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CLINICAL RESEARCH

EVALUATING KNEE FUNCTION POST-ACL RECONSTRUCTION: CONVENTIONAL VERSUS ALL-INSIDE TECHNIQUE USING LYSHOLM SCORE

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Key words: anterior cruciate ligament, graft, operative treatment, Lysholm scale, functional result

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Competing Interests: The author have declared that no competing interests

Abstract

Anterior cruciate ligament (ACL) reconstruction is a common surgical intervention. The aim of this paper was to make a comparison in terms of subjective symptoms that occur in a specific Lysholm scoring scale-in-progress before the operative period, 3 and 8 months after surgical treatment with two surgical methods. Materials and Methods: Eighty patients underwent primary ACL reconstruction at the Department of Orthopaedics and Traumatology in the City General Hospital "8th September" in Skopje in a period of two years. The first group (40 subjects) constituted the control group (CG), surgically treated with a standard method using a graft from ***m. semitendinosus*** and ***m. gracilis***. The second group (40 subjects) was the study group (SG) surgically treated with the ALL-INSIDE method using a ***m. semitendinosus*** graft. In all subjects preoperatively, at 3 and 8 months after surgical treatment, Lysholm scale was completed representing a designed questionnaire for evaluation of subjective symptoms. Results: Preoperatively, most patients from SG had a score lower than 65 to 55 % (22), while in CG between 65 and 83 – 50% (20). After 3 months of surgical treatment, SG patients had averagely a higher score than CG patients (88.60 ± 11.8 vs. 85.75 ± 17.8), but without statistical significance. Among SG and CG patients, 8 months after surgery (p = 0.043), SG patients had a significantly higher mean score than CG patients (97.62 ± 5.3 vs. 92.40 ± 15.1). Lysholm scale analysed qualitatively 8 months after surgical treatment showed no significant difference between them, i.e., the tested difference in the distribution of patients with a score of less than 65, from 65 to 83, from 84 to 90 and more than 90, and depending on the type of the surgical method was statistically insignificant (p = 0.123). Conclusion: The type of surgical technique used had no significant influence on the subjective complaints of patients after 3 months of surgical treatment. But after 8 months, a better functional result was obtained in SG patients.

КЛИНИЧКИ ИСТРАЖУВАЊА

ЕВАЛУАЦИЈА НА ФУНКЦИЈАТА НА КОЛЕНОТО СО LYSHOLM БОДОВНА СКАЛА ПО РЕКОНСТРУКЦИЈА НА ПВЛ:КОНВЕНЦИОНАЛНА НАСПРОТИ ALL- INSIDE ТЕХНИКА

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Цитирање: Зоран Несторовски, Зорица Вангеловска, Јасмин Циривири, Дарко Талевски, Ана- Марија Манева. Евалуација на функцијата на коленото со Lysholm бодовна скала по реконструкција на ПВЛ:конвенционална наспроти all- inside техника. Арх Ј Здравје 2024;16 (2) 5-17.

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Клучни зборови: преден вкрстен лигамент, графт, оперативен третман, Lysholm скала, функционален резултат.

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Печатарски права: ©2024. Зоран Несторовски, Зорица Вангеловска, Јасмин Циривири, Дарко Талевски, Ана- Марија Манева. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа торигиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Реконструкција на предниот вкрстен лигамент (ПВЛ) претставува честа хируршка интервенција. Целта на овој труд беше да се направи компарација во однос на субјективните симптоми кои се јавуваат кај пациентите преку специфична Lysholm бодовна скала во тек на предоперативниот период, 3 и 8 месеци по оперативниот третман со два оперативни метода. Материјали и методи: Осумдест пациенти беа подложени на примарна реконструкција на ПВЛ на Одделот за ортопедија и трауматологија во ГОБ „8-ми Септември" во период од две години. Првата група (40 испитаници) ја сочинуваа контролната група (КГ), оперативно третирана со стандарден метод со користење графт од *m. semitendinosus* и *m. gracilis.* Втората група (40 испитаници) ја сочинуваа испитуваната група (ИГ) оперативно третирана со методот ALL-INSIDE и користење графт од *m. semitendinosus.* Кај сите испитаници предоперативно, на 3 и на 8 месеци по оперативниот третман беше исполнета Lysholm скалата, која претставува дизајниран прашалник за евалуација на субјективни симптоми. Резултати: Предоперативно најголем дел пациенти од ИГ имаа скор понизок од 65 до 55 % (22), додека во КГ скорот беше помеѓу 65 и 83 – 50 % (20). По 3 месеци од оперативниот третман пациентите од ИГ имаа во просек повисок скор од пациентите од КГ (88,60 ± 11,8 vs, 85,75 ± 17,8), но без статистичка значајност. Осум месеци по оперативната интервенција (p = 0,043), пациентите од ИГ имаа значајно повисок просечен скор од пациентите од КГ (97,62 ± 5,3 vs 92,40 ± 15,1) Lysholm скалата анализирана квалитативно 8 месеци по оперативниот третман не покажа значајна разлика помеѓу групите, односно тестираната разлика во дистрибуцијата на пациенти со скор помал од 65, од 65 до 83, од 84 до 90 и повеќе од 90, а во зависност од типот на хируршкиот метод, беше статистички незначајна (p = 0,123). Заклучок: Типот на користена хируршка техника немаше значајно влијание врз субјективните тегоби на пациентите по 3 месеци од оперативниот третман. Но, по 8 месеци се доби подобар функционален резултат кај пациентите од ИГ.

Introduction

The knee joint intricately designed biomechanically, is susceptible to injuries, particularly the anterior cruciate ligament (ACL), a critical component coordinating knee joint motion. Despite its importance, the ACL is prone to injuries, necessitating surgical interventions for restoration[1]. The data confirm that ACL reconstruction can be recommended to patients older than 40 years who wish to maintain an active lifestyle or have symptomatic instability with daily activities. Patient-based outcomes scores were better in the operative studies compared to the single nonoperative study in this patient population[2]. Therefore, several previous studies have comprehensively evaluated the all-inside ACLR technique, analysing the clinical outcomes, graft rupture rates and rehabilitation protocols. While these studies have made significant contributions, there is for advancing new instrumentation and refined techniques to optimize this surgical approach and provide additional clinical advantages[3]. Many options are available for anterior cruciate ligament (ACL) reconstruction, including an autologous bone–patellar tendon–bone graft, a hamstring tendon graft and an allograft. The bone–patellar tendon–bone graft is more likely to result in normal knee joint laxity and less incidence of significant flexion loss. In contrast, hamstring grafts reduce the incidence of patellofemoral crepitus, kneeling pain and extension loss[4]. Surgeon experience, correct graft position, choice of graft fixation and postoperative rehabilitation confound the results of comparisons of ACL reconstruction[5]. Hamstring tendon grafts are the most common choice for anterior cruciate ligament (ACL) reconstruction (ACLR). Previous studies have provided evidence that offers conflicting opinions concerning the most favourable graft choice[6]. A disadvantage of using hamstring tendon autograft consisting of the semitendinosus and gracilis tendons for anterior cruciate ligament reconstruction is pain from tendon harvesting and persistent hamstring weakness. In the tendon-sparing all-inside technique, a quadrupled semitendinosus graft and adjustable-loop cortical fixation are suggested to give less postoperative flexion deficits while displaying overall similar clinical results to the traditional hamstring technique. Patients often expect to return to their preinjury functional status when they consent for ACLR surgery[7]. However, there are a limited number of high-quality studies comparing these techniques with inconsistent results[8]. In recent years, there has been considerable emphasis on the use of patient-reported outcomes to evaluate health care interventions. The Lysholm Knee Scale is an 8-item questionnaire scored on a 0-100 weighted scale measuring pain (25 points), instability (25 points), locking (15 points), swelling (10 points), limp (5 points), stair-climbing (10 points), squatting (5 points) and use of support (5 points). The scale was originally designed to assess ligament injuries of the knee[9].

The aim of this paper was to make a comparison in terms of subjective symptoms that occur in a specific

Lysholm scoring scale-in-progress before the operative period, 3 and 8 months after surgical treatment with two surgical methods.

Materials and Methods

A total of 80 patients who underwent primary ACL reconstruction using HS autograft (*m. semitendinosus - m. gracilis*) or HS autograft (m. semitendinosus) were included in this study. This study shows the results of patients treated in the City General Hospital "8th September" inSkopje at the Department of Orthopaedics and Traumatology. The first group (40 subjects) made up the control group (CG), surgically treated with a standard method using a graft in the form of duplication from the semitendinosus and gracilis muscles. The second group (40 subjects) consisted the study group (SG) surgically treated with a method in which only the semitendinosus muscle was used as a graft in the form of a quadruplication. The Lysholm scale was completed in all subjects preoperatively, three and eight months after surgical treatment, that is, it evaluated patients' subjective symptoms. The Lysholm scale is a designed questionnaire that gives data to the examiner about the impact of the change on the performance of daily activities: bending, support, pain, instability, blocking, swelling, climbing stairs, kneeling. The interpretation of the Lysholm scale is that if the score is less than 65 points, it indicates a poor functional result; from 65 to 3 points is considered enough. A score of 84 to 90 points is a good result. More than 90 indicates an excellent functional score.

Results

Patients from the study and control groups had preoperatively significantly different scores on the Lysholm scale, which expressed patients' subjective perception of the impact of the change on the performance of daily activities (p = 0.039) (Table 1). A significantly lower mean score on this scale was registered in SG (60.85 ± 15.1 vs. 69.0 ± 19.4) (Figure 1).

Table. 1 Preoperative Lysholm scale – SG and CG

Preoperative clinical examinations			
Group	Descriptive Statistics (Lysholm scale)		p-level
	mean ± SD	min – max	
SG	60.85 ± 15.1	22 – 91	t = 2.09
CG	69.0 ± 19.4	22 – 100	p = 0.039 sig

t (Student t-test for independent samples); SG (autograph m. *semitendinosus*); CG (autograph *m. semitendinosus* and *m. gracilis*)

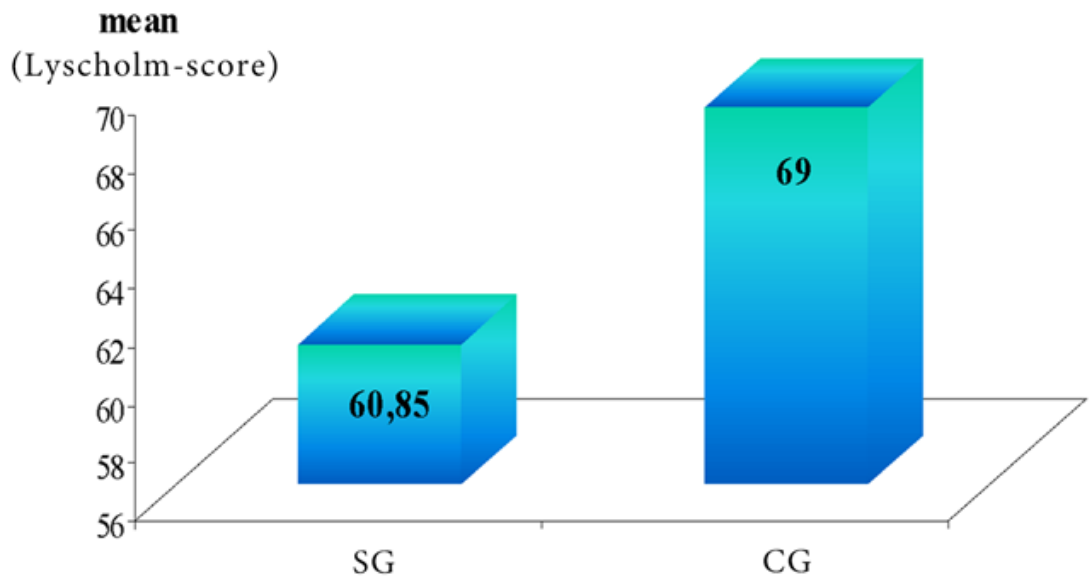


Figure. 1 Graphic representation of preoperative Lysholm scale – SG and CG

The results of the Lysholm scale were analyzed and qualitatively divided in 4 groups: score less than 65, from 65 to 83, from 84 to 90 and 90 and more (Table 2). According to the results displayed in Table 2, preoperatively most patients from SG had a scale score lower than 65 to 55 % (22), in CG most patients had a Lysholm score between 65 and 83 – 50 % (20).

Table. 2 Qualitative presentation of preoperative Lysholm scale – SG and CG

Lysholm scale	Groups		
	N	SG	CG
> 65 weak	34	22 (55)	12 (30)
65 - 83 good	35	15 (37.5)	20 (50)
84 - 90 very good	6	2 (5)	4 (10)
> 90 excellent	5	1 (2.5)	4 (10)

In accordance with the results obtained, patients from the study and control groups did not differ significantly in terms of Lysholm scale scores in a period of 3 months after surgical intervention (p = 0.4) (Table 3, Figure 2). SG patients had on average a higher score on this scale than CG patients (88.60 ± 11.8 vs. 85.75 ± 17.8), but without statistical significance. The type of surgical technique used had no significant influence on the subjective complaints of patients regarding the performance of daily activities after 3 months of surgical treatment.

Table. 3 Lysholm scale of the injured limb after 3 months postoperatively – SG and CG

After 3 months of postoperative treatment			
Group	Descriptive Statistics (Lysholm scale)		p-level
	mean ± SD	min – max	
SG	88.60 ± 11.8	44 – 100	t = 0.84
CG	85.75 ± 17.8	22 – 100	p = 0.4 ns

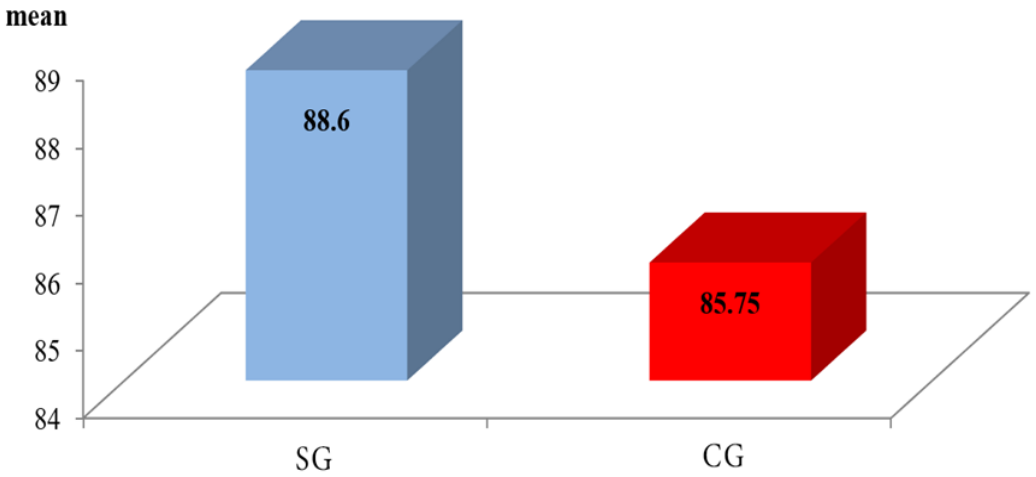


Figure. 2 Graphic representation of mean Lysholm score of the injured limb after 3 months postoperatively – SG and CG

A significant statistical difference was identified 3 months after surgical treatment, when the two groups were compared in terms of qualitatively expressed Lysholm scale scores (p = 0.02) (Table 4). SG patients more often than CG patients had a score from 65 to 83, indicating a sufficient functional result – 27.5% (11) vs. 5% (2), while SG patients more often had a Lysholm scale score from 84 to 90 – 32.5 % (13) vs. 12.5 % (5), which indicated a good functional result of the surgical intervention (Figure 3).

Table. 4 Qualitative representation of Lysholm scale of the injured limb after 3 months postoperatively – SG и CG

Lysholm scale after 3-months-postoperatively	Groups			p-level
	N	SG n (%)	CG n (%)	
Weak functional Result	6	3 (7.5)	3 (7.5)	X^2 = 9.81
Good	13	2 (5)	11 (27.5)	p = 0.0203 sig
Very good	18	13 (32.5)	5 (12.5)	
Excellent	43	22 (55)	21 (52.5)	

p(Pearson Chi-square)

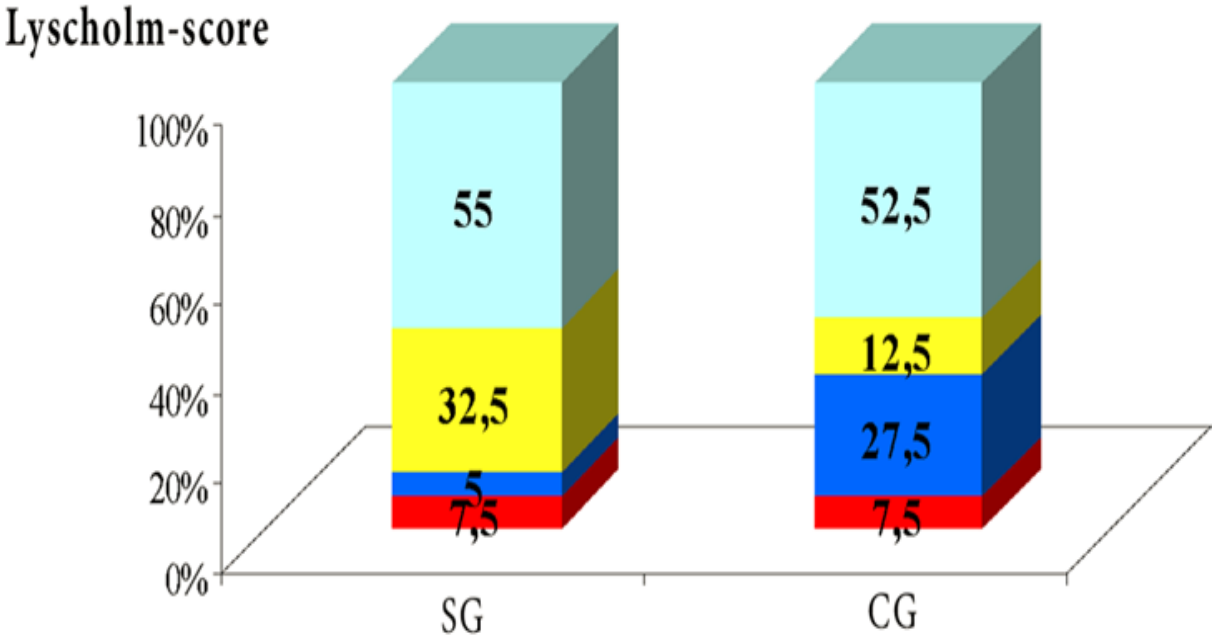


Figure. 3 Graphic representation of Lysholm scale of the injured limb after 3 months postoperatively– SG and CG

A statistically significant difference was identified between patients from the study and control groups regarding the Lysholm scale scores 8 months after surgical intervention (p = 0.043) (Table 5). SG patients had a significantly higher mean score than CG patients (97.62 ± 5.3 vs. 92.40 ± 15.1) (Figure 4). The type of surgical technique used had a significant impact on patients' subjective complaints regarding the performance of daily activities after 8 months of surgical treatment. According to the completed Lysholm scale, patients with a *m. semitendinosus* graft had a significantly better functional result after the intervention than patients with a *m. semitendinosus* and *m. gracilis graft*.

Table. 5 Lysholm scale after 8 months postoperatively – SG and CG

Eight months after postoperative treatment			
Group	Descriptive Statistics (Lysholm scale)		p-level
	mean ± SD	min – max	
SG	97.62 ± 5.3	73 – 100	t = 2.06
CG	92.40 ± 15.1	22 – 100	p=0.043 sig

t(Student t-tests for independent samples); SG (autograph *m. semitendinosus*); CG (autograph *m. semitendinosus* and *m. gracilis*)

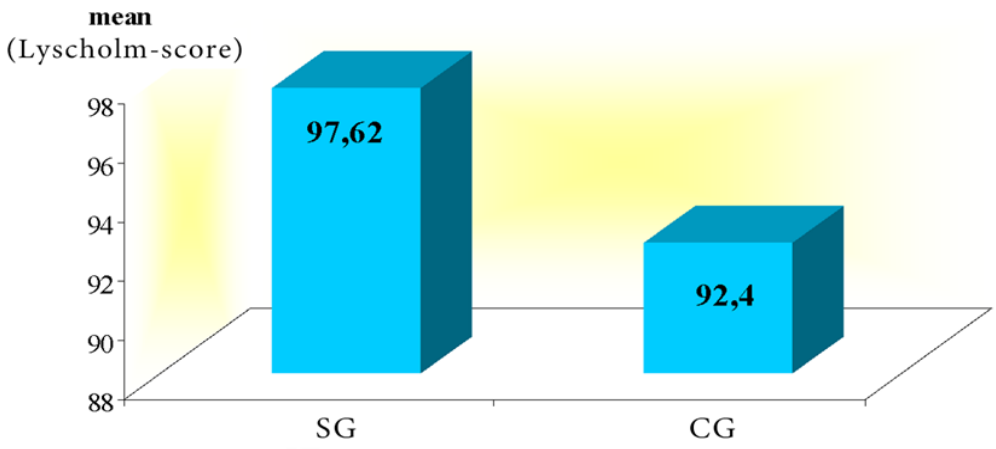


Figure. 4 Graphic representation of mean Lysholm score after 8 months of postoperative treatment – SG and CG

On the other hand, the comparison of the two groups of patients 8 months after surgical treatment in relation to the qualitatively analyzed Lysholm scale did not show a significant difference between them, i.e., the tested difference in the distribution of patients with a score on the Lysholm scale lower than 65, from 65 to 83, from 84 to 90 and more than 90, depending on the type of surgical method, was statistically insignificant (p = 0.123) (Table 6).

At the end of the observation, the majority of patients from both groups had a score greater than 90, which is equivalent to an excellent functional result in terms of performing daily activities, but insignificantly more often patients from SG had this result - 92.5% (37) vs. 72.5 % (29).

Table. 6 Qualitative presentation of Lysholm scale after 8 months postoperatively– SG and CG

Lysholm scale after 8-months-postoperatively	Groups			p-level
	N	SG n (%)	CG n (%)	
Unsatisfactory functional results	1	0	1 (2.5)	$X^2 = 5.77$
Sufficient	8	2 (5)	6 (15)	p = 0.123 ns
Good	5	1 (2.5)	4 (10)	
Excellent	66	37 (92.5)	29 (72.5)	

p(Pearson Chi-square)

The mean Lysholm score preoperatively was 60.85 ± 15.1, which is equivalent to a poor functional result, while in the control group the mean preoperative score was 69.0 ± 19.4, which indicates a good functional result (Table 7, Figure 5).

After the third and eighth months of surgical treatment, the mean Lysholm score was 88.60 ± 11.8 in SG and 97.62 ± 5.3 in CG; the mean Lysholm score was 85.75 ± 17.8 and 92.40 ± 15.1, respectively. Patients from both groups had an excellent functional result at the second control with the functional result being better in SG (Table 7, Figure 5).

For $p < 0.0001$, a significant increase in the Lysholm score was confirmed in both, the study and control groups (Table 7).

Table. 7 Lysholm scale – SG and CG

Group	Groups	
	SG mean ± SD	CG mean ± SD
Preoperative	60.85 ± 15.1	69.0 ± 19.4
After 3 months	88.60 ± 11.8	85.75 ± 17.8
After 8 months	97.62 ± 5.3	92.40 ± 15.1
p-level	X=78.6 p = 0.0000 sig	X = 53.6 p = 0.0000 sig

p (Friedman ANOVA and Kendall)

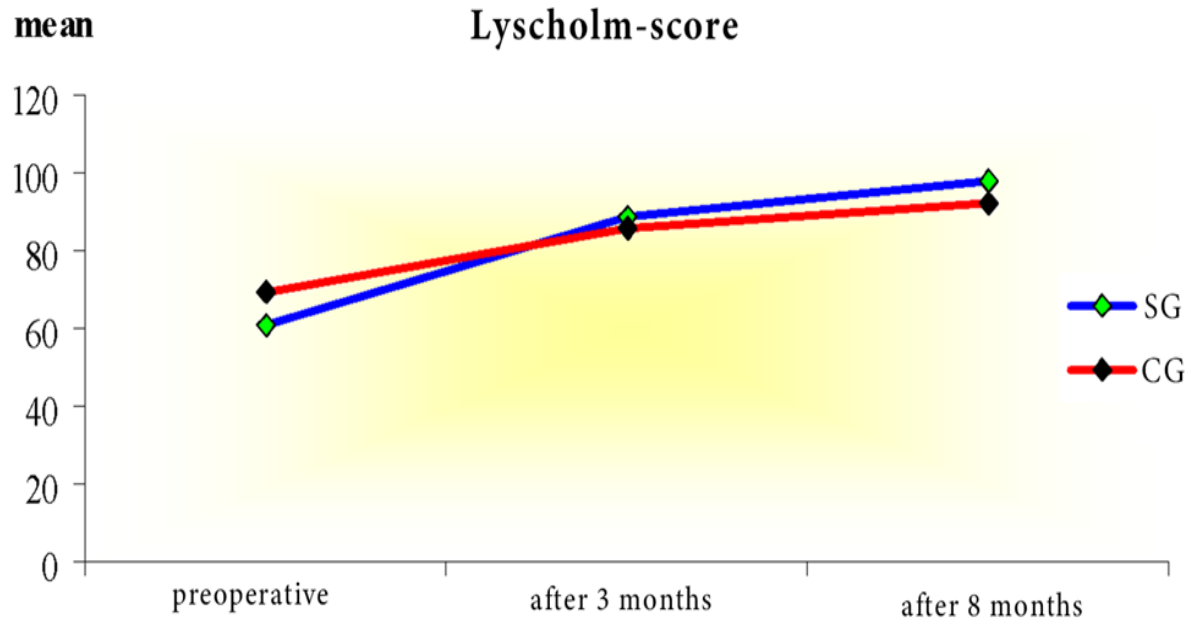


Figure. 5 Linear diagram for Lysholm scale in the examined period – SG and CG

Discussion

The Lysholm knee scoring scale is a commonly used subjective tool for evaluating outcome after anterior cruciate ligament reconstruction. The scoring scale evaluates the function and symptoms of patients, higher scores indicate a better result. The Lysholm knee scoring scale indicates knee function and symptoms on a scale of 0 to 100, with 100 indicating normal knee function, while 0 - complete knee dysfunction. Several studies indicate that the results obtained from the Lysholm knee scoring scale in patients in whom the all-inside technique was used were similar or better compared to patients in whom the standard technique was used. Vishal S Desai did a comparative study of 82 patients (mean ± SD age, 25.8 ± 10.2 years) who underwent all-inside reconstruction and 54 patients (mean ± SD age, 21.1 ± 7.3 years) who underwent complete tibial tunnel reconstruction. Patients were divided into 2 groups monitored over a period of 30 months. On the technique used, they received a score of 94.4 vs. 93.8 for patients in whom the all-inside technique was used 10. Anil Kumar Mishra and Girish S also conducted a study in which 120 patients were included (arthroscopy-assisted anterior cruciate ligament reconstruction with quadrupled semitendinosus tendon graft) in the period from March 2015 to March 2018. Lysholm score was recorded at 6 months, at the 1st year and 2nd year postoperatively. At the 2nd year of follow-up postoperatively, the mean postoperative Lysholm score improved from preoperative score of 66±5.2 to 88.70±5.54. The improvement in the mean preoperative and postoperative Lysholm scores was statistically significant. At the 2nd year of follow-up, 54 cases (45%) had excellent score (>90). Good score (84-90) was seen in 60 cases (50%). The overall satisfactory result (excellent + good) at 2 year-follow up was 95%. As a result of this, 111 patients (92.5%) were able to achieve preinjury activity level 11. Hee-Soo Kyung *et al.* evaluated 144 cases of single-bundle ACL reconstruction using an autologous hamstring tendon. The ST group included 85 cases and the ST/G group included 59 cases of reconstruction using a ST tendon and *a. gracilis* tendon. No significant differences were found between the ST and ST/G groups with respect to Lysholm scale[4]. George Kyriakopoulos *et al.* showed a similar result when examining 44 patients in two groups in a 3-year period. The first group was the all-inside group and the second was the classic with S-G graft. The Lysholm knee scores showed a significant improvement compared to the preoperative values in both groups. The preoperative values were almost identical in both groups with a mean of 57.6 and 57.2 points in the classic and the all-inside groups, respectively. The 24-month postoperative scores for the classic group increased significantly to an average of 87 ($p < 0.001$) and similar results were found in the all-inside groups, with a mean Lysholm score of 86.13 ($p < 0.001$). There was no significant difference between groups either in terms of postoperative values or percentile change[12]. Piero Volpi *et al.* conducted a pilot study between 2007

and 2008. Twenty patients were consecutively treated with ACL reconstruction using the all-inside transtibial technique with ST autograft and another 20 patients were consecutively treated with reconstruction with the traditional transtibial single-bundle procedure using ST-G autograft. This study suggests that in respect to return to sports and adequate articular function, there are no differences between the all-inside transtibial ACL reconstruction technique and the traditional transtibial ACL reconstruction using ST-G. Lysholm scale for traditional ACL technique showed a result of 94.9± 5.1 while for All Inside technique it showed 90.9 ± 8.8 (p value 0.09)[13]. In the study of Ignacio Manchado and Luci M. Motta, twenty-six patients underwent ACLR with a single bundle semitendinosus four-strand (ST group) arthroscopic all-inside reconstruction. The remaining 26 patients underwent arthroscopic ACLR with a single bundle combined doubled semitendinosus and double gracilis graft through a complete tibial tunnel (ST group). The Lysholm knee score at 5 years was similar between the ST-G and ST groups and the results were within the range of normative values for a population of this age. The preoperative vs. postoperative median values for the ST-G group were 58.5 (47.2–63) and 95 (94.2–100), respectively (p < 0.001). The preoperative vs. postoperative median values for the ST group were 52 (38.7–64.5) and 97.5 (95–99), respectively (p < 0.001).14 It is important to note that the results of these studies should not be generalized to all patients and that the difference between the all-inside technique and standard anterior cruciate ligament reconstruction should be based on individual patient needs and conditions. Research has shown that both reconstruction techniques can result in improving knee stability and function measured by this tool, i.e. scoring scale. In our study the results of the Lysholm scale were analysed qualitatively and divided into 4 groups (score less than 65, 65-83, 84-90 and more than 90). Patients completed the Lysholm scoring scale preoperatively, 3 and 8 months postoperatively. Preoperatively most of the patients in SG had a score lower than 65, while in CG most of them had a score between 65 and 83. Three months after the operation, the CG patients in relation to the SG had a score of 65 to 83, indicating a sufficient functional result, while the patients from SG had a score of 84 to 90, indicating a good functional result of the surgical intervention. Eight months after the operation the patients from SG had a significantly higher score than patients of CG (97.62 + 5.3 vs. 92.40 + 15.1) which represents a statistically significant difference between the examined and the control group in terms of Lysholm-scale values. Therefore, patients who were surgically treated only with a semitendinosus graft in the form of a quadruplication had a significantly better functional result compared to patients surgically treated with semitendinosus and gracilis grafts. The average preoperative Lysholm score was 60.85 ± 15.1, while in the control group the average preoperative score was 69.0 ± 19.4. On the third and

eighth month postoperatively, the average Lysholm score in SG was 88.60 ± 11.8 and 97.62 ± 5.3, respectively; in CG the average Lysholm score was 85.75 ± 17.8 and 92.40 ± 15.1, respectively. Patients from both groups had an excellent functional result at the second control, but the functional score was better in SG. For $p< 0.0001$ a significant increase in the Lysholm score was confirmed in the study and control groups. All-inside and standard techniques for ACL reconstruction are effective techniques, and which of these methods will be implemented depend on various individual factors, and mostly on the characteristics of the case. As doctors, it is important to give advice and guidance to patients, taking into account their individual needs and circumstances, supporting them throughout the entire process from preoperative evaluation to postoperative rehabilitation.

Conclusion

The type of surgical technique used had no significant influence on the subjective complaints of patients regarding the performance of daily activities after 3 months of surgical treatment. However, the type of surgical technique used had a significant impact on the subjective complaints of patients regarding the performance of daily activities after 8 months of surgical treatment. According to the completed Lysholm scale, patients with a *m. semitendinosus* graft had a significantly better functional result after the intervention than patients with a *m. semitendinosus* and *m. gracilis* graft. At the end of the follow-up, most patients from both groups had a score greater than 90, which is the equivalent of an excellent functional result in terms of performing daily activities, but patients from SG had this result insignificantly more often - 92.5% (37) vs. 72.5 % (29). The choice of technique may depend on patient-specific factors, recovery priorities and surgeon expertise.

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CLINICAL SCIENCE

SOCIOECONOMIC STATUS AND REPRODUCTIVE HEALTH OF MOTHERS FROM DIFFERENT ETHNIC GROUPS IN NORTH MACEDONIA

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Key words:social, reproductive health, ethnicity

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Abstract

A reproductive health framework would provide a broader programmatic focus that could bring needed attention to such issues as sexually transmitted diseases, infertility, abortion and women's empowerment generally. In order to analyze the elements of the reproductive health of our population, a one-year study was conducted that included 400 women in labor. Material and methods: Age, parity, number of pregnancies and deliveries antepartal controls, supplements intake, place of residence, etc. were analyzed. A descriptive analysis and statistical significance were made providing women's ethnicity. The results showed that the highest average age of women giving birth was registered among Macedonian women and it was 31.5 ± 5.4 years, and the lowest among Roma women 22.9 ± 5.4 years. The highest average number of deliveries among women in labor was observed in Roma and Bosnian women and it was 2.4±1.2 deliveries, and the lowest rate in Serbian women 1.3±0.6. The difference was statistically significant. It can be concluded that the emancipation of women, the level of education and the employment of women among all ethnic groups are the most important factors in the urban region. The traditions of religion and ethnicity are fundamental in family planning and have the main influence on women's reproductive life.

КЛИНИЧКИ ИСПИТУВАЊА

СОЦИОЕКОНОМСКИОТ СТАТУС И РЕПРОДУКТИВНОТО ЗДРАВЈЕ НА РОДИЛКИ ОД РАЗЛИЧНИ ЕТНИЧКИ ГРУПИ ВО РЕПУБЛИКА СЕВЕРНА МАКЕДОНИЈА

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Цитирање: Ливринова В. Социоекономскиот статус и репродуктивното здравје на родилки од различни етнички групи во Република Северна Македонија. Арх Ј Здравје 2024;16 (2) 18-25.

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Клучни зборови: социјален, репрудуктивно здравје, етникум

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Печатарски права: ©2024. Весна Ливринова. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа торигиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Со мерките за репродуктивно здравје би се обезбедил поширок програмски фокус со кој би можело да се привлече потребното внимание поврзано со сексуално преносливите болести, неплодноста, абортусот и генерално подобрување на состојбата на жените. Со цел да се анализираат елементите на репродуктивното здравје кај нашата популација, беше направена едногодишна студија во која беа вклучени 400 родилки. Следните варијабли беа анализирани: возраст, паритет, број на бремености и породувања, антепартални контроли, консумација на суплементи, место на живеење и др. Беше изработена дескриптивна анализа и определена статистичка значајност во зависност од етничката припадност. Резултатите покажаа: просечната возраст на родилките беше највисока кај Македонките и изнесуваше 31,5 ± 5,4 години, а најниската кај Ромките - 22,9 ± 5,4 години. Просечниот број на породувања кај родилките беше највисок кај Ромките и Босанките и изнесуваше 2,4±1,2 породувања, а најмалиот кај Србинките - 1,3±0,6. Разликата беше статистички значајна. Може да се заклучи дека еманципацијата на жените, нивото на образование и вработувањето на жените меѓу сите етнички групи се најважните фактори во урбаниот регион. Традициите на религијата и етничката припадност се фундаментални во планирањето на семејството кои имаат главно влијание врз репродуктивниот живот на жените.

Introduction

A reproductive health framework would provide a broader programmatic focus that could bring needed attention to such issues as sexually transmitted diseases, infertility, abortion, and women's empowerment generally[1]. One of the obvious benefits of economic development is the greater capacity of government to provide its people with basic social, material and other needs, such as food, clothing, shelter, education, access to basic health care and social services (Estes 1984, United Nations Economic and Social Commission for Asia and the Pacific - ESCAP 1998; World Bank 2006). As a result, social inclusion policies at both national and local levels have contributed to better maternity care and well-being of mothers and their infants. The UN Decade for Women (1975-1985) was a major impetus for all aspects of research on the role of women in society. It was during that period that demographic research began focusing on the links between women's status and fertility. High fertility was associated with low status, along with facts derived from various positive correlations of factors such as female education, literacy, and labor force participation, with smaller families, later marriage, and contraceptive use.

There is a substantial body of literature on the relationship between women's education and employment status and fertility, the status of women and family planning.

Moser (1989) proposes the strategy of empowerment. Empowerment is a process in which women become aware of and support by socioeconomic and cultural factors that decide their choices. Fertility care would include increasing understanding of the factors that figure out fertility[2].

At the Cairo Conference in 1994, reproductive health was defined as a state in which the reproductive process is brought to a state of complete physical, mental, and social well-being, and is not merely the absence of disease or disorders[3].

This implies that the right of women to make decisions related to reproduction and improving their socioeconomic status can enhance their reproductive health. Individuals admit imbalances in reproductive health services. Inequalities vary according to socioeconomic status, level of education, age, ethnicity, religion, and the resources available in their environment. It is possible, for example, that people with low incomes do not have the resources for proper health services and the knowledge to know what is proper for supporting reproductive health [4].

Ethnicity is associated in many ways with cultural and religious phenomena, so the concepts of culture, ethnicity and religion remain undefined in an exceedingly popular sense[5].

The aim of the paper was to identify the influence of demographic and socioeconomic factors on reproductive health in different ethnic groups.

Material and methods

This study analyzed women in labor who gave birth at the University Clinic for Gynecology and Obstetrics in Skopje during 2019. The study was designed as a cross-sectional study with random sampling. A total of 400 women in labor were included,

representing about 10% of the total number of births during 2019. Data for 30 to 40 parturient women were randomly selected. The randomization was done to avoid the influence of the seasonal nature of deliveries and the organization of work in maternity hospitals that refer patients for delivery to the University Clinic for Gynecology and Obstetrics in Skopje.

Data were taken from the obstetric histories of women, and the following parameters were analyzed: age, ethnicity, level of education, employment, place of residence (urban/rural), number of pregnancies, number of abortions, number of deliveries, stillbirths, infection.

The aim of the study was to evaluate the following parameters and their connection:

- Demographic data of patients (parturient women) - descriptive analysis;
- Elements of reproductive health in the study - descriptive analysis;
- Relation between ethnicity and reproductive health;
- Relation between socioeconomic status and reproductive health;
- Combined association of socioeconomic characteristics and ethnicity with reproductive health in parturient women.

Statistical analysis

The statistical program SPSS for Windows version 23 was used for data processing.

Numerical variables and qualitative variables were analyzed. They were processed with parametric and non-parametric tests and tests for comparison and correlation.

A p-value less than 0.05 was considered to be statistically significant.

The statistical significance of more than two variables and differences were analyzed with the analysis of variance – ANOVA. There is a wide selection of the so-called post-hoc tests that are performed after the ANOVA test presenting statistically significant results. These tests are also called multiple comparison tests. Their goal is to find out which difference (among most variables) manages the overall statistically significant result. The post-hoc Tukey HSD test was used in the study.

Results

Descriptive analysis of patients' data

A total of 400 women in labor took part in the study. According to ethnicity, the majority were Macedonian women - 50.5%, followed by Albanian women - 32.5%, Roma women - 10.5%, Turkish women - 3.75%, Bosniaks - 2.0% and Serbs - 0.75%

Of all patients, 71.5% were from the urban environment. According to the level of education, 44.0% had completed secondary education, 30.5% had higher education, 22.5% had primary education and 3.0% had no education.

Elements of reproductive health in the study - descriptive analysis

Infection was registered in 19.0% of women in labor, and 81.0% had no infection.

Supplements were taken by 92.25% of women in labor, and 7.75% did not take any supplements.

Malformations were registered in 4.5% of women giving birth, and 95.5% had no malformations.

Stillbirths were registered in 9.75% of women giving birth, and no stillbirths were registered in 90.25% of women.

In vitro fertilization was registered in 5.75% of women giving birth.

Correlation of ethnicity with patients' data

The highest average age of women giving birth was registered among Macedonian women and it was 31.5±5.4 years, and the lowest among Roma women - 22.9±5.4. The age ranged was from 15 years (Turkish and Roma women) to a maximum of 47 years (Macedonian women). According to the analysis of variance U test, the difference regarding the average age between ethnicities was statistically significant for $p<0.05$ ($p=0.000000$) (Table 1).

Table 1. Ethnicity and age of parturient women

Ethnicity	average	N	SD	minimum	maximum
Turkish	29.4	15	7.72	15.0	42.0
Macedonian	31.5	202	5.44	17.0	47.0
Albanian	29.0	130	5.43	19.0	45.0
Roman	22.9	42	5.40	15.0	36.0
Bosniaks	28.6	8	3.33	25.0	36.0
Serbians	33.7	3	1.52	32.0	35.0
total	29.7	400	6.03	15.0	47.0

The highest average number of pregnancies among women in labor was registered among Roma women and it was 2.8±15 pregnancies, and the lowest number among Serbian women - 1.7±1.1. The number of pregnancies ranged from one pregnancy among all ethnic groups taking part in the study to a maximum of 9 pregnancies among Albanian women. According to the analysis of variance U test, the difference in terms of the average number of pregnancies between ethnicities was not statistically significant for $p>0.05$ ($p=0.113517$).

The number of births ranged from 0 among Macedonian women to a maximum of 6 births among Albanian women. According to the analysis of variance U test, the difference regarding the average number of births between ethnicities was statistically significant for $p<0.05$ ($p=0.000786$) (Table 2).

Table 2. Ethnicity and number of births

Ethnicity	average	N	SD	minimum	maximum
Turkish	2.0	15	1.19	1.0	4.0
Macedonian	1.8	202	0.85	0.0	5.0
Albanian	2.2	130	1.14	1.0	6.0
Roman	2.4	42	1.16	1.0	5.0
Bosniaks	2.4	8	1.30	1.0	5.0
Serbians	1.3	3	0.57	1.0	2.0
total	2.0	400	1.03	0.0	6.0

The highest average number of abortions among women giving birth was among Macedonian women and it was 0.5±0.8 abortions, and the lowest among Bosnian women - 0.1±0.4. The number of abortions ranged from 0 among all ethnicities to a maximum of 5 abortions among Albanian women. According to the analysis of variance U test, the difference in terms of the average number of abortions between ethnic groups was statistically insignificant for $p>0.05$ ($p=0.687505$).

The highest average number of prenatal check-ups among women giving birth was found among Macedonian women and it was 9.1±2.1 check-ups, and the lowest among Roma women - 5.3±3.1. The number of prenatal check-ups ranged from 0 among Albanian and Roma women to a maximum of 15 prenatal check-ups among Macedonian women.

According to the analysis of variance U test, the difference regarding the average number of prenatal controls between ethnicities was statistically significant for $p<0.05$ ($p=0.000000$) (Table 3).

Table 3. Ethnicity and antenatal check-ups

Ethnicity/number of antenatal check ups	average	N	SD	minimum	maximum
Turkish	8.3	15	1.48	6.0	10.0
Macedonian	9.1	202	2.10	1.0	15.0
Albanian	8.5	130	1.81	0	12.0
Roman	5.3	42	3.14	0	10.0
Bosniaks	8.3	8	2.49	4.0	12.0
Serbians	8.7	3	1.52	7.0	10.0
total	8.5	400	2.40	0	15.0

The highest percentage of infection was registered among Roma women - 35.7%, followed by Macedonian women - 19.3%, Albanian women - 15.6% and Turkish women - 13.3%. A significant association was registered between infection onset and ethnicity of women giving birth for p<0.05 (Pearson Chi-square: 11.6338, df=5, p=.040166).

Over 94% of pregnant women took supplements as an addition to food. 23.8% of Roma women and 25.0% of Bosnian women did not take supplements. A significant association was registered between intake of supplements and the ethnicity of women giving birth for p<0.05 (Pearson Chi-square: 21.9354, df=5, p=.000539) (Figure 1.)

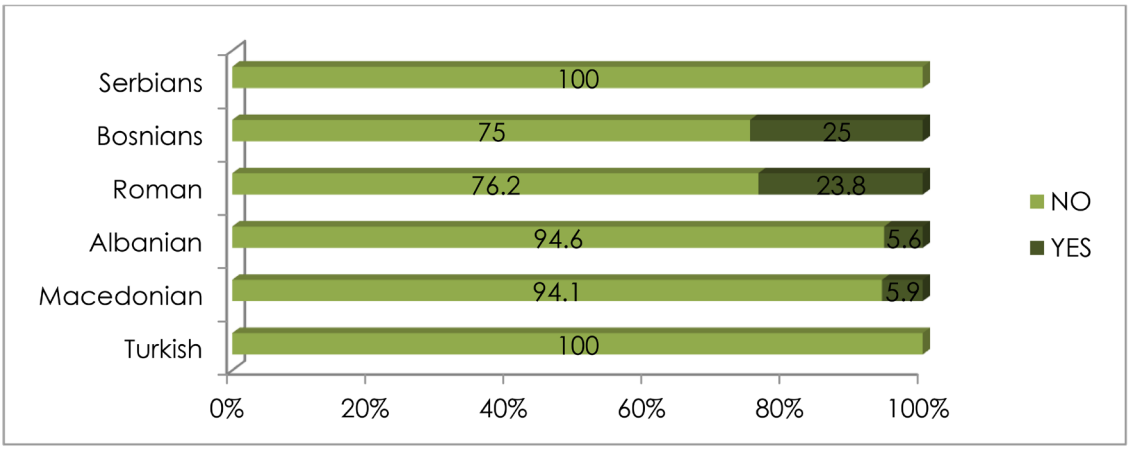


Figure 1. Ethnicity and supplements intake

Figure 1. Ethnicity and supplements intake

In 5.4% of Macedonian women, in 4.8% of Roma women - and in 3.8% of Albanian women malformations were registered-. No significant association was found between detected malformations and ethnicity of women giving birth for p>0.05 (1.78140, df=5, p=.878489).

Among women giving birth, 10.8% of Albanian women had stillbirths , 9.4% of Macedonian women, and 4.3% of Roma women -, and among women from other ethnicities, stillbirths were not registered. No significant association was registered between stillbirth and ethnicity of women giving birth for p>0.05 (Pearson Chi-square:.97146, df=5, p=.553532).

In vitro fertilization among women giving birth was registered among 3.1% of Albanian women, 8.9% of Macedonian women, and 12.5% of Bosnian women; such fertilization was not registered among women from other ethnicities. No significant association was registered regarding stillbirth and ethnicity of parturient women for p>0.05 (Pearson Chi-square: 9.77119, df=5, p=.081984).

Discussion

Religion and ethnicity tradition are predominant in family planning and they have the main impact on women's reproductive life [6,7], which has been shown in our studies, too.

Regarding literature data, the highest average number of deliveries among women in labor was reg-

istered among Roma and Bosnian women and it was 2.4±1.2 deliveries, and the lowest number was registered among Serbian women - 1.3±0.6. Our results with regard to number of pregnancies are similar to those in our neighborhood. In Albania, the birth rate is 2.05; it is under 1.5 in Bosnia, Serbia and Russia, and the highest rate is registered in Turkey-2.2 [8]. The descriptive analysis of data in this study suggests that ethnic affiliation of patients did not correlate absolutely with their representation at the national level. There is a wide range of reproductive age among female individuals, from 14 to 47 years.

The highest average age of women giving birth was recorded among Macedonian women and it was 31.5 ± 5.4 years, and the lowest among Roma women - 22.9 ± 5.4.

A study in Ethiopia discussed antenatal check-ups among all women, and one antenatal check-up visit was registered in 92.3% of pregnant women, four or more visits in 28.8%, but aur data suggest that our pregnant women had at least 4 antenatal check-ups[9].

Conclusion

The traditions of religion and ethnicity are fundamental in family planning. The efforts of the health care system in our country should be focused in providing preventive measures. It is necessary to reduce the number of giving childbirth under the age of eighteen in Roma population. There is increase in the age of women who give birth after 35 years when comorbidities are present. National strategies should promote a positive approach to maternal health and wellbeing, reducing the risk of complications in vulnerable populations.

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PUBLIC HEALTH

FAMILY SOCIOECONOMIC DIFFERENCES AMONG CHILDREN LIVING WITH OVERWEIGHT AND OBESITY IN NORTH MACEDONIA

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Key words: childhood obesity, socioeconomic status, health inequalities, WHO-COSI

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Abstract

Globally, the prevalence of overweight and obesity is increasing among children and adolescents. Halting the rise in obesity is a significant challenge because of the complex interplay of factors and influences. We aimed to explore the role of family socioeconomic status (SES) indicators in relation to overweight and obesity prevalence rates among primary school children in North Macedonia. Materials and methods: Data were collected on a nationally representative sample of children and their parent(s)/caregiver(s) participating in the 6th round of World Health Organization (WHO)-European Childhood Obesity Surveillance Initiative (COSI) in North Macedonia. Every child had their height and weight objectively measured and their family sociodemographic and SES data were obtained through a self-reported record form by their parent(s)/caregiver(s). According to COSI reporting, responses on three SES indicators (parental educational attainment, parental employment status and family-perceived wealth) were categorized in levels for data analysis. Overweight and obesity rates were estimated based on 2007 WHO growth references. Pearson's $\chi 2$-tests, corrected with the Rao-Scott method, were used to test differences in overweight and obesity across various subgroups. Results: The sample consisted of primarily native-born children (97.3%) and parents (mothers - 96.2%; fathers - 97.6%), living in urban areas (66.9%), in two-parent families (84.9%) and spoke Macedonian at home (59.8%). The majority of children lived in families with low to medium SES level. Prevalence of overweight was 30.5% [95% CI: 28.5-32.7], whilst of obesity 14.1% [95% CI: 12.3-16.0]. There were no significant differences observed across family SES indicators in overweight or obesity rates. Conclusion: Our findings contribute towards reporting on family SES among children living with overweight and obesity to better understand and address potential obesity risk factors. Future research should focus on exploring family SES within the long-term context of children's health-related behaviours.

ЈАВНО ЗДРАВЈЕ

СОЦИОЕКОНОМСКИТЕ РАЗЛИКИ ПОМЕЃУ СЕМЕЈСТВАТА НА ДЕЦА СО ЗГОЛЕМЕНА ТЕЛЕСНА ТЕЖИНА И ДЕБЕЛИНА ВО СЕВЕРНА МАКЕДОНИЈА

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Цитирање: Стаменова А, Силвер Волис Л, Михајлова К, Димитриевска Љ, Спироски И. Социоекономските разлики помеѓу семејствата на деца со зголемена телесна тежина и дебелина во Северна Македонија. Арх Ј Здравје 2024;16 (2) 26-36.

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Клучни зборови: детска дебелина, социоекономски статус, здравствени нееднаквости, СЗО-COSI

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Печатарски права: ©2024. Александра Стаменова, Лорејн Силвер Волис, Катерина Михајлова, Љубица Димитриевска, Игор Спироски. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа торигиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

На глобално ниво, стапката на преваленција од зголемена телесна тежина и дебелина кај деца и адолесценти се зголемува. Запирањето на порастот на дебелината е значаен предизвик поради комплексната интеракција на многу фактори и влијанија. Цел на студијата беше да се истражи улогата на социоекономскиот статус (СЕС) на семејството во однос на преваленцијата на зголемена телесна тежина и дебелина кај децата, ученици во основните училишта во Северна Македонија. Материјали и методи: Податоците беа собрани на национално репрезентативен примерок на деца и нивните родител(и)/старател(и), учесници во 6-от круг на СЗО - Европската иницијатива за следење на дебелината (COSI) во Северна Македонија. Телесната висина и тежина на секое дете беше објективно измерена, а социодемографските и СЕС податоци беа добиени од прашалникот за семејство пополнет од страна на нивните родител(и)/старател(и). Според претходни COSI публикации, одговорите за трите СЕС индикатори (степен на образование, работен статус и перцепции за економската благосостојба) беа категоризирани во нивоа за анализа на податоците. Стапките на зголемена телесна тежина и дебелина беа пресметани врз основа на СЗО референците за раст од 2007 година. Pearson-ов $\chi 2$-тест, коригиран со Rao-Scott методот, беа употребени за тестирање на разликите во стапките на зголемена телесна тежина и дебелина помеѓу различните подгрупи. Резултати: Примерокот за анализа се состоеше примарно од деца (97,3%) и родители мајка - 96,2%; татко - 97,6%) кои се родени во Македонија, живеат во урбани средини (66,9%), како дворoдителски семејства (84,9%), и зборуваат дома на македонски јазик (59,8%). Поголемиот број деца живееја во семејства со низок до среден социоекономски статус. Преваленцијата на зголемена телесна тежина беше 30,5% [95% CI: 28.5-32.7], додека на дебелина 14,1% [95% CI: 12.3-16.0]. Не беа забележани значајни разлики помеѓу индикаторите на семејниот СЕС и превалентноста на зголемена телесна тежина и дебелина. Заклучок: Нашите резултати придонесуваат кон евидентирање на социоекономскиот статус на семејството кај децата кои живеат со зголемена телесна тежина и дебелина со подобро разбирање и адресирање на потенцијалните ризик-фактори на дебелина. Идните истражувања треба да се фокусираат кон анализирање на семејниот СЕС во долгорочен контекст на поврзаноста со однесувањата поврзани со здравјето кај децата.

Introduction

Obesity is a significant public health challenge, which is often underestimated as priority by governments despite alarming evidence of adverse health outcomes and economic impact contributing to this complex disease[1]. Of particular concern are the growing overweight and obesity rates among youth; global estimates show that 390 million children and adolescents were living with overweight and obesity in 2022, while overweight (including obesity) prevalence doubled[2]. Data from the European Childhood Obesity Surveillance Initiative (COSI) highlights substantial differences in prevalence, especially as related to country income and paradoxically highest among children living in Mediterranean countries, as well as in North Macedonia.[3] Hence, the conditions in which children are born and grow as well as social determinants of health contribute to a complex interplay in childhood obesity risk.[4]

This is also supported by an overwhelming body of research which supports that despite strong genetic factors for obesity, environmental factors are crucial for expression of predisposition as well.[5,6] In essence, the perspective in understanding and prevention of obesity changed from individual towards socio-ecological approach and model (i.e., health-related behaviour is a result of personal factors, and interpersonal interactions at home, schools, community, as well as cultural and socioeconomic factors).[7]

The socioeconomic status (SES) is term in social epidemiology accessed through measuring the social position of the individual and associations between SES and health outcomes or mortality have been documented for centuries.[8] Previous studies and reviews have reported an inverse relationship between childhood obesity and high SES (i.e., parents education, employment, family income) in high-income countries, whilst a positive relationship has been observed in low-income and middle-income countries.[9-12] Children living in families with low SES have a greater risk of obesity regardless of the country's income.[13] Heterogeneous and inconsistent evidence are also observed, most likely as a result of the different methodology and indicators applied to measure and summarize SES in one value, which influences not only the results but conclusions on causality, and consequently policies.[14] Hence, understanding the local socioeconomic context of childhood obesity is essential for ensuring evidence-based public health action in halting obesity rates among children.

The aim of this study was to explore the role of family SES indicators in relation to overweight and/or obesity prevalence among a nationally representative sample of primary school children living in North Macedonia.

Materials and methods

Study Design and Data Collection Procedures

This study used data from the 6th round of World Health Organization (WHO) European Childhood Obesity Surveillance Initiative (COSI), conducted between October and December 2022 in North Macedonia. The Macedonian study protocol and data

collection procedures were in accordance with WHO-COSI methodology and standardized procedures.[15],[16] This system is implemented on the principles of 2002 International Ethical Guidelines for Biomedical Research involving human subjects.[17] Additionally, the national protocol was approved by the Ss. Cyril and Methodius University, Faculty of Medicine's Ethics Committee (approval: 03-2140/1 from 06.05.2022). This cross-sectional survey used a two-stage stratified cluster sampling approach in the recruitment of primary schools (second grade) and participants (children and parents/caregivers). In all previous WHO COSI rounds, primary schools in North Macedonia were stratified by location to ensure national representation, including socioeconomic diversity.

To address the purpose of this study, questions from the mandatory child and voluntary family forms were used. As part of the mandatory child form, each child's height and weight were measured according to WHO-COSI standardized procedures. Prior to data collection, parents were informed of study procedures and provided written informed consent for their child to participate. Data collection teams of trained physicians and nurses from regional and local Public Health Centres measured each child's body weight and height according to WHO-COSI standardized procedures after each child provided informed consent. Furthermore, each child's anthropometric measurements were performed in a private office and adhered to principles of confidentiality.

The voluntary family form includes a comprehensive battery of questions addressing both child and household characteristics. For the purposes of this study, questions addressing family sociodemographic (place of residence [urban or rural], child's place of birth, parent(s)/caregiver(s) place of birth, language spoken at home, and family living situation [one-parent, two-parents, extended family]) and socioeconomic characteristics were explored.

Classification of Children's Weight Status

Children's weight status was classified according to their BMI-for-age (BMI/A) Z-scores which were computed based on WHO growth references.[18,19] Overweight was defined as BMI/A ≥1 Z-score, while obesity was considered when BMI/A value ≥2 Z-score. Children with biologically implausible values were excluded from the analysis (i.e., BMI/A values below –5 or above +5 Z-scores) relative to 2007 WHO growth reference median.

Classification of Family Socioeconomic Status (SES)

The voluntary family record form included three questions addressing SES markers, including: (a) parental educational attainment, (b) parental employment, and (c) family-perceived wealth. Individual WHO-COSI questions for each SES marker and response options are presented in Table 1. For data analysis purposes, SES category levels were consistent with previous WHO COSI studies.[20]

Statistical Analysis

Multiple steps were employed to establish data quality assurance. Firstly, the national Macedonian COSI team reviewed and verified child and family forms for completeness. Next, data files were sent to the Regional European WHO Office for review and insertion of post-stratification weights to adjust for the complex sampling design, oversampling, and non-response error.

Descriptive analyses were calculated to depict children's sociodemographic characteristics, anthropometric measurements (BMI/A Z-scores and categories), and self-reported familial socioeconomic status. Prevalence estimates with 95% confidence intervals (CI) of overweight (including obesity) and obesity were calculated for the overall sample and by various subgroups (e.g., sex and family SES). Pearson's $\chi 2$-tests, corrected with the Rao-Scott method, were used to test differences in overweight and obesity across various subgroups. Statistical significance was set at $p<0.05$ *a priori*.

Table 1. World Health Organization (WHO) Childhood Obesity Surveillance Initiative (COSI) Predefined Family Socioeconomic Status (SES) Questions and Response Options

WHO COSI Family SES Questions and Response Options		Level of SES Categories for Data Analyses
Questions	**Response Options**	
Parental educational attainment		
What is the highest level of education you and your partner have completed? Please select one answer only for each of you	• Primary education or less (ISCED 0-1) • Lower secondary education (ISCED 2) • Upper secondary and post-secondary non-tertiary education (ISCED 3 and 4) • Short-cycle tertiary education or Bachelor's or equivalent level (ISCED 5 and 6) • Master's or Doctoral or equivalent level (ISCED 7 and 8)	(a) Low (both parents/caregivers reported education asISCED 0-1, 2, 3 or 4). (b) Medium (one parent with lower education and one parent with higher education) (c) High (both parents/ caregivers reported their education as ISCED 5, 6, 7, or 8).
Parental employment		
Which of the following best describes yours and/or your partner's main work over the last 6 months? Please select one answer only for each of you	• Full-time domestic housework/homemaker • Work full-time • Work part-time • Unemployed • Full-time education (i.e. student) • Sick/disabled • Something else	(a) Low (one or more parent(s) unemployed or economically inactive (i.e., comprises "full-time domestic housework/homemaker," "full-time education," "sick/disabled" and "retired" (b) High (both parents employed)
Family-perceived wealth		
Which of the following best describes your financial situation at home? Please select one answer only	• We barely make ends each month with our earnings • We have trouble making ends meet each month with our earnings • We get through the month without serious problems with our earnings • We easily get through the month with our earnings	(a) Low (those who barely or had trouble meeting the end of the month) (b) Medium (parents who met the end of the month with their earnings without serious problems) (c) High (those who easily met the end of the month with their earnings).

Results

The total sample included students (n=2783) present at school on the day of data collection who had completed information on age, sex, and anthropometric measures. Among those students, 96.4% (n=2683) returned at least a partially completed family form, with most (n=2667) returning a family form with completed SES indicators as well.

Family sociodemographic and socioeconomic characteristics are presented in Table 2. Overall, children and their parents/caregivers were born in North Macedonia. Most children lived in urban areas (66.9%), mainly in two-parent families (84.9%) and spoke Macedonian at home (59.8%). Approximately half of the families reported low educational level (49.4%), medium level of perceived wealth (52.8%), and current employment of both parents/caregivers (61.2%).

Table 2. Sociodemographic and socioeconomic characteristics of study sample

Sociodemographic characteristics		%
Residential urbanization	*Urban*	66.9
	Rural	33.1
Child's country of birth		
	Native-born child	97.3
	Foreign-born child	2.7
Parent(s)/Caregiver(s) country of birth		
	Native-born mother	96.2
	Foreign-born mother	3.8
	Native-born father	97.6
	Foreign-born father	2.4
Language spoken at home		
	Macedonian language	59.8
	Other languages	40.2
Family living situation		
	Two-parent family	84.9
	One-parent family	11.3
	Other or extended family	3.8
Socioeconomic characteristics		%
Parents/Caregivers educational attainment		
	Low	49.4
	Medium	21.6
	High	29.1
Parents/Caregivers employment status		
	Low	38.8
	High	61.2
Family-perceived wealth		
	Low	20.2
	Medium	52.8
	High	27.0

As shown in Table 3, overall prevalence of overweight (including obesity) was 30.5% [95% CI: 28.5-32.7], whilst obesity prevalence was 14.1% [95% CI: 12.3-16.0]. As compared to girls, significantly more boys were overweight/obese (34.2% *versus* 26.9%, *p*=.0010) and obese (16.4% *versus* 11.6%, *p*=.0016).

Table 3. Prevalence of overweight (including obesity) and obesity, according to WHO standard definitions

		Overweight (including obesity)		Obesity	
Child's sex	**Number of available observations**	**Prevalence (%) 95 % CI [lb-ub]**	**p value**	**Prevalence (%) 95 % CI [lb-ub]**	**p value**
Boys	1339	34.2 [31.9-36.6]	*.0010*	16.4 [14.4-18.7]	*.0016*
Girls	1328	26.9 [23.6-30.4]		11.6 [9.5-14.2]	
Total	2667	30.5 [28.5-32.7]		14.1 [12.3-16.0]	

Notes: Overweight (BMI/A ≥1 Z-score), Obesity (BMI/A value ≥2 Z-score), estimated based on the 2007 WHO cut offs. Prevalence of overweight includes obesity according to WHO definition

Overall, overweight and obesity rates in relation to family SES indicators are presented in Tables 4 and 5. For both overweight and obesity, there were no significant differences observed across family SES indicators.

Table 4. Prevalence of overweight (including obesity) according to WHO definition among school children in relation to family SES indicators

Overweight			
	Number of available observations	**Prevalence (%) 95 % CI [lb-ub]**	**p value**
Parents' educational attainment			
Low	1185	31.4 [28.2-34.7]	.4357
Medium	596	32.9 [28.8-37.3]	
High	693	28.8 [24.1-34.1]	
Parents' employment status			
Low	693	29.4 [24.6-34.8]	.1731
High	1428	33.4 [30.6-36.3]	
Family-perceived wealth			
Low	485	30.6 [26.0-35.6]	.8584
Medium	1312	31.4 [28.0-35.0]	
High	710	30.0 [26.1-34.2]	
Type of family			
Two-parent family	2205	30.1 [27.8-32.4]	.1126
One-parent family	238	33.9 [27.4-41.0]	
Other or extended family	83	41.2 [29.8-33.1]	

Table 5. Prevalence and 95% CIs of obesity according to WHO definition among school children in relation to family SES indicators

Overweight			
	Number of available observations	**Prevalence (%) 95 % CI [lb-ub]**	**p value**
Parents' educational attainment			
Low	1185	15.5 [12.7-18.7]	.1765
Medium	596	15.2 [12.3-18.5]	
High	693	11.8 [9.2-15.1]	
Parents' employment status			
Low	693	15.2 [11.7-19.6]	.6063
High	1428	14.2 [12.4-16.1]	
Family-perceived wealth			
Low	485	16.4 [12.0-22.0]	.4419
Medium	1312	13.4 [11.1-16.1]	
High	710	14.3 [11.8-17.2]	
Type of family			
Two-parent family	2205	13.9 [11.9-16.1]	.4577
One-parent family	238	16.0 [11.0-22.7]	
Other or extended family	83	19.3 [10.4-33.1]	

Discussion

The findings obtained in this study were drawn from a nationally representative sample. Each child's height and weight were objectively measured using standardized procedures and equipment. Additionally, family SES was assessed using previously validated questions applied in all COSI countries, warranting comparability.

Our findings showed high prevalence rates of both overweight and obesity among primary school children in North Macedonia. Consistent with previous COSI rounds, overweight and obesity were more prevalent among boys in North Macedonia.[21] No significant differences emerged between overweight and/or obesity and family SES in our study, which did not reflect findings from previous studies from the first and fourth COSI round exploring SES[20,22] in WHO/Europe region, where strong associations were reported for parental education level among European countries, except for Central Asian countries, as well as association between family-perceived wealth and overweight and/or obesity. For the other SES indicator: parental employment status, no associations were demonstrated in the majority of high-income countries, except in few Balkan countries, Georgia and Turkey.

We could not dismiss the family SES context of overweight and/or obesity among children living in North Macedonia merely on these findings. Obesity is manifested by re-

sponses not only to present family circumstances but to all stages of the life-course, especially influencing child development.[23] Therefore, it is of concern that the majority of children lived in families with low and medium SES levels, especially that 20% of the families had low level of perceived-wealth, meaning they could not get through the month with their own earnings. As shown in previous research, this leads to a psychological distress, and financial scarcity that impairs health-related behaviours, especially dietary habits, resulting in maladaptive behaviours to financial stress and long-term responses and could eventually lead to obesity.[24, 25] Furthermore, this is supported in cohort studies, which also report on significant associations between low-income families and increased risk for obesity in preschool children.[26]

Important aspects and limitations should be considered in the interpretation of the results. Firstly, family SES was based on self-reported data from parents or caregivers, and the formation of the questions with predefined answers may have introduced a reporting bias. Secondly, participants with incomplete family forms on SES information were excluded from data analysis, which may have resulted in selection bias. Thirdly, survey response options on SES indicators were categorized for data analyses; therefore, results may have varied if a different statistical strategy was employed. Finally, the small number of available observations in subgroups and large variations might have influenced these results as well.

Conclusion

To the best of our knowledge, this is the first study in North Macedonia reporting on family socioeconomic aspects in childhood overweight and obesity after the COVID-19 pandemic. Halting childhood obesity rates is a significant challenge as obesity is a complex disease with an interplay of numerous factors and influences. Our study contributes towards the importance of reporting on family SES among children living with overweight and obesity for better understanding and addressing obesity in the national context. Future research should focus on exploring the family SES and children's health-related behaviours, not only overweight and obesity prevalence rates. Moreover, data generated from past COSI rounds should be pooled to explore family SES and overweight and obesity trends over time.

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ORAL HEALTH

DECLARED FLUORIDE CONCENTRATION IN COMMERCIAL MOUTHWASHES: A MARKET ANALYSIS FROM NORTH MACEDONIA

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Abstract

The aim of this study was to determine the declared fluoride concentration in mouthwashes available on the market in the Republic of North Macedonia. Material and methods: To identify all available mouthwashes in the Republic of North Macedonia, a market analysis was conducted in the period between January 1, 2024 and July 1, 2024, including traditional markets and the online market. Two researchers recorded the ingredients declared by the manufacturer, while other two researchers verified the recorded ingredients. Results: There are 76 mouthwashes available on the market in the Republic of North Macedonia, out of which, 44 (57.9%) contained fluoride in the form of sodium fluoride or olaflur, or both. Of the 44 fluoride-containing mouthwashes, 9 (20.45%) did not declare the amount of fluoride. Most of the fluoride-containing mouthwashes used sodium fluoride alone or in combination with olaflur (n=42, 95.45%). The fluoride content in mouthwashes ranges from 98 ppm F to 475 ppm F, with the most common being 225 ppm F (n=9, 25.72%) and 250 ppm F (n=8, 22.85%). A total of 17 mouthwashes (51.42%) contain fluoride at a concentration of at least 230 ppm F. Conclusions: More than a half of the available mouthwashes contained fluoride in the form of sodium fluoride, olaflur or both. Among these, some of them did not declare the fluoride concentration despite stating the presence of sodium fluoride in their composition. Increased oversight by regulatory bodies is necessary to ensure the safety and proper labeling of these products.

ОРАЛНО ЗДРАВЈЕ

ДЕКЛАРИРАНА КОНЦЕНТРАЦИЈА НА ФЛУОРИДИ ВО КОМЕРЦИЈАЛНИТЕ ВОДИЧКИ ЗА ПЛАКНЕЊЕ НА УСТА: АНАЛИЗА НА ПАЗАРОТ ВО РЕПУБЛИКА СЕВЕРНА МАКЕДОНИЈА

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Клучни зборови: флуориди, водички за испирање на уста, натриум флуорид

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Печатарски права: ©2024. Киро Ивановски, Влатко Коколански, Марија Андоновска, Бојан Попоски, Спиро Спасовски, Мира Јанкуловска, Јулијана Николовска.. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа торигиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Целта на ова истражување беше да се утврди декларираната концентрација на флуориди во водичките за плакнење на уста достапни на пазарот во Република Северна Македонија. Материјали и методи: За да се идентификуваат сите достапни водички за плакнење на уста во Република Северна Македонија беше спроведена анализа на пазарот во период од 1 јануари до 1 јули 2024 година, која ги опфати традиционалните пазари и онлајн пазарот. Двајца истражувачи ги регистрираа состојките декларирани од производителот, додека други двајца истражувачи ги верификуваа регистрираните состојки. Резултати: На пазарот во Република Северна Македонија се достапни 76 водички за плакнење на уста, од кои 44 (57,9%) содржат флуориди во форма на натриум флуорид или олафлур или комбинација од натриум флуорид и олафлур. Од 44 водички за плакнење на устата што содржат флуориди, кај 9 (20,45%) не беше декларирана нивната концентрација. Повеќето водички за плакнење на устата што содржат флуориди, во својот состав имаа натриум флуорид или комбинација од натриум флуорид и олафлур (n=42, 95,45%). Концентрацијата на флуориди во водичките за плакнење на устата е во рамки од 98 ppm F до 475 ppm F, при што најчести се концентрациите од 225 ppm F (n=9, 25,72%) и 250 ppm F (n=8, 22,85%). Вкупно 17 водички за плакнење на уста (51,42%) содржат флуориди во концентрација од најмалку 230 ppm F. Заклучок: Повеќе од половина од достапните водички за плакнење на уста содржат флуориди во форма на натриум флуорид, олафлур или комбинација од натриум флуорид и олафлур. Од нив, некои производители не ја декларирале концентрацијата на флуориди и покрај тоа што навеле присуство на натриум флуорид во нивниот состав. Неопходен е зголемен надзор од страна на регулаторните тела за да се осигура безбедноста и правилното декларирање на овие производи

Introduction

For millennia, oral care has been crucial across diverse populations and cultures worldwide. Effective oral hygiene requires controlling bacteria that cause dental plaque and bad breath, while also fortifying and protecting teeth to prevent dental caries[1]. Proper oral hygiene, including brushing, flossing, a suitable diet, and hydration, is foundational for a healthy oral cavity. Additionally, various adjunctive oral hygiene products like irrigators, tongue scrapers, and mouthwashes enhance oral care effectiveness. Mouthwashes, in particular, are widely used and there is a vast array of products available[2]. A mouthwash is defined as a non-sterile aqueous solution primarily used for its deodorant, refreshing, or antiseptic properties. Mouthwashes are intended to reduce oral bacteria, remove food particles, temporarily alleviate bad breath, and provide a pleasant taste. They are generally categorized as either cosmetic or therapeutic, or a combination of both. Cosmetic rinses are commercial products that eliminate oral debris before or after brushing, temporarily mask bad breath, reduce bacteria, and leave a refreshing taste. Therapeutic rinses, while also offering cosmetic benefits, contain active ingredients (such as fluoride or chlorhexidine) that help prevent or treat certain oral diseases[3,4]. Some mouthwashes are used for preoperative surgical treatment5, postoperative wound care[6,7], and during fixed orthodontic treatment[8]. Recently, commercial or over-the-counter mouthrinses have become one of the fastest-growing sectors in the oral care industry[9]. Mouthwashes contain various ingredients including oral health substances, solvents, surfactants, thickeners, sweeteners, plant extracts, preservatives, colorants, and flavoring agents. Several groups of oral health substances have been identified, with fluorine compounds being a notable inclusion[2]. Fluoride is naturally present in the environment and is a common part of daily life. It is found in water, soil, and air, and exposure occurs through diet, respiration, and supplements. While toxic at extremely high concentrations[10], fluoride is proven to prevent cavities or tooth decay. The role of fluoride in caries prevention was first noted by Black and McKay in the early 20th century[11]. The addition of fluoride to community water supplies and oral care products like toothpaste and mouthwash has been a significant public health measure (PHM), considered one of the top ten public health achievements of the 20th century[12]. Studies have shown that fluoride concentrations in community water supplies of 0.8-1.5 mg/L can reduce dental caries by over 60%. However, in the Republic of North Macedonia, drinking water, particularly in larger cities, usually contains fluoride concentrations lower than 0.2 mg/L[13]. Fluorides are categorized into systemic (such as fluoridated water, milk, salt, and supplements) and topical forms (including toothpaste, mouthwashes, varnishes, gels, foams, and slow-release devices)[12]. Fluoride strengthens the tooth's enamel. Despite concerns about potential adverse effects from excessive use, especially in young children who might ingest more toothpaste, appropriate use of fluoride products remains highly effective for caries prevention with minimal risk. Studies by Nakamoto *et al.*[14]

and Dhar *et al*.[15] highlight risks like dental fluorosis and systemic toxicity from excessive fluoride intake. Nonetheless, when used correctly, fluoride products are the most effective means of caries prevention with minimal adverse effects. According to the World Health Organization, dental caries affect 60-90% of school-age children and nearly 100% of adults worldwide[16]. Comprehensive prevention programs, including the use of fluoride-containing products like toothpaste, mouthwashes, gels, foams, and varnishes, have been shown to significantly reduce caries prevalence[17]. Regular mouthrinsing with fluoride solutions has proven to be an effective caries prevention method for schoolchildren[18]. Marinho *et al*.[19] reviewed 37 trials from various countries, confirming the effectiveness of supervised use of fluoride mouthrinses in reducing caries in permanent teeth. They also noted limited data on adverse effects and treatment acceptability. In Japan, where water fluoridation is not practiced, a school-based fluoride mouth-rinsing program (S-FMR) began in Niigata Prefecture in 1970 and expanded nationwide by 2005[20]. Matsuyama *et al*.[21] conducted a study across all 47 Japanese prefectures, finding that high S-FMR utilization significantly correlated with lower DMFT (Decayed, Missing, Filled Teeth) rates in 12-year-olds. Yonezawa and Yagi[22] concluded that participation in the FMR program during elementary school offered a significant protection against dental caries. This paper aimed to determine the declared fluoride concentration in mouthwashes available on the market in the Republic of North Macedonia.

Materials and methods

Between January 1, 2024, and July 1, 2024, a market analysis was conducted in the Republic of North Macedonia. This study encompassed traditional markets (pharmacies, cosmetic chains, and consumer goods markets) as well as the online market. Four researchers (VK, KI, SS and BP) carried out this research, aiming to identify all available mouthwashes. One to three packs of each mouthwash were purchased directly from vendors without requesting free samples from manufacturers or importers. Mouthwashes were selected based on the following inclusion criteria: intended for maintaining oral hygiene, preventing oral diseases, or having a therapeutic effect; available over-the-counter; and in the pharmaceutical forms of either a solution intended for direct use or a concentrate to be dissolved in water, regardless of their regulatory status (medicine, medical device, cosmetic product). The exclusion criteria were: tablets that dissolve in water or other liquids, chewing tablets, saliva substitutes; products containing antibiotics, steroids, parasympathomimetic saliva stimulants, topical local anesthetics, and other prescription drugs; liquids taken orally but not intended for maintaining oral hygiene; liquids in the form of sprays, toothpastes, gels, powders, foams, homeopathic products, and products without a fully available composition.

Two researchers (MJ and JN) recorded the ingredients declared by the manufacturer in an Excel spreadsheet (Microsoft Corporation, Redmond, Washington, United States). The

other two researchers (KI and MA) verified the recorded ingredients to eliminate errors. The manufacturers were not contacted to request missing data about fluoride concentrations, assuming the accuracy of the provided data. Frequency analysis of substances was performed using Microsoft Excel v. 2016 (Microsoft Corporation, Redmond, Washington, United States) and SPSS Statistics v23 for Windows (IBM Corp., Armonk, NY), while the difference between the proportions means was performed with Difference test in StatSoft STATISTICA v12.5 (StatSoft, Inc., Tulsa, Oklahoma, United States).

Results

There are 76 mouthwashes available on the market in the Republic of North Macedonia. A comprehensive list of these mouthwashes, including those with declared fluoride content and the specified amount of fluoride (expressed in ppm F), is provided in Annex 1. Out of the 76 mouthwashes, 44 (57.9%) contained fluoride in the form of sodium fluoride or olaflur, or both. There is a statistically significant difference in the number of available mouthwashes containing sodium fluoride compared to those that do not ($p<0.001$). Table 1, based on the analysis of fluoride forms in mouthwashes, shows the number of products declaring fluoride in their composition and the specific form of the fluoride component.

Table 1. Frequency of the type of fluorine compounds

Type of fluorine compounds	Number of mouthwashes (%)
sodium fluoride	37 (84.1%)
olaflur	2 (4.54%)
sodium fluoride and olaflur	5 (11.36%)
Total	**44 (100%)**

Of the 44 fluoride-containing mouthwashes, 9 (20.45%) did not declare the amount of fluoride. Most of the fluoride-containing mouthwashes used sodium fluoride alone or in combination with olaflur (n=42, 95.45%).

Table 2 displays the declared fluoride concentrations (in ppm F) and the frequency of mouthwashes with various fluoride concentrations.

Table 2. Frequency of declared amount of fluorides

Concentration of fluoride	Number of mouthwashes (%)
98 ppm F	1 (2.86%)
100 ppm F	1 (2.86%)
135 ppm F	1 (2.86%)
220 ppm F	5 (14.28%)
225 ppm F	9 (25.72%)

230 ppm F	1 (2.86%)
250 ppm F	8 (22.85%)
450 ppm F	8 (22.85%)
475 ppm F	1 (2.86%)
Total	**35 (100%)**

The fluoride content in mouthwashes ranges from 98 ppm F to 475 ppm F. The most common fluoride concentrations are 225 ppm F (n=9, 25.72%) and 250 ppm F (n=8, 22.85%). A total of 17 mouthwashes (51.42%) contain fluoride at a concentration of at least 230 ppm F. There is a statistically significant difference in the number of mouthwashes with fluoride concentrations between 220 and 250 ppm F compared to others (n=23; 65.71%, p=0.086).

Discussion

This is the first study that evaluated the declared fluoride concentration in mouthwashes in the Republic of North Macedonia. The market analysis in our study identified a total of 76 available mouthwashes. As mentioned before, based on the presence or absence of chemically active ingredients, mouthwashes can be classified as cosmetic (absence of chemically active ingredients) and therapeutic (presence of chemically active ingredients, such as cetylpyridinium chloride, chlorhexidine, fluoride, or hydrogen peroxide)[23]. Initially, we separated the mouthwashes containing fluorides as a chemically active ingredient, which comprised 44 out of the available 76 (57.9%). The fluoride ion concentrations in the available mouthwashes ranged from 98 to 135 ppm (8.58%), 220 to 250 ppm (65.71%) and 450 to 475 ppm (25.71%), with 9 out of 44 fluoride-containing mouthwashes (20.45%) not declaring the fluoride concentration. In general, sodium fluoride (NaF) is the most commonly used fluoride agent in mouthwashes[24], but from the available literature we know that mouthwashes can also contain other fluoride compounds such as stannous fluoride (SnF2), sodium monofluorophosphate (SMFP), acidulated phosphate fluoride (APF), amine fluoride (AmF), olaflur (C27H60F2N2O3), nicotinyl alcohol HF (fluorinol, nicomethanol hydrofluoride) (C6H8FNO), fluorohydroxyapatite (Ca10(PO4)6F2), potassium fluoride (KF), and calcium fluoride (CaF2)[2]. The use of various fluoride preparations has a long history, with sodium fluoride being the first used in solutions. Subsequently, stannous fluoride was introduced, and since 1960, organic fluorides (AmF) have been clinically applied, followed by other complex fluoride compounds over the years[25]. The market analysis we did in the Republic of North Macedonia in this study identified that sodium fluoride, alone or with olaflur, was the most prevalent fluoride compound in the mouthwashes (n=42, 95.45%). Only 2 of the 44 fluoride-containing mouthwashes (4.55%) did not contain sodium fluoride. In Poland, a study by Radzki *et al.*2 found that 63.5% of mouthwashes contained fluoride compounds, including olaflur (11.8%), nicotinyl alcohol HF (2.0%), fluorohydroxyapatite (1.3%), sodium monofluorophosphate (6.5%), sodi-

um fluoride (86.9%), potassium fluoride (1.3%), stannous fluoride (1.3%), and calcium fluoride (0.7%). The fluoride ion concentrations ranged from 98 to 135 ppm (9.8%), 187 to 250 ppm (66.7%), 400 to 500 ppm (11.8%), 900 to 1136 ppm (5.2%), and 1450 ppm (0.7%), with 5.9% not declaring fluoride concentration. Sodium fluoride was the predominant fluoride compound 2, known for its high solubility and proven effectiveness[26]. In Turkey, Yazicioglu *et al.*[27] identified 28 mouthwashes containing sodium fluoride (62.22%), one with olaflur (2.22%), one with stannous fluoride (2.22%), and two with sodium monofluorophosphate (4.44%). Sodium fluoride concentrations ranged from 217 to 500 ppm in 23 of 45 different mouthwashes, with some containing significantly lower percentages. In Saudi Arabia, Aldrees *et al.*[28] evaluated the fluoride concentration in commercial mouthrinses, finding that most provided topical fluoride at levels below the manufacturers' label values but above the recommended 0.05%. There were discrepancies within and between batches, indicating variability in fluoride content. In the Russian Federation, researchers compared active and total fluoride concentrations in 10 mouthwashes. Using direct potentiometry, they found that most mouthwashes contained sodium fluoride, with other fluoride sources being Na2PO3F, AmF, and AlF3. The study highlighted the need for methods that better reflect in vivo conditions to accurately evaluate free fluoride content[17]. In the Netherlands, van Swaaij et al. found that 32 of 54 mouthwashes (59%) contained fluoride, mostly sodium fluoride (78%), sodium monofluorophosphate (9%), and a combination of amine fluoride and sodium fluoride (13%). The total soluble fluoride ranged from 229 to 500 ppm, with discrepancies between labeled and measured concentrations, indicating higher soluble fluoride than labeled[29]. In Thailand, a study on 19 children's mouthwashes found fluoride concentrations ranging from 0.00 ppm to 106 ppm. Only four brands had concentrations matching their labels, with one brand providing lower than labeled values. The authors recommended labeling fluoride concentrations and pH for better dental advice[30]. Valdivia-Tapia *et al.*[31] evaluated fluoride concentration in 20 mouthrinses from Chile and Brazil, finding that the fluoride concentrations were close to those declared by manufacturers. The results indicated consistency with regulatory standards. Most mouthwashes in the European Union are classified as cosmetic products, subject to regulation (EC) No. 1223/2009, which mandates specific conditions for fluoride oral products. The maximum concentration of fluoride in ready-to-use preparations is limited to 0.15% (as F)[32]. The European Academy of Paediatric Dentistry (EAPD) recommends daily use of 0.05% NaF (225 ppm F) for primary teeth and weekly use of 0.2% NaF (900 ppm F) for permanent teeth, under supervision, as part of preventive programs for children[33]. The NHS Public Health guidance in England recommends 0.05% fluoride mouthwash (230 ppm) for children from age 8 years onwards, and adults at a higher risk of caries[34]. Despite these recommendations, global studies still call for further research on fluoride mouthwash effectiveness in various populations[23]. Our results indicate

that 51.42% of commercially available mouthwashes in North Macedonia with labeled fluoride concentrations contain at least 230 ppm F, aligning with NHS recommendations. Additionally, 77.14% contain at least 225 ppm F, meeting EAPD guidelines. No mouthwashes had concentrations above 475 ppm F, precluding the implementation of 900 ppm F weekly application programs recommended by the EAPD.

At last, our study has several limitations. We did not perform chemical analysis of the fluoride concentrations, but instead, we used the data indicated on the packaging by the manufacturer. There is a possibility that not all mouthwashes available on the market were found, but we took measures to reduce bias, and the market research was carried out by 4 researchers. It is possible that the manufacturer did not declare the fluoride components on the packaging, which is against the national regulation, but we worked with the assumption that the data provided by the manufacturers were accurate.

Conclusion

In the Republic of North Macedonia, more than a half of available mouthwashes contained fluoride in the form of sodium fluoride or olaflur, or both. Among these, some of them did not declare the fluoride concentration despite stating the presence of sodium fluoride in their composition. Increased oversight by regulatory bodies is necessary to ensure the safety and proper labeling of these products, irrespective of whether they are classified as medicines, medical devices, or cosmetic products.

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Annex 1: List of the available mouthwashes with non-declared and declared fluoride content and the specified amount of fluoride (expressed in ppm F)

	Commercial name	Fluoride concentration (ppm F)
1	Doctor's Mint Mouth Wash	/
2	Doctor's HERBAL MOUTH WASH	/
3	Doctor's ANTITARTAR MOUTH WASH	/
4	Doctor's PROPOLIS MOUTH WASH	/
5	Doctor's SMOKERS MOUTH WASH	/
6	Alur Care Mouthwash cool mint	non-declared
7	Bilka Dent Expert Classic Parodont Protect	/
8	Alverde Pro Climate 5 in 1 Mondspulung	450 ppm F
9	Dontodent Protect & Care 10 in 1 Rundumschutz	450 ppm F
10	Dontoent Zahnfleisch Intensiv - Pflege	450 ppm F
11	Dontodent Sensitive Intensiv - Schutz	450 ppm F
12	Dontodent Neue Rezeptur Mundwasser Konzentrat	/
13	Bilka Homeopathy Grapefruit Mouthwash	/
14	Dontodent Junior Lerneffekt - spulung	/
15	Dontodent Junior mund - spulung	250 ppm F
16	Parodontax Active Gum Health	225 ppm F
17	Betadine Gargle	/
18	Stomatidin	/
19	Oralsept	/
20	Elmex Caries Protection	250 ppm F
21	Elmex Sensitive	250 ppm F
22	Colgate Plax ICE	225 ppm F
23	Lacalut Micellar Sensitive Mouthwash	non-declared

24	Lacalut Micellar tartar protection micellar water	non-declared
25	Listerine Total Care Clean Mint 6 in 1 Mild Taste	450 ppm F
26	Listerine Total Care Clean Mint 6 in 1	450 ppm F
27	Listerine Natural Enamel protect	220 ppm F
28	Listerine Naturals Sabor Suave	/
29	Listerine Advanced Defence Sensitive	220 ppm F
30	Listerine Advanced White Mouthwash Mild Taste	220 ppm F
31	Listerine Green Tea Mild Taste	220 ppm F
32	Listerine Total Care Tartar Protect	220 ppm F
33	Listerine Teeth&Gum Defence	non-declared
34	Listerine Smart Rinse	100 ppm F
35	Listerine Cool Mint	/
36	Listerine Fresh Burst	/
37	Astera Total All-in-one	225 ppm F
38	Parodont Active	450 ppm F
39	Oral B Pro-Expert	98 ppm F
40	Gengigel Oral Solution	/
41	Colgate Cool Mint	225 ppm F
42	Colgate plax white+charcoal	225 ppm F
43	Colgate max white	225 ppm F
44	Colgate plax soft mint	225 ppm F
45	Edel+White Fresh+Protect	250 ppm F
46	Lacalut Micellar Whitening Mouthwash	non-declared
47	Lacalut Multi-Effect Micellar Mouthwash	non-declared
48	Lacalut Flora	non-declared
49	Lacalut Aktiv	225 ppm F
50	Lacalut white	135 ppm F
51	Lacalut Sensitive	250 ppm F
52	Curaprox Perio Plus Balance CHX 0.05	230 ppm F
53	Curaprox Perio Plus + Protect CHX 0.12	/
54	Curaprox Perio Plus Forte CHX 0.20	/
55	Curaprox Regenerate CHX 0.09	/
56	Alkmene Tea Tree Mouthwash	475 ppm F
57	Aquafresh Fresh & Minty	250 ppm F
58	Ben & Anna Natural Mouthwash Sensitive	/

59	Eco Denta Refresh & Protect Mouthwash	non-declared
60	Natura Siberica Whitening & Enamel Protection	/
61	Natura Siberica Plaque Control & Fresh Breath	/
62	Natura Siberica Strong Teeth & Gums	/
63	Cosmos Organic People Mouthwash Coconut & Mint	/
64	Maxlab Silver Water	/
65	Aquafresh Big Teeth Mouthwash	225 ppm F
66	Intermed Unisept Mouthwash	/
67	Intermed Chlorhexil Extra 0,20% Mouthwash	/
68	Intermed Chlorhexil 0.12% Mouthwash	/
69	Intermed Kids Mouthwash	non-declared
70	ESI Aloe Fresh Collutorio	/
71	Limes Rosa Fresh Concentrate	/
72	Dr. Silver Mouthwash Total Care	/
73	Green Fresh Concentrate Mouthwash	/
74	FrezyDerm Sensitive Teeth Mouthwash	250 ppm F
75	FrezyDerm Plaque&Tartar Mouthwash	250 ppm F
76	Oral B Gum & Enamel Care Fresh Mint	450 ppm F

ORAL HEALTH

ENDODONTIC TREATMENT AS A RISK FACTOR AFFECTING THE TOOTH STRENGTH

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Key words: tooth fracture strength, tooth fracture resistance, endodontic instrumentation, risk factors of tooth fracture

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Abstract

Endodontic instrumentation is a critical step in root canal therapy that involves cleaning and shaping the canal system. While it effectively removes infected tissue and shapes the canal for obturation, it also impacts the fracture strength of the treated tooth. So, endodontically treated teeth are considered to have a lower survival rate compared to vital teeth. Objective: This study aimed to evaluate the rate of influence of the factor endodontic treated and root-filling to the fracture strength of the tooth compared to the intact tooth. Materials and methods: After applying criteria for selection, fifty extracted single-root noncarious teeth were randomly divided into 2 groups and 4 subgroups: 1a) intact teeth, 1b) decoronated teeth, 2a) instrumented with Hedstrom file and obturated, 2b) instrumented with Hedstrom file and insert fiber post. After instrumentation, irrigation and obturation, all specimens were placed into EXMAL 1 models. Then, the fracture strength was tested with the Universal testing machine. Results: The intact teeth had the highest mean value of the fracture pressure among the specimen groups, i.e. 1346.9± 320.25 (min 954, max 2030), while the endodontic instrumentation decreased the tooth strength. At the same time, they had (instrumented and obturated group of specimens) the lowest rate of pressure 867.23± 108.76 (min 647, max 1051). Fiber post subgroup had 802.13± 95.04 (min 647, max 963) force of fracture pressure in comparison to instrumented and obturated subgroup 932.33± 79.93 (min 806, max 1051), which had a higher rate of fracture resistance. Conclusion: The major risk factor that influence on the fracture resistance of the tooth is the endodontic instrumentation. Intact teeth have the highest rate of strength. Gutta-percha/Endometasone N single cone technique showed higher strength than obturated teeth and reinforced with fiberglass post.

ОРАЛНО ЗДРАВЈЕ

ЕНДОДОНТСКИОТ ТРЕТМАН КАКО РИЗИК ФАКТОР КОЈ ВЛИЈАЕ ВРЗ ЦВРСТИНАТА НА ЗАБИТЕ

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Клучни зборови: цврстина на заб, отпорност на заб на кршење, ендодонтска инструментација, ризик-фактори за фрактура на заб

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Печатарски права: ©2024. Верица Тонева-Стојменова, Лидија Поповска, Ивона Ковачевска, Марко Младеновски, Павле Апостолоски, Соња Роголева, Љупка Арсовски, Сандра Атанасова, Љупчо Ѓорѓиевски. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа торигиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Ендодонтската инструментација е важен чекор во коренската канална терапија која вклучува чистење и обликување на каналниот систем. Додека од една страна ефикасно го отстранува инфицираното ткиво и го обликува каналот за оптурација, од друга страна влијае врз фрактурната цврстина на третираниот заб. Па така, ендодонтски третираните заби се сметаат дека имаат пониска стапка на преживување во споредба со виталните заби. Цел: Оваа студија има за цел да го евалуира влијанието на факторот ендодонтско обработување и полнење на забот врз фрактурната цврстина на забот во споредба со интактните заби. Материјал и методи: По примената на селективни критериуми, 50 извадени еднокорени, некариозни заби, по пат на случаен избор беа поделени во 2 групи и 4 подгрупи: 1а) интактни заби, 1б) декоронирани заби, 2а) инструментирани со Hedstrom file и оптурирани, 2б) инструментирани со Hedstrom file и поставено фиберглас колче. По направената инструментација, иригација и оптурација, сите примероци беа поставени во EXMAL 1 модели. Потоа беше тестирана фрактурната цврстина со универзална тестирачка машина. Резултати: Интактните заби имаа најголема средна вредност на сила на притисок на кршење меѓу сите испитувани групи, т.е. 1346,9± 320,25 (min 954, max 2030), додека, пак, ендодонтската инструментација ја намали цврстината на забот. Исто така, тие имаа (инструментирана и оптурирана група на примероци) најниска просечна сила на притисок на кршење 867,23± 108,76 (min 647, max 1051). Подгрупата со фибер колче имаше 802,13± 95,04 (min 647, max 963) сила на притисок на кршење во споредба со иструментирана и оптурирана подгрупа 932,33± 79,93 (min 806, max 1051), која споредбено имаше повисока стапка на фрактурна резистенција. Заклучок: Главен ризик-фактор кој влијае врз фрактурната резистенција на забот е ендодонтската инструментација. Интактните заби имаат повисока стапка на цврстина. Gutta-percha/Endometasone N single cone техниката покажа повисока цврстина на забите отколку оптурираните и зајакнати заби со фиберглас колче.

Introduction

The strength of instrumented teeth is affected by several predisposing factors such as excessive loss of tooth structure due to endodontic instrumentation, dehydration of teeth, trepanation preparation, negative effects of irrigation and preparation for intraradicular post[1-3]. Experimental studies have shown that excessive removal of dentin during root canal preparation, preparation for the intracanal post and obturation increase susceptibility to root fracture[4,5]. Clinically, the fracture may decrease the long-term survival rate of the tooth. Although the reasons are multifactorial, the loss of tooth structure during root canal treatment plays a major role in the long-term survival of the tooth. Endodontic instrumentation is a critical step in root canal therapy that involves cleaning and shaping the canal system. While it effectively removes infected tissue and shapes the canal for obturation, it also impacts the fracture strength of the treated tooth. So, endodontically treated teeth are considered to have a lower survival rate compared to vital teeth[6]. Instrumentation removes dentin from the canal walls, which directly weakens the tooth structure. Over-preparation, especially with wide tapers or excessive coronal flaring, leads to thinner dentin walls, making the tooth more susceptible to fracture. The dentin near the cervical third (pericervical dentin) of the root is critical standing occlusal forces. Aggressive preparation in this area significantly compromises fracture strength. Preservation of a larger amount of tooth structure not only increases fracture resistance, but also maintains the structural integrity of post-endodontically-restored teeth[7-10]. This study aimed to evaluate the rate of influence of the factor endodontic treated and root-filling to the fracture strength of the tooth compared to the intact tooth.

Material and methods

Fifty extracted single-root noncarious, permanent teeth were selected. After their extraction, they were stored in a medium with 100% humidity and at room temperature. After applying selective inclusion and exclusion criteria, the teeth were examined in detail with magnification and transillumination. During preparation and testing phases of the experiment, care was taken to prevent dehydration. Teeth were randomly divided into two groups:

- I group/negative control group (G1) (n=20) – intact teeth that were neither trepanned nor instrumented;
- II group/experimental group (G2) (n=30) – endodontically treated teeth with endodontic hand instrument Hedstrom file and obturated.

Then, the first group was subdivided into: 1a) and 1b).

1a) were completely intact with no prior preparation. They were not decoronated, trepanned, or instrumented. (n=10);

1b) were only decoronated (n=10).

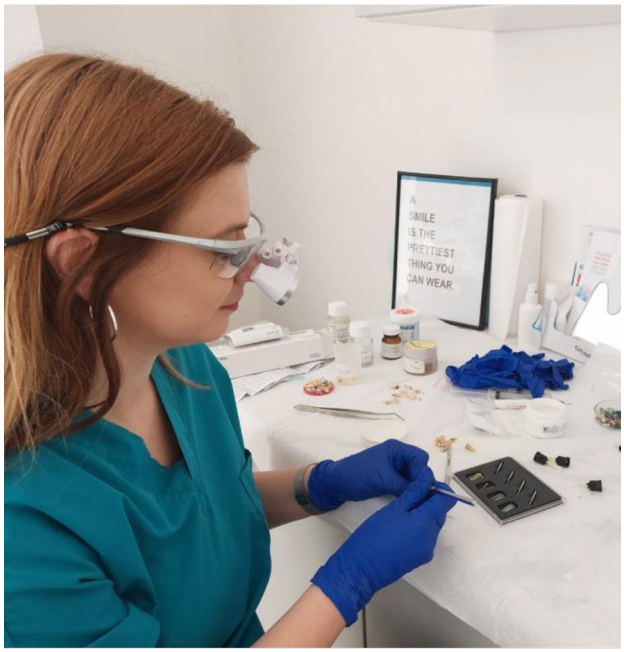
The second group was subdivided into: 2a) and 2b).

2a) endodontically treated with endodontic hand instrument Hedstrom file and obturated with gutta-percha single cone-technique and Endomethasone N (n=15);

2b) endodontically treated with endodontic hand instrument Hedstrom file and obturated with gutta-percha single cone-technique and Endomethasone N and insert fiber post 2/3 of the length of the canal. The cement used for fiber post was SpeedCEM®Plus translucent (Ivoclar, Vivadent). (n=15)

The decoronation was made for 1b, 2a, and 2b specimens. A diamond separator (Rotary Dental Instruments, NTI-Kahla GmbH, Germany) was used for decoronation. In those subgroups, after trepanation, depulping was performed with a nerve extirpator (Dentsply Maillefer, Ballaigues, Switzerland), the glide path was established and the working length was determined. The glide path was achieved with a #10 size K-file (Dentsply Maillefer, Ballaigues, Switzerland). The working length was determined by inserting a size #15 K-file (Dentsply Maillefer, Ballaigues, Switzerland) into the canal until the tip of the instrument was visible at the apical opening, after which the working length was established by retracting it back for 1 mm.

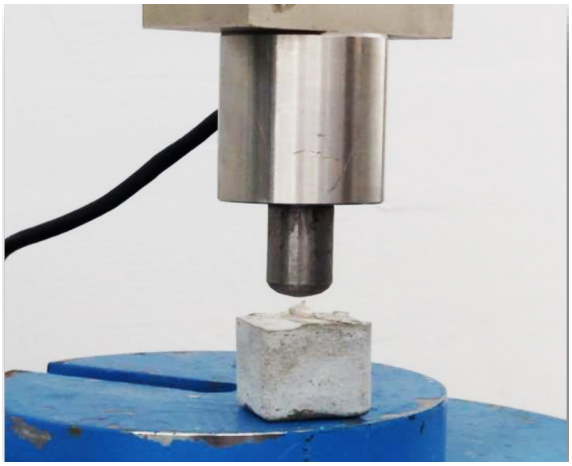
Parallel to the instrumentation with Hedstrom files, irrigation was made. Irrigation was carried out according to a classic modern protocol. Then, the samples were dried with paper points. Obturation was performed according to the principle of the single cone technique.



Picture 1. Specimen preparation

After that, the samples were placed in blocks of the EXMAL 1 (ADING AD, Skopje) material and were properly coated with 2 layers of varnish to isolate them from humidity. In order to avoid dehydration of the samples, they were kept at room temperature and 100% humidity until the time of testing.

The samples were subjected to static, compressive and vertical pressure using a universal testing machine fully automatic in Geodesign Engineering Laboratory, Skopje. Each sample was individually subjected to pressure.



Picture 2. Testing the specimen strength

After receiving the data, a statistical analysis was made with IBM SPSS 27.

Results

The distribution of examined teeth according to groups and subgroups is summarized in Table 1.

Table 1. Distribution of examined teeth according to groups and subgroups

Specimens			**N**
Groups	N1	Intact teeth	20
	N2	Instrumented teeth	30
Subgroups	N1a	Intact teeth	10
	N1b	Decoronated teeth	10
	N2a	Instrumented and obturated teeth	15
	N2b	Instrumented teeth and place fiber post	15

Table 2 shows the mean value, standard deviation, minimum and maximum force of pressure among the specimens of the groups. The intact teeth had the higher mean value of the fracture pressure among the specimen groups, i.e. 1346.9 ±320.25 (min 954, max 2030), while the endodontic instrumentation decreased the tooth strength. At the same time, they had (instrumented and obturated group of specimens) the lowest rate of pressure 867.23 ±108.76 (min 647, max 1051).

Table 2. Mean value of force of fracture pressure according to tooth samples

Specimens	**Mean value of fracture pressure**				
	n	$\overline{X}$	**σ**	**min**	**max**
N1 – intact group	20	1346.9	320.25	954	2030
N2 - instrumented group with Hedstrom file 2% and obturated	30	867.23	108.76	647	1051

n-number, $\overline{X}$ – mean value, σ - standard deviation, min – minimum, max - maximum

Regarding the subgroups, although we expected the fiber post subgroup to be on the better position than the obturated subgroup, it was not the case. Fiber post subgroup had 802.13±95.04 (min 647, max 963) force of fracture pressure in comparison to instrumented and obturated subgroup 932,33±79.93 (min 806, max 1051). As we expected, the intact subgroup of teeth had the highest value of fracture force 1624.4±186.68 (min 1323, max 2030). This is shown in Table 3 and Figure 1.

Table 3. Distribution of examined teeth according to groups and subgroups

Subgroups	Mean value of force of fracture pressure				
	N	$\overline{X}$	σ	min	max
Intact teeth **(1a)**	10	1624.4	186.68	1323	2030
Decoronated teeth **(1b)**	10	1069.4	102.66	954	1323
Instrumented with Hedstrom and obturated **(2a)**	15	932.33	79.93	806	1051
Instrumented with Hedstrom and place fiber post **(2b)**	15	802.13	95.04	647	963

n-number, $\overline{X}$ – mean value, σ - standard deviation, min – minimum, max – maximum

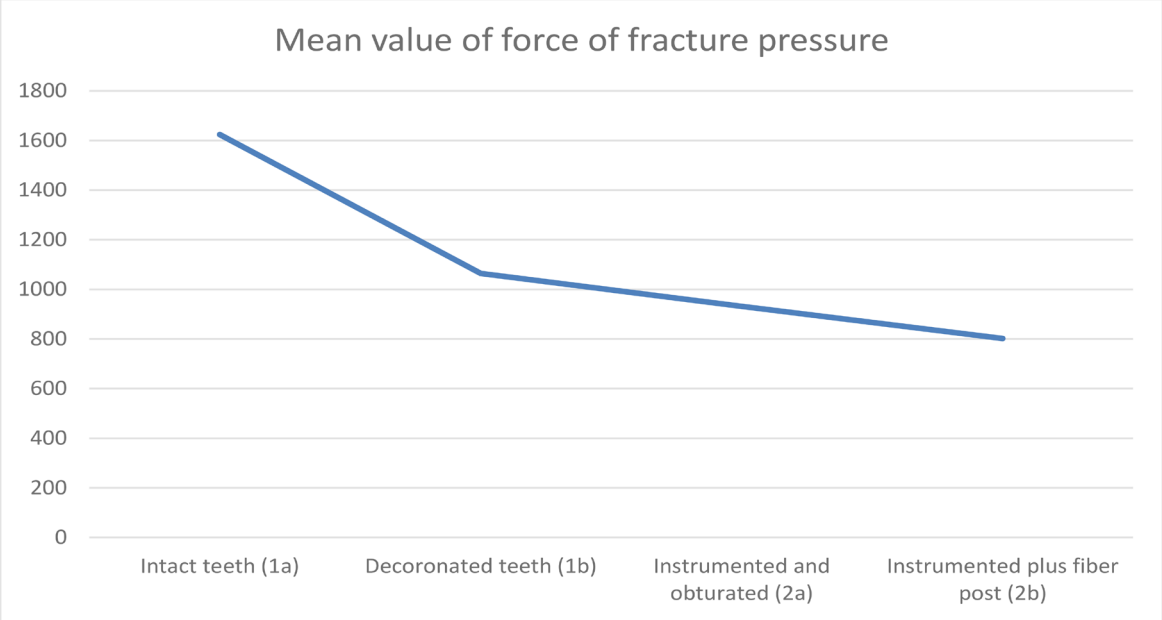


Figure 1. Mean value of force of fracture pressure according to subgroups

Discussion

The fracture strength of a tooth is a critical factor in its longevity, especially after endodontic treatment[11]. Endodontic preparation, which involves access cavity creation and canal instrumentation, directly influences the structural integrity of the tooth. Fracture strength refers to the tooth's ability to resist breaking under masticatory or occlusal forces[12]. After endodontic treatment, teeth are inherently weaker. This is because of loss of natural dentin and enamel during cavity access and shaping altered structural properties of dentin due to dehydration and exposure to irrigants and the absence of pulp, which provides internal support and hydration to dentin[13]. If not managed well, these changes can lead to catastrophic failures, such as vertical root fractures[14]. Endodontic procedures produce substantial effects on the relative stiffness of the tooth, so endodontic procedures appear to be the major contributor to clinical fractures. Although long-term functional survival rates can be high for initial endodontically-treated permanent teeth, they are generally more susceptible to fracture intact teeth[14,15]. As we saw from the results obtained in our study, the roots were significantly weakened by the instrument preparation. Similar conclusions were made by Zandbiglari *et al.*,[16]. Another study found that although there was no statistically significant difference in the average value of the pressure, there was higher fracture pressure in the control group than in the instrumented group[17].

On the other hand, the type of obturation interference to the fracture strength of the tooth[18]. According to Amal *et el.*, the total fill group showed slightly better fracture resistance (734.62 N) than AH Plus group (728.29 N), but with no statistically significant difference between them. This would suggest that the total effect of endodontic obturation is not great and in fact it makes no big difference in the choice of canal obturation.

According to placement of the fiber post, contrary to our view is the view of Bitter et al. They think that root-filled teeth without post placement show lower fracture resistance compared to the others[19]. The same opinion share Jurema *et al.*[20] They, as well as many other authors, think that use of glass fiber posts increases the fracture resistance of endodontically treated and restored teeth[21,22]. However, there is a need for reinforcing the tooth soon after root canal therapy to prevent fractures and reduce the incidence of fracture occurrence. No matter the type of treatment, conventional obturation or fiber post insertion, one is certain, tooth stiffness is reduced as a result of endodontic procedure.

Conclusion

As a result of this investigation, the following conclusions can be drawn: Canal instrumentation can significantly impact the fracture strength of a tooth by removing dentin, inducing increase in the fracture rate, and altering its mechanical properties. Adopting minimally invasive techniques and timely obturation helps preserve tooth integrity and reduce the risk of fractures. The major risk factor that influences on

the fracture resistance of the tooth is the endodontic instrumentation. Intact teeth have the highest rate of strength and more restorable fractures than all the other ones. Guttapercha/Endometasone N single cone technique showed higher strength than obturated teeth and reinforced with fiberglass post.

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REVIEW

BUILDING RESILIENCE TO COPE WITH HEAT WAVES AND EXTREME WEATHER EVENTS IN THE REPUBLIC OF NORTH MACEDONIA

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Key words: climate change, heat waves, extreme weather events

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Abstract

High ambient temperatures have a significant impact on society and population health, including a rise in morbidity and mortality. Episodes of heat lasting for several days are often referred to as heat waves and can be associated with tens of thousands of premature deaths. In the Republic of North Macedonia, the most striking weather anomaly was in 2007, when the national government declared a nationwide heat-wave emergency. The content of this inspirational example outlines a wide range of coordinated actions at community and system levels to adapt, anticipate and manage the many problems caused by heat waves. The example shows the need of intersectional action to build adaptive, absorptive, anticipatory and transformative resilience capacity in both communities and institutions in order to effectively fight against the harmful health effects of heat waves. There were several heat waves in the country during 2007-2023 and public health activities to prevent and minimize adverse health effects.

ПРЕГЛЕД НА ЛИТЕРАТУРА

ГРАДЕЊЕ НА ОТПОРНОСТ ЗА СПРАВУВАЊЕ СО ТОПЛОТНИ БРАНОВИ И ЕКСТРЕМНИ ВРЕМЕНСКИ НАСТАНИ ВО РЕПУБЛИКА СЕВЕРНА МАКЕДОНИЈА

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Цитирање: Кочубовски М. Градење на отпорност за справување со топлотни бранови и екстремни временски настани во Република Северна Македонија. Арх Ј Здравје 2024;16 (2) 57-65.

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Клучни зборови: климатски промени, топлотни бранови, екстремни временски настани

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Печатарски права: ©2024. Михаил Кочубовски. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа торигиналниот(ите) автор(и) и изворот.

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Извадок

Високите амбиентални температури имаат значително влијание врз здравјето на населението и општеството, вклучително и пораст на морбидитетот и морталитетот. Епизодите на топлина кои траат неколку дена често се нарекуваат топлотни бранови и може да се поврзат со десетици илјади предвремени смртни случаи. Во Република Северна Македонија, највпечатлива временска аномалија имаше во 2007 година, кога националната влада прогласи вонредна состојба заради топлотен бран низ целата земја. Содржината на овој инспиративен пример прикажува широк опсег на координирани дејства на нивоа на заедницата и системот за да се приспособат, предвидат и управуваат со многуте проблеми предизвикани од топлотните бранови. Овој пример ја покажува потребата од интерсекторски активности за да се изгради капацитет за отпорност и во заедниците и во институциите со цел ефикасно да се спротивстави на штетните здравствени ефекти од топлотните бранови. Имаше неколку топлотни бранови во земјата од 2007 до 2023 година и јавноздравствени активности за спречување и минимизирање на негативните здравствени ефекти.

Introduction

During the summer of 2007, daily temperatures reached 43°C and caused more than 1000 excess deaths at national level (compared to the averages of 1994–2008). In Skopje, the capital city with around 600 000 inhabitants, temperatures in July 2007 were 3.4°C above the monthly average, and deaths were 16.5% higher than the average between 1994 and 2008. The direct health effects of heat waves could become a significant problem, especially with more than 60% of the population living in cities while urbanization is increasing.

The heat cut-off point for the maximum temperature for Skopje was 30.8°C. Under heat-wave conditions, an increase of 1°C above the heat cut-off point for Skopje increased the total mortality by 4.8%. The increased mortality during heat waves is higher among older people with chronic diseases, and cardiovascular and respiratory diseases[1]. Compared to the baseline period (1986–2005), heat-related mortality in Skopje is projected to more than double in 2026–2045, and more than quadruple in 2081–2100[2].

It has been estimated that the expected impact in the country will be much larger than if temperatures remain at the observed historical levels. During the period 2071–2099, an overall excess of 305 and 871 attributable deaths per year is expected under the Representative Concentration Pathway (RCP) 4.5 and RCP 8.5 scenarios, respectively, in addition to 14 attributable deaths estimated under the historical scenario[3]. Under anticipated future warming conditions, the length, frequency and intensity of heat waves are expected to increase. Taking into consideration that the national population is aging, an increase in heat-attributable deaths is a serious risk. In order to avoid such negative scenarios, effective adaptation measures must be taken. Policies and plans for heat mitigation and adaptation are urgently needed in European countries in order to prevent the expected increase of heat-related deaths in the coming decades[4].

Action

A National heat–health action plan was developed within the country's Strategy to adapt the health sector to prevent health consequences associated with extreme heat due to climate change[5,6]. Its goal is to reduce morbidity connected with heat waves by issuing heat and health warnings, encouraging planning in the relevant sectors, prioritizing health in all policies, raising public and health sector workers' awareness and mobilizing resources for managing heat effects.

A national framework was established to build adaptive capacity for climate change resilience in the public health community to better address the effects of climate change and to oversee activities. A national, multisectoral steering committee and a technical working group were established, and they defined the scope of the national adaptation plan, methods, peer review process and process for defining priorities using a WHO comprehensive framework for developing national climate change health adaptation strategies[7]. The WHO framework incorporates an assessment of climate change im-

pacts, a vulnerability assessment, the modelling of projected health impacts, an evidence-based evaluation of intervention options, a strategy for implementing interventions and systematic evaluation of all activities in an iterative manner.

A team from the Institute of Public Health, supervised by the national steering committee, conducted a scoping exercise to identify readily available information and data on the heat-associated health exposures and risks to population health, and vulnerability and impact assessments. A variety of qualitative and quantitative methodologies were used in the assessment: literature reviews, interviews, focus groups, time series and regression analysis, damage and adaptation cost estimation, and scenario-based assessment.

Other areas addressed by the national health adaptation strategy include: adapting the health care infrastructure (hospitals, nursing homes) to be more resilient to the effects of heat, fires and floods; developing local "Safety Hospital" plans to cope with disasters; and increasing awareness of how people can adapt to changes in climate. Developing the strategy underscored the need of greater emphasis on climate change and its impacts; the need governments to focus on this problem; and measures individuals can take to mitigate the effects of climate change on their health.

In order to increase the resilience of the health sector to cope with health impacts of climate change and to strengthen national capacity for assessing these impacts, the following activities took place:

- the training of more than 300 health and environmental professionals, journalists and other profiles on health effects of climate change, with an emphasis on heat waves;
- an assessment of health effects of climate change in the country;
- a study that examined the impact of heat waves on morbidity in summer months in the country in the period 1994–2009;
- a study on the correlation between the occurrence of Salmonella infection and average weekly temperature distribution in the period 1996–2009;
- a study on the presence of the vector *Aedes albopictus* in the country, published in 2011;
- a study on the impact of climate change on pollen micro flora related to the respiratory allergies among the adult population in Skopje, published in 2011; and
- a publication on health effects of climate change in the Republic of Macedonia, available in English and local languages.

Climate change mitigation efforts by the health sector include implementation of activities on energy efficiency and promotion of the use of renewable energy sources in hospitals and health institutions. Such measures were initiated by the Ministry of Health with the WHO support in 2009 in two pilot municipal hospitals in Gostivar and Shtip. Furthermore, the Government adopted measures for refurbishment of all hospital facilities at secondary and tertiary levels in the country, including energy efficiency measures. These measures help to reduce greenhouse gas emissions at mu-

nicipal level and raise awareness of health managers and staff on the effects of climate change. Hospital staff training regarding energy saving and environmental protection strategies is to be done.

One of the main proposed solutions was the implementation of a structured system for timely heat-wave announcements (alert system), particularly during the period from 1 May to 30 September (5). This includes: the set-up of a responsible body, a 24–48 hour early heat warning, specific thresholds for action, and priorities for vulnerable populations, workers' health and communication. The alert system is part of the broader approach designed by the national heat–health action plan. Further elements are:

- coordination body for plan implementation;
- communication plan to inform the public and the health and social sectors about protection during heat waves, along with recommendations given by the Ministry of Health addressed to health workers, general population and at-risk groups;
- recommendations and (medium-term and short-term) strategies for reducing exposure to heat inside health and social institutions, and special protection plans for vulnerable population groups; and
- long-term planning for preparedness of the health and social care systems, including: planning and training of personnel, appropriate health protection, creating green areas, improving the energy efficiency of hospitals and reducing the emission of greenhouse gases.

Regarding implementation, monitoring and evaluation of the plan, certain activities have taken place. Firstly, a heat–health watch system operates during the summer months, with advice from the National Institute of Public Health and the Ministry of Health, with four levels of response and appropriate advice. The heat–health action plan provides a summary of key measures to be undertaken by the responsible sectors and institutions. These measures aim to decrease morbidity connected with heat waves by issuing heat and health warnings from the Hydrometeorological Institute to encourage planning in the relevant sectors and to raise public and health worker awareness, as well as to mobilize the resources for managing the heat effects. The action plan consists of a set of previously agreed upon activities and preparations to be carried out by the health sector and institutions, in order to raise awareness and reduce heat risks. Furthermore, the plan gives guidance for the responsibilities of the institutions and individuals in terms of taking measures after a heat-wave announcement.

Secondly, information leaflets for protection against heat waves, aimed at the general population, managers in health and social institutions, general practitioners and workers were prepared and printed. The Red Cross, regional public health institutes and their local branches, municipalities and the Labour Inspectorate distributed the information.

Thirdly, an application for Android mobile phones providing heat and

health warnings and related recommendations was also developed. The Government endorsed the heat–health action plan in February 2012, and it is now fully in effect, following the successful piloting of specific heat-protection actions in the summers of 2010 and 2011 7. Representatives of the Macedonian Red Cross distribute information during the heatwave in Skopje.

Impact

While there have been specific project benefits, such as increasing the awareness among health professionals with regard to health impacts of climate change, and the development of the heat–health action plan and the cold health action plan, the broader benefit has been in the increased engagement of key stakeholders and policy-makers with this agenda[8]. Before the process was initiated, climate change and health topics were largely marginalized, with activities happening in silos. Creating such cooperative and supportive environments is crucial for strengthening resilience as recommended by Health 2020 and its priority area four[9].

In the current implementation period, this collaborative approach has proven to work well.

The heat–health action plan was evaluated in 2015, and 100% of survey participants from all implementing institutions (N=38) agreed that proposed activities and approaches were appropriate. At the time of the evaluation, more than half of the proposed activities were implemented (52%); lack of staff and funding, as well as staff indifference, accounted for the other half. Of the respondents, 83% called for more field visits, targeted and tailored action for groups and capacity building at local level: general practitioners, social care workers, employers, inspectors etc. Most respondents (96%) would like the heat–health action plan to continue but with more funding from the central budget. Many of the successes in the country's climate

change health assessment have already begun to have an impact. Nevertheless, building adaptive and anticipatory resilience capacity remains an ongoing concern. Throughout the process, a number of tools were utilized which allowed practitioners to organize information on the hazards and at-risk populations in order to prioritize responses. These successes provide an ongoing foundation for future collaboration and activity. In 2020, under the EU Project SCORCH, another evaluation of the heat–health action plan was made, and it was concluded that organizational structure, warning system, communication plan, measures for emergency management and acre for vulnerable groups were very well developed and implemented.

The study in Skopje calculated the projected average annual mortality attributable to heat in the absence of adaptation or acclimatization during specific time windows, and evaluated the contribution of each source of uncertainty on the final impact[2]. Improvements in infrastructures and health care services together with heat-adaptation measures have beneficial effects on reducing the impact of heat on mortality. It can be accomplished by reducing heatwave-related morbidity and mortal-

ity through heat–health warnings, especially for the most vulnerable groups: older people, infants and children up to five years old, the chronically ill, people who are overweight, people who work outdoors, and those whose social factors (nationality, profession, educational level etc.) make them particularly vulnerable.

In order to strengthen preparedness for crisis situations and climate change-related emergencies, a simulation exercise took place on 22 May 2013, in the Strumica Region in the country. The key stakeholders were the Ministry of Health, Strumica General Hospital (an important regional hospital centre), emergency medical services, the Crisis Management Centre, the Red Cross, fire rescue units, the Ministry of the Interior, the Ministry of Defence and WHO. Prior to the simulation exercise, preparatory meetings were held to establish the parameters of the exercise such as the number of expected casualties, trigger indicators for activating the emergency response plan, triage and patient traffic flow, as well as the responsibilities of hospital and emergency medical staff. The simulation allowed the authorities to test general preparedness and also the implementation of the national heat–health action plan [10].

Moreover, a partial reduction in health impacts is an expected benefit as a result of adaptation measures implemented (in this case a heat–health action plan). Investment costs such as infrastructure, equipment and training are important for effective health preparedness and response. In the country, the main one-off investment is made by the Ministry of Health, and social infrastructure and lesser investments are made by local governments. These costs include energy efficiency measures, air-conditioning and water fountains in hospitals and nursing homes, and communication and awareness-raising for medical staff and the general public. The total cost of health damage attributed to climate change and heat for the selected outcomes in the country was estimated at 170 million local currency units (LCU) per year. A cost–benefit analysis compared the damage costs of the increase in disease cases and of deaths not averted with the costs of adaptation and its expected reduction of negative health effects. The adaptation cost is estimated to be 12 million LCU. When compared with the total damage costs (170 million LCU per year), the adaptation costs appear to be relatively small[11].

Due to climate change, an extreme weather event as a freakishly violent rainstorm that Macedonia's top weather official called a "water bomb" ravaged Skopje, Republic of North Macedonia on 6th of August 2016, collapsing streets, inundating vehicles and drowning trapped motorists and homeowners, most of them caught by surprise.

Torrential rainfall caused flash flood 33/l/m^2 in the first 30 minutes, and /93 l/m^2 in the following 2 hours. Flood has caused 22 deaths in Skopje's region. The Ministry of Health, the Institute of Public Health and all other health institutions (primary, secondary and tertiary health care) from the first moment were providing proper health care to endangered people in the flooded areas. They were also providing environmental

health surveys and epidemiological surveillance on the terrain, delivering recommendations and conducting monitoring of drinking water quality, disinfection, desinsection and deratization of properties and goods, as well as on the contaminated areas. Epidemiological situation was stable. According to the proposal by the Governance Committee for coordination and management of crisis, emergency state was declared by the Government with duration of 15 days (07-22.08.2016). First responders on the ground were units for first response (Ministry of Interior, fire brigade and emergency medical services-EMS), and due to the meteorological situation, human loses and damaged areas, the President of the Republic of Macedonia activated the armed forces to take response actions. Protection and Rescue Directorate activated the reserve forces. The Ministry of Health, Red Cross of the Republic of Macedonia and all relevant governmental institutions and self-governmental institutions with their public enterprises started with their filed activities for preparation and distribution of food and safe drinking water (bottled and water tanks), clothes, hygienic means, etc.

Surface Urban Heat Island (SUHI) is a documented urbanization-driven phenomenon, causing higher temperatures in cities than in surrounding rural areas. Global warming, rapid urbanization, and UHI amplify thermal stress and endanger public health. A cross-sectional study was conducted, in Skopje, Republic of North Macedonia from 22.07 to 28.07. 2022. Monitoring temperatures thrice daily, we compared locations with and without tree coverage. Utilizing Landsat-8 data on July 22, 2022, we extracted SUHI patterns. Four of nine locations studied displayed (UHI) effects. The largest temperature difference, 7.9°C, occurred between a treeless one-way street and City Park. On average, temperature differences between the hottest and coolest spots were 6.8°C. All tree-covered areas showed lower ambient temperatures. Green spaces, like parks and tree-lined gardens, play a crucial role in mitigating thermal stress and counteracting UHI's adverse impact on public health. This study emphasized the importance of urban planning and incorporating green infrastructure to combat UHI's detrimental effects amidst climate change and urbanization challenges. Policies promoting and preserving green spaces are essential for creating climate-resilient and sustainable cities prioritizing inhabitants' well-being [12].

Lessons learnt

In order to ensure effective implementation of planned actions and impact, organizational arrangements are crucial. The Ministry of Health has overall responsibility for implementing the heat–health action plan. The Climate Change and Health Commission was established within the Ministry of Health in June 2009. The Commission has participated in the preparation of the national heat–health action plan, in the execution, surveillance and evaluation of the plan. The Commission is responsible for coordinating the involvement of institutions during the implementation of the plan's activities, as well as for promoting multisectoral cooperation. One rec-

ommendation is that, when necessary, people from other relevant institutions should be included in the Commission. The following institutions and organization are included: the Institute of Public Health and Public Health Centres, the Institute of Occupational Medicine (WHO Collaborating Centre for Occupational Health), the Crisis Management Centre, the Hydrometeorological Institute, the Directorate for Protection and Rescue, departments that improve the living environment within municipalities (in the first phase, active participation of the city of Skopje), the Ministry of Transport and Communications, the Ministry of Labour and Social Policy, the Ministry of Education and Science, the Macedonian Red Cross, the media and the non-governmental sector. Community awareness and engagement are very important. Intensifying the dissemination of information through workshops, roundtables, preparation of brochures, leaflets, campaigns, the use of electronic and print media, social networks, etc., should serve in increasing the community awareness of the problem of heat waves, other extreme weather events and climate change.

Using preventive interventions and policies to reduce the health risks and the potential effects of climate change and extreme weather events on population health requires further capacity building in the health sector. This is especially relevant in the field of environmental health.

Capacity should be strengthened in order to better provide, recognize, assess and control the changes in the environment and the related hazards. Furthermore, increased focus on modelling and adaptive management and effective use of local community resources and assets is needed to strengthen the resilience of the community as part of building an integrated, efficient and effective public health approach.

Professors at the Faculty of Medicine, Ss. Cyril and Methodius University in Skopje employed at Institute of Public Health of the Republic of North Macedonia have developed a Chapter on Climate and Health in the Curricula of the Faculty of Medicine in Skopje for medical students and published a handbook entitled "Hygiene and Environmental health" in 2008[13].

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REVIEW

ROBOTIC SOLUTIONS FOR POST-STROKE RECOVERY – LITERATURE REVIEW

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Abstract

Stroke stands as a widespread and severe health concern worldwide, often resulting in profound motor and cognitive impairments. Its impact is particularly pronounced in the Republic of North Macedonia, posing significant social and economic challenges. Beyond acute-phase treatments like medication and surgery, rehabilitation emerges as a pivotal component of stroke management. Robotic technology offers distinct advantages over conventional physical, occupational, and speech therapies, increasingly becoming a preferred option in post-stroke recovery. By integrating rehabilitation robots, not only does the burden on healthcare professionals decrease, but also the outlook for stroke patients improves. In this review, we provide a concise examination of the role played by therapeutic robots in the rehabilitation of individuals post-stroke. Our focus will encompass outlining the fundamental distinctions among various robotic rehabilitation devices and assessing the merits and drawbacks of employing robotic rehabilitation specifically for lower extremity rehabilitation.

ПРЕГЛЕД НА ЛИТЕРАТУРА

РОБОТСКИ РЕШЕНИЈА ЗА РЕХАБИЛИТАЦИЈА ПО МОЗОЧЕН УДАР – ПРЕГЛЕД НА ЛИТЕРАТУРАТА

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Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Мозочниот удар претставува широко распространет и сериозен здравствен проблем ширум светот, често резултирајќи со значајни моторни и когнитивни оштетувања. Неговиот импакт е особено изразен во Република Северна Македонија, предизвикувајќи значајни социјални и економски последици. Покрај третманот во акутната фаза, кој опфаќа примена на лекови и хируршки интервенции, рехабилитацијата се издвојува како клучна компонента во менаџментот на мозочниот удар. Роботската технологија нуди посебни предности во споредба со конвенционалната физикална терапија, работна терапија и логопедски третмани, и сè повеќе станува приоритетна опција за закрепнување на пациентите по прележан мозочен удар. Со интеграција на уреди за роботска рехабилитација, не само што се намалува оптоварувањето врз здравствените работници, туку и се подобрува прогнозата за пациентите со мозочен удар. Во овој труд, даваме краток преглед за улогата на роботската рехабилитацијата кај пациентите по прележан мозочен удар. Нашиот фокус ќе биде насочен кон преглед на основните разлики помеѓу различните уреди за роботска рехабилитација и проценување на предностите и недостатоците од употребата на роботска рехабилитација, особено за рехабилитација на долните екстремитети.

Introduction

Stroke is a clinically defined syndrome of acute, focal neurological deficit attributed to vascular injury (infarction, haemorrhage) of the central nervous system. Stroke is a huge and increasing global health challenge. Worldwide, stroke is the leading cause of acquired physical disability in adults, and the second leading cause of mortality in middle- to high-income countries.

People with stroke are in need of access to efficient rehabilitation therapy. The goal of the rehabilitation in these patients is to restore the motor functional mobility, cognitive functions, to improve balance, walking ability and to return to daily activities.

Motor recovery after stroke is a complex, dynamic and multifactorial process. It includes genetic, pathophysiological, sociodemographic and therapeutic factors that determine the course of the recovery.

Parallel to the development of a large number of manual-assisted techniques, now we are in a modern technological era when technology has been largely developed and has found its place in the rehabilitation of post-stroke patients. Thus, today in the rehabilitation of patients with stroke robotics and virtual reality can be applied. The use of technology in rehabilitation of patients has been very efficient in improving the functional mobility of post-stroke patients by decreasing the costs for workforce, increasing the patients' motivation and functional monitoring of the progression of the rehabilitation process.[1] The integration of robotic rehabilitation in the conventional neurological rehabilitation has proven some level of efficacy in rehabilitation of post-stroke patients.[2]

After stroke, the most common problems that patients encounter are walking difficulty and poor balance. Hence, we have made a literature search on the use of modern technology in rehabilitation of walking ability and balance.

The aim of this review is to analyze the principal differences in the robotic devices for rehabilitation and to present the advantages and drawbacks of robotic lower limb rehabilitation.

Technological advancement of robotic rehabilitation devices

Robotic devices are technological revolution in the rehabilitation medicine. As representatives of the technology they assist, improve and accelerate the recovery, enhance the quality of life and independence of the patient.[3] Robotic-assisted gait training (RAGT) has been in use since 1980 for assisted gait in patients with walking difficulty caused by neurological disorders.[4] This treatment is based on the principle of body-weight supported treadmill (BWSTT) and by successive repetition of different gait phases, the functional motor learning is achieved.[5] Repeating the same movement enables the nervous system to create a better communication between the central and peripheral nervous system.[6] After stroke, the brain can be influenced by intensive sensorimotor training through neuroplasticity that has impact across the subacute and chronic phases of the post-stroke recov-

ery. Rehabilitation of patients after stroke based on the BWSTT principle includes one or two physical therapists that facilitate the desired movement while the patient is on a treadmill, where the robot provides partial or full body weight support to the patient's lower limbs.[7] BWSTT, in comparison with the conventional mode of rehabilitation, has proven to be better since patients increase walking distance as well as the number of steps performed, resulting in more repetitions of the gait cycle.[8]

Rehabilitation robots are programmed, multifunctional electromechanical devices, divided into robotic exoskeleton and endoskeleton.[9] Exoskeleton robotic device is attached parallel to the patient's lower limbs and allows movements of all joints of the lower limbs. Robotic endoskeletons are attached to the distal segment of the limbs and they help in movements of only those segments; they are the so-called end-effectors.[10,11] The end-effector is a series robot mechanism, which has larger movement space and provides more freedom of the patient's movements.[12] Unlike the end-effectors types, robotic exoskeletons are installed outside the patient's body. The joints of the robot have a direct correspondence with those of the human body, that is, with the limbs. This portability of the exoskeleton makes it a good choice for rehabilitation of patients who have sustained a stroke. Although there are problems in adjustment with the anatomical axis of the human body, robotic exoskeletons are widely used in robotic rehabilitation and have reached a significant development in recent years. Exoskeletons are increasingly becoming a major option in clinical treatment compared to end-effectors.

Rehabilitation robots can also be classified to upper and lower limb robotic rehabilitation devices depending on the affected area.[13]

Virtual reality is a rehabilitation platform that enables creation of a virtual world for the patient during the process of robotic rehabilitation treatment. In the virtual world, the patient performs tasks that are a constituent part of the rehabilitation process. Virtual reality can be an individual choice of rehabilitation or additional assistance during robotic rehabilitation. Therefore, the third division of robotic devices is made according to the level of interaction between the patient and virtual environment. Consequently, they are divided into traditional and robots using virtual reality.[14]

Review of robotic rehabilitation devices for lower limbs

In recent years, various types of robotic devices have been developed for the rehabilitation of patients with impaired motor function, including those with paralyzed limbs or individuals who have had a stroke.

The existing robots designed for physical therapy are most commonly included in the neuromotor training of patients suffering from neurological diseases.[15] Verticalization of a patient and maximum independence are priorities of the rehabilitation process. The major problem in the lower limb rehabilitation is that patients are not able to maintain balance and to walk independently.[16] Robotic systems provide stability to patients.[17] In addition, these systems

participate actively in the patient's lower limb motion by an integrated software system that is coordinated with sensors, thus imitating the work of the therapist. These robotic systems are usually exoskeleton type devices.

In 2001, the Swiss Federal Institute of Technology developed the exoskeleton rehabilitation robot Lokomat. It was produced by Hocoma, and is an advanced type of a robot developed to recover the function of the lower limbs in adults and children with partial or total loss of the lower limb function. The device consists of an integrated running treadmill with dynamic (body-weight) support system, a computerized gait orthosis, and a hardware control system.[18] In an entertaining and interactive way, by using video games, Lokomat stimulates the patient to make certain motions several times that leads to faster patient's recovery. Locomat moves the patient's legs in a repeated cyclical gait motion in the sagittal plane.[19] Additional motivation for the patient is the biofeedback, that is, the precise measure through sensors located on the knees and hips. Thus, a clear insight into the patient's functionality and course of the recovery can be obtained.

LokoHelp is a gait-training robot that was produced and developed by a German company. It consists of three components: a device to which the feet or limbs are tied, a running treadmill, and a body-weight support system. This robot can provide basic gait rehabilitation. It has a modular design that is easily assembled, dismantled and adjusted for allowing vertical up and down motion of the patients. Clinical and experimental studies about LokoHelp have shown that the influence of rehabilitation of this robotic system is almost identical to the conventional method of gait rehabilitation training, but it significantly reduces the human resources and provides physical relief to the therapists.[20]

Andago robot provides stability and a sense of safety while enabling safe walking, ensuring quality body posture that results in the elimination of patients' fear of free walking.[21] Andago is the safest robotic device.[22] It affords control of the functional rehabilitation that allows patients to walk without fear of falling. This gait-training device automatically presents the graphic functional recovery that can be stored in the patient's digital memory card.[23]

C-Mill and virtual reality (VR) is a robotic device that combines virtual technology with a running treadmill developed for training and assessment of the patient's gait and balance for safe daily walking. There are three types: C-Mill, C-Mill VR and C-Mill VR +. Although C-Mill VR and C-Mill VR + types use elements of virtual technology for stimulating patients, their final goal is different. Robotic C-Mill VR device is used in training of automated movements whereas C-Mill VR + is a thorough/ detailed solution for rehabilitation with body-weight support on gait and balance.[24]

ALEX (Active Leg Exoskeleton)robotic system consists of a treadmill, exoskeleton orthoses for lower limbs and a control system. It has four degrees of freedom assisting free movements, two degrees of freedom assisting the hip movements, one degree of freedom for the knee and

one for the ankle. It uses a balancing mechanism for human body's gravity, and hence, it can help patients achieve balance.[25] However, it has a major drawback – it puts a great deal of physical labor to both therapists and patients, and one or two therapists are needed to assist the patient by manually guiding limb movements and providing trunk stability. Manual help during the training process varies from one therapist to another and thus it is difficult to be consistent in each training session.[26]

Walkbot G is a robotic rehabilitation system for gait training assisted by double robotic orthoses compatible for adults and children. It uses a mode for dynamic body-weight support in real time with distant remote control.

Ekso GT is a robotic exoskeleton constructed by Ekso Bionics and approved to be used for hemiplegic patients after stroke. Ekso is a wearable robot powered by batteries, made of 30 carbon fibers that uses a hydraulic system for charging. This exoskeleton is bilaterally attached to the lower limbs and has electrically movable joints for the hips and the knees, and passive ankle articulation.[27] Built-in sensors are placed around the patient's body and respond to the patient's muscle performances. Ekso robot works in several modes depending on the necessary degree of assistance required by the patient, and it also assists in training motions such as standing up from a chair, walking and sitting down, and vice versa.[28]

Advantages and drawbacks in the application of robotic rehabilitation

Robotic rehabilitation as a new technology has its own advantages, but also its limitations. Advantages include patients' greater motivation, program dynamics and shorter duration of the entire rehabilitation process, greater objectivity and possibility to modify a larger number of parameters. The advantage of robotic rehabilitation is the option to quantify and monitor the patient's motor improvement. It provides precision in the therapeutic engagement and precise measurement of the achieved results. It improves the coordination and helps in reaching the desired scheme of motions.[29] During robotic-aided training, the patient's body weight is supported by a belt system thus eliminating the need of therapeutic assistance. Robotic exoskeletons have proven to be an attractive tool not only in the gait rehabilitation, but also improving the level of patients' physical activity after motor deficits.[30] Robotic hardware enables control of the treadmill, control of the belt and harness system so that different techniques can be applied adjusted to the need of the patient. The software enables programming of the devices for movement control. It regulates the precision and intensity of the movements as well as the mode of interaction of the patient by monitor's virtual reality. Software applications allow collecting, interpretation and sending information regarding the progress of the patient in a real time.[28] This allows doctors and therapists to (continually) monitor and analyze the patient's performance and to individualize

the training session. Many of the rehabilitation robotic devices include software (video) games that make the rehabilitation sessions more interesting and fun for the patient. Patients are additionally motivated and the outcome rehabilitation results are improved.

Along with advantages, there are disadvantages when using rehabilitation robots. Newer technologies have not yet been thoroughly investigated in clinical trials; then, the price of the devices is very high; they occupy more space; require a specific education of physical therapists. End-effectors robots have been associated with more technical drawbacks.[31,32]

Over the last ten years, there has been a dramatic advancement in the field of robotic rehabilitation, and when reviewing the literature, every year there is more research on this topic.

Rehabilitation robotics in lower limb function

In recent years, there has been significant development in lower-limb rehabilitation robotics, which have become indispensable in assisting stroke patients by improving motor function in paralyzed limbs. These robotic systems enable structured and efficient training to enhance motor skills in affected limbs.[33]

Most randomized controlled trials have utilized exoskeleton robots, either alone or with combined endeffector devices (end – effector).[34,35] Additionally, there have been studies involving gait robots based on the end-effector principle, where a vest supports the patient's weight, and their feet are fastened to the system using two platforms to simulate gait movements.[36,37] Most robots developed to enhance patients' walking or stair-climbing capabilities in the lower limbs typically provide three degrees of freedom. This allows independent rotation at the hip joint, knee joint, and ankle joint within the sagittal plane. Some robotic systems integrate harnesses to aid patients in supporting a portion of their body weight while walking with the device. In the study by van Dellen F et al. the participants had stroke stages ranging from acute to sub-acute and chronic phases. The experimental group used a robot, either alone or in combination with traditional rehabilitation techniques, while the subjects in the control group applied only traditional rehabilitation methods. The result of the study showed that robot-assisted gait training with body weight support effectively improved the walking ability of stroke patients.The result of the study indicates that robot-assisted gait training with body weight support effectively improved the gait of stroke patients.[39]

Lower-limb rehabilitation robots do not appear to beeffective in improving the spasticity status of the lowerlimbs. The Modified Ashworth Scale (MAS) is commonly usedto assess lower-limb spasticity in stroke patients. Li et al. discovered that patients who underwent robot-assisted gait training with exoskeletons for 4 weeks did not experience greater improvements in MASthan thosewho received traditional training.[26]

The study by Hesse S. et al indicatedthatrobot-assisted practice of gait and stair climbing did notprovide any

benefits in reducing lower extremity (LE)muscle tone in stroke patients[37] However,Park et al. suggested that utilizing an inventivehumanoid robot capable of coordinating interlimb movementbetween the ankle, knee, and hip joints, can significantlyincrease active and resistive forces in these jointscompared with physical therapy. They observed that resistivestiffness in the hip extension, knee extension, ankledorsiflexion, and ankle plantarflexion muscles had a moderatecorrelation with spasticity, suggesting that RAGT (Robotic assisted gait training) mighthelp reduce spasticity, stiffness, and abnormal synergistic(extensor) gait patterns in thelower limbs[39]. In summary,further research is necessary to confirm the efficiency of thelower limb rehabilitation robots for lower limb spasticity.

Only a small number of randomized controlled trials (RCTs) have explored the impact of lower limb rehabilitation robots on muscle strength. Lin et al.were the only ones to observe notable improvements within the Robot-Assisted Gait Training (RAGT) intervention group. However, no significant disparity in manual muscle test (MMT) scores was detected between the intervention group and the control group undergoing conventional rehabilitation[40].

In general, therapeutic robots designed for lower limb rehabilitation have generated mixed evidence regarding their effectiveness in improving active functional movement of the lower limbs. The Fugl-Meyer Assessment of Lower Extremity (FMA-LE) serves as a widely accepted standard for evaluating motor function post-stroke[42]. Results regarding the effectiveness of RAGT compared with the conventional rehabilitation, as measured by FMA-LE, have varied. While some studies have reported significant improvements in the RAGT group[43,41]others have not observed significant differences between the two groups[41,42,43]. When itcomes to assessing walking ability, the Functional Ambulation Classification (FAC) of stroke patients in the acute orsub-acute phase showed improvements following RAGT, but no significant difference was observed betweenexperimental and control groups.

Furthermore, Mayr et al. concluded that an early treatment protocol involving conventional physical therapy in addition to RAGT is not superior to that of adding conventional gait training intervention for improving locomotion in stroke patients, as measured by the modified Emory Functional Ambulation Profile. In summary, the effectiveness of lower-limb rehabilitation robots in improving lower limb motor function remains uncertain.

Regarding lower limb coordination and balance among stroke patients, Kim et al. observed a notable improvement in coordination function within the Robot-Assisted Gait Training (RAGT) group compared to the conventional training group.[35] However, research on the efficacy of rehabilitation robots for improving balance function in lower limb rehabilitation has not consistently produced positive outcomes. Concerning balance in the standing position, rehabilitation robotic therapy exhibited improvement only within the group, with no significant distinction between groups compared

to conventional therapy.[43]

Summary and future perspectives

This review article has given insight into the application of robotic-assisted rehabilitation, its advantages and drawbacks and its efficacy in rehabilitation post-stroke. In summary, robotic technology holds significant promise in aiding the motor recovery of individuals post-stroke. Robotic rehabilitation allows patient's active participation in walking while overcoming interesting challenges and biofeedback as well as providing a safe support. By utilizing rehabilitation robots, healthcare professionals can alleviate the demands of intensive training tasks. With their precision and reliability, these robots present an efficient avenue to improve outcomes for stroke patients.

Although some results point to the superiority of robotic rehabilitation over manual one, i.e., one-on-one rehabilitation, the effect of the therapy is best when combining both methods of rehabilitation.

Literature search has shown the necessity of new, more detailed research in order to define the right time when to start with robotic-assisted rehabilitation after stroke and to determine the dynamics of its application.

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REVIEW

STROMATOGENESIS AND ANGIOGENESIS, TWO ESSENTIAL PROCESSES OF TUMOR INVASION IN MALIGNANT EPITHELIAL NEOPLASMS - A BRIEF REVIEW OF PLANOCELLULAR SKIN CARCINOMA

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Abstract

Each neoplasm creates its own unique micro-environment in which the tumor grows and modifies. Although majority of host cells in the neoplasm stroma have obligatory tumor suppression ability, the stroma changes during the malignant process and even promotes growth, invasion and metastasis. The genetic changes that occur during cancer evolution, driven by malignant cells, lead to changes in the stroma of the host. At the same time angiogenesis occurs, and formation of new vascular net from the existing normal capillaries. The stroma in the neoplasm does not only give mechanical support to the tumor, but also provides metabolically rich and active environment where the cancer cells survive and multiply. It also contributes to tumor growth and through the newly formed vascular pathways enables further guidance to the circulation, so that the four features of the cancers are achieved: migration, invasion, angiogenesis and metastasis. The understanding of the molecular events in the process of stromatogenesis and angiogenesis is essential for clinical research.

ПРЕГЛЕД НА ЛИТЕРАТУРА

СТРОМАТОГЕНЕЗА И АНГИОГЕНЕЗА, ДВА БИТНИ ПРОЦЕСИ ВО ТУМОРСКАТА ИНВАЗИЈА КАЈ МАЛИГНИТЕ ЕПИТЕЛНИ НЕОПЛАЗМИ - КРАТОК ОСВРТ НА ПЛАНОЦЕЛУЛАРЕН КАРЦИНОМ НА КОЖАТА

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Печатарски права: ©2024. Љубица Ташева, Ирена Костадинова-Петрова, Наташа Стојковска, Елида Митевска, Лена Какашева-Маженковска. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа тоориналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Секоја неоплазма создава своја единствена микросредина во која туморот расте и се модифицира. Иако повеќето клетки на домаќинот во стромата на неоплазмата имаат задолжителна способност за супресија на туморот, стромата се менува за време на малигниот процес, па дури и почнува да промовира раст, инвазија и метастазирање. Генетските промени кои се случуваат за време на еволуцијата на неоплазмата, поттикнати од малигните клетки, доведуваат до промени во стромата на домаќинот. Исто така, во исто време се јавува ангиогенеза, формирање на нова васкуларна мрежа од постојните нормални капилари. Стромата во неоплазмата не дава само механичка поддршка на туморот, туку обезбедува и метаболички богата и активна средина каде што канцерозните клетки преживуваат и се размножуваат. Придонесува и за раст на туморот, и преку формираните васкуларни патишта овозможува понатамошно водење на циркулацијата, така што се постигнуваат четирите карактеристики на карциномот: миграција, инвазија, ангиогенеза и метастаза. Разбирањето на молекуларните настани во процесот на строматогенезата и ангиогенезата е од суштинско значење за клиничките истражувања.

Introduction

The skin is placed on the body`s surface, between the internal environment of the human organism and the external habitat. It is considered a morphologically complex and multifunctional organ, the largest in the human body.

Sun exposure, i.e. the ultraviolet radiation, polluted environment, use of different chemical substances, alcohol, nicotine, arsenic poisoning, the process of industrialization in the bigger cities, chemical substances such as vinyl chloride, poly-cyclic aromatic hydrocarbons, HPV infection etc., are some of the factors that cause various skin changes[1,2]. 95% of skin cancers present as non-melanoma cancer and squamous cell carcinoma account for 20% of them. Squamous cell carcinoma can cause metastasis and death, and therefore it is in the top five causes of cancer death around the world[3].

Squamous cell carcinoma

Squamous cell carcinoma (SCC) is a malignant tumor of the epidermal epithelium. This type of neoplasm, depending on the location in the body, presents with different symptomatology, origin, prognosis and treatment[4,5].

The main etiological factors in the occurrence of squamous cell carcinoma are: ultraviolet B radiation, previous skin burns, HPV infections, radiological radiation, inflammatory lesions and long-term skin ulcerations and arsenic poisoning.

People who have undergone immunosuppression therapy as a result of organ transplant are more likely to develop squamous cell carcinoma. This type of cancer appears mostly on the uncovered body parts that are directly exposed to sun, such as: forehead, face, ears, scalp, neck, arms and lips (vermillion). SCC has a higher occurrence rate in light-skinned people and in elderly people. The incidence is higher in countries near the equator. This cancer rarely appears in dark-skinned population.5 There were 2,402,221 global incidence cases and 356,054 deaths of SCC in 2019. Data from the Institute of Public Health of the Republic of Macedonia cover two categories of malignant skin neoplasm: malignant melanoma of the skin and other malignant neoplasm of the skin that include squamous cell carcinoma, basal-cell carcinoma and malignant neoplasm of the sweat and sebaceous glands.

Squamous cell carcinoma skin changes can be detected by eye as shallow ulcers, often crusted on top and elevated, with an indurated surrounding, as plaques or nodules[6].

This type of carcinoma is composed of nests, sheets and strands of squamous epithelial cells that invade the epidermis and extend into the dermis with variable depth. The cells have rich eosinophilic cytoplasm, a large vesicular nucleus with notable nucleolus; some of them are hyperchromatic and show numerous mitosis. There is variable central keratinization and horn pearls formation, depending on tumor differentiation. The level of anaplasia in the nests is used to determine the tumor differentiation and the categorization of well differentiated, moderately and poorly differentiated tumors. Squamous cell carcinomas occasionally infiltrate along nerve sheaths, the adventitia of blood vessels, lymphat-

ic system and fascial planes. The presence of perineural lymphocytes is a sign of cancer spreading in the deeper parts.[6] In the periphery of the neoplasm, a variable quantity of inflammatory infiltrate may exist. Rare histological variants of SCC include clear cell, signet-ring, pigment, basaloid and rhabdoid types. The cells of squamous cell carcinoma are positive to the epithelial membrane antigen and cytokeratin.[6,7]

Skin squamous cell carcinoma is a locally aggressive tumor, which can appear in several modalities. It has an aggressive course in patients infected by HPV. If the tumor invasion is severe, poorly differentiated, it is more likely to recur or metastasize. The risk of metastasis in the skin damaged by sun radiation is low and is around 0.5%, while in cancers in areas unexposed to the sun the risk is higher and is between 2-3%. Lesions located on the lips, penis, vulva, perineum, as well as on the so-called Marjolin's ulcer, radiation scar or thermal burns have even higher potential for metastasizing. The depth of tumor invasion is a prognostic factor. Lesions invading less than 2 mm in the skin can rarely metastasize; tumors between 2 and 5 mm invasion depth have a medium risk of around 5% chance to lead to metastases, while tumors invading deeper than 5 mm have a high risk to metastasize, around 20%. Tumors that are larger than 2 cm in diameter have a higher risk of recurrence and metastasis, compared to smaller lesions.8

The aim of this paper was to evaluate the current evidence that science has had confirmed by now, regarding the role of stromatogenesis and angiogenesis in the evolution of epithelial malignancies with reference to squamous cell carcinoma.

Tumor stroma

The histological architecture of the tumor includes parenchyma, specific for each tumor type, which is composed of tumor cells, and stroma, a structural mass built of connective tissue, blood vessels and inflammatory cells, which originates from the host. Without the presence of the stroma, the cancer cells cannot sustain themselves, because it supplies them with nutrients essential for their survival, growth and spreading.[9]

A network of blood vessels, specialized mesenchymal cells, cancer-associated fibroblasts (CAFs)/ myofibroblasts, immune cells, mastocytes, macrophages, leukocytes and adipocytes, all together incorporated in the extracellular matrix (ECM), are the main components of the stroma. (On the other hand) the principal elements of the extracellular matrix are structural proteins (collagen and elastin), specialized proteins (fibrillin, fibronectin and elastin) and proteoglycans. The process of the cancer development leads to genetic changes guided by the malignant cells. These genetic changes alternate the stroma of the host. In the process of tumor development and invasion, the basal membrane is deteriorated and the stroma becomes more dynamic as a result of an increased number of fibroblasts, inflammatory infiltrates and newly composed capillaries. The previously mentioned tissue elements are in direct contact with tumor cells. These changes lead to cancer invasion.[10]

Stromatogenesis represents formation of a new, specific type of tissue located around active tumor cells as a vital part of the invading process. Tumor stromatogenesis is managed by the tumor cells themselves with absolute tolerance and participation of host's local fibroblasts. Tumor stromatogenesis differs from the usual reactive fibrosis that surrounds benign lesions (fibrous capsule) and the formation of avascular connective tissue that forms the scar tissue.

Carcinogenesis is defined as uncontrolled replication of tissue cells with a monoclonal character, implying origin from a single cell mutation. These monoclonal cells are in fact tumor cells that interact with the surrounding tissue including the ECM growth factors and cytokines. The monoclonal cells are associated with the ECM, as well as with the nearby endothelial cells, fibroblasts, macrophages, mastocytes, neutrophils, pericytes and adipocytes. The mitigation of the tumor cells, tumor invasion, metastasis and angiogenesis are reliant on the tumor microsurrounding. The key players in this process are matrix metalloproteinases (MMP), enzymes that break cell adhesion molecules, change the connections between the cells and the connections of the cells with the ECM.[11,12]

The following mechanisms of the malignant cells are believed to lead to breaking the normal tissue barriers and causing invasion:

- Rapid growth and replication of the malignant cells cause mechanic pressure on the surrounding tissue with the least resistance;
- Tumor cells lose the surface molecules of the cadherins and integrins, which leads to weakened tumor cell adhesions;
- Tumor cells become more motile through secretion of mitogen cytokines and increase the number of growth factor receptors;
- The extracellular matrix is degraded by the release of more proteolytic enzymes such as metalloproteases, collagenases, plasminogens, cathepsins, etc.
- The secretion of the vascular endothelial growth factors (VEGF) and thymidine phosphorylase (TP) stimulates angiogenesis, providing survival of the tumor cells and their penetration in the circulation.[11]

The matrix metalloproteinases (MMP) provide proteolytic activity necessary for breaking down the physical barriers in the surrounding tissue, which contributes to tumor expansion and intravasation in the nearby blood vessels. MMPs locally stimulate the production of the so-called invadopodia that support the invasion, localized on the surface of the cells. The invadopodia are found in places where ECM degradation happens.

MMPs are also involved in the tumor cell proliferation by modifying the bioavailability of the growth factors and the functions of the surface cell receptors. The members of the MMP release cell membrane precursors for the insulin-like growth factor (IGF) and the epidermal growth factor (EGF) that support the proliferation. MMP-1, -2, -3, -7, -9, -11 and -19 connect to the IGF connecting pro-

tein and regulate the bioavailability of the growth factor.[13]

Many authors have pointed out to the association between glycose aminoglycans, matrix metalloproteinase and growth factors. Glycosaminoglycans (GAGs) induce the matrix metalloproteinase (MMPs) to release growth factors (GFs) from the cell surface that leads to proliferation of the cancer cells.

MMP are also involved in the tumor angiogenesis. MMP-9 increases the bioavailability of the vascular endothelial growth factor, which is a potent mediator in the tumor vasculature, and human basic fibroblast growth factor (bFBGF), by degradation of the extracellular components such as collagen type IV, VIII and perlecan. MMPs also release tumstatin, endostatin, angiostatin and endorepellin - products of the degradation of collagen type 4 and type 17, as well as plasminogen and perlecan. By releasing the previously mentioned products of degradation, MMPs regulate the balance of angiogenesis. MMP-2, -3, -9, -13, -14 reduce the intracellular interactions and increase the migrational capacity of the epithelial cells. During this process, the epithelial cells lose their polarity and take on mesenchymal phenotype. Breaking the cell adhesions results in cell migration; also the connections between the cells are disturbed because of the elimination of e-cadherins.[14]

As a result of the degradation of EMC and other extracellular molecules, fragments with new bioactivities appear which can suppress angiogenesis. For example, active endostatin appears in the process of ripping collagen type XVIII caused by MMP-3, -7, -9, -13, -20. Also, pathological vascularization and increased tumor growth can be found in mice with MMP-9 deficiency. MMP-2, -9 and -12 degrade plasminogen and this process produces angiostatin which has anti-angiogenic function. It means that the MMP can generate angiogenesis inhibition, as well as angiogenesis stimulation. MMPs also play a role in the process of lymphangiogenesis. Studies have reported that the MMPs expand the bioavailability of the vascular endothelial growth factor, which also supports the lymphangiogenesis and promotes the metastasis spreading in the lymph. This has been confirmed in experiments done in fragments of ductus thoracicus of mice incorporated in collagen, that resulted in formation of lymph capillaries in the lumen. The increased level of MMP-1, -2 and MMP-3 is associated with the lymph invasion and metastasis in the lymph nodes. The inhibition of MMP-2, -9 and -14 decreases the angiogenesis, lymphogenesis and reduces the appearance of metastasis in the lymph nodes.[15,16]

MMP-9 was found in the stroma of the invasion surroundings in the micro-invasive squamous cell carcinoma.[17] The MMP-2 level can serve as a predictive factor in the appearance of metastasis in the oral squamous cell carcinoma, and the high level of MMP-2 and -9 correlates with the level of invasion of the squamous cell carcinoma.[18,19] MMP-1 can be found in neoplastic nests of the SCC and in the stroma fibroblasts which surround the tumor epithelial cells.[20] The increased expression of MMP-9 and -7 detected in the cancer cells is in correlation with deeper tumor invasion.[21]

Most of the epithelial tumors accumulate connective tissue cells and extracellular material in their surroundings. This appearance/phenomenon is called a stromal reaction. The key element of the stromal reaction are myofibroblasts. Myofibroblasts are in fact fibroblasts with acquired capacity for expression of alpha smooth muscle actin, (a-SMA), which are vascular smooth muscle cells. Myofibroblasts are capable of synthesizing collagen and other extracellular components and play a key role in the connective tissue remodeling that occurs during wound healing and development of fibrosis.[22] These cells can remodel the connective tissues, but can also react with the epithelial cells and other connective tissue cells, and control processes such as tumor invasion and angiogenesis. Fibroblasts and myofibroblasts produce collagen and extracellular proteins, thus creating desmoplastic reaction.[23] Desmoplasia is a process in which host cells respond to the inductive stimulus of the tumor cells. The stroma cells produce collagen, ECM proteins and initiate desmoplastic reaction for mediation in the invasion process of the tumor cells. Therefore, a question is raised whether the stroma around the cancer cells acts as a protective mechanism, or it accelerates the tumor activity. The stromal collagen is accumulated by the myofibroblasts during the cancer invasion, which is associated with desmoplasia. Myofibroblasts produce paracrine motility factor and cytokines such as hepatocyte growth factor (HGF) and fibroblast growth factor (FGF) also initiate growth of blood vessels and increase the cancer invasion and the metastasis potential[24,25] (Figure 1).

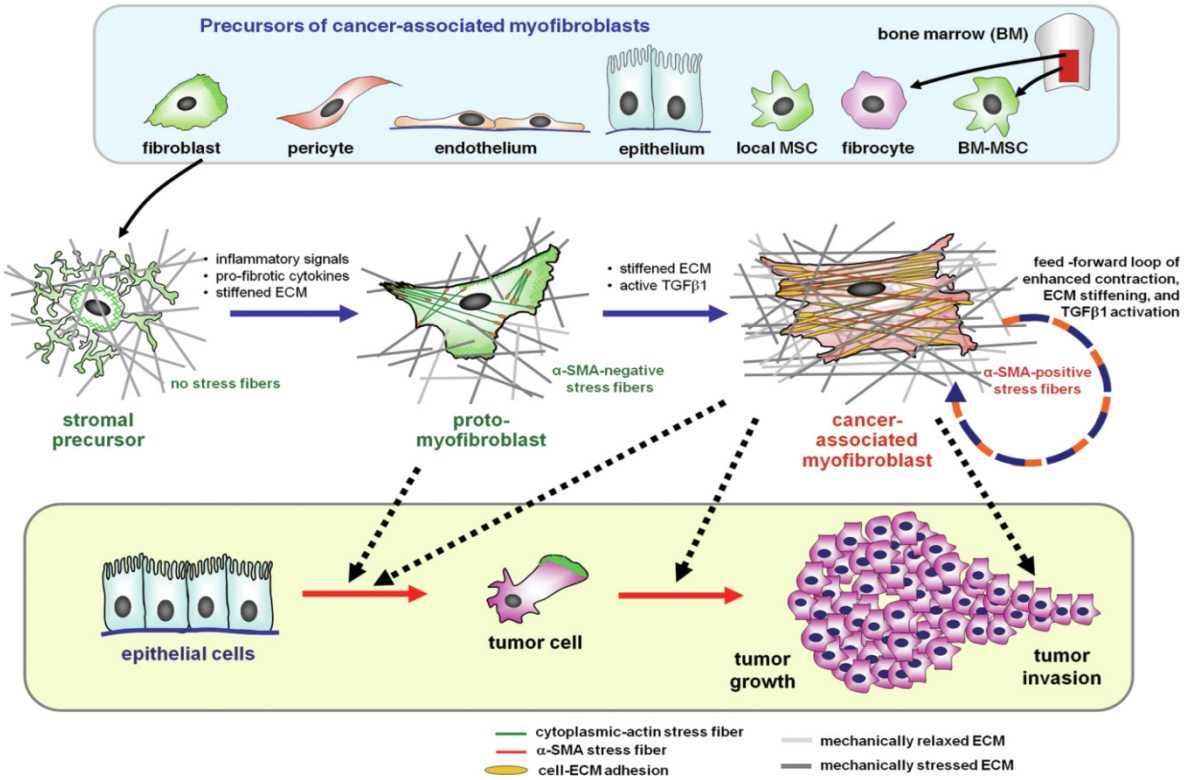


Figure 1 Myofibroblast in the tumor stroma
(See ref. Otranto M. *et al.*[39])

A study that analyzed samples from oral leukoplakia and squamous cancer stained immunohistochemically with a-SMA, confirmed that there were no myofibroblasts in the normal mucosa and in the oral leukoplakia, but were found occasionally in samples of squamous cell carcinoma. Myofibroblastic presence was more frequently found in the more invasive squamous cell carcinoma compared to those with smaller invasion.[26] The analysis of myofibroblasts marked with alpha smooth muscle actin and CD34 in the non-metastatic and metastatic oral squamous cell carcinoma has shown more a-SMA positive fibroblasts in the metastatic group of carcinomas.[27] It has been confirmed that myofibroblasts are strong indicators of the invasion and the proliferation of oral squamous cell carcinoma.[28] Analyzing the myofibroblasts and examining their presence in the stroma in keratoacanthoma and squamous cell carcinoma, it was found that these were significantly more common in the stroma of squamous cell carcinoma.[29]

Angiogenesis

Angiogenesis is the process of formation of new blood vessels from the existing normal capillaries. The higher the angiogenesis activity is, the more aggressive the tumor is, which leads to a poor prognosis for the patients.[30] It is believed that tumors which have more blood vessels than the others are angiogenetic. Tumors also show ability for expression of angiogenesis growth factors such as VEGF, TP, etc.[31]

Stromal and tumor-associated macrophages produce molecules which activate proliferation of endothelial cells, their migration and maturation by forming vascular channels. These growth factors are mainly VEGF. Also, the increased presence of hepatocyte growth factor, the basal fibroblast growth factor and some other interleukins may manifest angiogenesis activities. Weidner *et al.* used immunochemical staining of the endothelial cells in order to differentiate neoplastic lessons into rich angiogenesis and poor angiogenesis tumors. Tumors with increased vascular density have higher chance of metastasizing and have worse postoperative prognosis.[32]

Endothelial cells, which compose the inner lining of the tumor blood vessels, are vital in delivering nutrients and oxygen to the malignant cells. The VEGF expression by endothelial cells amplify vascular permeability. This occurrence assists in the extravasation of fluids and macromolecules, which leads to tumor development and metastasis. The process mentioned above encourages the development of a tumor vasculature, establishing a continuous supply of oxygen and nutrients to support neoplastic proliferation. Research has shown that the TME of SCC often exhibits increased angiogenesis.[33] Thompson *et al.* described the vascular density in breast adenocarcinoma. They found that angiogenesis dominated on the invasion front of the tumor and even more it was found on the border between the normal tissue and the malignant tissue. This finding helped the authors understand that the tumors get the blood supply by the blood-vessel joining, and not by its proliferation.

The vascular density of the hot spots in the tumor periphery was appointed as T1; the area in the middle (between the periphery and the center) was marked as T2 and T3 was named the vascular density area in the center of the tumor. T1 area had the highest vascular density, and it was decreasing going towards the internal part of the tumor, with variations depending on the different types of neoplasm. This occurrence of the vascular regression has also been confirmed by immunochemical staining used for VEGF and kinase insert domain receptor (KDR) complex. VRGF and KDR are present on the surface of the vascular endothelium and VEGF/KDR positive vascular density is higher in the periphery of the tumor and on places where it touches the normal tissue. This finding suggests that angiogenesis activity occurs also in the normal tissue near the invasive tumor front.[34]

Angiogenesis and stromatogenesis are parallel processes in the active tumor cell invasion. The newly formed stroma is edematous and convenient for endothelial cell migration and proliferation of tumor cells. These overlapping processes along with the invasive tumor cells form a well-organized tumor. Angiogenesis and stromatogenesis happen at the same time with the tumor cell invasion and are closely related with tumor metastasis. The conditions in the tumor micro-surrounding, as oxygen level, acidity level and the amount of nutritious products are dominant specifications of the tumor environment. From the above mentioned, a question is raised on how the tumor cells survive in the central parts of the neoplasm when the conditions are less appropriate compared to the peripheral parts of the tumor. The presumption would be that the tumor cells and the young blood vessels are more tolerant to hypoxia by activation of the glycolytic anaerobic pathways.[35] Tumor hypoxia is a microenvironment factor that causes cancer development and resistance to cancer treatment. Approximately 60% of tumors show evident levels of hypoxia or anoxia in tumor tissues. The adaption to hypoxia environment is the base for cancer tissue survival and growth. Abnormal and dysfunctional tumor blood vessels are unable of restoring oxygenation because of the loss in the transportation of oxygen, therefore sustaining hypoxia, which results in promoting cancer progression, metastasis, and resistance to antitumor therapies.[36]

During hypoxia, cancer cells change their metabolism by shifting from oxidative phosphorylation to aerobic glycolysis that results in acidification of the extracellular space. Acidosis is a major link associated with hypoxia which allows selected cells to adapt to acidic conditions. As proliferation of tumor cells occurs, the consumption of energy increases prompting oxygen deprivation. Oxygen deprivation leads to metabolic shift into aerobic glycolysis, known as Warburg effect, by converting glucose into lactate, subsequently fermenting lactic acid in the cytosol. The pH of tumors can decrease to 5.7 in comparison to the pH of healthy tissues which is 7.4.[37]

The tumor potential to withstand lower blood flow in its central parts depends on the ability for production of proteins with anti-apoptotic

features. Proteins are produced and secreted from the tumor and the endothelial cells that determine an important feature of the tumor, the so-called vascular survival ability (VSA). The blood vessels that supply the peripheral part of the tumor are typical blood vessels. But the blood vessels in the internal part of the tumor are irregularly shaped, dilated, tortuous and can have dead ends. These blood vessels are not organized in venules, arterioles and capillaries, but rather have chaotic arrangement. The blood vessels of the vascular network formed in the tumors contain wide splots and this is the cause of bleeding in the surrounding tissues. The perivascular cells often become loosely associated or less abundant. Tumor vessels have cancer cells incorporated in its walls. The blood flow is irregular, with slower and sometimes even oscillating course. The reason for this peculiar occurrence is unknown, but it is believed to be a result of disorder in the appearance and functioning of the angiogenesis factors.

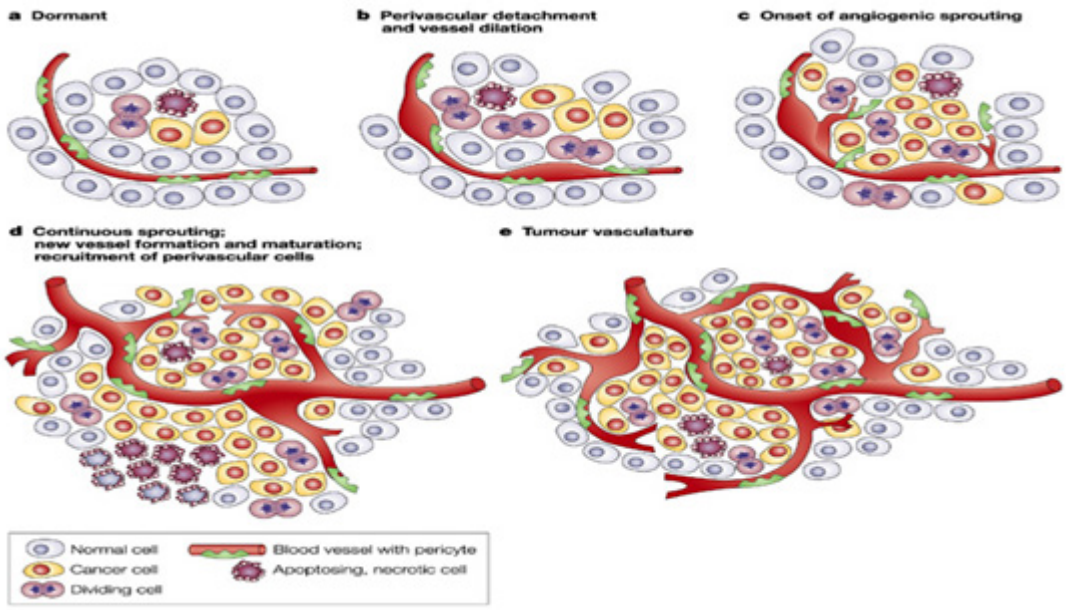


Figure 2 Classical angiogenic switch
(See ref. Bergers G. *et al.*[33])

In oral squamous carcinoma association between the micro-vascular density and positive lymph node metastasis indicates that the angiogenesis plays an essential role in the oral carcinoma.,[38] Angiogenesis is a constitutive part of tumor progression which plays a key role in tumor growth and metastasis. In the 1970s, Professor Folkman stated that tumor growth and metastasis depend on angiogenesis, and targeting its angiogenesis can be used as a therapeutic strategy for tumor treatment.[40]

Conclusion

The stroma in the neoplasm does not only give mechanical support to the tumor, but also provides metabolically rich and active environment where the cancer cells survive and multiply. It also contributes to tumor growth and through the newly formed vascular pathways enables further guidance to the circulation, so that the four features of the cancers are achieved: migration, invasion, angiogenesis and metastasis. The understanding of the molecular events in the process of stromatogenesis and angiogenesis is essential for clinical research. Studying the anti-angiogenesis or blocking of the enzymes included in the complex cell matrix interactions can provide relevant information that would be further included in the treatment protocol of the neoplasm.

Squamous cell carcinoma as a more common type of skin cancer needs further research, taking into consideration that most of the published studies are related to the oral squamous cell carcinoma. Cutaneous squamous cell carcinoma with the mechanisms of its invasion and metastasis, as well as the interactions between the epithelium and the stroma still remains unclear and can be considered as an interesting field of research, not only because of the frequent occurrence of this tumor, but also because of the access to materials for research. The elaboration of the abovementioned mechanisms has not only academic value, but could be considered as a basis for determination of prognosis and treatment modality.

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CASE REPORT

CILIATED VULVAR CYST IN A 13-YEAR-OLD GIRL- CASE REPORT

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Key words: ciliary cyst, Miller's tissue, vulva

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Abstract

Vulvar cysts are rare, mostly benign lesions in childhood, originating from Miller's embryonic tissue and associated with progesterone action. The interior of the cysts is lined with columnar epithelium with cilia. They can be asymptomatic until they reach a size that causes heviness and pressure on the surrounding tissue and aesthetic deformity of the vulva. Case report: A 13-year-old girl presented with a large elongated cystic structure originating from the right labia majora of the vulva, with a length of about 20 cm, without significant symptoms, except for discomfort in the external genitalia. The cyst was surgically removed and the histopathological findings confirmed the existence of a ciliary vulvar cyst, originating from Miller's structures. After the operation, the cosmetic result was excellent and the young patient felt relieved. Conclusion: Vulvar cysts are a rare finding in childhood and puberty, but they can also reach large sizes. The treatment is surgical excision, which provides a cure, correction of the normal anatomy of the vulva, and histological confirmation of the diagnosis.

ПРИКАЗ НА СЛУЧАЈ

ЦИЛИЈАРНА ЦИСТА НА ВУЛВА КАЈ 13- ГОДИШНО ДЕВОЈЧЕ

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Клучни зборови: цилијарни цисти, Милерови структури, вулва

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Печатарски права: ©2024. Анета Сима, Весна Наунова, Слаѓана Симеонова- Крстевска, Драге Дабески, Лазо Јовчески, Тони Ристески, Благица Крстеска. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа торигиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Вулварните цисти се ретки, најчесто бенигни промени во детската возраст, со потекло од Милеровите ембрионални структури и се поврзани со дејството на прогестерон. Внатрешноста на цистите е обложена со колумнарен епител со трепки. Можат да бидат асимптоматски сé додека не постигнат големина за да предизвикаат тежина и притисок врз околното ткиво, како и естетски деформитет на вулвата. Приказ на случај: Тринаесетгодишно девојче дојде на преглед со голема цистична структура која потекнуваше од десната голема усна на вулвата, со должина од околу 20 см, без значајни симптоми, освен дискомфорт во надворешни гениталии. По сооветна подготовка, цистата беше хируршки отстранета- хистопатолошкиот наод потврди постоење на цилијарна вулварна циста, со потекло од Милеровите структури. Постоперативниот тек помина уредно, со одличен козметички резултат и олеснување за младата пациентка. Заклучок: Вулварните цисти се редок наод во детска возраст и пубертет, но можат да достигнат и големи димензии. Третманот се состои во хируршка ексцизија со која се постигнува лекување, корекција на нормалната анатомија на вулвата, како и хистолошка потврда на дијагнозата.

Introduction

Vulvar cysts are a unique entity in pediatric gynecology with an often confusing clinical appearance. Although relatively rare in pediatric population, they can have significant implications on the health and well-being of young patients and therefore require special attention due to their anatomical and physiological characteristics[1,2]. The exact etiology of the vulvar cysts with cilia remains to be further investigated. Current research is focused on the most probable origin from epithelial remnants of the Mullerian ducts, the embryonic precursors of the female reproductive tract. However, it is widely believed that these result from incomplete involution or fusion, abnormalities of Mullerian ducts during embryogenesis. This incomplete regression can lead to the formation of cystic structures, typically located in the vulvar region[3,4]. Furthermore, hormonal influences can also play a role in developing vulvar ciliary cysts. Changes in hormone levels, especially estrogen, can affect the growth and maintenance of these cystic structures. This is especially relevant in adolescent patients, where fluctuations in hormonal levels are common[5,6].

Case report

We describe the case of a 13-year-old patient who presented with a large elongated cystic formation localized on the right labia majora(Figure1), 20cm long and filled with liquid content. The cystic formation did not fluctuate in size and was connected to the skin of the labia majora with a narrow stalk. According to the patient's history, the cystic formation appeared 3 years ago and gradually grew without causing any particular symptoms. However, she complained that it became so large that she felt uncomfortable wearing jeans and a bathing suit in public. She was afraid and shy, so she didn't share any information with her family and physician, at least not until the cyst grew significantly. She had her first menarche at the age of 12 years, and she has a regular menstrual cycle. On clinical examination, the inguinal region was free without signs of hernia and the hymen was intact. Surgical excision was indicated and she was scheduled for elective removal of the lesion.

The patient underwent surgery with general anaesthesia. She was placed in a modified frog-leg position. The excision boundaries were marked and the entire cyst was excised at the level of the stalk-skin attachment. Right labial skin edges were sutured with continuous interlocking suture with monofilament, absorbable suture (Figure 2). The patient tolerated the procedure well and there were no complications.

The entire cyst was sent for histopathologic examination After complete processing of the pathohistological and immunohistochemical examinations, the cut section of the specimen revealed a cystic space filled with serous fluid (Figure 4). The wall of the cyst was lined by one layer of pseudostratified ciliated epithelium with focal squamous metaplasia. There was no significant inflammation in the cyst wall.



Figure 1. Before operation



Figure 2. Post-operation

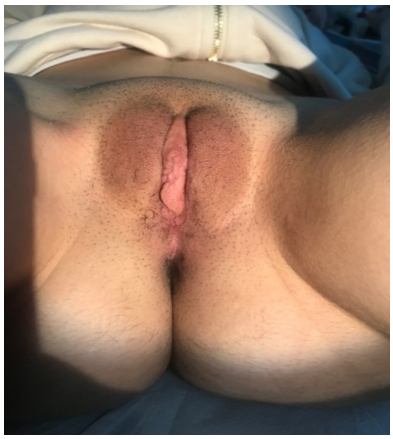


Figure 3. One month after

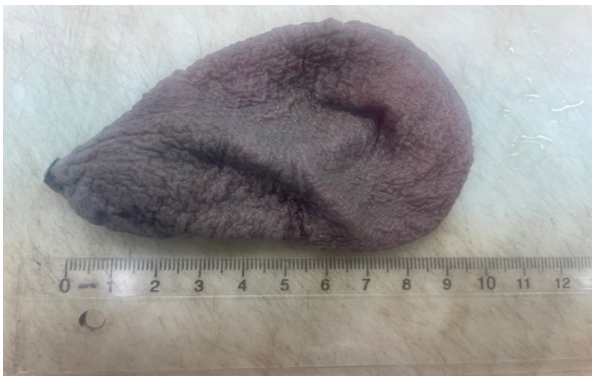
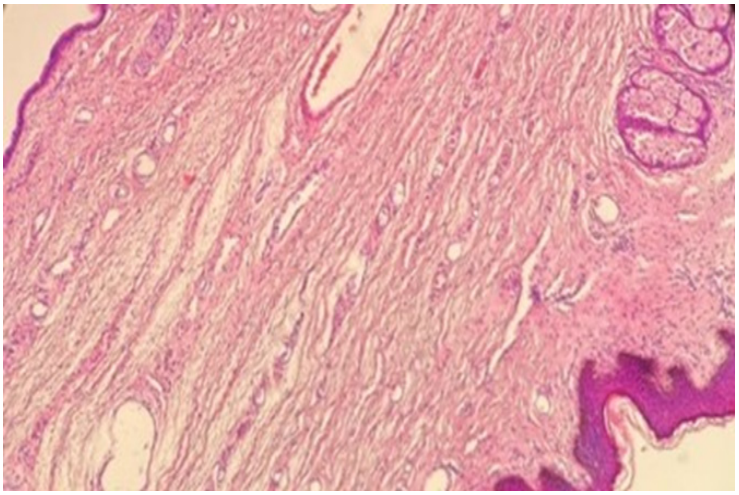




Figure 4. The cut section of the specimen revealed cystic space filled with serous fluid

Teratoma elements were not identified. Immunohistochemical analysis showed that the ciliated cells were positive for estrogen receptor (ER), progesterone receptor (PR), cytokeratin 7 (CK7), PAX8 and WT1 which confirmed the Mullerian origin (Figure 5).



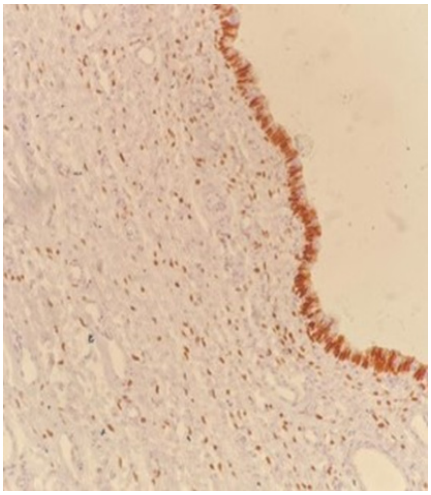


Figure 5. A benign Müllerian cyst lined with ciliated epithelium with ER positivity

No complications were observed postoperatively, and at the 4-week follow-up visit, the patient was in a good clinical condition (Figure 3). She was very satisfied with the esthetic outcome and was psychologically relieved.

Discussion

The clinical presentation of vulvar cysts can vary greatly, which often leads to challenges in the diagnosis. Various pathohistological entities can present clinically with a similar appearance as a vulvar "polypoid cystic lesion". These cysts may be asymptomatic and discovered incidentally during routine physical examinations or tests for other conditions. However, when they are symptomatic, they can manifest in several ways: vulvar mass or swelling, pain or discomfort, dyspareunia, localized redness or inflammation, urinary symptoms and recurrent infections[7]. Diagnosis can be confirmed by physical examination of the vulvar region as the first step in the evaluation of a suspected vulvar ciliary cyst. Palpation is necessary to assess the size, location and consistency of the cystic mass[8]. Transabdominal or transperineal ultrasound is often the modality of choice for evaluating cystic lesions of the vulva. The ultrasound can provide valuable information about the size, location, contents and characteristics of the cyst, helping to differentiate it from other vulvar masses. In the cases where ultrasound findings are indistinct or require additional characterization, magnetic resonance imaging can offer detailed imaging of the cystic lesion and its relationship with the surrounding structures. A biopsy of the cystic lesion is rarely performed, although in some cases it can be necessary. Histopathological examination after complete surgical excision is a gold standard in the diagnosis[4,6].

Differential diagnosis- considering the varied clinical presentation of vulvar ciliary cysts, it is essential to consider several differential diagnoses when evaluating a pediatric patient with a vulvar mass8. The following are some situations that can imitate this situation: cyst or abscess of the Bartholin's gland, hemangioma or vascular malformations, epidermal inclusion cyst, lipoma, sebaceous cyst, inguinal hernia(in pediatric patients, an inguinal hernia can manifest as a bulge or swelling in the groin or labial region). This condition requires rapid evaluation and surgical intervention if symptomatic[5,6,9].

Conclusion

Comprehensive clinical evaluation and wisely chosen imaging techniques can help in the differentiation of vulvar cysts. Histopathological examination is the most preferred way of distinguishing vulvar ciliary cysts from other vulvar masses in pediatric patients. Therefore surgical excision is the preferred approach to treatment, it is curative while also providing significant restoration of the appearance of external genitalia.

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CASE REPORT

PEDIATRIC ECHINOCOCCOSIS: DIAGNOSIS, URGENT SURGICAL INTERVENTION, AND TREATMENT

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Key words: ecchinococcosis, children, imaging methods, treatment, surgery

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Abstract

Echinococcus tapeworms cause human echinococcosis, which causes hydatid cysts, most commonly in the liver and lungs but also in other organs. Delays in symptom onset can lead to diagnostic issues, especially in children. Pediatric cases are rare and often lead to unintentional diagnoses. Living in a rural area increases risk. Imaging and serological testing are essential for diagnosis. This case is rare since it involves pediatric echinococcosis. Children rarely get echinococcosis, and symptoms are often vague; thus, diagnosis is mainly by accident. Case report: A 10-year-old female child developed symptoms and signs such as tachycardia, fever, and facial urticaria. On the first clinical examination, classic signs of an acute abdomen were present, indicating a possible abdominal emergency. Laboratory results showed significantly high levels of inflammatory markers, including CRP and WBC, indicating an active inflammatory process, most likely caused by infection or tissue injury. Imaging examinations, particularly a contrast CT scan of the abdomen, revealed two burst liver cysts in the peritoneal cavity, confirming the diagnosis of echinococcal cysts in the liver. We undertook an urgent surgical intervention to address the burst cysts and avert potential complications like peritonitis or sepsis. Post-operative treatment included constant monitoring of the patient's condition, antibiotic and antihelminthic medication to control infection, pain management, and supportive measures to help with recovery. Echinococcosis in children manifests as nonspecific symptoms, which often leads to a rare suspicion and coincidental diagnosis. Echinococcosis is often considered a possible cause of stomach discomfort. The standard treatment for echinococcosis usually involves a combination of antiparasitic medication and surgical removal of the cyst.

ПРИКАЗ НА СЛУЧАЈ

ПЕДИЈАТРИСКА ЕХИНОКОКОЗА: ДИЈАГНОЗА, ИТНА ХИРУРШКА ИНТЕРВЕНЦИЈА И ТРЕТМАН

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Печатарски права: ©2024. Шабан Мемети, Харис Сулејмани, Лазар Тодоровиќ, Наталија Цоклеска- Шунтов, Анила Рацај, Њомза Љумани-Бакиу, Маријан Камиловски, Сања Ѓуриќ, Рецеп Селмани, Ќемал Рушити. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа торигиналниот(ите) автор(и) и изворот.

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Извадок

Ехинококни црви предизвикуваат ехинококоза кај луѓето, што резултира со формирање на хидатидни цисти, најчесто во црниот дроб и белите дробови, но и во други органи. Одложувањето на појавата на симптомите може да доведе до компликации во дијагнозата, особено кај децата, каде случаите се ретки и често доведуваат до дијагностички потешкотии. Живеењето во рурални области го зголемува ризикот од инфекција. Имиџинг методите и серолошките тестови се клучни за точна дијагноза. Овој случај е значаен поради вклучувањето на ехинококоза во педијатриската популација, која е ретко присутна, а симптомите обично се нејасни, поради што дијагнозата често се открива случајно. Десетгодишно девојче беше донесено на Универзитетската клиника за детска хирургија со симптоми и знаци како тахикардија, температура и уртикарија на лицето. На првиот клинички преглед беа присутни класични знаци на акутен абдомен, што индицираше за можна абдоминална итност. Лабораториските резултати потврдија значително зголемени нивоа на инфламаторни маркери, вклучувајќи CRP и покачени леукоцити, што укажуваше на активен инфламаторен процес, најверојатно предизвикан од инфекција или повреда на ткивото. Имиџинг испитувањата, особено компјутеризираната томографија (КТ) на абдоменот со контраст, идентификувале две распукани цисти во црниот дроб во перитонеалната шуплина, што ја потврди дијагнозата на ехинококни цисти во црниот дроб. Реализиравме итна хируршка интервенција за да ги елиминираме распуканите цисти и да спречиме потенцијални компликации како перитонитис или сепса. Постоперативната нега вклучуваше континуирано следење на состојбата на пациентот, примена на антибиотици и антихелминтски препарати за контрола на инфекцијата, намалување на болката и поддршка за закрепнување. Ехинококозата кај децата се манифестира со неспецифични симптоми, што често доведува до сомнителна дијагноза. Ехинококозата често се смета за можна причина за абдоминална непријатност. Стандардното лекување на ехинококоза обично вклучува комбинација на антипаразитски лекови и хируршко отстранување на цистата.

Introduction

Human echinococcosis is a zoonotic disease that spreads between animals and humans. Tapeworms, specifically those of the species Echinococcus, spread it. Humans serve as accidental intermediate hosts, meaning that they become infected in the same way as other intermediate hosts but do not contribute to the infection transmission to the final host. Echinococcus granulosus cysts are most common in the liver and lungs but can also affect the bones, kidneys, spleen, muscles, and CNS. Symptoms may not appear for years until the hydatid cysts become large enough. Hydatids in the liver cause stomach discomfort, nausea, and vomiting. Dyspnea, thoracic discomfort, and persistent cough are lung involvement symptoms.[1]

Both alveolar and cystic echinococcosis are life-threatening conditions; however, cystic echinococcosis is especially severe and has a poor prognosis and a high mortality rate if left untreated. Although the parasite develops sophisticated evasive tactics to ensure its survival, the host does mount a substantial immune response during the initial phases of infection. Furthermore, the majority of echinococcosis cases exhibit a prolonged period of clinically asymptomatic status.[2]

The nature of the pathogen makes hydatidosis more common in areas where people keep dogs to guard and herd livestock. Some people have cysts that go unnoticed for years, while others rupture spontaneously or as a result of trauma and disappear altogether. Hosts may remain infected for months or years without exhibiting any infection-related signs or symptoms.[3]

Imaging techniques are critical for identifying, screening, and monitoring hydatid cysts in humans. Ultrasonography and X-rays routinely diagnose lung cysts and liver lesions, respectively. Serological assays, with varying degrees of sensitivity and specificity for antigen and antibody detection, can serve as a confirmation step in definitive and intermediate hosts. The current treatment guidelines for echinococcosis recommend a combination of medicine and surgery, as well as long-term case follow-up.[4]

Surgery was the only available treatment for echinococcal cysts until 1980. New treatments, including cyst puncture, aspiration, chemical injection, and re-aspiration, are replacing surgery. Benzimidazole-based chemotherapy is also available. Complete hydatid cyst removal via surgery is the best technique to eradicate them and recover quickly. The usual treatment is pericystectomy.[5]

Puncture, aspiration, injection, and reaspiration (PAIR) constitute an additional therapeutic intervention. Certain physicians utilize this ultrasound-guided technique as an alternative to surgical intervention or in situations where surgery is contraindicated. Surgery is always the primary treatment option for symptomatic and complicated cysts. Surgical procedures frequently include liver resections, either anatomical or non-anatomical, such as cystopericystectomy. Surgery is a radical form of treatment that allows for the possibility of recovery.[6]

Benzimidazole compounds can serve as the sole anthelmintic treatment or in conjunction with surgery for

treating simple hydatid cysts with a diameter of less than 1 cm. Nearly one-third of the patients who had this type of treatment indicated that the cyst had entirely and permanently disappeared, while nearly half reported that the cyst size had greatly diminished. However, 20–40% of people do not react favorably.[7]

Case report

The pediatric surgery department admitted a 10-year-old female child to the intensive care unit. On the initial clinical examination, the patient was conscious, contactable, and tachycardic (HR = 154/min), febrile (37.8), urticaria in the facial region was detected, and typical signs of acute abdomen. Laboratory findings showed a highly increased value of the inflammatory parameters CRP and WBC (Table 1). We found higher than normal potassium levels, suggesting hypokalemia, and higher than predicted glucose levels, indicating hyperglycemia (Table 1). These findings prompted additional examination and therapeutic options designed to address the underlying metabolic abnormalities associated with echinococcosis in pediatric patients.

Initial abdominal ultrasounds detected two liver cysts. The initial therapy consisted of fluid resuscitation, antibiotics, analgesic therapy, and gastroprotective therapy. We treated the urticaria with corticosteroids and antihistamine therapy. We performed a brain, lungs, and abdominal CT scan. The intraoperative finding confirmed the CT scan (Figure 1).

Two liver cysts ruptured into the peritoneal cavity, with dimensions of 103 x 44 mm and 50 x 40 mm. The patient got urgent surgical treatment. We removed both cysts, performed abdominal lavage with a hypertonic saline solution, and placed two abdominal drains under the liver and in the douglas cavity.

Table 1. Lab reports during hospitalization

	RBC	WBC	LYMP	PLT	TotalP	Albumin	ALT	AST	Sodium	CRP
06.01	4.96	5.9	8.0	358	75	42	5	14	134	60.8
07.01	4.59	8.7	5.2	308	55	29	87	201	147	201.9
08.01	3.67	9.1	4.1	229	52	27	47	45	141	272.4
09.01	3.57	8.8	7.9	248	56.94	31.68	28.44	13.47	138.4	195.35
10.01	3.68	7.24	13.4	255	51.78	27.98	17.42	27.98	136.15	70.34
11.01	3.97	8.3	19.4	347	57	30	17	11	138	43.8

RBC -red blood cells normal ranges 4.20–5.50 10^12\L, WBC - white blood cells 4.00-9.00 10^12\L, LYMP-lymphocytes normal ranges 15-50 %, **PLT**-platelets 150-450 10^9\L, **TotalP**-total proteins normal ranges 63-83 g/l, **Albumins**-normal ranges 35-50 g/l,**ALT**-alanine aminotransferase normal ranges 10-45 U/L,**AST**-aspartate aminotransferase normal ranges 10-34 U/L, **Sodium**-normal ranges 137-154 mmol/l,**CRP**-C-reactive protein normal ranges <6 mg/l.

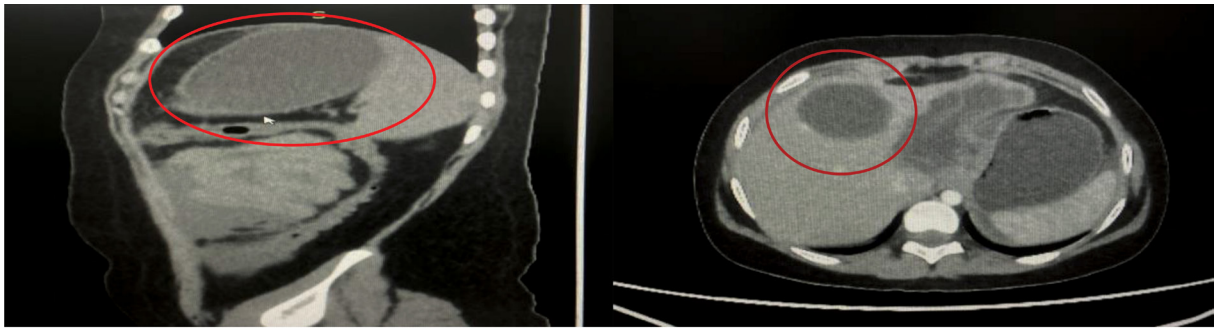


Figure 1. CT imaging - cystic echinococcosis

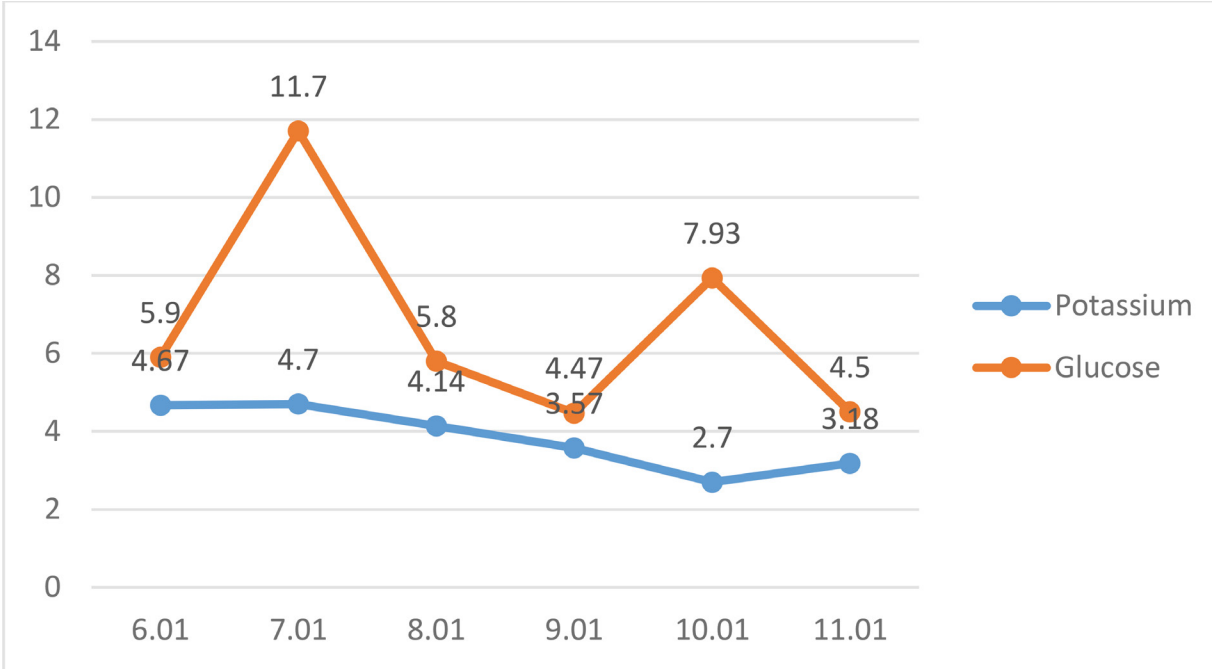


Figure 2. Progression of selected laboratory parameters: Potassium (normal ranges 3.8-5.5 mmol\L), Glucose (normal ranges 3.5-6.1 mmol/L)

During hospitalization, the patient received antibiotic, analgesic, gastroprotective, and rehydration therapy. We performed regular laboratory analyses and used the results to prescribe suitable substitute treatments. Following protocol, we administered Albendazole tablets (2x400 mg) on the first postoperative day. We released the patient in good overall health, with adequate wound healing.

Discussion

Echinococcal infection in humans occurs accidently when a person comes into close conttact with a reservoir host and is not a necessary stage in the parasite's life cycle. Because the parasite has evolved mechanisms to avoid host immunity, the infection is usually asymptomatic until a mechanical complication occurs, such as rupture (into the biliary tree, bronchial tree, or peritoneum), compression of vital structures, hemorrhage, or tissue failure (especially with bone involvement).[8]

Many people get the condition in childhood but don't show symptoms until late adulthood. As demonstrat-

ed in our case and earlier studies, abdominal mass is the most common liver involvement complaint. Untreated cysts can grow, calcify, and die, but they usually merely grow. Hydatid cyst fluid is extremely allergenic and can cause anaphylaxis, making intraperitoneal cyst rupture a life-threatening emergency.[9]

Research shows that children in rural regions are more likely to suffer severe impacts than those in urban areas, with proportions of 74.3% vs. 25.7%, respectively. Though some patients came from neighboring peri-urban areas or had a history of frequent travel to high-risk rural areas where ideal conditions for CE transmission exist, the high frequency of CE in urban settings can be overstated.[10]

Our patient had hyperglycemia and hypokalemia. Following adequate patient rehydration, hypokalemia spontaneously resolved. Additionally, we treated hyperglycemia by administering dextrose-free solutions over a two-day period, which resulted in correction without the need for additional therapy. This demonstrates the effectiveness of hydration as well as targeted treatment options for addressing electrolyte imbalances and metabolic abnormalities in our clinical setting.

Before surgery, an antihelmintic medication course (like Albendazole 2 x 400 mg) may be used. An older cyst still has a significant role in cyst recurrence because it tends to develop more daughter cysts. Medical treatment may reduce the risk of spreading and prevent a recurrence. The preferred surgery is a cystectomy, which involves a complete excision of the cyst without any contents spilling out.[11]

Typically, sonography or imaging tests performed for other purposes (possible appendicitis) in children unintentionally uncover the suspicion of CE, which typically affects the liver. Adverse events in pediatric patients are uncommon.[12]

Conclusion

The manifestation of echinococcosis in children differs from that in adults. Children rarely suspect echinococcosis due to the non-specific nature of its symptoms. However, it is frequently considered a possible cause of stomach pain. Typically, the discovery of echinococcosis is coincidental. Children in rural regions face a higher risk of significant damage compared to children in urban areas. Surgical removal is the gold standard for hydatid cyst treatment.

Ethical Approval and Consent to participate

Ethical approval is not applicable. The patient's parents/legal guardians provided written informed consent for the publication of their cases and associated imagery.

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CASE REPORT

BLEEDING DUODENAL ULCER IN A PATIENT WITH HEMOPHILIA A

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Abstract

Hemophilia A is a hereditary bleeding disorder characterized by excessive musculocutaneous hemorrhage due to a congenital deficiency of factor VIII. While upper gastrointestinal bleeding in patients with hemophilia A has been reported globally, specific literature on this topic remains scarce, emphasizing the need for further research. Case presentation: A 38-year-old male presented at the Univesrity Clinic of Gastroenterhogepatology, reporting a recent episode of black stool three days prior to admission. His digital rectal examination was unremarkable, and levels of blood urea and nitrogen (BUN) were within normal ranges. Apart from Helicobacter pylori infection, the patient lacked significant risk factors for duodenal ulcers. An esophagogastroduodenoscopy (EGD) revealed a duodenal ulcer (classified as Forest Ib), and endoscopic hemostasis was performed using 9ml adrenaline solution. Coagulation factor VIII was administered prior to the procedure. Following the EGD, the patient was treated according to the duodenal ulcer protocol and hospitalized at the University Clinic. Conclusion: Recognizing risk factors, such as Helicobacter pylori infection and the use of nonsteroidal anti-inflammatory drugs, is crucial in managing duodenal bleeding ulcers in patients with Hemophilia A. Screening for Helicobacter pylori infection can significantly reduce the risk of ulcer-related bleeding episodes and enhance overall patient health. Further research and the development of clinical strategies are essential to optimize the management of duodenal ulcers in this patient population.

ПРИКАЗ НА СЛУЧАЈ

КРВАРЕЧКИ ДУОДЕНАЛЕН УЛКУС КАЈ ПАЦИЕНТ СО ХЕМОФИЛИЈА А

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Клучни зборови: дефицит на фактор VIII, гастроинтестинално крварење, хемофилија А

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Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Хемофилија А е наследно хеморагично заболување кое се презентира со прекумерни мускулно-кутани крварења настанати поради вроден дефицит на фактор VIII. На глобално ниво се застапени горнодигестивни крварења поради хемофилија А, но постои недостиг на стручна литература и опишани случаеви со што се нагласува потребата од понатамошни истражувања. Приказ на случај: 38- годишен маж се јавил на Универзитетската клиника за гастроентерохепатологија, со податок за епизода на црна столица три дена пред приемот. Дигиталниот ректален преглед беше незабележителен, а уреата и азот во крвта (BUN) беа со нормални вредности. Освен инфекција со Helicobacter pylori, пациентот немаше други значајни ризик фактори за појава на дуоденален улкус. Направена беше езофагогастродуоденоскопија (ЕГД) која откри дуоденален улкус (класифициран како Forest Ib), а ендоскопска хемостаза беше извршена со употреба на адреналински раствор (9мл). Пациентот прими коагулационен фактор VIII пред ендоскопската процедура. По извршената ЕГД, пациентот беше третиран според протоколот за дуоденален улкус и хоспитализиран на Универзитетската клиника. Заклучок: Препознавањето на ризик факторите како инфекција со Helicobacter pylori и конзумирањето на нестероидни антиинфламаторни лекови кај пациентите со хемофилија А се клучни за ефикасно справување со дуоделаните улкуси. Скринингот за инфекција со Helicobacter pylori може да помогне да се намали ризикот од епизоди на крварење поврзани со чир на дуоденум како и подобрување на целокупното здравје на пациентот. Потребни се понатамошни истражувања и клинички стратегии за развивање и усовршување на менаџментот на дуоделаните улкуси кај пациентите со хемофилија А.

Introduction

Hemophilia A is a hereditary bleeding disorder characterized by excessive musculocutaneous hemorrhage caused by a congenital deficiency of factor VIII[1].

Recurrent joint and soft tissue bleeds are prevalent in patients with hemophilia A, representing hallmark manifestations of the condition[2]. Among the potential sources of gastrointestinal bleeding in this population, duodenal ulcer stand out, necessitating careful consideration of both bleeding risk and therapeutic interventions[3]. Although upper gastrointestinal bleeding associated with Hemophilia A is recognized globally, there is a scarcity of literature specifically addressing duodenal bleeding ulcers in these patients, highlighting the necessity for further research and clinical insights to enhance patient care and outcomes[4].

In this context, we present a case report of 38-year-old male patient with hemophilia A, who experienced an episode of duodenal bleeding ulcer. We outline the multidisciplinary management approach used to address this clinical challenge.

Case presentation: A 38-year-old male patient presented at the University Clinic of Gastroenterohepatology, reporting a recent episode of black stool three days prior to admission.

The patient has hemophilia A and has not been prescribed any medications for chronic diseases. Additionally, he is a non-smoker and abstains from alcohol consumption.

During the examination, no symptoms besides the primary complaint were observed upon reviewing the patient's systems. On physical inspection, he appeared acutely unwell, with slightly pale skin and conjunctiva. There were no signs of scleral jaundice or enlargement of the liver or spleen. His digital rectal examination was unremarkable, and blood urea and nitrogen (BUN) levels were within normal ranges. Vital signs were within normal limits, with blood pressure measuring 115/75 mm Hg, pulse rate of 90 beats per minute, respiratory rate of 20 breaths per minute, and body temperature of 37.4 ℃. An electrocardiogram revealed sinus tachycardia.

Laboratory results showed a minimal increase in leukocyte count and normal hemoglobin levels of 14.2g/dL. The prothrombin time (PT) was recorded at 11.2 seconds, while activated partial thromboplastin time (aPTT) was 39.7 seconds, indicating prolonged aPTT values. The factor VIII antihemophilic globulin level was measured at 11.5%.

Diagnosis and Management

The patient had no significant risk factors for duodenal ulcers, except for a suspected Helicobacter pylori infection. Therefore, an Esophagogastroduodenoscopy (EGD) was preformed to evaluate the upper gastrointestinal tract.

Before the procedure, the patient received coagulation factor VIII, due to low levels of the factor. During the EGD, normal mucosa was observed in the esophagus, while the stomach exhibited hematin patches, suggesting prior bleeding or irritation. Further examination revealed a duodenal linear bleeding ulcer located on the bulb of the duodenum (classified

as Forrest Ib), necessitating immediate intervention (Fig.1.). Endoscopic hemostasis was achieved using a 9ml adrenaline solution to stop the bleeding and promote ulcer healing.

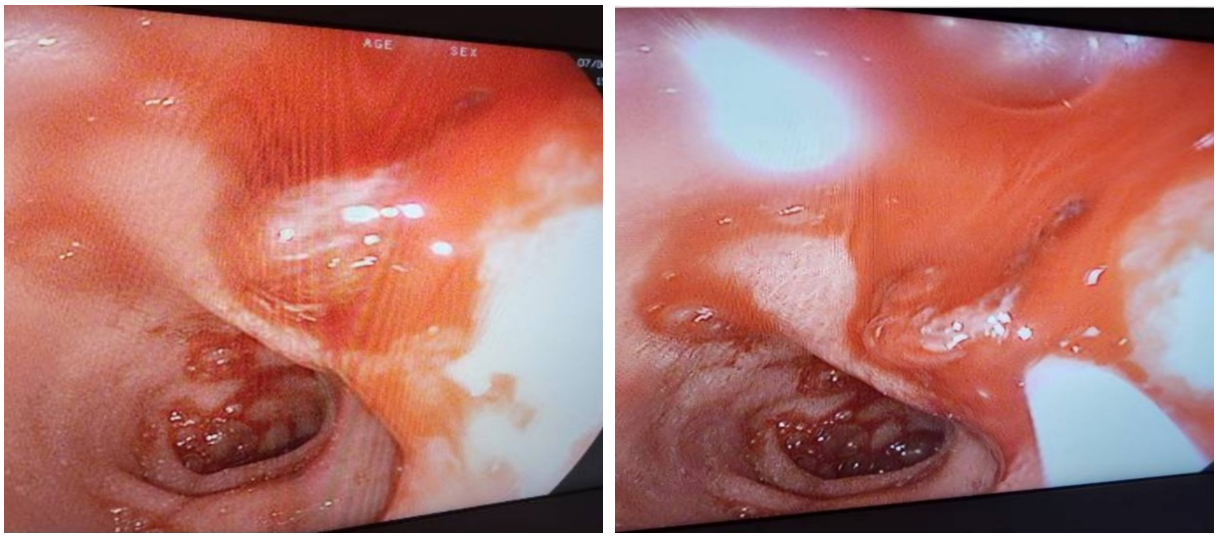


Figure 1. Endoscopic findings: Duodenal linear bleeding ulcer located on the bulb of the duodenum

Following the procedure, serological testing for Helicobacter pylori infection was conducted, with positive results confirming our suspicion.

During the hospitalization, the patient received parenteral nutrition for three days before transitioning gradually to oral intake. The patient began quadruple therapy for Helicobacter pylori infection, which included intravenous antibiotics (metronidazole, tetracycline and bismuth subsalicylate) and proton pump inhibitors (PPIs) for a duration of 14 days.

Throughout the entire treatment period, the patient received Factor VIII to manage his hemophilia A. Control EGD were performed during hospitalization to monitor ulcer progression and assess for recurrent bleeding episodes. The examinations revealed a notable reduction in ulcer size and signs of healing, indicating a positive response treatment and promising prognosis for the patient's gastrointestinal health.

After discharge, the patient continued attending regular follow-up appointments at the gastroenterohepatology clinic, including esophagogastroduodenoscopies. These follow-up examinations confirmed ulcer cicatrization and signs of healing, with no evidence of infection. The urease breath test for Helicobacter pylori infection, performed three months later, showed negative results. The patient was advised to continue using PPI inhibitors and to undergo follow up H2 antagonist therapy for continued care.

Discussion

In patients who have hemophilia A, the correlation between Helicobacter pylori infection and duodenal bleeding ulcers presents a complex and critical aspect of gastrointestinal management.

Hemophilia A, characterized by a deficiency in clotting factor VIII, significantly impairs the body's ability to form blood clots, rendering patients particularly vulnerable to the bleeding complications. When combined with the risk of duodenal ulcers induced by Helicobacter pylori, the clinical management becomes even more challenging.

Helicobacter pylori is gram-negative bacterium known for its role in the development of chronic gastritis and peptic ulcers, including duodenal ulcers. This bacterium colonizes the gastric mucosa, leading to persistent inflammation and increased acid secretion, which contributes to the formation of ulcers in the duodenum. The chronic inflammation induced by Helicobacter pylori weakens the mucosal barrier, making it more susceptible to damage from gastric acid and exacerbating ulcer formation[5].

In addition to Helicobacter pylori, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) can further aggravate ulcer formation and bleeding risk by compromising the mucosal defenses of the gastrointestinal tract [6]. However, Helicobacter pylori remains a primary concern due to its direct role in the development and exacerbation of duodenal ulcers.

For patients with hemophilia A, the presence of Helicobacter pylori is particularly alarming due to the additional burden it places on their already compromised hemostatic system. The development of duodenal ulcer in these individuals can result in significant gastrointestinal bleeding, a serious complication exacerbated by their impaired clotting ability[7]. The bleeding risk is compounded by the fact that these patients may experience delayed or insufficient clot formation, making even minor gastrointestinal hemorrhages potentially life-threatening.

The interaction between Helicobacter pylori and duodenal ulcers in hemophilic patients underscores the importance of early diagnosis and intervention. Active screening for Helicobacter pylori infection should be conducted in patients with hemophilia A who present with gastrointestinal symptoms such as abdominal pain, black stools, or vomiting blood. Early detection and eradication of Helicobacter pylori are crucial in managing ulcer-related complications[8].

Treatment typically involves a combination of antibiotics and proton pump inhibitors (PPIs). Quadruple therapy, which includes metronidazole, tetracycline, bismuth, and PPIs is often employed to effectively eradicate Helicobacter pylori and reduce acid secretion, thereby promoting ulcer healing. This therapeutic approach not only addresses the underlying infection but also mitigates the factors contributing to ulcer formation and bleeding[9].

Moreover, managing bleeding risk in these patients involves careful control of their hemophilia A. Factor VIII replacement therapy is essential to ensure adequate hemostasis during and after ulcer treatment. Endoscopic interventions may be required to control active bleeding and asses the severity of ulcers, while ongoing monitoring is necessary to prevent recurrence and manage any potential complications[10].

Conclusion

Recognizing risk factors like Helicobacter pylori infection and the use of nonsteroidal anti-inflammatory drugs in patient with Hemophilia A is crucial for effectively managing duodenal bleeding ulcers. Screening for Helicobacter pylori infection can help reduce risk of the ulcer-related bleeding episodes and improve overall patient health. Further research and clinical strategies are needed to develop and refine optimal management of duodenal ulcers in patients with hemophilia A.

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