oldest record confirming that Lalangue was certainly in Croatia in early November 1771 (22, 23). According to historical sources, the first Croatian Masonic Lodge was founded on the territory of the Military Border (according to the Turkish Empire) in Glina in 1759, under the name "War Friendship". The founding of the Varaždin

Masonic Lodge in 1772, a year after Lalangue arrived from Vienna, is associated with his arrival in Croatia's then-capital Varaždin. The Zagreb Lodge was founded a year later in 1773 (2, 13, 22, 23). According to historical sources from the second half of the 18th century, Lalangue was one of the most agile Freemasons in Croatia and he is considered an ardent supporter of Drašković's faction (2, 13, 23).

Lalangue's Freemasonry activity in Varaždin and Croatia

Given that Lalangue settled permanently in Varaždin, recent research also confirms his accession to the Varaždin Masonic Lodge, which is understandable. Certainly, his educational and Freemason involvement is inextricably linked to his public health, social and publishing work. Based on the aforementioned recent knowledge, we can form a much better understanding of Lalangue's work, his life and especially his publishing work, through which he greatly indebted Croatian medicine and public health, as well as numerous other segments of social activity. In his further Masonic engagement in 1784, John the Baptist Lalangue became the elder of the Varaždin Masonic Lodge Vorsicht (Vigilance), under the secret name Hippocrates (22). The first Varaždin Masonic Lodge was founded in 1772 and was called the "Perfect Alliance" (L´ Union Parfaite). After two years the Lodge changed its name to "Sloboda" (Libertas, Freiheit). In 1784 the Lodge changed its name again to the "Good Council" (Zum Guten Rat) and moved from Varaždin to the Hungarian Zalaegerszeg based on the decision of Emperor Joseph II on placing Freemasonry lodges under direct state-police administration (22). The first Varaždin Freemasonry Lodge was founded in January 1772 at the instigation of Count Ivan Drašković, along with Lalangue and Captain Breščić (Bresci) of Russian origin, Count Stjepan Niczky and Varaždin lawyer noble Pavel Kugler. Count Stjepan Niczky (1747 – 1777) was the first elder of the Varaždin Masonic Lodge "Perfect Alliance", while Lalangue was the first supervisor (Niczky was later recorded as the great prefect of Križevci). Antun noble Holzman (1744 –) succeeded Lalangue as the supervisor of the Varaždin Lodge. Holzman was a secretary in the state administration, while Aleksander von Pasthory (1749 – 1798) was the secretary of the Lodge. Antun noble Holzman worked as a registrar for the Trade and Economic Commission in Varaždin at the Croatian Royal Council (from its founding in 1769 until his transfer to Zagreb in 1776). The Croatian Royal Council operated in Zagreb, as the capital, from 1776 to 1779 when it was abolished and annexed to the Hungarian Royal Council (23–26). Alexander von Pasthory served as an adviser to Field Marshal, Governor and Ban Francis Count Nadaždi, after whose death he led the Lodge until 1779. Based on the mentioned historical sources and facts, the reasons why Lalangue dedicated his debut to the Ban and Masonic brother Franjo Nadaždi, thanks to whom he came to Croatia and to whom he became a personal physician and a very close associate, become clear. We can also gain a better understanding of why his midwifery debut is dedicated to Stephen's wife, Countess Eleonora Niczky. Niczky himself, as a Masonic brother and close associate, and his wife, wholeheartedly assisted Lalangue in his public health work, especially in the field of midwifery and publishing. Therefore, it is clearer why all of Lalangue's books were printed by Johann noble Trattner, his Masonic brother, who contributed significantly to the great popularization of Lalangue's works and ideas, and not only by the fact that he had the imperial privilege of printing and selling books throughout the Monarchy (23–26). This explains why Lalangue dedicated his literary debut to his Masonic brother Ban Nadaždi and his midwifery debut to Countess Niczky, whose husband, like Lalangue, was a very respectable and influential Freemason. It is also clear that Trattner was a very influential Freemason (also Lalangue's friend) with whom Lalangue published all his medical professional original works in Croatian during his lifetime. Historical sources best explain the lucky circumstances that favored the remarkable achievement of John the Baptist Lalangue. Croatia and Croats were lucky that a man like John the Baptist Lalangue lived and worked in their area. Through his Freemasonry activities,

he made many positive changes important for the life of the Croatian people, especially in the field of public health. We have not yet realized the true greatness of John the Baptist Lalangue and his true valorization is something we have yet to do and which Lalangue undoubtedly deserves (23–26). These documents prove that Lalangue was a very prominent and engaged Freemason of his time and that he was also associated with the most prominent minds of the second half of the 18th century, who also largely belonged to the Freemasons. The social environment that was changed under the influence of the Freemasons of Lalangue's time is largely responsible for the development of science, economy, culture, medicine and all areas of social activity. It is certain that without engagement, unquestionable sensitivity for the loved ones and the desire to change the difficult feudal framework, to which the Freemasons of Lalangue's era truly contributed, there would be no progress in the modern world for a long time. It is also interesting to note that van Swieten's son Gottfried Freiherr van Swieten (Leiden, Luxembourg, 29 October 1733 – Vienna, Austria, 29 March 1803), was a distinguished Mason and also a diplomat, a famous librarian and a government officer who served the Habsburg Monarchy during the 18th century. He was a great lover of music and a patron. He supported and was a patron of three great musical geniuses (also Freemasons): Wolfgang Amadeus Mozart (Salzburg, Austria, 27 January 1756 – Vienna, Austria, 5 December 1791), Ludwig van Beethoven (Bonn, Germany, 16/17 December 1770 – Vienna, Austria, 26 March 1827) and Joseph Haydn (Rohrau, 31 March 1732 – Vienna, Austria, 31 May 1809). A large number of the greatest minds of the 18th century belonged to the Freemasons. The aforementioned Enlightenment ideals, embraced by a great number of people with open hearts and minds, including Freemasons like John the Baptist Lalangue, had changed and improved living conditions, including advancements in the field of public health in Europe, the Habsburg Monarchy and in Croatia. Lalangue dedicated his life to these ideals, particularly in his beloved Varaždin (1, 2, 23–26).

This work builds on the work of the great Croatian medical historian Lujo Thaller, who stated that Lalangue was a Freemason (27). Encouraged by this, in our research we have confirmed the research of Branko Šömen that Lalangue was a high-ranking member of the Freemasons in Croatia (28). All of the above fits into the context of the time and the educational activities carried out by the Freemasons of that time. This emphasizes the weight and significance of Ivan the Baptist Lalangue's contributions to public health, education, humanism and Freemasonry. It is indisputable that all of this is connected to the implementation of the imperial law on public health and improving the health of the population, which Skenderović and colleagues write about in their research (29).

Conclusion

From the aforementioned new insights, we received additional confirmation that John the Baptist Lalangue was not only a successful and famous physician but also a very prominent educator and Freemason. New insights have been of great help for a better understanding of the greatness of his work, helping us to valorize a truly impressive literary work in the field of medicine in the Croatian language. Both the circumstances that prevailed in Croatia and in the Habsburg Monarchy in the second half of the XVIII century are not comparable to today, especially in terms of socio-economic conditions but also the technological achievements that we enjoy today. With all of the technological possibilities of today, it would be almost impossible for us to publish in such a short time a truly impressive literary work as Lalangue's. Based on the above, Lalangue's greatness is even more brilliant. Certainly, Lalangue's progressive Enlightenment engagement is also creditable for the fact that we had original printed medical debuts in the Croatian language in the second half of the 18th century, which only a few nations in the world can be proud of. Based on the above, we must believe that his Enlightenment and Masonry activity and affiliation were of great help to him, which was extremely progressive and

commendable in his time. Lalangue's heritage is truly exceptional and the data of the latest research are especially important to us, which complete the data on his exceptional educational and Freemasonry activities. In addition to the fact that he was a truly exceptional doctor, the aforementioned knowledge about Dr Lalangue was not sufficiently known and researched until now and it was also not valued and represented enough in the scientific literature. The aforementioned recent research certainly completes and complements the data on the work and Lalangue's life. Therefore, the scientific and professional public receives invaluable data, very significant for the further valorization of Lalangue's public health, social, educational, Freemasonry, publishing, journalistic and medical activities. It is indisputable that Lalangue's exceptional involvement, as an inimitable individual and through the significant work we inherit today, brought a touch of the most modern European aspirations to Croatia in the second half of the 18th century, marking the entire Habsburg Monarchy. These activities changed the difficult feudal conditions, which prevailed until the middle of the 19th century and improved public health conditions in Croatia and the Habsburg Monarchy.

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Prosvjetiteljstvo i slobodno zidarstvo u životu i djelu liječnika Ivana Krstitelja Lalanguea

Podaci o obrazovnim i slobodnozidarskim aktivnostima doktora Joannisa Baptistae Lalanguea do sada su relativno skromno predstavljeni u znanstvenoj literaturi. Na temelju nedavnih istraživanja, došli smo do spoznaja koje stvaraju novi kontekst za Lalangueov život i rad, posebno s aspekta njegove društvene aktivnosti. Sve navedeno imalo je vrlo značajne reperkusije na cijeli njegov rad u javnom zdravstvu, a posebno na njegovo spisalačko i izdavačko djelovanje. Ivan Krstitelj Lalangue bio je uspješan liječnik, tijekom studija medicine u Beču prepoznao ga je barun van Swieten, prvo ime u medicini Habsburške Monarhije. Nedavna saznanja govore o njegovom vrlo zapaženom prosvjetiteljskom i slobodnozidarskom radu, što je uvelike odredilo njegov život i rad. Lalangue je stvorio doista impresivno književno djelo, koje je usko povezano s njegovim aktivnim prosvjetiteljskim i javnim slobodnozidarskim angažmanom. Navedeni progresivni prosvjetiteljski angažman također je zaslužan za činjenicu da smo zahvaljujući Lalangueu već u drugoj polovici 18. stoljeća imali tiskanu medicinsku originalnu stručnu literaturu na hrvatskom jeziku. To je izravno promijenilo uvjete u društvu, prvenstveno na području javnog zdravstva, na bolje, ne samo u Hrvatskoj, već i u cijeloj Habsburškoj Monarhiji..

Review article

The Effectiveness of Bupropion in Cigarette Smoking Cessation – A Narrative Review

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Abstract

Smoking is still a large indirect cause of premature death worldwide. The first line of treatment for smoking cessation is nicotine replacement therapy (NRT). Bupropion, a drug primarily developed as an antidepressant, in some countries is the first drug licensed for smoking cessation that is not associated with nicotine. The drug acts mostly through its inhibition of dopamine reuptake in the neuronal synapses, but other effects of bupropion may also have a role in smoking cessation. There have been many clinical studies of bupropion that have shown impressive results in helping patients with smoking cessation. Because of its antidepressant role, it is useful in smoking cessation in patients with depression. Through the years bupropion has proven to be a potential cost-effective alternative to NRT.

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Introduction

Although smoking prevalence among adults has been in decline for the last couple of decades (1) it is still a serious health issue associated with the death of around 8.7 million people every year of which 1.3 million were estimated non-smokers and it stands among the top preventable causes of premature deaths (2). It is estimated that a smoker attempts quitting 30 times or more before successfully quitting for at least 1 year (3). Nicotine exerts most of its effects by binding to neuronal nicotinic acetylcholine receptors (nAChRs) located on the presynaptic membrane and causing the release of neurotransmitters dopamine, noradrenaline, acetylcholine, glutamate, γ-aminobutyric acid (GABA), serotonin and endorphins. There are a lot of subtypes of these receptors and the most important one associated with nicotinic addiction is the $\alpha 4 \beta 2$ receptor (4,5). The first step in an attempt to quit smoking is always counseling and cognitive behavioral therapy which both promote smoking cessation by giving patients information, guidance and skills for the prevention of a relapse. For many smokers, this approach alone is not enough so pharmaceutical intervention aids in the process of quitting (5). The main principles by which pharmaceutical intervention can aid in smoking cessation are the reduction of nicotine withdrawal symptoms, reduction of the rewarding pathway of nicotine by blocking or desensitizing nicotine receptors and providing a substitute for smoking with an alternative source of nicotine in controlled doses (5). Nicotine replacement therapy (NRT) is recommended by many clinical guidelines as the first-line therapeutic drug for smoking cessation (6). NRT is available in forms of transdermal patches, gums, inhalers, lozenges and nasal sprays which are most effective in a combination and deliver nicotine in controlled doses to the neural synapses thus reducing the urge to smoke and exposure to dangerous substances found in cigarettes. These doses should be low enough to reduce symptoms associated with nicotine withdrawal syndrome while not high enough to sustain addiction (7,8,9). Since the development of NRT, there have been a lot of clinical trials trying to find a cost-effective and safe alternative. Today, bupropion and varenicline are also licensed as first-line treatment options in many countries, with clonidine and nortriptyline being second-line options (10,11,12). The goal of this study is to explain the effectiveness of bupropion as a first-line smoking cessation pharmaco-therapy intervention.

Methods

For this narrative review, a comprehensive literature search was conducted predominantly in the medical database PubMed. The search was restricted to papers written in English that contained the words "bupropion" and/or "smoking cessation" and/or "tobacco cessation" and/or "nicotine withdrawal" in the title, abstract or body of the article. The review included open-access articles published in peer-reviewed journals. No date limits were applied to the articles included in the search. Additionally, a hand search of the references of full-text papers was obtained. This paper is a non-systematic review of existing literature on the topic of our interest in which retrieved articles were analyzed and key results were discussed in summary.

Mechanism and pharmacology

Bupropion, previously known as amfebutamone, was synthesized in 1966 by Burroughs Wellcome as an atypical antidepressant chemically distinct from the tricyclics (TCAs) or the selective serotonin reuptake inhibitors (SSRIs) with similar efficacy but with lesser side-effects related to sympathomimetic, cholinolytic or monoamine oxidase inhibitory properties (13,14). Bupropion is a monocyclic phenylbutylamine of the amino ketone group with tertbutyl moiety attached to the amine group and a chlorine group attached to the position 3' of the aromatic ring (15). The synthesis includes the reaction of 3-chlorobenzonitrile with ethylmagnesium bromide to produce 3-chloropropiophenone. Bromination of 3-chloropropiophenone gives 3-chloro-α-bromopropiophenone which reacts with tert-

butylamine and finally produces bupropion (16). While structurally unrelated to TCAs or SSRIs, the core structure is similar to that of neurotransmitters dopamine and norepinephrine but also to psychoactive substances diethylpropion, cathinone and amphetamine. The psychostimulant activity and abuse potential are reduced by the phenyl ring substitution and the size and branching of the N-alkyl group. Bupropion is a weak base (pKa: 7.9 at 25) available as a racemic mixture of R-()-bupropion and S- (þ)-bupropion and dispensed as hydrochloride (HCl) salt (15,17). Bupropion comes in three different, bioequivalent forms: immediate release (IR), sustained release (SR) – bupropion incorporated in a methylcellulose matrix and the extended-release (XL) – bupropion incorporated by controlled-release and moisture-barrier coatings (15).

The development of slow-release formulations with prolonged absorption that can be taken once a day largely decreased the prevalence of seizure activity that appeared with immediate form (14). Bupropion sustained release used for treating nicotine craving (generically Zyban) should be initiated 1 to 2 weeks before the quit date (while the patient is still smoking), usually started at the lowest dose of 150 mg daily for 3 days and then increased and continued at 300 mg per day for the next 6 to 12 weeks. The maximum single dose is 150 mg and the time interval between successive doses should be at least 8 hours. The maximum daily dose is 450 mg (18). Because it is a small and highly lipophilic molecule, bupropion is rapidly absorbed and distributed throughout the body, followed by a slower elimination phase (biphasic distribution). However, its bioavailability is reduced due to the extensive, stereoselective metabolism that eliminates the majority of parent compounds with less than 1% of bupropion excreted unchanged in the urine (19). Hepatic enzymes produce three primary metabolites: (2S,3R)- and (2S,3S)-hydroxybupropion, (R,R)- and (S,S)-threo-bupropion, and (R,S)- and (S,R)-erythro-bupropion (20). Hydroxybupropion is formed through hydroxylation of the side chain tert-butyl group of bupropion by hepatic cytochrome P450 (CYP) 2B6, and diastereoisomers threohydrobupropion and erythrohydrobupropion through reduction of the side chain ketone group by carbonyl reductase (19). Compared to bupropion, its major active metabolites reach higher plasma concentrations and have 25–50% potency and therefore have a significant impact on its efficacy and pharmacological and toxicological effects (15,19). Since bupropion has an extensive metabolic pathway and CYP2B6 is a catalyst for many biotransformation reactions there is high potential for drug interactions. Both bupropion and its metabolites are inhibitors of CYP2D6, increasing the levels of drugs metabolized by this enzyme (21). Because it crosses the blood-brain barrier and human placenta and is also excreted in human breast milk, bupropion belongs to pregnancy class C and requires caution in breastfeeding (15).

Bupropion sustained-release (bupropion SR)

Bupropion was primarily licensed as an antidepressant but during its use in the treatment of major depressive disorders in the late 1980s, it has been noted that some of the patients who smoked coincidentally quit smoking. Later through clinical trials, it has proven to be an effective smoking cessation aid (22,23). As an antidepressant, it was first used in its IR form, but in the treatment of nicotine addiction, it is used in ER form which is further divided into the SR form administered in 2 doses daily and the XL form administered as a single daily dose (24). With its inhibition of the reuptake of dopamine and noradrenaline, it simulates the effect of nicotine by elevating the concentrations of these neurotransmitters in the synapse. It also acts as a nicotine antagonist on the $\alpha 4\beta 2$ subtype receptor and with this mechanism lowers the dependence on nicotine (5,25,26). Some studies have shown that continuous bupropion SR therapy is associated with a reduction in smoking and shorter periods between attempts to quit (27). Another first-line drug therapy for tobacco cessation is varenicline. Compared to bupropion, varenicline is a partial agonist of the $\alpha 4\beta 2$ subtype receptors which are responsible for the major

nicotinic effects and as such it acts as an agonist, having half the efficacy of nicotine and thus relieving the symptoms of nicotine withdrawal syndrome. Meanwhile, as an antagonist, it inhibits the nicotinic reward pathway (28). Many studies have shown that bupropion has similar effectiveness as single-use NRT, but less than varenicline in smoking cessation, which in most cases outperformed both but did not prove to be more effective than combination NRT, but further research is necessary for confirmation (29,30). Combined bupropion SR and NRT therapy have shown to have somewhat higher abstinence rates than bupropion SR solely but were statistically of no significance compared to single NRT, where efficacy was much higher in the combination therapy (31). Unlike NRT, bupropion SR treatment should be started while the person is still smoking, ideally 2 weeks before the patient begins abstinence. It is normally used in doses of 100 to 300 mg daily and bupropion SR in particular is given typically in 2 doses of 150 mg per day. It is administered only orally and the maximum dose is 450 mg a day (32). Using bupropion SR alone or in combination with NRT reduces the normal weight gain that happens in smoking cessation. These effects last even after the end of long-term treatment whereas for short-term treatment, they last only during the active treatment (31).

Bupropion SR in smokers with mental illnesses

Nicotine addiction is common among people diagnosed with mental illnesses such as major depression, anxiety disorder and schizophrenia. There may be a connection in genetic predisposition between nicotine addiction and mental illness. The self-medication hypothesis suggests that psychiatric patients smoke cigarettes to lessen their symptoms (33,34). Some substances in cigarettes other than nicotine inhibit the functions of monoamine oxidases (MAO), enzymes that facilitate the breakdown of certain neurotransmitters, thus leading to their higher concentrations and enhancing the nicotine effects (35). Since MAO inhibition is used for the treatment of depression, this suggests that in some patients smoking might have positive effects in the short-term management of symptoms. Some studies have shown that patients with a history of depression were at higher risk of developing depressive episodes after smoking cessation (36). Even though in the early stages of abstinence they tend to develop anxiety and other depressive symptoms, it was observed that in the long term, smoking cessation improves the mood, and reduces stress, depression symptoms and anxiety equally in smokers with and without mental illnesses (37). Smoking cessation may be as effective as antidepressant therapy in the management of anxiety disorders. Although smoking is common in these patients there is little information about the safety and effectiveness of smoking-cessation medicamentation and further research is necessary. In clinical trials, bupropion showed a short-term reduction in depressive symptoms but the effect was of no significance in the long term after ending the treatment. While heavy smokers with higher nicotine dependence showed a bigger reduction in depressive symptoms during the treatment, after the end of treatment they experienced more severe depression symptoms than the less dependent smokers (38). Bupropion SR may show equal efficacy in patients with anxiety disorders as in the general population but without any significant reduction in depressive symptoms (39). There were some concerns of increased psychosis when using bupropion for smoking cessation in patients with schizophrenia but some studies refute these concerns and show that bupropion is acceptable in the treatment and may even relieve depressive symptoms (40). One study which included a clinical trial and meta-analysis has shown contradictory results that bupropion SR did not have any effect during the clinical trial but did show efficacy in the meta-analysis in smoking cessation in patients with schizophrenia. However, the conclusion was that bupropion was effective and tolerable in smoking cessation in patients with schizophrenia (41). It is suggested that the same treatment for smoking cessation including pharmaceutical intervention in the general population is of the same efficacy in smokers

with mental illnesses without significant risk of worsening their mental disease (42).

Drug interactions

As already mentioned, bupropion is metabolized in the liver by CYP2B6. Bupropion moderately inhibits enzymes such as CYP2D6 which is responsible for its pharmacokinetic interactions with other drugs. As CYP2D6 is responsible for the metabolization of other antidepressants such as venlafaxine, if used in combination with bupropion the effects but also the risk of side effects associated with venlafaxine are increased. Most second-generation antipsychotics are in the same way as antidepressants metabolized by CYP2D6 and bupropion could have similar interactions (43,44). On the other hand, CYP2D6 metabolizes some other medications to their active forms like opiates or tamoxifen. Bupropion used concomitantly with opiates like codeine, oxycodone and tramadol may lower their efficacy in analgesia (45,46). With tamoxifen only some SSRIs have proven to lower the efficacy of the drug and further research is needed to evaluate the potential effect of bupropion. There is not enough information on whether bupropion should be used with tamoxifen, but it is advisable to avoid it (47). Anticonvulsants phenobarbital, carbamazepine and phenytoin are strong CYP inducers including the CYP2B6 which lowers the concentration of bupropion and may reduce its effects (48,49).

Contraindications

Bupropion is contraindicated in patients who are allergic or hypersensitive to it. Because of drug interaction, it should not be prescribed in combination with MAOIs (50). Bupropion should be avoided in smokers with a present seizure disorder, a history of seizures or any other increased risk for seizures, which includes patients with central nervous system tumors, patients undergoing acute abstinence from alcohol or discontinuation of benzodiazepines and patients diagnosed with bulimia or anorexia nervosa. The only indication to use bupropion in these patients is when the benefits of smoking cessation surpass the seizure risk. Bupropion should not be prescribed in patients on medications that lower the seizure threshold such as antipsychotics, antimalarials, tramadol, quinolones, some antidepressants, etc. Alcohol abuse or a previous head trauma also lowers the seizure threshold (51,52).

Side effects

Bupropion is mostly safe to use and tolerable in the dose of 100 to 300 mg a day in most smokers up to 45 weeks. The most common side effects observed when used for smoking cessation are insomnia and dry mouth which mostly resolve on their own and can be controlled with dose regulation. Other less common side effects include headache, nausea, anxiety, pruritus, constipation and pharyngitis. Compared to placebo, bupropion SR did not show any higher frequency rates of side effects associated with the cardiovascular system such as hypertension, tachycardia, postural hypotension and vasodilation. In patients with preexisting cardiovascular diseases, it has proven to be as safe as in the general population. The most feared side effects of bupropion are seizures and hypersensitivity reactions. These are serious complications with a rare occurrence, but mostly not life-threatening. As seizures seem to be dose-related, bupropion SR should not be prescribed in higher doses than allowed. It is also contraindicated in patients who use medication that lowers the seizure threshold, have any other kinds of predispositions for seizures or have a history of seizures. Even though there have not been any clinical comparisons between SR and IR forms, it was observed that bupropion SR may have lower seizure rates (24,31,53,54). One of the rare side effects of bupropion is angioedema, a potentially serious complication that normally affects the head and neck and should be further studied (55). While most antidepressants are associated with sexual dysfunction as a side effect, bupropion is one of the exceptions (32). Some smokers tend to develop depression after the use of bupropion SR for smoking cessation which could be caused by bupropion itself or as part of nicotine withdrawal syndrome (51).

Discussion

To summarize, tobacco smoking is a global public health challenge with profound implications for individuals and societies. It stands at the top among preventable causes of death in the world. Beyond its direct health consequences, smoking exerts a substantial economic burden and carries significant social implications. The societal costs extend to secondhand smoke exposure, affecting non-smokers and exacerbating health disparities. Understanding the multifaceted nature of smoking provides a foundation for exploring interventions aimed at reducing its prevalence and mitigating its impact on health and society. Behavioral interventions form a cornerstone of smoking cessation efforts. These approaches target the psychological and behavioral aspects of smoking addiction. Cognitive-behavioral therapy, for example, focuses on identifying and modifying thought patterns and behaviors associated with smoking. Support groups, counseling sessions and motivational interviewing are additional examples of behavioral therapies that aim to empower individuals in their journey towards tobacco-free living. Pharmacological interventions play a pivotal role in smoking cessation, aiding individuals by addressing the physiological aspects of addiction. NRT, such as patches, gum, lozenges and nasal sprays, provide controlled doses of nicotine to alleviate withdrawal symptoms. Additionally, prescription medications, including varenicline and bupropion, have been developed to target nicotine receptors in the brain, reducing cravings and withdrawal symptoms. Bupropion, originally approved as an antidepressant, has found a prominent role in smoking cessation since its approval. Bupropion, an aminoketone antidepressant, exhibits a mechanism of action not fully elucidated. Although its impact on monoamine uptake is limited, it inhibits the reuptake of norepinephrine and dopamine, particularly affecting the latter. The heightened dopamine reuptake inhibition contributes to its clinical manifestations. Bupropion also acts on nicotinic receptors to a lesser extent as an antagonist. The onset of therapeutic effects varies based on the formulation (immediate, sustained or extended-release). Bupropion is administered orally as a hydrochloride salt. The recommended dosage for smoking cessation usually starts at 150 mg daily, with careful titration to a maintenance dose of 300 mg per day. The maximum daily dose is 450 mg, administered in divided doses. The most significant adverse effects include a lowered seizure threshold and potential hypersensitivity. Seizures, although rare, are more likely with higher doses, especially in the immediate-release form. The clinician should carefully monitor patients for these adverse effects, especially those with a history of seizures or mood disorders. Several contraindications limit the use of bupropion. Patients hypersensitive or allergic to bupropion or its constituents should avoid its use. Bupropion, through many trials in clinical practice, has proven to be more effective than single NRT and shows even more efficacy if combined with it. It is safe to take in people with mental illnesses such as depression, anxiety disorders and schizophrenia as it does not worsen the patients' mental health but helps with the management of some of their symptoms.

Conclusion

Understanding the mechanism of action, adverse effects and contraindications of bupropion is crucial for healthcare professionals involved in smoking cessation efforts. With careful monitoring and consideration of individual patient factors, bupropion can be a valuable tool in the comprehensive approach to tobacco addiction treatment. The subsequent exploration of scientific literature further enhances our understanding of the risks and benefits associated with the use of bupropion in smoking cessation. These programs may include a combination of behavioral therapies, pharmacological aids and ongoing support to tailor the approach to individual needs.

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Provision of study materials or patients: MP, FP, IP, MFB, RR

Učinkovitost bupropiona u prestanku pušenja cigareta – pregledni rad

Pušenje je i dalje velik neizravan uzrok prerane smrti širom svijeta. Prva linija liječenja s ciljem prestanka pušenja terapija je nadomjeskom nikotina (NRT). Bupropion, lijek prvobitno razvijen kao antidepresiv, u nekim je zemljama prvi lijek licenciran za prestanak pušenja koji nije povezan s nikotinom. Lijek djeluje uglavnom kroz inhibiciju ponovnoga unosa dopamina u neuronskim sinapsama, ali drugi učinci bupropiona također mogu imati ulogu u prestanku pušenja. Provedene su mnoge kliničke studije bupropiona koje su pokazale impresivne rezultate u pomaganju pacijentima s prestankom pušenja. Zbog svoje antidepresivne uloge, koristan je u prestanku pušenja kod pacijenata s depresijom. Kroz godine, bupropion se pokazao kao potencijalno isplativa alternativa NRT-u.