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Betimi i Hipokratit

Në çastin kur po hy në radhët e anëtarëve të profesionit mjekësor premtoj solemnisht se jetën time do ta vë në shërbim të humanitetit. Ndaj mësuesve do ta ruaj mirënjohjen dhe respektin e duhur. Profesionin tim do ta ushtroj me ndërgjegje e me dinjitet. Shëndeti i pacientit tim do të jetë brenga ime më e madhe. Do t'i respektoj e do t'i ruaj fshehtësitë e atij që do të më rrëfehet. Do ta ruaj me të gjitha forcat e mia nderin e traditës fisnike të profesionit të mjekësisë.

Kolegët e mi do t'i konsideroj si vëllezër të mi.

Në ushtrimin e profesionit ndaj të sëmurit tek unë nuk do të ndikojë përkatësia e besimit, e nacionalitetit, e racës, e politikës, apo përkatësia klasore. Që nga fillimi do ta ruaj jetën e njeriut në mënyrë apsolute. As në kushtet e kërcënimit nuk do të lejoj të keqpërdoren njohuritë e mia mjekësore që do të ishin në kundërshtim me ligjet e humanitetit. Këtë premtim po e jap në mënyrë solemne e të lirë, duke u mbështetur në nderin tim personal.

The Oath of Hippocrates

Upon having conferred on me the high calling of physician and entering medical practice, I do solemnly pledge myself to consecrate my life to the service of humanity. I will give my teachers the respect and gratitude which is their due. I will practice my profession with conscience and dignity. The health of my patient will be my first consideration. I will respect the secrets which are confided in me, even after the patient has died. I will maintain by all the means in my power, the honor and the noble traditions of the medical profession.

My colleagues will be my brothers.

I will not permit considerations of religion, nationality, race, party politics or social standing to intervene between my duty and my patient. I will maintain the utmost respect for human life from its beginning even under threat and I will not use my medical knowledge contrary to the laws of humanity. I make these promises solemnly, freely and upon my honor

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Original scientific paper

HULUMTIMIEPIDEMIOLOGJIKDHEKLINIKIUROLITIAZËS NË LUGINËN E PRESHEVËS

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Medicus 2017, Vol. 22 (3): 271-273

HYRJE

Urolitiaza është proces patologjik - sëmundje e cila karakterizohet me formimin e gurëve në sistemin urinar.

Urolitiaza është sëmundje tek e cila shkalla e incidencës ka rritje të vazhdueshme. Llogaritet se 15% e njerëzve gjatë jetës mesatare 75 vjet, formojnë gurë në sistemin urinar, ku nga kjo sëmundje nuk kursehen banorët e asnjë shtrirje gjeografike, grupeve etnike apo edhe moshe. Klinikisht manifestohet në mes të decenies së tretë dhe gjashtë të jetës.

Urolitiaza është sëmundje e proceseve të shumta multifaktoriale e cila përbëhet nga faktorët socio-ekonomik, faktorët gjenetik dhe faktorët konstitucional.

Lugina e Preshevës, përfshin tri komunat në jug të Serbisë me 67 fshatra dhe 3 qendra urbane (Presheva, Bujanovci dhe Medvegja), e cila shtrihet në një sipërfaqe rreth 1250 km katrorë dhe me rreth 100.000 banorë.

MATERIALI DHE METODAT

Në periudhën mars-prill të vitit 2002-2014 janë bërë hulumtime epidemiologjike të popullatës së kësaj treve (Lugina e Preshevës) ku është përfshirë në anketim një numër i popullatës sipas kritereve të njejta epidemiologjike.

Anketimi i banorëve është bërë nga vetë autori i këtij punimi ku janë anketuar 441 familje në të cilat janë kryer intervistat dhe të dhënat janë marrë për 2506 anëtarë të familjeve, prej të cilëve 1687 ose 67.3% të gjinisë mashkullore dhe 819 ose 32.7% të gjinisë femërore. Me X2-test kemi fituar dallim me sinjifikancë të rëndësishme statistikore sipas gjinisë (X2=53.1, P<0.001).

FLET ANKETIM PËR UROLITIAZË

I Nr. telefoni: fiks _____ celular _____

1. Emri _____ Mbiemri _____ Komuna _____

A Kryefamiljar B Familjar

2. A Qyteti _____ B Fshati _____ C Migruar_____

3. Në familjen tuaj a ka dikush gurë në veshka: PO JO

4. Si quhet personi që ka gurë _____ Viti i lindjes _____

5. Prej kur e din se ka gurë në veshka Viti _____

6. A ka qitur spontanisht dikush gurë në familjen tuaj Viti _____

7. Guri është dokumentuar me Rengen PO JO

8. Ka thyer gurë me aparat ESWL-i Qyteti _____

9. A është operuar personi që ka gurë PO JO

10. Në cilën anë të veshkës ka patur gurë Djathtë Majtë

11. Ka patur gurë në kanale të veshakve (ureter) Djathtë Majtë

12. Ka patur përsëritje të formimit të gurit PO JO

13. Sa familjar kanë pasur gurë në familjen tuaj _____

14. Gjendja ekonomike e juaj Lartë Mesme Vobekt

15. Gjithsejt sa anëtarë në familje jeni _____

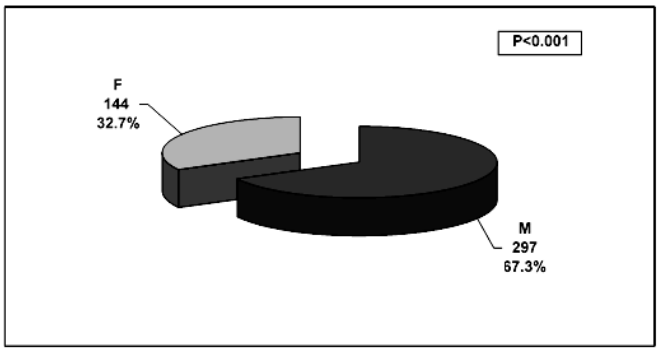
Qyteti, fshati _____ Data_____ Nënshkrimi_____

REZULTATET

Nga 2506 anëtarët e anketuar, prej tyre me urolitiazë janë 441 persona, prej të cilëve 297 ose 67.3% të gjinisë mashkullore dhe 144 ose 32.7% të gjinisë femërore. Me X2-test kemi fituar dallim me sinjifikancë të rëndësishme statistikore sipas gjinisë (X2=53.1, P<0.001), (Tabela 1).

Tabela 1. Të hulumtuarit sipas gjinisë

Gjinia	N	%	X^2-test
M	297	67.3	X^2=53.1 P<0.001
F	144	32.7	
Gjithsj	441	100.0	



Grafiku 1. Struktura e të hulumtuarëve sipas gjinisë

Mosha mesatare e të hulumtuarëve ishte 45.9 vjet (DS ± 13.4), rangu 14-90 vjet. Mosha mesatare e të hulumtuarëve të gjinisë mashkullore ishte 46.3 vjet (DS ± 12.4 vjet), rangu 14-90 vjet. Mosha mesatare e të hulumtuarëve të gjinisë femërore ishte 44.9 vjet (DS ± 15.2 vjet), rangu 19-89 vjet (Tabela 2).

Tabela 2. Mosha mesatare e të hulumtuarëve sipas gjinisë

Mosha (vjet)	Gjinia		Gjithsej
	M	F	
N	297	144	441
Mesatarja	46.3	44.9	45.9
DS	12.4	15.2	13.4
Min	14	19	14
Max	90	89	90
Mann-Ëhitney test	P=0.027		

Familjet në luginën e Preshevës janë zakonisht familje të mëdha 27.4% kanë nga pesë anëtarë në familje, 25.4% nga gjashtë anëtarë, 13.6% nga shtatë anëtarë dhe 11 familje kanë qenë me 10 e më shumë anëtarë.

Nga 2506 anëtarët e anketuar 246 raste ose prevalenca e gurëve në veshka ishte 9.8%. Nga të gjitha rastet me gurë në veshka 107 ose 43.7% kishin gurë në veshkën e djathtë, 98 ose 39.8% majtas, 41 ose 16.5% kishin gurë në të dy veshkat. Ndërsa sipas gjinisë, meshkujt më shumë kishin gurë në anën e djathtë 58 ose 43.3%, po ashtu dhe femrat më shumë kishin në anën e djathtë 30 ose 41.7% (Tabela 3).

Tabela 3. Pervalenca e gurëve në veshka në familjet e anketuara

	N	%
Gjithsej të anketuar	2506	**100.0**
Gjithsej me gur në veshka	246	9.8

Nga 2506 anëtarët e anketuar 56 raste ose prevalenca e gurëve në ureter ishte 2.2%. Të dy gjinitë më së shpeshti kishin gurë në ureterin e djathtë (M 17.2% vs. F 12.5%), pastaj në të majtin (M 11.2% vs. F 6.9%), dhe në të dy anët (M 1.5% vs. F 2.8%), (Tabela 4).

Tabela 4. Pervalenca e gurëve në ureter në familjet e anketuara

	N	%
Gjithsej të anketuar	**2506**	**100.0**
Gjithsej me gur në ureter	56	2.2

Nga të gjitha rastet me gurë në veshka 88 ose 42.7% kishin gurë në veshkën e djathtë, 80 ose 38.8% majtas, 34 ose 16.5% kishin gurë në të dy veshkat dhe 4 ose 1.9% nuk kishin gurë në veshka në momentin e diagnostikimit por vetëm në ureter. Ndërsa sipas gjinisë, meshkujt me shumë kishin gurë në anën e djathtë 58 ose 43.3%, po ashtu dhe femrat më shumë kishin në anën e djathtë 30 ose 41.7%. Me X^2-test nuk kemi fituar dallim me sinjifikancë të rëndësishme statistikore në anën e gurëve në veshka sipas gjinisë (X^2=0.096, P=0.953 pra, P>0.05), (Tabela 5).

Tabela 5. Të hulumtuarit me gurë në veshka sipas lokalizimit të gurit

Veshka me gurë	Gjinia				Gjithsej	
	M		F			
	N	%	N	%	N	%
Djathtë	58	43.3	30	41.7	88	42.7
Majtë	54	40.3	26	36.1	80	38.8
Të dy anët	22	16.4	12	16.7	34	16.5
Jo ne veshka	-	-	4	5.6	4	1.9
Gjithsej	**134**	**100.0**	**72**	**100.0**	**206**	**100.0**
X^2-test	X^2 = 0.096 , P=0.953					

Nga 206 të anketuar (134 meshkuj dhe 72 femra) me gurë në veshka dhe ureter 7.8% e tyre kanë kanë deklaruar se i kanë thyer gurët me ESWL. Femrat i kanë thyer më shpesh gurët me ESWL 8.3% krahasuar me meshkujt 7.5% (Tabela 6).

Tabela 6. Përgjegjet e të anketuarëve në pyetjen: Keni/ kanë thyer gurë me ESWL? sipas gjinisë

Ka thyer gurë me ESWL?	Gjinia				Gjithsej	
	M		F			
	N	%	N	%	N	%
Po	10	7.5	6	8.3	16	7.8
Jo	124	92.5	66	91.7	190	92.2
Gjithsej	**134**	**100.0**	**72**	**100.0**	**206**	**100.0**
X^2-test	X^2=0.821, P=0.365					

Siç shihet në tabelën 7, 7.8% e rasteve me gurë në veshka ose ureter kanë deklaruar se janë operuar. Meshkujt janë operuar më shpesh 9.0% krahasuar me femrat 5.6% por me X^2-test nuk kemi fituar dallim me sinjifikancë të rëndësishme statistikore (X^2-test=0.356, P=0.551, pra P>0.05).

Tabela 7. Përgjegjet e të anketuarëve në pyetjen: A jeni/ janë operuar për shkak të gurëve në veshka? sipas gjinisë

	Gjinia				Gjithsej	
	M		F			
Operuar	N	%	N	%	N	%
Po	12	9.0	4	5.6	16	7.8
Jo	122	91.0	68	94.4	190	92.2
Gjithsej	**134**	**100.0**	**72**	**100.0**	**206**	**100.0**
X^2-test	X^2=0.356 , P=0.551					

PËRFUNDIME

Lugina e Preshevës është e njohur si zonë endemike për urolitiazë ku mund ta vërtetojmë edhe në bazë të rezultatit të incidencës së lartë me urolitiazë të të anketuarëve me 7.6% ku si sëmundje atakon në grup-moshën më produktive të popullsisë 45.9 vjet dhe zbulimi i hershëm i kësaj sëmundjeje trajtohet me aplikimin e metodave më moderne si ESWL, URS lithotripsy si dhe nefrolitholapaksi perkutane.

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Original scientific paper

SERUM MARKER CTX (CARBOXY-TERMINAL COLLAGEN CROSSLINKS) AND BONE HEALING OF ORAL SURGICAL DEFFECTS IN PATIENTS WITH DIABETES MELLITUS

СЕРУМСКИ МАРКЕР CTX (CARBOXY-TERMINAL COLLAGEN CROSSLINKS) И ЗАРАСНУВАЊЕ НА ОРАЛНО-ХИРУРШКИ КОСКЕНИ ДЕФЕКТИ КАЈ ПАЦИЕНТИ СО DIABETES MELLITUS

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ABSTRACT

The bones are complex, dynamic connective tissue with a triple function: structural support, organs protection and maintenance of mineral homeostasis.The bone remodeling is a lifelong active metabolic process involving osteoclasts and osteoblasts. The balance between bone resorption and bone formation can be detected by tracing the circulating proteins (formative and resorptive markers). Diabetes is mentioned as one of the cause factors of metabolic bone disorder. The aim of the study was to determine the value of resorptive bone marker CTX (carboxy-terminal collagen crosslinks) and its possible influence on bone mineralization of oral surgical defects in patients with diabetes. Prospective clinical study was made including 100 subjects divided into two groups, patients with diabetes and control group. The serum values of CTX and the percent of relative bone healing in oral surgical defects were followed for over a 12 months period. Serum values of CTX in diabetic patients suggested reduced activity of bone metabolism with no influence on bone mineralization process followed by bone density increase in oral surgical defects.

Key words: bone metabolism, CTX, spontaneous bone healing

АПСТРАКТ

Коскеното ткиво претставува комплексно, динамично, минерализирано потпорно ткиво на еден организам со тројна функција: структурна поддршка на телото, протективна улога на внатрешните органи и одржување на минерална хомеостаза. Коскеното ремоделирање е активен метаболен доживотен процес во кој учествуваат остеокласти и остеобласти. Балансот помеѓу коскената ресорпција и коскената формација може да се проследи преку циркулирачки протеини (формативни и ресорптивни маркери). Дијабетесот се споменува како еден од факторите кој може да предизвика коскено-метаболно нарушување. Целта на оваа студија беше да се одреди вредноста на ресорптивниот коскен маркер CTX

(carboxy-terminal collagen crosslinks) и неговото можно влијание врз минерализацијата на оралнохируршките коскени дефекти кај пациенти со дијабетес. Беше изработена клиничка студија со 100 испитаници поделени во две групи,испитаници со дијабетес и контролна група. Во период од 12 месеци беа проследени серумските вредности на CTX и процентот на релативно коскено зараснување на вилични дефекти.Серумските вредности на CTX кај испитаници со дијабетес укажуваат на намалена активност на коскениот метаболизам без влијание врз динамиката на пораст на коскената густина на дефектите.

Клучни зборови: коскен метаболизам, CTX, спонтано коскено зараснување

INTRODUCTION

The bones are complex, dynamic and supporting mineralized tissue of an organism with a triple function: structural support, organs protection and maintenance of mineral homeostasis. Bone tissue is composed of several cell types, proteins, blood vessels, nerve elements and bone mineral matrix that allow an operation called metabolism, regulated by many factors. The bone remodeling is a lifelong active metabolic process involving osteoclasts and osteoblasts on the same place. While osteoclasts absorb the old bone, osteoblasts form a new one. Imbalance between these activities, for any reason, results in metabolic bone disorder (1-2).

The balance between bone resorption and bone formation can be detected by tracing the circulating proteins (biological markers) in serum and urine. Bone markers are divided in two groups of formative and resorptive markers (3).

The most analysed marker of resorptive markers group is ë crossLaps((carboxy-terminal collagen crosslinks-CTX), high sensitive marker of bone resorption, stable in serum and urine. Collagen cross links are released during bone matrix resorption (early breakdown of collagen type 1) and can be detected by specific tests. (4-5).

Hossein-Nezhad et al. (6) show different bone resorptive markers including CrossLaps. It is one of the most sensitive markers formed directly with the onset of collagen type 1 degradation (Figure1). In bone physiology, C-terminal telopeptide-CTX can be used as bone turnover serum biomarker. The detecting test of CTX marker, named serum CrossLaps, is used more often than any other currently available test for bone resorption process determination (7-8).

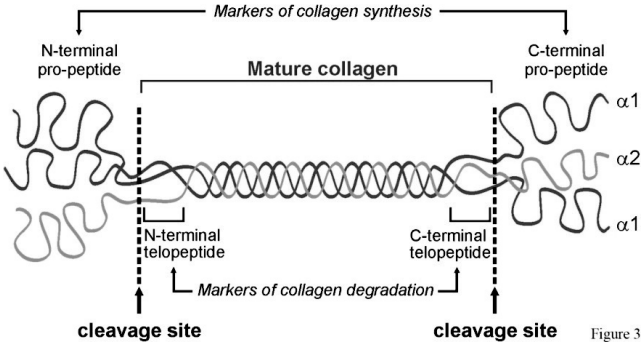

Figure1. Structure of collagen molecule (Presented by Dong Fan et al.[8] Cardiac fibroblasts, fibrosis and extracellular matrix remodeling in heart disease. Fibrogenesis&Tissue repair, 2012;5:15).

This specific protein sequence is separated from the osteoclasts during bone resorption. Therefore the serum CTX levels are proportional to the osteoclastic activity in the time when blood sample was taken (9).

Reference intervals of CTX in menopausal women are well studied, but in other age groups there is much less information (healthy children show variations associated with the age). Despite these shortcomings, serum CTX, fully or partially meets all the criteria for a reference bone resorption marker (10).

The values of bone turnover markers obtain clinically usable informations about either normal or pathological processes affecting bone cells activity (11).

Biochemical markers are used in medicine for osteoporosis treatment initiation. The serum marker of osteoclastic activity (CTX) is used to evaluate bone resorption degree (12,13). In oral and maxillofacial surgery CTX is used for risk prediction of jaws osteonecrosis development after oral surgical procedures in patients receiving oral bisphosphonate therapy and evaluation of bone mineral density in elderly patients.

In the early years of the 21st century, the relationship between bisphosphonate usage and impaired bone physiology was observed. The strong inhibition of the osteoclast function caused by bisphosphonate therapy leads to bone metabolism inhibition with impaired wound healing after trauma (such as dental surgery) or jaw bone fractures. Because bisphosphonates are primarily deposited in bones with a high rate of metabolism, it is possible to have increased levels of bisphosphonates in the jaw bones (14).

Diabetes is mentioned as one of the cause factors of metabolic bone disorder. Diabetic alterations in mineral and bone metabolism result in bone mass decrease. (15-16).

Diabetes affects bones through diabetic microangiopathy leading to blood supply reduction and reduced formation of collagen fibers due to osteoblast inhibition. The reduced amount of bone collagen matrix is followed by reduced deposition of mineral salts resulting in prolonged bone healing(17).

Based on the presented literature we set the aim of this study: to determine the serum values of CTX (as a direct indicator of bone resorption process) and its possible impact on bone mineralization followed up by bone density increase in oral surgical defects in patients with diabetes and to determine the correlation between serum markers representative (CTX) with type

of diabetes, duration of diabetes and diabetes regulation degree.

MATERIAL AND METHODS

Prospective clinical study was done at the Clinic of Oral Surgery, University Dental Clinical Center and the Department of Oral Surgery at the Faculty of Stomatology in cooperation with University Clinic of Endocrinology, diabetes and metabolic disorders in Skopje.

The survey included 100 respondents divided into two groups: participants with diabetes (60) and a control group without diabetes (40). For each patient detailed medical history, clinical examination and radiographic analysis was performed, leading to indication for oral surgical intervention.

Each patient was voluntarily involved in the research confirmed by a signature on the prepared consent form.

For biochemical analysis (HbA1C, CTX) blood sample from the antecubital vein was taken from each patient. Biochemical analyzes were conducted at the University Clinic of clinical biochemistry in Skopje.

Oral surgical interventions were performed at the Clinic for Oral Surgery respecting the specified operative protocol.

After 24 hours x-ray verification of the oral surgical defect was made (panoramic radiography). Panoramic radiographs were repeated after 6 and 12 months. The subsequent radiographs were digitized through professional photo scanner, Epson perfection V 600, and analyzed by Adobe Photoshop 7.0 for Windows 7 using the gray scale histogram where illumination intensity of the measured field is converted and expressed in pixels.

Converting the area of interest in gray scale enables accurate estimation of increased or decreased bone density which is equivalent to the degree of bone defect mineralization.

The percentage was calculated using the formula presented in Ihan Hren, Milijavec[18]analysis:

$$\text{Relative bone healing} = \frac{\text{NB (new bone formation density) X 100}}{\text{SB (surrounding bone density)}}$$

The statistical programs STATISTICA 7.1 and SPSS 17.0 were used for the statistical analysis.

Numerical series were analyzed with average and standard deviation. In numerical series where there is no deviation from the normal distribution, the significance of the difference is tested with the Difference Test, and where there is a deviation from the normal distribution, the significance of the difference is tested with the Mann-Whitney U test.

Correlative relationships were realized using the Pearson correlation coefficient (r).

A multiple regression analysis was used to determine the relationship between the dependent variable and the system of predictor variables of interest.

RESULTS

The results obtained from the research analysis showed that the average value of bone resorption marker (CTX) in the control group was 0.3 ± 0.1ng/ml (minimum 0.115ng /ml, maximum 0.657ng/ml), while in experimental group was lower at 0.2 ± 0.09ng/ml (minimum 0.113ng/ml, maximum 0.645ng/ml) (Table1). The difference between the values of CTX is statistically significant for $p < 0.05$.

Table1. Average values of serum marker CTX in tested groups

group	average	Num.	St dev	min	max
KG	0.3	40	0.1	0.115	0.657
DG	0.2	60	0.09	0.113	0.645

Mann-Whitney U test					
	Rank Sum	**Rank Sum**	**U**	**Z**	**p-level**
CTX	2234.000	2816.000	404.0000	-5.60064	0,000000

Additional parameters for CTX values correlation (type of diabetes, the duration of diabetes and diabetes regulation degree) were included in the study.

The diabetes regulation degree was determined by the values of glycosylated hemoglobin-HbA1C. In our research we set value of HbA1C at 7.0% as good glycemic control under research of Petrovski(22).

In our research, immutability of resorptive marker CTX depending on diabetes regulation degree was shown (Table 2).

Table 2. Correlation between serum marker CTX versus duration of diabetes and HbA1C

CTX	duration of diabetes	HbA1C
DG	r=-0.2866	r=-0.0508
	p=0.026	p=0.700

The duration of diabetes in our study showed statistically significant negative correlation with the values of the serum marker CTX (Table 3).

In this study values of CTX between respondents with different types of diabetes did not show statistical significance The average value of CTX in type 2 diabetes group was 0.2 ± 0.1 ng/ml, while in type 1 diabetes was 0.2 ± 0.07 ng/ml (Table 3). The difference is statistically insignificant for p> 0.05.

Table 3. Average serum marker CTX in different types of diabetes

Diabetes / CTX	**average**	**number**	**St.dev**	**min**	**max**
Diabetes type 2	0.2	31	0.1	0.123	0.645
Diabetes type 1	0.2	29	0.07	0.113	0.329
Mann-Whitney U test					
	Rank Sum	**Rank Sum**	**U**	**Z**	**p-level**
CTX	927.500	902.5000	431.5000	-0.266268	0.790033

In our research, the average percentages of bone density in the defect versus density of the surrounding healthy bone on immediate radiography in the experimental group is 29.7 ± 5.1%, on the radiographic control image after 6 months bone density increased to 54.4 ± 7.1% and on the control after 12 months reaches a value of 77.2 ± 8.7% (Table 4).

Table 4. Average radiographic analysis (%) of bone healing compared to the surrounding healthy bone in both groups

	group	**average**	**number**	**St dev**	**min**	**max**
RTG immediate	DG	29.7	60	5.1	18.4	44.9
	KG	23.8	40	5.2	17.4	36.0
RTG afer 6 months	DG	54.4	60	7.1	38.0	68.5
	KG	52.5	40	7.3	35.2	69.1
RTG afer 12 months	DG	77.2	60	8.7	62.0	96.0
	KG	84.5	40	9.0	65.8	97.8

The average percentages of bone density in the defect versus surrounding healthy bone on immediate radiography in the control group is 23.8 ± 5.2%, on the radiographic control image after 6 months bone density increased to 52.5 ± 7.3% and on the control after 12 months reaches a value of 84.5 ± 9.0% (Table 6).

After 12 months, different bone healing between the groups was shown (77.2 ± 8.7 in the test group versus 84.5 ± 9.0% in the control group). The result is statistically significant for p <0.05 (Table 5).

Table 5. Different bone healing between the groups after 12 months (Mann-Whitney U test)

	Rank Sum	Rank Sum	U	Z	p-level
Immediate	3732.500	1317.500	497.500	4.942773	0.000001
After 6 months	3267.500	1782.500	962.500	1.67104	0.0947
After 12 months	2500.500	2549.500	670.500	-3.72555	0.000195

We confirmed our results with another statistical method - MRA (multiple regression analysis). Multiple regression analysis in patients with diabetes determined connection between the values of bone healing (%) compared to the surrounding healthy bone (dependent variable) and the system of independent variables (type of diabetes, duration of diabetes, the degree of regulation-HbA1C, CTX).

The analysis of independent variables showed a significant impact of duration of diabetes on the percentage of bone healing.

For the independent variable-duration of diabetes, the coefficient of partial regression analysis was 0.323 and tested with t -test shows that the impact on bone

healing (%) compared to the surrounding healthy bone is statistically significant for p = 0,013 (Table 6).

Table 6. Multiple regression analysis (%) of bone healing compared to the surrounding healthy bone in patients with diabetes

INDEPENDENT VARIABLES	R = 0,749 F = 4.539	R^2 = 0,561 p= 0,000063	
	Beta	t – test	p - level
gender	0.127266	1.12802	0.265162
age	0.047782	0.41075	0.683161
BMI	-0.154686	-1.29397	0.202136
Type of diabetes	-0.223339	-1.76261	0.084609
Duration of diabetes	-0.323594	-2.57356	**0.013354***
HbA1C	-0.170630	-1.37227	0.176633
CTX	-0.224291	-1.83379	0.073159

DISSCUSION

By abandoning the concept of bone tissue inertness as the mainstay of an organism, rich metabolic activity of bone tissue is frequently mentioned, provided by the the composition of tissue involving multiple cell types and collagen matrix.

Bone metabolism is regulated by bone cells. The bone cells activity and bone metabolism indirectly can be followed through the values of serum bone formation and resorption markers (osteocalcin and ßcrossLaps-CTX).

Serum marker of bone resorption ßcrossLaps-CTX (Collagen cross links), released from the bone matrix after resorption (early breakdown of collagen type 1), is one of the most sensitive markers of this group.Collagen type 1makes about 90% of the bone organic matrix . It is helical protein associated with short bridges of N-amino and C-carboxy molecule terminals. Osteoclasts secrete a mixture of acidic and neutral protease during bone resorption that degrades the mature collagen in molecular fragments including C-terminal telopeptide (CTX). These CTX fragments, released into the bloodstream during bone resorption, serve as a specific marker for mature collagen type 1 degradation. Elevated serum concentrations of CTX has been reported in patients with increased bone resorption (19).

Numerous studies have analysed the CTX marker and they all agree with the fact that in diabetic patients, CTX concentrations changes occur. These changes provide an information about the bone tissue condition in patients with this metabolic disorder.

Reduced values of bone resorption, indicated by significantly lower CTX values, indicate reduced general bone turnover, consistent fact with the findings of Linde[20].

On the contrary, histomorfometric studies from Brandi[5] did not show changes in the bone resorption in diabetic patients. Changes are reflected only in the process of bone formation, supported by the results of the bone markers values (osteocalcin and CTX).

The diabetes regulation degree was determined by the values of glycosylated hemoglobin-HbA1C. Glycosylated hemoglobin is formed in a reaction between hemoglobin and glucose in the blood. It is a direct indication of the glucose serum levels for a period of 2-3 months, as the half-life of hemoglobin in blood circulation. Because it is called “golden standard” in glicoregulation assessment (21).

In studies of Thrailkill[23]; McCaeb[24]; Capoglu[25] and Winhofer[26], correlation with our data was shown, which means immutability of resorptive marker CTX depending on diabetes regulation degree. The analyzes of these studies indicate normal bone resorption, sometimes even reduced, while bone formation is significantly reduced, confirmed by decreased osteocalcin serum levels. Opposing views were found in the study of Achemlal[27], where values of CTX are in significant negative correlation with HbA1C values.

Long duration of diabetes leads to clinical manifestation of some chronic complications. If microangiopathy occupies the renal tissue (diabetic nephropathy), renal hyperfunction and microalbuminuria will occure. Most of the complications occur after 15-25 years of having diabetes. This data is used in the study of Hossein-Nezhad et al.[6] where increased urinary excretion of CTX is the reason for reduced values of the indicated tag.

The duration of diabetes in different studies shows variously interpreted influence on osteogenesis and concentrations of bone serum markers. Brandao et al.[28] did not show correlation between bone serum markers and duration of the diabetes. Patients with short duration of diabetes (recently diagnosed diabetes) have affected bone formation due to the absence of insulin anabolic effect (in case of diabetes type 1). In case of diabetes type 2, long asymptomatic existence of hyperglycemia may lead to chronic vascular complications that have an impact on bone metabolism. Therefore, the duration of diabetes (in

time of its diagnosis) may not be a relevant indicator for bone metabolism condition screened through analysis of serum markers. (29-31)

Different type of diabetes affect bone metabolism by various mechanisms leading to different results in terms of serum bone markers, but we still need to keep attention on the different quality and quantity of bone tissue that shows changes in the bone structure and bone density (20, 32)

Hongbing et al.[33] show changes in the microarchitecture of the bone tissue, causing increased fragility of bones and decreased remodeling ability, which helps us to understand increased risk of bone damage, typical for this type of patients with unchanged bone quantity and bone density.

Metabolic aspects of diabetes as systemic disorder, directly affect the healing of bone fractures and defects in the jaw bone occurred by osteotomy or through a pathological process (34-36). Bone healing takes place in three phases: the inflammatory phase, the phase of repair and the bone remodeling phase. After the remodeling phase the bone gets its previous building, structure and mechanical durability.

The time required for healing of alveolar bone defects (occurring after operative extraction of impacted teeth, apicotomy or cystectomy) is different and depends on numerous local and general factors including diabetes (37, 23, 38).

Through the above mentioned biochemical analysis, we focus on three main steps of osteogenesis:

- synthesis of extracellular organic matrix (osteoid)

- matrix mineralization

- remodeling (resorption and formation)

Reduced values of bone resorption indicated by significantly lower values of bone resorption marker in subjects with diabetes, suggest reduced bone turnover in this group of respondents. These findings correlate with the findings of Sun[17], Hwang[39], Lappin[40], Bao[41] and Linde[20].

Opposite to our results are the histomorfometric studies of Brandi[5] which did not show changes in bone resorption.

The results of MRA did not show significant impact of CTX on percentage of bone healing in both groups of respondents.

CONCLUSION

Serum values of bone resorption marker CTX in diabetic patients suggested reduced activity of bone metabolism with no influence on bone mineralization process followed by bone density increase in oral surgical defects.

Type of diabetes, duration of diabetes and the degree of regulation (HbA1C) may have an impact on CTX values. The results showed a statistically significant negative correlation between CTX and duration of diabetes. Different types of diabetes do not affect the CTX levels.

The awareness of the possible impact of diabetes and its complications on the mineralization and remodeling of oral-surgical defects followed by simple biochemical analysis will contribute to adequate treatment of these patients in terms of prevention of postoperative complications

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Original scientific paper

INCIDENCA DHE PREVALENCA E HEPATITIT A DHE B NË RAJONIN E GOSTIVARIT 2010-2015

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ABSTRAKTI

Definicioi: Hepatitet virale janë infeksione sistemike që prekin kryesisht mëlçinë, duke shkaktuar dëmtime inflamatore, të cilat histologjikisht karakterizohen nga nekroza parenkimale dhe infiltracionet inflamatore.

Qëllimi: Të analizohet numri i përgjithshëm i pacientëve me Hepatit A dhe B sipas gjinisë dhe grup moshës gjatë periudhës kohore 2010-2015 në Spitalin e Përgjithshëm të Gostivarit.

Materiali dhe metodat: Është analizuar dokumentacioni i pacientëve të regjistruar në Spitalin e Përgjithshëm të Gostivarit në periudhën kohore 2010-2015.

Rezultatet: Tregojnë se Hepatiti A më tepër paraqitet te meshkujt me 59% të rasteve dhe me pak te femrat me 41% të rasteve. Ndërsa Hepatiti B më tepër paraqitet te meshkujt me 71% të rasteve dhe me pak te femrat me 29% të rasteve.

Përfundimi: Hepatiti A është një semundje e cila atakon kryesisht grupmoshat 20-24 vjeç dhe 15-19 vjeç. Hepatiti B atakon më shumë grupmoshat 35-44 vjeç dhe 25-34 vjeç

Fjalët kyçe: Hepatiti A, Hepatiti B

Regjistri i shkurtesave: VHA (Virus i Hepatitit A); VHB (Virus i Hepatitit B)

SUMMARY

Definicion: Viral hepatitis are systemic infections affecting primarily the liver, causing inflammatory damage, which is histologically characterized by parenchymal necrosis and inflammatory infiltration.

Intetion: To analyze the total number of patients with hepatitis A and B by gender and age group during the time period 2010-2015 in Gostivar General Hospital.

Materials and methods: The documentation of patients enrolled in Gostivar General Hospital during the time period 2010-2015 was analyzed.

Results: Show that Hepatitis A appears more in men in 59% of cases and less in women with 41% of cases. While Hepatitis B is more present in men with 71% of cases and less in women with 29% of cases.

Conclusion: Hepatitis A is a disease which mainly attacks the age groups 20-24 years and 15-19 years. While Hepatitis B attacks more age groups 35-44 years and 25-34 years.

Key Word: Hepatitis A, Hepatitis B

HYRJE

Hepatitet virale janë infeksione sistemike që prekin kryesisht mëlçinë, duke shkaktuar dëmtime inflamatore, të cilat histologjikisht karakterizohen nga nekroza parenkimale dhe infiltracionet inflamatore.

Viruse të vërtetë që shkaktojnë dëmtim të hepatocitit, deri më sot njihen: Virusi i Hepatitit A, virusi i Hepatitit B, virusi i Hepatitit C, virusi i Hepatitit D (delta), virusi i Hepatitit E, ndoshta dhe virusi i Hepatitit G.Për sa i përket ekzistencës së viruseve të tjera si virusi F, tani për tani është një hipotezë.Citomegaloviruset, virusi herpe0s simplex, virusi i varicelës dhe herpes zoster, viruset koksaki, virusi i etheve të verdha, Epstein-Barr etj, përgjithësisht quhen hepatite virale vetëm se shkaktojnë alteracione histologjike ne mëlçi.

Hepatiti A

Hepatiti akut A është inflamacion akut i mëlçisë, i vetshërueshëm, me ecuri të mirë e cila gati kurrë nuk kalon në formë kronike.

Sëmundja shkaktohet nga virusi i Hepatitit A (VHA), që është ARN virus.

Virusi i Hepatitit A ne bazë të vetive fiziko-kimike dhe të ngjashmërisë morfologjike, radhitet në familjen Picornaviridae, gjinia Hepatovirus. Virusi veçohet me fekale, në tëmth dhe në mëlçinë e infektuar. Ai ka formë sferike, është pa mbulesë, ka përmasa 27 deri 28 milimetra. Grimca virale mund të ketë struktur të plotë, por edhe të pjesshme.

Virusi i Hepatitit A është i pranishëm në melçi, në bilë, në fece dhe për një kohë të shkurtër në gjak gjatë fazës së fundit të periudhës së inkubacionit. Ky lloj virusi nxit prodhimin e dy lloj antitrupave; në fillim të simpatomalogjisë kemi përgjigje të antitrupave specifikë kryesisht të tipit IgM, ndërsa në periudhën e konvaleshencës mbizotëron prodhimi i antitrupave IgG. Antitrupat IgM vazhdojnë të qëndrojnë në titra të latrë edhe për disa muaj pas episodit akut; ndërsa antitrupat e klasës IgG shfaqen me vonesë por persistojnë për një kohë të gjatë, ndoshta dhe për gjithë jetën. Prania e antitrupave të klasës IgG ndaj VHA është tregues i një infeksioni të kaluar dhe gjendjes imunitare ndaj VHA.

I vetmi burim infeksioni është njeriu i sëmurë, i cili eliminon ne mjedisin e jashtëm me materiet fekale virusin. Për këtë sëmundje nuk ka portatorë kronikë, por virusi eliminohet vetëm nga njeriu i sëmurë qoftë me forma të dukshme të sëmundjes, qoftë në forma të lehta asimptomatike. Eliminimi i virusit nga këta të sëmurë bëhet për një kohë të shkurtër.

Hepatiti A është i përhapur kudo, sëmundja mund të paraqitet si në formë sporadike ashtu dhe epidemike. Përhapjen e infeksionit e favorizojnë kushtet e këqija higjieno-sanitare, prandaj infeksioni dhe sëmundja është më e perhapur në vendet me nivel social-ekonomik të ulët.

Patogjeneza e hepatitit viral te tipit A ende nuk është bërë e qartë.

Simptomat:

Shenjat dhe simptomat e Hepatitit A shfaqen disa javë pas mbartjes së virusit dhe janë:

1. Lodhje
2. Përzierje dhe të vjella
3. Dhimbje barku dhe siklet, sidomos në zonën e mëlçisë, në anën e djathtë nën brinjët e poshtme
4. Ngjyrë e errët e urinës
5. Verdhësim i të bardhës së syve dhe i lëkurës
6. Tepmeraturë e ulët trupore.

Mjekimi:

Për hepatitin viral akut ende nuk ekziston ndonjë mjekim secifik, por për mjekimin e tij mbështetemi kryesisht në regjimin e pushimit dhe në dietën. Regjimi i pushimit për një kohë të gjatë në shtrat nuk është i nevojshëm.

Parandalimi:

Nënkupton respektimin e masave normale higjieno-sanitare për parandalimin e sëmundjeve fekale orale. Imunoprofilaksa pasive rekomandohet për mbrojtje pas kontaktit me të sëmurin deri në dy javët e para të kontaktit dhe ipet në dozë prej 0.02ml/kg të peshës trupore. Mbrojtja është efektive për 3 deri 6 muaj.

Hepatiti B

Hepatiti B është hepatiti më i shpeshtë dhe prek çdo moshë.

Hepatiti B është quajtur edhe hepatit nga serumi, për arsye se sëmundja ishte parë të zhvillohej në personat që kishin marrë gjak apo produktet e tij ose për shkak të përdorimit të shiringave të infektuara me gjak të infektuar. Ky emërtim u përdor për të dalluar këtë lloj hepatiti nga ai që quhej hepatiti “epidemik” ose hepatiti A.

Shkaktar i sëmundjes është virusi i Hepatitit B (VHB)

Virusi i Hepatitit B bën pjesë në familjen e Hepadnaviridae, është virus hepatotrop që përmban ADN dyfishe. Në serumin e të sëmurëve me Hepatit B janë zbuluar tri forma të grimcave virale: sferike, cilindrike dhe Dane. Grimcat sferike dhe cilindrike janë mbizotëruese,por nuk janë infektive; grimcat Dane janë forma infektuese e virusit.

Shenjuesit serologjikë të një infeksioni akut nga VHB bëhen të pranishëm në serum disa javë pas infektimit dhe shumë përpara shfaqjes së shenjave klinike të një hepatitis akut.

Shënjuesi i parë që shfaqet në serum është antigjeni sipërfaqësor i VHB- HBsAG dhe prania e tij në serum është tregues i infeksionit për të ndjekur efektin e trajtimeve antivirale në hepatitet kronike.

Megjithëse patogjeneza e Hepatitit B nuk është plotësuar përfundimisht, shumica mendojnë se ndryshimet hepatocitare që ndodhin si gjatë fazës akute, ashtu edhe asaj kronike janë pasojë e përgjigjes imunitare të organizmit të strehuesit ndaj infeksionit. Sëmundja përhapet me rrugë parenterale, përmes gjakut dhe produkteve të tij, marrëdhënie seksuale të pambrojtura, transmisionit vertikal nga nëna te fëmiu etj.

Simptomat:

1. Urinë e errët
2. Ethe
3. Humbje e oreksit
4. Përzierje dhe të vjella

Dobësi, lodhje dhe verdhësim i lëkurës dhe të bardhës së syve

Mjekimi:

Mjekimi i hepatitit B është simptomatik dhe higjieno-dietik me regjim shtrati. Barnat që mund të përdoren për Hepatitin B janë: Interferoni alfa dhe Lamivudina.

Parandalimi:

Parandalimi i sëmundjes sot bëhet me vaksinim aktiv me tre doza të vaksinës së prodhuar me inxhiniering gjenetik. Vaksinimi fillon pas lindjes dhe është i obligueshëm me ligj.

QËLLIMI I PUNIMIT

- Qëllimi i këtij punimi qëndron në analizën e numrit të përgjithshëm të pacientëve me Hepatit A dhe B;

- Të tregohen llojet e Hepatitit;

- Të tregohet numri i të sëmurëve sipas gjinisë;

- Të tegohet numri i të sëmurëve sipas grup moshës;

- Të gjitha këto të dhëna të marra në Spitalin e Përgjithshëm të Gostivarit me rrethinë të analizohen në mënyrë grafike dhe tabelare.

MATERIALI, METODAT DHE PËRPUNIMI STATISTIKOR

Është analizuar dokumentacioni i gjithsej 39 pacientëve me Hepatit A dhe 13 pacientëve me Hepatit B në grup mosha të ndryshme në Spitalin e Përgjithshëm të Gostivarit.

- Paraqitja grafike dhe tabelare.

Detektimi i Hepatitit A dhe B bëhet përmes aparateve: Abot, Murex, Humana, me metodë të punës Elisa e cila bëhet :

- Mënyra rapide
- Pisiar metoda
- NAT – nukleare
- Riad metoda

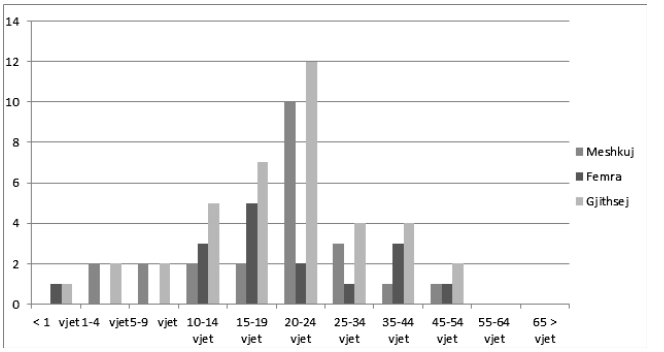
REZULTATET

Në këtë temë është analizuar dokumentacioni i 39 pacientëve me Hepatit A dhe 13 pacientëve me Hepatit B.

Tabela 1. Paraqet numrin e pacientëve me Hepatit A sipas grupmoshës në Spitalin e Përgjithshëm të Gostivarit me rrethinë gjat periudhës kohore 2010-2015

	< 1 vjet	1-4 vjet	5-9 vjet	10-14 vjet	15-19 vjet	20-24 vjet	25-34 vjet	35-44 vjet	45-54 vjet	55-64 vjet	65 > vjet	Gjithsej	
M	0	2	2	2	2	10	3	1	1	0	0	**M**	**F**
F	1	0	0	3	5	2	1	3	1	0	0	23	16
GJ	1	2	2	5	7	12	4	4	2	0	0	39	

Grafikoni 1. Paraqet numrin e pacientëve me Hepatit A sipas grupmoshës

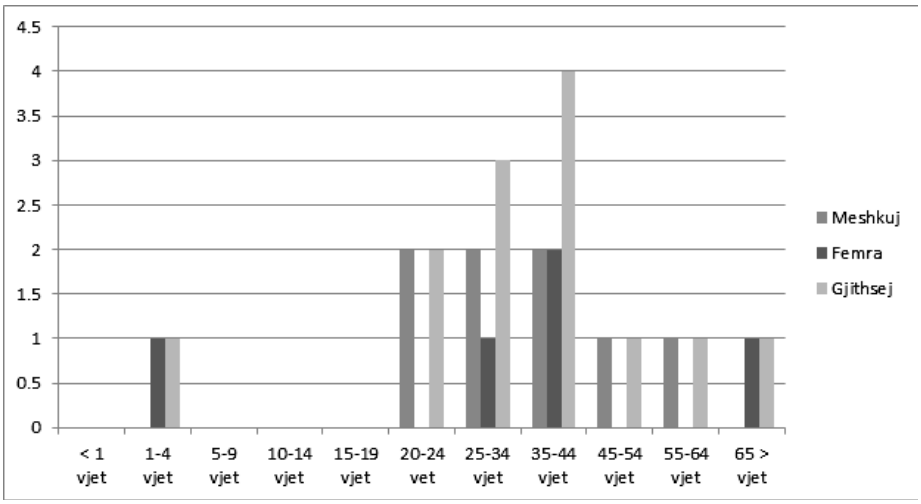


Koment: Në tabelë 1 dhe grafikonin 1 shihet se më të prekur janë pacientët e grupmoshës 20-24 vjet, ku 10 prej tyre janë meshkuj dhe 2 femra.

Tabela 2. Paraqet numrin e pacientëve me Hepatit B sipas grupmoshës në Spitalin e Përgjithshëm të Gostivarit me rrethinë gjat periudhës kohore 2010-2015

	< 1 vjet	1-4 vjet	5-9 vjet	10-14 vjet	15-19 vjet	20-24 vjet	25-34 vjet	35-44 vjet	45-54 vjet	55-64 vjet	65 > vjet	Gjithsej	
M	O	0	0	0	0	2	2	2	1	1	0	**M**	**F**
F	0	1	0	0	0	0	1	2	0	0	1	8	5
GJ	0	1	0	0	0	2	3	4	1	1	1	13	

Grafikoni 2. Paraqet numrin e pacientëve me Hepatit B sipas grupmoshës

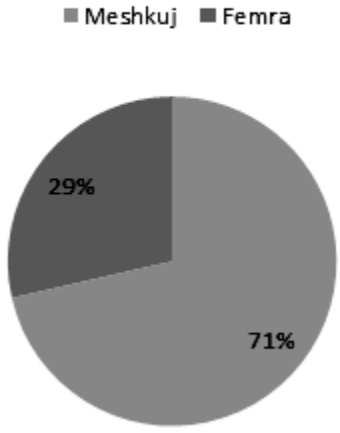


Koment: Nga Tabela 3 shihet se prej 39 pacientëve me Hepatit A, 23 pacientë janë meshkuj dhe 16 pacientë janë femra. Ndërsa nga Grafikoni 3 shihet se 59% e pacientëve me Hepatit A janë meshkuj dhe 41% janë femra.

Tabela 4. Tregon numrin e përgjithshëm të pacientëve me Hepatit B meshkuj dhe femra të marrë nga Spitali i Përgjithshëm i Gostivarit me rrethinë gjatë periudhës kohore 2010-2015

Meshkuj	Femra	Gjithsej
8	5	13

Grafikoni 4. Tregon numrin e përgjithshëm të pacientëve me Hepatit B meshkuj dhe femra të marrë nga Spitali i Përgjithshëm i Gostivarit me rrethinë gjatë periudhës kohore 2010-2015



Koment: Nga Tabela 4 vërehet se prej 13 pacientëve me Hepatit B, 8 pacientë janë meshkuj dhe 5 pacientë janë femra. Ndërsa nga Grafikoni 4 shihet se 71% e pacientëve me Hepatit B janë meshkuj dhe 29% janë femra.

5. PËRFUNDIMI

Në bazë të rezultateve mund të përfundojm si vijon:

1. Hepatiti A është rasti më i shpeshtë i Hepatitit dhe paraqitet kryesisht te pacientët meshkuj me 59% të rasteve.
2. Më shpesh paraqitet te pacientët e grupmoshës 20-24 vjeç.

Shkaktarë të Hepatitit A janë kushtet e këqija higjieno-sanitare ndërsa shkaktarë të Hepatitit B janë përdorimi i shiringave të infektuara me gjak të infektuar, mardhëniet seksuale të pambrojtura etj.

Në këtë punim janë analizuar 39 pacientë me Hepatit A dhe 13 pacientë me Hepatit B, të cilët ishin evidentuar në listë e pacientëve me Hepatit në Spitalin e Përgjithshëm të Gostivarit gjatë periudhës kohore 2010-2015.

Nga 39 pacientë me Hepatit A janë 23 meshkuj ose 59% dhe 16 femra ise 41%, ndërsa nga 13 pacientë me Hepatit B janë 8 meshkuj ose 71% dhe 5 femra ose 29%.

Sa i përket grup moshës, grup mosha më e atakuar me Hepatit A është grup mosha 20-24 vjeç, ku prej tyre 10 pacientë janë meshkuj dhe 2 pacientë janë femra, ndërsa grup mosha më e atakuar me Hepatit B është grup mosha 35-44 vjeç, ku prej tyre 2 pacientë janë meshkuj dhe 2 pacientë janë femra.

6. LITERATURA

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Original scientific paper

INCREASED COX2 GENE EXPRESSION IN COLORECTAL CANCER: CLINICAL AND MOLECULAR STUDY

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ABSTRAKTI

Objective: Colorectal cancer (CRC) is most frequent malignant disease of the gastrointestinal tract with multifactorial etiology. Multiple genetic abnormalities are involved in the molecular transformation of the normal to neoplastic colorectal epithelium. Expression of cyclooxigenase-2 gene (COX2) is reported to be increased in CRC, but the results from different studies are rather contradictory. The aim of this study was to investigate the correlation of COX2 expression levels with the main clinicopathological parameters in a group of patients with CRC.

Methods: A total of 65 patients with histopathologically confirmed CRC was included in the study. Total RNA was isolated form matched tumor and normal colorectal mucosa from each patients and quantitative real-time PCR was used to determine the COX2 expression levels normalized to mucosa levels. Correlation of COX2 expression with tumor location, histopathological grade of differentiation and TNM stage was calculated by logistic regression and Mann-Whitney test.

Results: No statistically significant differences were observed regarding the COX2 gene expression values and tumor location or grades of malignancy ($p>0.05$). However, the differences were significant when subgroups of patients with different TNM stages were compared ($p=0.003$).

Conclusions: The results from our study indicates that COX2 gene expression increase with TNM stage in CRC patients and could be used as a potential biomarker for tumor progression and dissemination.

Key words: colorectal cancer, COX2 gene, gene expression

INTRODUCTION

Colorectal cancer is most frequent malignant disease of the gastrointestinal tract and has a multifactorial etiology where genetic background, environmental factors, inflammatory diseases and other factors contribute to malignant alteration of the normal epithelium of the colonic mucosa through multiple stage process of genetic and epigenetic alterations accumulation. It is already established for more than 25 years that the step-by-step progression of normal epithelium to malignant transformed carcinoma in-situ and to invasive carcinoma is followed by consecutive chain of molecular and genetic abnormalities (1). The results of huge number of conducted studies confirmed that single molecular abnormalities such as gene mutations, changes of the gene expression levels, single nucleotide polymorphisms (SNPs), DNA methylation, genomic instability and chromosomal aberrations contribute to this transformation processes (2).

Cyclooxygenase (COX) is an enzyme that is involved in the biosynthesis of prostaglandins and thromboxanes, which are key regulators of inflammation, cell proliferation and angiogenesis. Thus far, two functional cyclooxygenase isoforms were discovered: COX-1, with constitutive tissue expression, and COX-2, which has an inducible expression regulation and is associated with different pathological processes (3). COX-2 (PTGS2) gene is located in chromosomal locus 1q25.2-q25.3 and encodes the cyclooxygenase-2 enzyme that has a key role in the synthesis of prostaglandins and thromboxanes which further stimulate inflammation, cell proliferation and angiogenesis. All these processes have important role in the pathogenesis of colorectal cancer (4). The results of several studies indicated that the overexpression of

COX-2 gene is frequently found in more than 80% of patients and therefore is correlated with significantly worse prognosis and high probability for metastasis of CRC (5, 6). Anatomic disproportion of the increased COX2 expression regarding the left and right colon was reported by some authors (7). In addition, the determination of the intratumoral COX2 expression levels were found to be a predictive factor for effectiveness of the adjuvant chemotherapy in CRC patients (8).

The published studies investigating the COX-2 gene expression correlation with matched patients' clinical and laboratory data have frequently leaded to rather contradictory results. The main goal of this study is to establish the correlation of COX-2 gene expression levels with major clinical and pathological parameters among the population of Macedonian patients with colorectal cancer.

METHODS & MATERIAL

Patients and samples

In this study we have investigated the tumor and matched normal mucosa tissue samples derived from a total of 65 randomly selected patients that were treated at the University Clinic for Digestive Surgery in Skopje from March 2015 to August 2016. After signing the written consent for participation in the study and its approval by the Ethics Committee at the Medical Faculty, patients with histopathologically confirmed diagnosis of colorectal adenocarcinoma were recruited in the study. The tumor samples were taken from the central tumor mass immediately after intervention and normal mucosa sample were excised at least 10 cm from the visible tumor edge.

Quantitative Real-Time PCR assay of *COX2* mRNA levels

Total RNA was isolated from each matched tumor and normal mucosa samples by TRIzol reagent (Life Technologies) following the manufacturer's protocol. Subsequently, the RNA concentration was determined in each isolate quantitatively by Qubit fluorimeter and broad range RNA reagent (Life Technology).

A two-step quantitative Real-Time PCR (qRT-PCR) was used for determination of COX2 expression levels. In the first step, the complementary DNA (cDNA) was synthesized by High-Capacity cDNA Reverse Transcription Kit with RNase Inhibitor (Applied Biosystems) using 1 μg of isolated RNA from each sample and random hexamer primers, according to the instructions of the manufacturer. The samples were incubated at 20°C for 10 min and 42°C for 60 min, and reverse transcriptase was inactivated by heating at 95°C for 10 min.

In the second step, cDNA was amplified by TaqMan Gene Expression Master Mix (Applied Biosystems) in StepOne Real-Time PCR System (Thermo Fisher). The following primers and probe were used: COX2, 5'-GAA TCA TTC ACC AGG CAA ATT G-3' and 5'-TTT CTG TAC TGC GGG TGG AAC-3'; COX2 probe, 5' FAM-TTC CTA CCA CCA GCA ACC CTG CCA-NFQ 3'; 18SrRNA, 5'-CGG CTA CCA CAT CCA AGG AA-3' and 5'-GCT GGA ATT ACC GCG GCT-3'; 18SrRNA probe, 5' VIC-TGC TGG CAC CAG ACT TGC CCC TC-NFQ 3' as described elswere (9). Both oligonucleotide primers and fluorescent probes, as well as qRT-PCR consumables, were ordered from Applied Biosystems.

The following amplification run protocol was used: activation of DNA polymerase at for 10 min, following by 40 cycles, each consisting of: denaturation at 95°C for 15 s and combined annealing and elongation at 70°C for 1 min). In addition, a non-template control (ddH_2O control) was included for each master mix.

The quantitative gene expression levels were estimated as a $\log_{10}$ of relative quantity (RQ) values calculated by the $2^{-\Delta\Delta Ct}$ method described by Livak (10). The ΔCt value was calculated by subtracting the Ct parameter (threshold cycle) for the housekeeping 18SrRNA gene from the Ct value of the target COX2 gene in the same RNA sample. The ΔΔCt represented the difference between the matched tissue samples from the same patient, calculated as ΔΔCt = (ΔCt of tumor sample - ΔCt of normal mucosa). Triplicate measurements of each sample were included in the calculations. The folds of differential expression of the COX2 gene in a tumor sample compared to the normal mucosa sample (i.e. RQ) was calculated by the formula: $2^{-\Delta\Delta Ct}$. In our study, we have presented the final COX2 gene expression values for each patient as a logarithm of RQ with base 10, i.e. as: $\log_{10}(RQ)$.

STATISTICAL ANALYSIS

Normality of data distribution of each series was estimated by Shapiro-Wilk test. Comparison of COX2 gene expression levels between the groups of patients with different clinicopathological characteristics was calculated by non-parametric two-tailed Mann-Whitney test with applied continuity correction. Correlation between the TNM stages (as ordinal variables) and the quantitative COX2 expression levels was calculated using logistic regression model at 95% confidence interval. The statistical significance threshold was set to $p < 0.05$.

Statistical analyzes were performed using the XLStat 2016 software extension installed on Microsoft Excel 2016.

RESULTS

The basic demographic and clinicopathological parameters for the 65 patients with CRC that were investigated in our study are shown in the Table 1.

Conclusion: Hepatitis A is a disease which mainly attacks the age groups 20-24 years and 15-19 years. While Hepatitis B attacks more age groups 35-44 years and 25-34 years.

Table 1. Basic demographic and clinico-pathological patients' data

Parameter	**Values**	
Age: average ± SD (range)	64.82 ± 9.20 years (39 - 86)	
Gender	n	**%**
Males	38	58.46
Females	27	41.54
Total	65	100.00
Tumor location	n	**%**
Proximal	13	20.00
Distal and rectum	52	80.00
Total	**65**	**100.00**
TNM Stage	**n**	**%**
I	5	7.69
Iia	17	26.15
Iib	3	4.62
Iic	0	0.00
IIIa	1	1.54
IIIb	22	33.85
IIIc	12	18.46
Iva	2	3.08
Ivb	3	4.62
Total	65	100.00
Tumor Grade	**n**	**%**
Low	2	3.08
Intermediate	60	92.31
High	3	4.62
Total	65	**100.00**

SD = standard deviation

Regarding the clinicopathological parameters, differences between the COX2 gene expression values were compared among the subgroups of patients using logistic regression analysis (Figure 1, Table 2). Differences regarding the tumor location in proximal (caecum, colon ascendens, colon transversum until the splenic flexure) vs. distal/rectal (from the splenic flexure, colon descendens, colon sigmoideum and rectum) anatomical location were not statistically significant (p= 0.876).

According to histopathological analysis, all investigated tumor samples were characterized as low, intermediate and high grade of malignancy. No statistically significant difference was observed between the subgroups of patients with those 3 grades of malignancy (p= 0.940).

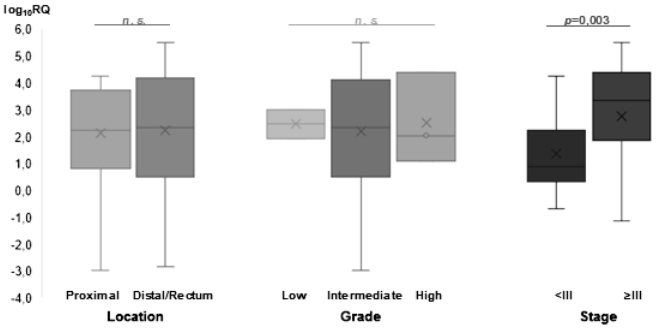

Figure 1. Differences between the COX2 gene expression values among different clinicopathological subgroups of patients depicted in box-plot format. n. s. = non-significant.

However, comparison of the subgroups of patients with different TNM stages revealed that the differences were significant analyzing the COX2 gene expression values (p=0.003). Considering that the number of patients with some of the TNM stages was low (stages I, IIb, IIIa, Iva and IVb) or zero (stage IIc), the analysis was additionally performed comparing the COX2 expression with a subgroup of patients having stages lower than III (abbreviated as <III on the figure), with those having stages III and above (depicted as ≥III). This analysis was performed using Mann-Whitney test and the differences were found to be statistically significant (p=0.004).

Table 1. Statistical parameters of COX2 gene expression values among different clinicopathological subgroups of patients

Parameter	Location		Grade			Stage	
Values	**Prox.**	**Dist. / Rect.**	**Low**	**Inter.**	**High**	**<III**	**≥III**
n	13	52	2	60	3	25	40
Mean	2,12	2,24	2,46	2,19	2,50	1,36	2,75
Max	4,26	5,51	3,02	5,51	4,38	5,22	5,51
Min	-2,97	-2,85	1,91	-2,97	1,08	-2,85	-2,97
SD	2,05	2,24	0,78	2,26	1,69	1,74	2,29
SE	0,57	0,31	0,55	0,29	0,98	0,78	0,56

Abbreviations: Prox.=proximal; Dist. /Rect.=distal/rectum; Inter.=intermediate; Max=maximal; Min=minimal; SD=standard deviation; SE=standard error.

DISCUSSION

Colorectal cancer is a major health issue with increasing global incidence. Despite the advances in diagnosis and treatment, CRC is associated with unacceptably high mortality (11). At molecular level, one of the numerous genetic abnormalities described in CRC is deregulation of COX2 gene expression. Consequences of this phenomenon are numerous, considering the cyclooxygenase enzyme is involved in the biosynthesis of prostaglandins and thromboxanes, which are regulators of biologic processes such as inflammation, cell proliferation and angiogenesis (12).

In our study, we have determined the normalized COX2 expression levels in 65 patients with CRC and analyzed the possible correlation with tumor location, grade of differentiation and TNM stage. We found statistically significant differences of COX2 gene expression values in subgroups of patients with different TNM stages, but not in subgroups differing in the tumor location or grades of malignancy. However, our patient sample size was rather low and substratification into grade and stage subgroups leads to further reduction of statistical analyses strength. Nevertheless, the significant correlation of COX2 expression with TNM stage indicates involvement of this gene in tumor progression and aggressiveness.

Previous studies indicates that the expression of COX2 gene is normally absent in most non-neoplastic cells in both humans and animals (13). Various pro-inflammatory and proliferation-stimulatory agents and stimuli could lead to immediate induction of COX2 expression that, consequently, result in increased synthesis of PGE2 (14). Reports of COX2 gene overexpression in CRC are published more than 20 years ago (15). In that study, Ebehart et al. investigated COX2 gene expression on mRNA level using Northern blotting and found that the expression of this gene is markedly increased in 86% of CRC samples and in 43% of adenomas, compared with normal mucosa. Many other studies indicated similar results, demonstrating correlation between different patient and tumor characteristics, survival and prognosis with COX2 gene expression (16-19). These studies indicates that COX2 gene is overexpressed in approximately 80% of CRC samples and has been associated with tumor invasiveness, resistance to apoptosis, as well as to the increased tumor angiogenesis. Increased COX2 gene expression levels were identified in premalignant and malignant neoplasms and there are an evidence that that could have tumor-promoting effects and is associated with reduced survival of patients with different cancer types (20). Clinical studies that demonstrated the CRC-risk reducing effects of non-steroid anti-inflammatory drugs (NSAID) such as aspirin and other COX-inhibitors was first direct indication of the relationship between COX2 gene expression and colorectal cancer (21).

The results of some animal genetic studies (Oshima et al., 1996) indicates that there is a significant decrease in intestinal polyposis in COX2-deficient mice (22). The results from those studies leads to idea that long-term gene overexpression is pathological and advocate pharmacological COX2 inhibition in order to inhibit the CRC development and progression.

However, although COX2 inhibitors lower the incidence of CRC and other neoplasms, its long-term administration is associated with reduced survival in patients which already have CRC and with other adverse effects (12).

In summary, our study indicates the correlation of COX2 expression with TNM stages in Macedonian patients with CRC and further support the role of abnormally increased COX2 gene expression in tumor progression and dissemination. Potential use as a biomarker is possible after validation in larger patient size studies.

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Original scientific paper

GENITO URINARY ADVERSE EFFECTS FOLLOWING RADIATION THERAPY TREATING PELVIC MALIGNANCY

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ABSTRACT

Introduction: The objective of study is to evaluate and analyze acute and late toxicity of GU genito-urinary tract, estimating GFR as a marker of kidney function, and investigate adverse effect of treatment according RTOG scoring system at the at 3-rd and 6-th month of treatment.

Material and methods: This study is done at Clinical Center of Kosovo, Oncology Department. 75 patients are evaluated where several variables have been investigated: sex, age, type of primary malignancy, Median TD (tumor dose) evidence over 50 and above 50 Gy. At the beginning, at 3rd and 6th of the treatment patient have been followed by fulfilling in the questioner according RTOG scoring system. Chemotherapy have been employed based on primary tumor site concurrently with radiotherapi Median follow up (FU) have take 6 months.

Excluding criteria: Patients with PGUM (Pre Treatment GenitoUrinary Morbidity). G0 of RTOG score at the beginning of treatment to all patients

Results: Our cohort consist of 75 patients with pelvic tumors of which 53 or 70.7% were female and 22 or 29.3% of male. The average age of the patients involved in the research was 57.5 years (SD ± 11.2 years) range 33-77 years. The average age of the female patients involved in the research was 56.1 years (DS ±11.1 years), range 33 – 77 years. The average age of the male patients involved in the research was 60.8 years (SD ±11.1years), range 37 – 74 years. Females are with 3 various types of carcinomas (cervical and endometrial) and males with only 1 (rectal). The 75 patients involved in the research 30 or 40.0% were rectal carcinomas, 28 or 37.3% were cervical carcinomas and 17 or 22.7% were endometrial carcinomas. Conclusions: No significant differences in treatment related site effects between radiotherapy and hemoradiation groups were found. In the follow up after 3 months from 75 patients involved in the research, 11 patients (14.7 %) had G1 GU toxicity that did not need any kind of treatment. 5 patients (6.7%) had G2 GU toxicity. Whereas in the follow up after 6 months 15 patients (20%) had G1 GU toxicity, 7 patients (9.3%) G2 GU toxicity and 4 patients (5.3%) had G3 GU toxicity.

Compering grade of toxicity between follow up 3 and 6 months no significant differences have been appeared according RT treatment.

Key words: Urinary toxicity, adverse effects RTOG, pelvic radiotherapy.

INTRODUCTION

The American Cancer Society estimate for 2016 in the USA tumors arising in the pelvic including uterus, cervix, rectum account for 168,260 new cases will be diagnosed[1].

Concurrent hemoradiation has improved survival of patients with cervical carcinoma and rectal carcinoma.

The development of radioactivity by Henri Becquerel in 1896 and the discovery of radium by Marie and Pierre Curie in 1898 led to a new period in medical technology[2]. Pelvic radiotherapy (RT) now plays an important role in the management of these cancers. This treatment modality has been shown to have both early and late morbidity. The radiation-induced damage to tissue architecture develops in a linear threshold model. Damage to the basement membranes of blood vessels can lead to occlusion, thrombosis and neovascularization. The atrophy and contraction of tissue results from increased proliferation

of fibroblasts[3]. All these changes have the potential to cause significant urinary tract injury. Bladder damage and loss of capacity can cause significant urinary symptoms. Neovascularization is an important factor for radiation cystitis and subsequent hemorrhagic cystitis. Replacement of the corpus spongiosum with fibrosis and subsequent occlusion of the urethral lumen is an important factor for the increased incidence of urethral strictures after RT[2].

Acute and late urinary adverse effects (AEs) are usually graded using the Radiation Therapy Oncology Group (RTOG) system, which grades AEs on a scale of 0-4.

RTOG Acute Radiation Morbidity Scoring Criteria[4]

0. No change
1. Frequency of urination or nocturia twice, pretreatment habit/dysuria, urgency not requiring medication.
2. Frequency of urination or nocturia, that is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic.
3. Frequency with urgency and nocturia hourly or more frequently/dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/gross hematuria with/without clot passage.
4. Hematuria requiring transfusion/acute bladder obstruction not secondary to clot passage, ulceration or necrosis.

MATERIALS AND METHODS

This is a retrospective study for the patients that have been finished treatment of RT or CCRT.Follow up have been done after 3 and 6 months . This study has been done in Institute of Oncology in Prishtina, Kosovo.

Including criteria

1. pelvic carcinomas, cervical endometrial and rectal treated based on criteria for adjuvant treatment according NCCN Guidelines version 2. 2015.

Excluding criteria:

1. patients with PGUM (Pre Treatment Genito Urinary Morbidity).
2. patients that in the beginning of treatment have had G score from RTOG more than 0

Our cohort consist of 75 patients with pelvic tumors of which 53 or 70.7% were female and 22 or 29.3% of male. The average age of the patients involved in the research was 57.5 years (SD ± 11.2 years) range 33-77 years. The average age of the female patients involved in the research was 56.1 years (SD ±11.1 years), range 33 – 77 years. The average age of the male patients involved in the research was 60.8 years (SD ±11.1years), range 37 – 74 years.

Gynecological cancer and rectal cancer were treated with adjuvant radiotherapy or concurrent radio chemotherapy depends by stage and site of cancer.

The radiation therapy technique and doses were strictly defined and identical for all regimens.

Patients have been treated by whole pelvic RT with different site of pelvic carcinomas, following the International Commission on Radiation Units and Measurements (ICRU) No. 50 recommendations[5].

The clinical target volume (CTV) have been define as pelvic lymph nodes and primary tumor region and have been contoured on individual axial CT slices. The lymph node regions have been determine by encompassing the blood vessels with a 2 cm margin and based upon primary tumor site. The planning target volume (PTV) have been create expanding the CTV by 1 cm. The dose have been prescribe, to encompass at least 95% of the PTV, ranged from total dose of 45 Gy or 50 Gy, administrated in 1.8 -2 Gy per fraction delivered in 25 to 30 daily fraction. Treatment planning have been generate using the Xio software for 3D RT. Dose volume restrictions used for pelvic OARs have been described.

In the 3D CRT, whole pelvic irradiation was delivered by anterior-posterior and posterior-anterior parallel ports or a four field box technique utilizing x-ray energies of 15 MV. Plans have been based on pelvic isocentric conformal fields with energy of 15-MV and patients have been treated with a Simens linear accelerator, equipped with 80-leaf multileaf collimator. The pelvic field extended from the upper margin of L5 to the midportion of the obturator foramen or the lowest level of disease with a 3 cm margin and laterally 1.5 to 2 cm beyond the lateral margins of the bony pelvic wall (at least 7 cm from the midline). For lateral fields, the anterior border was the pubic symphysis and the posterior border was the space between S2 and S3. The fields have been modified to include areas of known tumor.

Modification as necessary to include areas of known tumor where allowed according RTOG.

Measurements for renal function before treatment were: urea, creatinine, GFR (Cockroft-Gault), urological echo and urine sediment.

CreatClear = Sex * ((140 - Age) / (SerumCreat)) * (Weight / 72)

Equation parameters such as Sex have two or more discrete male 1, female 0.85 values that may be used in the calculation[6].

After 3DCRT, patients were followed up between 3 and 6 months with. Image studies were done when specific complaints occurred. Urinary Toxicity – acute urinary toxicity was considered three months of the end of 3DCRT, late urinary toxicity was considered after six months of the end of 3DCRT, and was graded according questioner on Table-1. Information about patient complaint was obtained by physician interview.

Questioner

Adverse Event: Date of Treatment: Course Number:

Date of onset: Grade at onset:

Date of first change in grade: Grade:

Date of next change in grade: Grade:

Did adverse event resolve? Yes_____ No _____

If so, date of resolution of adverse event:

Date of last observation

(if prior to recovery):

Reason(s) observations stopped

(if prior to recovery):

Was patient retreated? Yes_____ No _____

If yes, was treatment delayed for recovery? Yes _____ No _____

Date of next treatment?

Doe reduced for next treatment? Yes _____ No _____

Follow up was done at 3 and 6 months with: urea, creatinine, GFR (Cockroft-Gault), urological echo and urine sediment, cystoscopy where needed.

Data processing was done with statistical package SPSS. The obtained data are presented with tables and graphs. From the statistical parameters are calculated index structure, the arithmetic mean, and standard deviation, minimum and maximum values.

Testing of qualitative data was done with X2 – test, quantitative data that did not have a normal distribution with the Kruskal -Wallis test and Mann - Whitney test. Testing of quantitative data that had normal distribution with One Way ANOVA and T - test .Verification of tests was made with 99.7 % confidence level (P < 0:01) and the reliability of 95% (P<0.05).

RESULTS

Table 1. Patients involved in research by group and gender

Age (years)		Sex				Total	
		F		M			
		N	%	N	%	N	%
30-39		5	9.4	2	9.1	7	9.3
40-49		9	17.0	1	4.5	10	13.3
50-59		17	32.1	5	22.7	22	29.3
60-69		15	28.3	10	45.5	25	33.3
70+		7	13.2	4	18.2	11	14.7
In total	N	53	100.0	22	100.0	75	100.0
	%	70.7	-	29.3	-	100.0	-

Table 2. Acute toxicity of GU Tract according to the RTOG scoring system at 3 and 6 months

Gender	No	G 0		G 1		G 2		G 3		G 4	
Follow up		3 mths	6 mths	3 mths	6 mths	3 mths	6 mths	3 mths	6 mths	3 mths	6 mths
F	53	41	35	10	11	2	5	0	2	0	0
M	22	18	14	1	4	3	2	0	2	0	0

From 75 patients involved in the research, at 3 months follow up 11 patients had G1 toxicity that did not need any kind of treatment. They appear minor symptoms. 10 from them are female and 1 male. With G2 toxicity are 5 patients that needs simple outpatient management.

Whereas follow up on 6 months 15 patients had G1 toxicity, 7 patients had G2 toxicity and 4 G3 toxicity from which 3 of them have need hospitalization daily catheterization and 1 of them requiring nephroureterectomy.

Table 3. Acute toxicity of GU Tract according to group Age

Group Age	No	G 0		G 1		G 2		G 3		G 4	
Follow up		3 mths	6 mths	3 mths	6 mths	3 mths	6 mths	3 mths	6 mths	3 mths	6 mths
30-39	7	6	4	0	1	1	2	0	0	0	0
40-49	10	8	8	2	2	0	0	0	0	0	0
50-59	22	16	14	5	6	1	1	0	1	0	0
60-69	25	21	16	2	4	2	2	0	3	0	0
over 70	11	8	7	2	2	1	2	0	0	0	0

Table 4. Acute toxicity of GU Tract according site of treatment – diagnoses

Diagnoses	No	G 0		G 1		G 2		G 3		G 4	
Follow up		3 mths	6 mths	3 mths	6 mths	3 mths	6 mths	3 mths	6 mths	3 mths	6 mths
Endometrial cancer	17	13	11	3	2	1	3	0	1	0	0
Rectal Cancer	30	26	20	1	5	3	3	0	2	0	0
Cervical Cancer	28	20	18	7	8	1	1	0	1	0	0

Table 5. Acute toxicity of GU Tract according to treatment

Treatment	No	G 0		G 1		G 2		G 3		G 4	
Follow up		3 mths	6 mths	3 mths	6 mths	3 mths	6 mths	3 mths	6 mths	3 mths	6 mths
CCRT	50	39	35	8	9	3	3	0	3	0	0
RT	25	20	14	3	6	2	4	0	1	0	0

Table 6. Acute toxicity of GU Tract according to dose of treatment

Doses	No	G 0		G 1		G 2		G 3		G 4	
Follow up		3 mths	6 mths	3 mths	6 mths	3 mths	6 mths	3 mths	6 mths	3 mths	6 mths
Over 50 Gy	35	25	7	8	3	2	2	0	1	0	0
Under 50 Gy	40	34	7	3	3	3	2	0	0	0	0

DISCUSSION

Grade 1 and 2 AEs are commonly managed with observation or medical therapy and have minimal impact on quality of life. Grade 3 and 4 AEs are considered severe. These are often managed with a procedure and have a significant impact on quality of life.

In this retrospective study, we examined the incidence of acute and late radiation-induced side effects among patients curatively treated for cervical cancer, rectal and endometrial cancer that were followed fora 6 month period of time. The results revealed that grade 2 radiation-induced side effects occurred in a relatively large proportion of patients of which the majority suffered from urinary tract toxicities.

We expect to see urinary AEs following RT for rectal cancer due to the close proximity of the rectum to the bladder, as well as its blood and nerve supply. One trial reported urinary AEs such as frequency, cystitis, incontinence, urinary retention, and ureteral stricture[7].

CONCLUSION

Urinary AEs can manifest long after RT, and there is a paucity of studies describing rates of these long-term AEs. It is important that the possible complications of RT are recognized by providers and properly managed.

Grade 1 and 2 are relatively frequent side effects in curatively treated patients, but are not enhanced by the addition of chemotherapy. Their negative impact on health-related quality of life stresses the importance of new radiation techniques, that can reduce side effects.

Compering grade of toxicity between follow up 3 and 6 months no significant differences have been appeared according RT treatment.

Grade 3 AEs mostly have been appeared according to locally advanced cancer and progression after treatment.

Conflict interest statement.

There is no conflict interest of author and coauthor.

The work for publication is sent only to your Journal.

ABBREVIATION

GFR – Glomerular Filtration Rate

AEs – Adverse Effects

OAR - Organ At Risk

RT – Radio Therapy

GU – Genito Urinary

3DCRT – 3D Conformal Radio Therapy

TD – Tumor Dose

FU – Follow Up

PGUM - Pre Treatment Genito Urinary Morbidity

SD – Standard Deviation

CCRT - Concurrent chemo-radiotherapy

Gy – Grey

CTV - Clinical Target Volume

PTV - Planning Target Volume

RTOG – Radiation therapy oncology group

NCCN – National comprehensive cancer network

ICRU - International Commission on Radiation Units and Measurements

ANOVA – Analysis of Variance statistical test

SPPS – Software Package For Statistical Analysis

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Profesional paper

SOME DATA ABOUT ECTOPARASITES INFECTION OF DOGS FROM TETOVA, MACEDONIA

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ABSTRACT

The data about the ectoparasites in dogs of Tetova region, Macedonia are very few. The aim of this study was to identify tick species infecting dogs of this region. Ectoparasites were collected from 126 dogs during 2017; the specimens were identified and separated according to species. Rhipicephalus sanguineus was found on 47.6% of the dogs and Ixodes ricinus in18.2%, they were the most frequent tick species found in the dogs taken into study. The presence of the ectoparasites in the dogs may have implications for their health and may have also zoonotic importance.

Key words: dogs, ectoparasites, infection, prevalence.

INTRODUCTION

Ectoparasites are a common and important cause of skin diseases in dogs worldwide. The aim of this study was to identify tick species infecting dogs of Tetova region in Macedonia and determine their prevalence. Ectoparasites cause important diseases as life-threatening anemia and occasionally hypersensitivity disorders (Araujo et al. 1998). Some ectoparasites of dogs can also infect humans so they are zoonosis and may cause dermatitis and transmit vector-borne diseases (Scott et al. 2001). Cases of human parasitism such as Astrakhan fever have been reported by Rhipicephalus sanguineus from southeastern Europe (Fournier et al. 2003). Ticks cause paralysis, the condition caused by toxins found in the saliva of ticks (Xhaxhiu et al. 2009). Health routine check-ups and measures taken from the vets protect pets from ectoparasites infection.

MATERIALS AND METHODS

In the present investigation, ectoparasites were collected from 126 dogs from different breeds and age (6 months– 10 years). The dogs were examined for ectoparasite infection by a complete examination of the skin. The skins of all dogs were palpated and visually inspected thoroughly for the presence of ticks. All ticks were manually removed carefully to ensure that the mouthparts remained intact and collected together with any fleas and lice in the comb. The ticks removed from the animals were stored in 70% ethanol. The ticks are identified microscopically at 40× using the diagnostic keys (Anon 1966, Estrada-Pena et al. 2007).

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RESULTS

A total of 126 dogs were randomly selected from Tetova region, Macedonia during the four time periods. Samples were collected in spring, summer, autumn and winter seasons. 83 out of 126 referred dogs (65.8%) were positive for external ectoparasites. The most common ectoparasites found were ticks Rhipicephalus sanguineus on 60 dogs followed by Ixodes ricinusx in 23 dogs. The calculation prevalence was for Rhipicephalus sanguineus 0.48 and for Ixodes ricinus 0,37. According to our results the infection was more prevalent during the spring and summer period. The prevalence of infection was higher in dogs <1 year old and there was not observed any difference between the sexes. Large dog breeds were more frequently affected by all ectoparasites than the smaller breeds. The most common clinical sign among the animals examined was pruritus.

DISCUSSION

Ectoparasites live on, feed on and inhabit the external body surfaces of vertebrates, including dogs (Wall, 2001). The ectoparasites also are vectors for a variety of infectious agents such as Babesia spp., Ehrlichia spp., Anaplasma spp., Rickettsia spp., etc or act as intermediate hosts. Some of this infectious agents cause serious diseases in dogs and people in contact with them (Little, 2009). They sometimes can be highly pathogenic and according to parasitism intensity and the host's immunological condition may even cause death (Scott et al., 2001). In the dog with tick infections common founds are eosinophilia and low hematocrit levels. The present study presents the prevalence of infestations in companion dogs Tetova, Macedonia. It was revealed that 65.8 % of the dogs analysed were infected to ectoparasites. From a total of 126 dogs the species of ectoparasites identified and their prevalence rates were: R. sanguineus 0,48 and for I. ricinus 0.37. These results indicate that ectoparasites are relatively common in this area, as many parts of the world. And also according to our study R. sanguineus and I. ricinus were the most abundant ectoparasites found. The ticks feed on a wide range of hosts however; all stages of R. sanguineus are primarily associated with dogs (Dantas-Torres 2008) and this parasite is a very common finding on the dogs of our study. Because older animals may acquire immunity, puppies taken in the study appeared to be most susceptible to ectoparasites but of course the difference was not significant. Also the sex of the dog's did not showed any significant differences. Summer-autumn was the period when the most positive dogs infected was found, this is understandable knowing that this period is the most appropriate for the parasites due to the higher temperature and humidity. It is a known fact that ectoparasites require a specific temperature and humidity for their survival (Wall 2001). The majority of the infections were recorded in large breeds. It is not easy to diagnose the ectoparasites disease and as in other causative agents diagnose it is important to take the anamneses, for example the appearance of the pruritus as a common manifestation of ectoparasite presence or the present of alopecia or any weight loss. Pruritus in infected dogs was observed to be the main clinical signs which come as results of the hypersensitivity reactions (Halliwell et al., 1987). Also important information to take is the source of the suspected infection; most of the ectoparasites are transmitted by direct contact with infected animals. After the history a thorough clinical and dermatological examination has to be undertaken also the lesions and their distribution if are present should be recorded, it is important to know that there are no pathognomonic skin lesions for ectoparasitic skin diseases, since a variety of both primary and secondary ones are usually present depending on the duration of the infection, the parasite species involved and the specific immune response of the dog. Some ectoparasites are zoonotic agents so to prevent the possibility of continued transmission of ectoparasites from pet animals, the veterinarians should advice pet owners to pay attention to and be aware of them.

CONCLUSION

In the present study was indicated the prevalence of endoparasites infections in dogs of Tetova region, Macedonia. This study provides some information about the most frequent dog ectoparasite species found, their seasonal occurrence some infection characteristic and clinical signs. In this study are analyzed 126 dogs for the parasites presence. According to our results R.

sanguineus and I. ricinus were the most frequent tick species in dogs. They presence were more prevalent in spring and summer with a significant relationship between season and infection. It is important to never underestimate the importance of ectoparasites presence and also the preventive and therapeutic measures to be taken routinely all year round. Also pet owners have to pay attention and be aware of ectoparasites of zoonotic importance.

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Profesional paper

DETERMINING FACTORS IN THE APPROACH OF THE SURGICAL AND ORTHODONTIC TREATMENT OF IMPACTED MAXILLARY CANINE

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ABSTRACT

Maxillary canine impaction is a frequently encountered clinical problem, the treatment of which usually requires an interdisciplinary approach, and that involves surgical exposure of the impacted tooth, followed by orthodontic traction to guide and align it into the dental arch. Bone loss, root resorption, and gingival recession around the treated teeth are some of the most common complications. Because of this and many other reasons a detailed plan for surgical exposure as well as the way of orthodontic tractions should be well determined. The purpose of this paper is identification of factors that affect the approach of the surgical and orthodontic treatment of the impacted maxillary canine through presentation of clinical cases.

Material and methods: 18 cases of maxillary canine impaction treatment with different position, direction and depths, in patients aged 13 to 25 years old, are presented. Determination of the position, direction and depth of impaction, as well as age of the patient is done with anamnesis, clinical examination and X-ray. Evaluation of space needed for canine placement in dental arch is made by analyzing the dental arch with the metric analysis in dental casts. In cases where there wasn't enough space for canine placement, necessary space for canine alignment was gained first. In 13 cases surgical exposure – denudation was required. Traction of labially impacted canines was done using the force of 30 grams, whereas traction of those in palatal position with the force of 50 grams.

Results: From all cases seven of them were diagnosed in labial position, while eleven with palatal position. Four of the cases with labial position of impacted canine and age 13 - 16 years, resulted in spontaneous eruption of the tooth after creating the necessary space. But in all other cases with labial position of the impacted canine and age 16 - 25 years, as well as all in cases with palatal position denudation and then orthodontic traction was done. After 18 - 24 months of treatment the correct position of the canine in dental arch was achieved and no root resorption, hyalinization mass or other side effects were observed. In one of the cases with labial position gingival recession was identified whereas gingival hyperplasia was seen in one of the cases with palatal position of the impacted canine.

Conclusion: For successful orthodontic treatment of impacted maxillary canine surgical and orthodontic approach must be predetermined. Therefore it should be taken into account several factors and the interaction between these factors.

INTRODUCTION

Maxillary canine impaction is a frequently encountered clinical problem, whose treatment usually requires an interdisciplinary approach. This includes surgical exposure of the impacted tooth, followed by orthodontic traction to guide and align it into the dental arch.

Although management of impacted teeth is a routine task for most orthodontists, certain impactions can be frustrating and aesthetic results can be unpredictable if the surgeon exposes the impacted tooth in an irregular manner. On the other hand, if the right method for surgical exposure of the tooth is chosen, eruption process can be simplified, resulting in a predictable, stable and esthetic result (1).

Maxillary canines are most commonly impacted teeth second only to third molars (2, 3). The most common position of impaction is the palatal position. (4) Etiology of the impaction of canines is still unknown (5). Potential causes may be local or systemic factors depending on the position of the impaction which can be labial or palatal.

Labial impaction of maxillary canine may be caused as a result of ectopic migration of canine over the root of a lateral incisor or due to deviation of the mid line though reducing the space for canine eruption (1). Different authors have suggested conservative approaches to correct this kind of anomaly whether through extraction of the deciduous teeth or creation of space using routine orthodontic methods, but when these methods are inefficient then surgical exposure of canine must be performed. (3, 6).

There are two main theories regarding the causes of palatal impaction of the canine, the genetic theory and guidance theory. The genetic theory points to genetic factors as a primary origin of palatally displaced maxillary canines and includes other possibly associated dental anomalies, such as missing or small lateral incisors. Also there were reports connecting palatal impaction with other dental anomalies such as enamel hypoplasia and aplasia of the second premolar (7-9). Whereas, the guidance theory proposes that the canine erupts along the root of the lateral incisor, which serves as a guide, and if the root of the lateral incisor is absent or malformed, the canine will not erupt. (5).

Regarding the treatment of palatal impacted canine, spontaneous eruption after conservative methods does not occur, therefore surgical exposure should be performed. Surgical exposure of the impacted canine can be done with the:

- flap opening technique, and

- window shaped opening technique.

In the flap the flap was raised and the crown of the unerupted canine was exposed and surgical osteotomy was performed around the greatest circumference of the tooth taking in consideration not to expose the amelo-cemental junction. Whereas, in the window technique, first identification of tooth position is done which directs us to the line of incision. A semi-lunar incision is made along cusp of canine and is extended by 0.5 cm on both sides of the tooth. This is done in order to expose the largest circumference of the tooth and always taking care not expose the cervical part (10-13).

Variations of maxillary canine displacement are often encountered in dental practice. In such cases, because of his devious path to get in the right position in the dental arch, it often remains impacted and it becomes difficult to bring him in occlusion. Orthodontist and surgeons should intend an early diagnosis, to design a plan, to surgically expose the canine and use all eligible orthodontic methods to bring it to occlusion (14).

Apical gingival migration and long clinical crowns after treatment of the impacted maxillary canine cause unequal anterior gingival margins, which can be unaesthetic in patients with high smile line (15).

The introduction of CBCT has enabled better diagnosis and evaluation as well as better determination of the surgical approach and orthodontic treatment of impacted maxillary canine (13).

Loss of bone, root resorption and gingival recession around treated tooth are some of the most common complications. Because of this and many other reasons a detailed plan for surgical exposure as well as the way of orthodontic tractions should be determined.

The aim of this paper is identification of the factors that affect the approach of the surgical and orthodontic treatment of the impacted maxillary canine through presentation of clinical cases.

MATERIAL AND METHODS

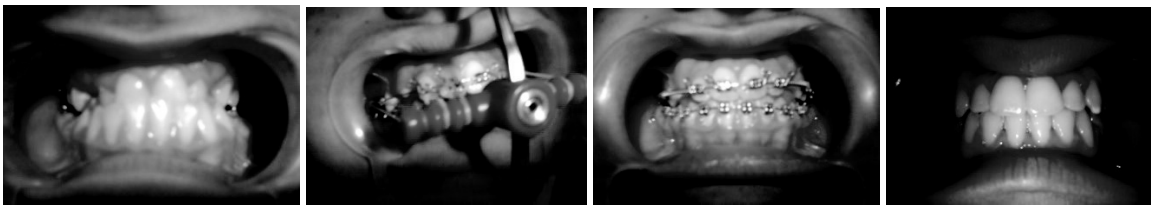
18 cases of maxillary canine impaction treatment with different position, direction and depths, in patient aged 13 to 25 years old, are presented. Two of them were bilateral impactions. Determination of the position, direction and depth of the impaction as well as age of the patient is done with anamnesis, clinical examination and X-ray. Evaluation of space needed for canine placement in dental arch is made by analyzing the dental arch with metric analysis in dental casts. In cases where there wasn't enough space for canine placement, necessary space for canine alignment was gained first.

In 13 cases surgical exposure – denudation was required. Traction of impacted canine in labial side was done using the force of 30 grams, whereas traction in palatal side with the force of 50 grams.

RESULTS

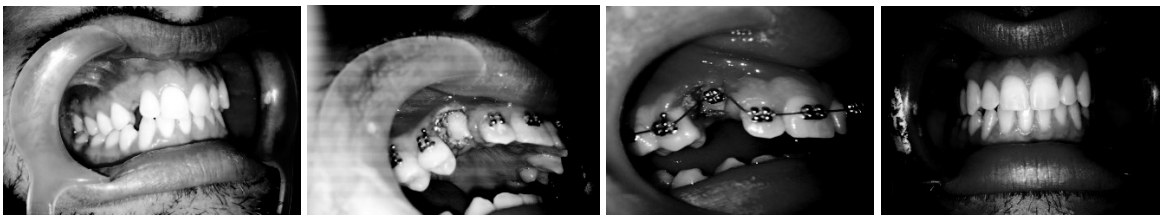
From all impaction cases, seven of them were diagnosed in labial position, while eleven in palatal position. Four

of the cases with labial position of the impacted canine aged 13-16 years, resulted in spontaneous eruption of the tooth after creating the necessary space. But in all other cases with labial position of the impacted canine aged 16-25 years, as well as all in cases with palatal position denudation and afterwards orthodontic traction was done. After 18-24 months of treatment was achieved correct position of the canine in dental arch, and no root resorption, hyaline mass or other side effects were observed. In one of the labial position cases gingival recession was identified, whereas gingival hyperplasia was seen in one of the palataly positioned canine.



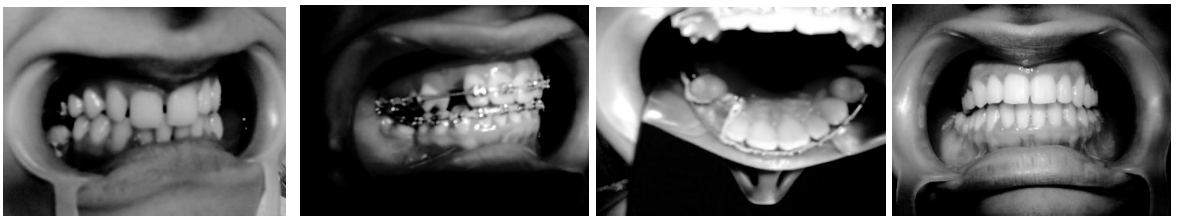
a. b. c. d.

Case 1. The patient 15 years old with bilateral impaction of maxillary canines in labial position, as well as endomaxilla: a. before treatment; b. and c. after creating space help with facemask, following spontaneous eruption on both sides; d. after treatment with fixed orthodontic appliance in both jaws.



a. b. c. d.

Case 2. The patient 23 years old with right side unilateral impaction of maxillary canine in labial position: a. before treatment; b surgical exposure in window shape; c. direct orthodontic traction in order to align the tooth in the arch; d. after treatment with fixed orthodontic appliance only in upper jaw.

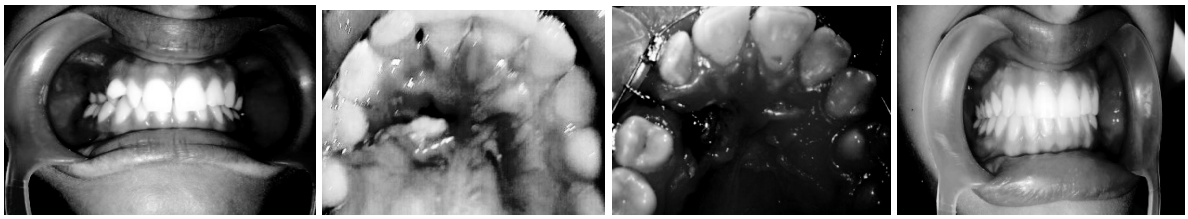


a. b. c. d.

Case 3. The patient 18 years old with right side unilateral impaction of maxillary canines in palatal position: a. before treatment; b. space gaining; c. indirect orthodontic traction in order to align the tooth in the arch; d. after treatment with fixed orthodontic appliance in both jaws.

a. b. c. d.

Case 4. The patient 16 years old with right side unilateral impaction of maxillary canines in palatal position: a. before treatment; b. surgical exposure; c. indirect orthodontic traction in order to align the tooth in the arch; d. after treatment with fixed orthodontic appliance only in upper jaw.



a. b. c. d.

Case 5. The patient 17 years old with unilateral impaction of maxillary canine in palatal position, as well as lateral crossbite in the right side: a. before treatment; b. surgical exposure with flap, and smooth traction; c. repeated opening, but in window shape and with indirect orthodontic traction was continued in order to align the tooth in the arch; d. after treatment with fixed orthodontic appliance in both jaws.

DISCUSSION

Correct surgical and orthodontic treatment of impacted maxillary canine can only be done by primarily analyzing the determinant factors of the approach of treatment for this kind of anomaly. The factors that are noted to determine the approach of orthodontic and surgical treatment of maxillary impacted canines are:

- labial or palatal position of impacted canine;

- direction or angulation which can be vertical, horizontal, or inclined relative to the Frankfort plane;

- depth of the impaction;

- unilateral or bilateral impaction;

- the remaining spaces for the canine alignment in the arch;

- the patient's age and early diagnosis;

- orthodontic appliances that will be used during treatment and amount of force for canine traction;

- presence of other malocclusions; and

- interaction between different factors.

If the direction or angulation of the impacted canine in relation to the Frankfort plane is suitable and the depth of impaction is not very expressed, i.e. if it is found near the root of the lateral incisor, it can come to spontaneous eruption of the impacted canine, especially in the labial position, and that complies with our conclusions. This is also described in the literature for the impacted canine in palatal position, but does not correspond with our findings.

Regarding position and age factor, for labialy positioned cases, patient's young age represents a favorable factor for treatment course, whereas in palataly positioned cases, especially in those with unfavorable direction and degree of depth of the impacted tooth, the patient's age, does not represent determining factor of the treatment approach.

The results of this study show that palatal impaction of maxillary canine is more frequent than labial impaction, which coincides with the findings of many authors (4,7,10), but does not coincide with the findings of others (8).

Concerning unilateral or bilateral impactions, our findings are consistent with the most previous researches suggesting that unilateral impaction are more prevalent than bilateral ones (16, 17, 18, 19), even though some of the other authors suggested that bilateral impactions are more common (20). This is a positive element considering that the treatment of bilateral impactions is more complicated and lasts longer.

CONCLUSION

For successful orthodontic treatment of impacted maxillary canines surgical and orthodontic approach must be predetermined. Therefore it should be taken into account several factors, such as:

1. Labial or palatal position of impacted canine affects the surgical exposure as well as orthodontic treatment method;
2. If angulation of the impacted canine is suitable and the depth of impaction is not very expressed, it can come to spontaneous eruption of the tooth. They, also have an impact on the surgical exposure method and duration of treatment;
3. Age of the patient in cases with canine impaction in labial position, represents a very important factor, whereas in palatal position cases, it has very little or no impact.
4. Bilateral impaction preferably are treated first in one and then on the other side, to avoid complications recurrences. This should be taken into account during treatment planning.
5. Creating the necessary space for canine, the traction to

align it in the arch, and the choice of the orthodontic appliance to be used, are factors that affect the planning of treatment.

6. The presence of other malocclusions, and the interaction between various factors must also be taken into account when we approach the treatment of impacted maxillary canines.

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Profesional paper

SUGAR – A PREDISPOSING FACTOR FOR TOOTH DECAY IN 7-YEAR-OLD CHILDREN

ШЕ́КЕРИ - ПРЕДИСПОНИРАЧКИ ФАКТОР ЗА КАРИЕС КАЈ ДЕЦА НА СЕДУМ ГОДИШНА ВОЗРАСТ

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ABSTRACT

Good nutrition education for children as one of the important elements for caries prevention in primary and permanent teeth and preservation of health from their early age is very important.

Aim: To present the fact that food rich in sugar has great influence on teeth depending on the frequency and the quantity of consuming.

Material and Methods: For realization of the goal, we made a survey on diet and consumption of sugars and systematic examination (dental checkups) of teeth in the second grade pupils in urban and rural schools. The pupils in the urban schools were educated in the first grade and the pupils in the rural schools were educated in the second grade. After that examination was done.

Results: According to the survey of children from urban areas, slightly more than half of them occasionally consumed foods containing sugars, but the hygiene was at high level and a high percentage of teeth without caries was present.

According to the survey, children from rural areas consumed large quantity of different kinds of food containing sugar and did not take care of their teeth. At the examination we concluded poor oral hygiene and a small number of children with healthy teeth. DMFT is 0.89.

Conclusion: A diet high with sugar has negative effect on the health of your teeth without proper care and hygiene.Education is a very important element in the health care.

Key words: Food with sugar, caries, the first permanent molar, DMFT, education, oral hygiene, children

АПСТРАКТ

Добрата едукација кај децата за правилна исхрана и ставање под контрола на шеќерите, како и редовната хигиена на забите е важна во превенирање на кариес кај млечните и трајните заби уште од најмала возраст.

Цел: Да укажеме на фактот дека, храната богата со шекери влијае на здравјето на забите во зависност од фреквенцијата и времето на нејзино конзумирање.

Материјал и методи: Направена е анкета за начинот на исхрана кај ученици од второ одделение од училиште од градско и рурално подрачје. Анкетата е направена после првично извршена едукација на децата од градското подрачје кога тие посетувале градинка и на почетокот на прво одделение, а кај децата од руралното подрачје едукацијата беше направена само во прво одделение. После едукацијата беше извршен и систематски преглед на забите.

Резултати: Кај децата од градска средина според анкетните листови (анкета) за видот на исхрана, консатиравме дека: повеќе од половина деца повремено конзумирале храна која содржи шеќери, а систематскиот преглед покажа добра орална хигиена и висок процент на здрави млечни и стални заби.

Кај децата од рурална средина од анкетата дознавме дека голем број од децата секој ден конзумирале разни видови храна што содри шеќери и не воделе грижа за хигиената на забите. На прегледот констатиравме: лоша орална хигиена и мал број на деца со здрави заби. КЕП изнесува 0.89.

Заклучок: Исхраната богата со шеќери влијае на здравјето на забите доколку неправилно се конзумира . Едукацијата на децата за правилна исхрана е многу битен елемент.

Клучни зборови: Храна со шеќери, кариес, прв траен молар, КЕП (ДМФТ), едукација, орална хигиена

INTRODUCTION

Dental health is part of overall health of the body and proper nutrition is one of the factors for the achievement and maintenance of health. All scientific studies suggest that diet is one of the important factors which condition the appearance of teeth cavities. Even in the II century BC Galen noted that tooth decay was caused by improper diet. The primitive lifestyle enabled consuming raw and fresh food. The manner and living conditions changed many centuries ago, and thus began the food processing and thus food became poorer in vitamins and minerals and the need for chewing food decreased. [11]

Food containing sugar causes tooth decay. But also other physical characteristics of the food, its solubility, stimulating the secretion of saliva, chemical changes in it, size and structure of the particles in it are important about cariogenicity of food. Food rich in carbohydrates that lingers longest around teeth is the most harmful.

The most adequate example of cariogenicity of carbohydrates in drinks with sugar is "Baby bottle caries" with children that are fed with bottle (picture 1).

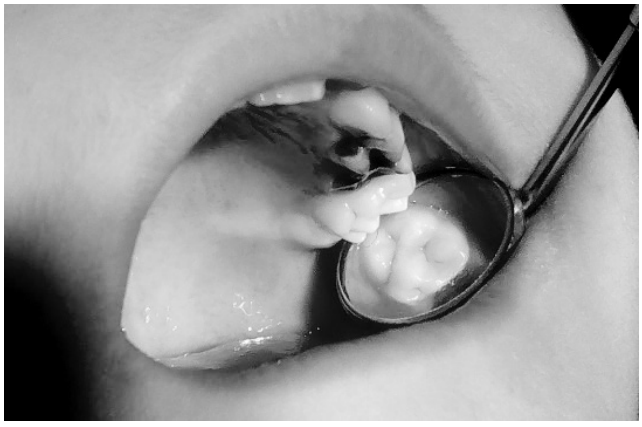
Even in children that are breast-fed mostly in the late hours, circular caries is spotted.

Picture No. 1 Little child sleeping with bottle after a meal

The term sugar associates many people with the one we use domestically (saccharose). Under the term sugar all sugar types are included: monosaccharides (glucose, fructose and galactose), disaccharides (sucrose, lactose and maltose) and polysaccharides (starch). [12] [13]

For the occurrence of dental decay the amount of intake of sugars is not the most important factor, but the physical form in which it is fed sucrose, presence of bacteria in dental plaque, frequency and timing of intake (consuming sugar before bed) [5]. Food which highly contains starch without addition of other sugars plays a minor role in the creation of dental caries. [3]

It is thought that sucrose facilitates colonization and growth of bacteria in plaque (Streptococcus mutans). This bacterium breaks down sucrose to acids, reduces the permeability of the plaque thus incapacitating saliva to neutralize the acids in the deeper parties of dental plaque and thus begins enamel demineralization. If cariogenic food lasts longer in the mouth the demineralization stops and remineralization will not begin until carbs are not eliminated from the mouth. High frequency of carbohydrate intake during the demineralization increases and the duration of remineralization is reduced thus conditions for occurrence of tooth decay are created. [1] [2] [5] [8] [10] [11]



Picture No.2 Decay of first permanent molar

Both children and parents should be advised to reduce the amount and frequency of intake of sweetened foods

(sweets, juices). Especially they should avoid sugary snacks between meals and just before bedtime.[5][7][8]

The aim of the paper is to point out the importance of proper nutrition as one of the conditions for good health of teeth in children and the importance of children learning from an early age how to properly care for the health of their teeth.

MATERIAL AND METHODS:

For the realization of this study 90 children were included, seven-year-olds of both sexes in a school from urban areas and 93 school children of the same age from rural areas.

Children who were from the urban areas were educated about proper nutrition in the period of kindergarten and again in first grade, and children who were from rural areas, the education was carried out only when the children were in first grade. Education was to make children understand they should avoid food with sugar (chocolate, foods that are with white flour, various crackers and salty snacks that stick to your teeth and juices containing sugar) and if consumed, they should brush their teeth .Also children that eat at school were advised to eat healthy foods and to avoid meals that are sticky and unhealthy. After the education, to see the effect we did an inquiry to see how often the children use food rich in sugar to see the effect of the cariogenic food. We used Klein-Palmer system or KEP.

Every condition that we found in every child was registered in order to make a comparison between the two groups.

Children from the urban areas at the systematic examination usually arrived with their parents, so the data in the survey on nutrition we received was from parents and children, whereas children from the rural areas were not with their parents, but with their teachers and carried the snacks with them. Data on diet among these children was received from teachers and also we were able to see it for ourselves - the snacks were with them. All data was also registered in the questionnaires. Most snacks which the children had consisted of croissants, cakes, crisps, sugary juices, and we received direct insight into the diet of each child.

From the materials for systematic examination we used: mirror, probe, brushes and pastes for polishing teeth, flyers and fuji triage, and for the survey a questionnaire for each child in which all the data on the diet was entered, the type of food, the number and the amount of meals.

RESULTS

After the education about proper nutrition in both groups we noticed the following: two-thirds of children from urban areas understood well the contents of the education about proper diet and control of sugar intake. Whereas, with the children of the rural areas, the situation was totally different. Of these, two-thirds did not bother to mind what they were eating and continued to consume sweets (tables 1 and 2).

Table 1: Participants from urban areas - second-grade pupils from PS Vlado Tasevski according to the questionnaire for proper nutrition

Grade no of children				rare usage of sugars			occasional usage			constant usage		
	m	f	all	m	f	all	m	f	all	m	f	all
IIa	14	6	20	1	1	2	7	3	10	5	3	8
IIb	10	9	19	1	0	1	10	4	14	1	3	4
IIc	14	12	26	4	2	6	8	6	14	1	5	6
IId	12	13	25	3	2	5	6	6	12	3	5	8
All	50	40	90	9	9	14/ 15.6%	31	19	50 / 55.6 %	10	16	26/ 28.8%

Table 1 shows the children from the urban areas, where it can be seen that more than half of them (55.6%) occasionally used sugars in the diet. Whereas 15.6 % of children used organic food and rarely consumed sugar

Respondents from rural areas were children / pupils from second grade from two schools, of which pupils from three villages were attending PS Naim Frasheri (villages: Bukovikj .Arnakija and Chajlane) and in PS Ibe Palikuka the pupils were from the villages Laskarci and Panichari.(Table 2).

Table 2: Participants according to the questionnaire for proper nutrition in rural areas:

Grade no of children				rare usage of sugars			occasional usage			constant usage		
	m	f	all	m	f	all	m	f	all	m	f	all
II-1B.	6	13	19	0	0	0	1	2	3	2	12	14
II-2B.	11	6	17	0	0	0	1	0	1	12	6	18
IIAr	8	12	20	1	0	1	1	2	3	6	10	16
IICha	6	5	11	0	0	0	4	3	7	2	2	4
IILa	9	13	22	1	2	3	1	1	2	7	10	17
IIPa	3	1	4	0	1	1	2	0	2	1	0	1
All	43	50	93	2	3	5/ 5.4%	8	8	18/ 19.4%	30	40	70/ 75,2%

Legend: B: -Bukovik, Ar.-Arnakia, Cha-Chajlane, La.-Laskarci, Pa.-Panicari

Table 2 shows the children from rural areas where consuming sugar is present with 75% of the children i.e. 70 children consumed food rich in sugar daily. Negligible numbers of children who rarely use sugars in the diet is only 5.3% of the surveyed children.

Table 3: General state of the teeth after the examinations in the school Vlado Tasevski:

Grade	IIa	IIb	IIc	IId	all
Examinees	20	19	26	25	90
Children with healthy teeth	9	8	10	15	42- (46.7%)
Children with caries	11	2	2	9	24- (26,6%)
Teeth with fillings	0	9	14	1	24- (26.6%)
(All 360 first molars)					
Molars with fillings	43	67	99	79	288- (80%)
Teeth with cavities	3	3	5	6	17- (4.72%)
Extracted molars	0	2	0	1	3- (0.8%)
Impacted molars	34	4	0	14	52- (14.4%)

At the examinations the children from the urban areas had great oral hygiene. In 4.72% of the kids had treated caries on the permanent molars and the percentage of untreated caries was 26.6%. The DMFT is 0.45 (table 3).

Significant fact is that 46.7 % of the pupils from the school Vlado Tasevski had completely healthy teeth (table 3).

Table 4: General state of teeth condition after the examinations in the rural areas:

Grade	Bukovic	Arnakia	Cajlane	Laskarci	Panicari	All
Examinees	36	20	11	22	4	93-(100%)
Healthy teeth	4	1	0	3	1	9- (9.67%)
Teeth with caries	31	14	7	15	3	70- (75.2%)
Teeth with fillings	1	5	4	4	0	14-(15%)
All 372 teeth examined						
Filled molars	99	44	26	83	12	264- (71.0%)
Filled molars	2	4	0	0	0	6- (1.6%)
Extracted teeth	0	1	1	3	2	7- (1.9%)
Impacted teeth	12	4	9	1	0	26- (7.0%)
Molars with caries	31	27	8	1	2	69-(18,5%)

With the children from the rural areas we noticed that the percentage of caries in the first molar was 16.4%. These children have high percentage of filled molars and in 1.9 % we had extracted teeth. Just 9.67 % of the children had healthy teeth. DMFT is 0.89

DISCUSSION:

According to these facts in relation to the results of our survey it is certain that the care for oral health should start from an early age as many other authors consider. Implementation of preventive measures, proper nutrition, control of the intake of sugars, the removal of harmful habits, regular, proper and sufficiently long-time implemented oral hygiene, regular fluoride prophylaxis and regular visits to the pediatric dentist and the family dentist will provide satisfactory results. Also carbohydrates, i.e. sweets should be consumed after the main meal and not before the main meal.

It is generally accepted that the prevalence of caries is associated with the form of food (sticky and sweet food, chips, cookies, crackers, small chocolate cakes and sweets), the frequency of input of the same and how long the teeth are exposed to the cariogenic food. [1] [2] [4] [7] [8]

The type of sugar entering is very important, except frequency of input as Burt highlights, and the results are in line with our received results in the incidence of tooth decay.

Children in kindergarten in the urban areas in most cases rarely consumed meals containing sugar. They paid attention to their oral hygiene whilst children living in rural areas despite the fact they had the possibility to be fed healthier, they consumed food which contains a high amount of sugar few times daily. They did not pay attention to their oral hygiene especially before going to bed. According to our results we can see that more than half of the children living in the urban areas have healthy teeth, sealed molars or 88%. The number of sealed teeth and teeth decay is not high, the KEP index is 0.45. That means that the education gave results.

Nutrition with food containing sugar is a very important factor for the oral health and it coincides with the results given by Doichinova where 100 children were examined and in 54% a bad oral condition was determined due to unhealthy nutrition.

Paula Movnihan Petersen also highlights that nutrition with food highly rich in sugar is one of the factors causing bad oral health in many countries around the world.

Many of the examined children living in rural areas did not quite understand the need for proper nutrition and many of them consumed meals containing sugar so that the oral condition was bad in most of the children and the percentage of healthy permanent molars was 9.67%. The

number of children with milk tooth decay and not sealed first permanent molars was high as well as the number of children that had not visited a dentist. Among the children were a few of them that had extracted the first permanent molars. The KEP index was higher unlike the KEP index for the children living in urban areas.

Parents have a very important role in the training and education of young children concerning healthy eating habits. Nowadays many parents are informed and aware of the harmful effects of sugar and also believe that poor oral hygiene can cause cavities. The education about the importance of regular dental visits can prevent dental diseases in children. Yet the need for health education of parents and children exists because there is a discrepancy between dental knowledge, attitudes of parents and dental practice. . [1] [4] [10] Proper nutrition and avoiding foods containing sugar as some of the preventive measures are part of the educational activities included in the preventive measures to preserve oral health as part of the national strategy for the prevention of oral diseases in children 0-14 years. In RM the education of children of five, six and nine years are implemented in all preschool and school facilities. [8]

Children from urban areas who were strongly influenced by the education and the parents, teachers, and doctors mastered the lesson successfully and understood that health comes from proper nutrition.

Children from rural areas even though live in a region with opportunities to feed healthily, fed more with processed foods purchased in shop. In both cases the crucial part was played by the parents.

Providing good education about proper nutrition and control of the food that contains sugar allow us to create a generation that will have a solid oral health.

CONCLUSION

Although sugar itself is a factor for dental diseases it must be emphasized that it is not the only factor that leads to tooth decay. Its more frequent consumption accompanied by bad oral health are factors that lead to milk and permanent teeth decay.

The education of children should be a priority for every dentist.

It should be informative, educational so that children can receive proper knowledge about the importance of the oral health and how to maintain the same with proper nutrition and education so that children can receive proper knowledge about the importance of the oral health and how to maintain the same with proper nutrition and oral hygiene. Certainly parents should be included.

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Profesional paper

VALUE OF SODIUM DODECYL SULFATE POLYACRILAMIDE GEL ELECTROPHORESIS IN EVALUATION OF PEDIATRIC URINARY TRACT INFECTIONS

ВРЕДНОСТА НА SODIUM DODECYL SULFAT ПОЛИАКРИЛАМИД ГЕЛ ЕЛЕКТРОФОРЕЗАТА ВО ЕВАЛУАЦИЈА НА ПЕДИЈАТРИСКИ УРИНАРНИ ИНФЕКЦИИ

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ABSTRACT

Urinary tract infections (UTI) represent frequent health problem, especially in developing countries. Clinical signs are different based on the location of infection. An interesting ethical and professional question arises: how to treat febrile children who previously received antibiotic therapy and have sterile urine culture in presence of pyuria. Is that a pyelonephritis and are further invasive imaging studies needed?

Objectives: To analyze the electrophoretic patterns of urinary proteins in children with proximal respectively distal UTI and to evaluate the value of sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) in acute febrile respiratory infections (AFRI) without signs and symptoms of UTI.

Material and methods: The study included 79 children aged 1-16 years: 36 with proximal UTI (15 with culture positive APN, respectively 21 with culture negative APN), 23 with cystitis (7 with hemorrhagic cystitis) and 20 children with AFRI without symptoms of UTI. Separation of urinary proteins was performed by SDS-PAGE.

Results: Children with culture positive and culture negative APN had incomplete tubular proteinuria (24-67 kDa) which was transient. Hemorrhagic cystitis was characterized by the typical presence of 28 kDa band (apolipoprotein A-1). In the group AFRI without symptoms of UTI, there was no observed pathological electrophoretograms.

Conclusions: SDS-PAGE is useful laboratory technique for separating proteins by their molecular size. The presence of incomplete tubular proteinuria indicates the renal origin of the fever. Detection of apolipoprotein A-1 in children with hemorrhagic cystitis allows differentiation in relation to glomerular cause bleeding. Despite these facts, in the literature there are few reports on SDS-PAGE in diagnosis of various renal diseases including urinary tract infections.

Key words: proteinuria, SDS-PAGE, urinary tract infection, respiratory infection, children

АПСТРАКТ

Вовед: Инфекциите на уринарниот тракт во детската возраст претставуваат чест здравствен проблем особено во земјите во развој. Клиничките знаци се различни во зависност од фактот каде е локализирана инфекцијата. Се наметнува етичка и професионална дилема кај фебрилно дете претходно лекувано со антибиотска терапија при стерилна уринокултура, а присутна пиурија. Дали е тоа пиелонефрит и дали е потребно додатно да се реализираат имиџинг техники.

Цели: Да се анализираат електрофоретските профили на уринарните протеини кај деца со проксимална односно дистална уринарна инфекција (УИ) како и да се евалуира вредноста на sodium dodecyl sulfat полиакриламид гел електрофорезата (SDS-ПАГЕ) на уринарните протеини кај акутни фебрилни респираторни инфекции (АФРИ) без знаци и симптоми за УИ.

Материјал и методи: Во студијата беа вклучени 79 деца на возраст од 1-16 години: 36 деца со проксимална УИ (15 со акутен документиран односно 21 со недокументиран пиелонефритис), 23 со циститис од кои 7 имаа хеморагичен цистит, како и 20 деца со АФРИ без знаци и симптоми за УИ.

Резултати: Кај децата со документиран односно недокументиран пиелонефритис беше констатирано постоење на инкомплетна тубуларна протеинурија (24-67 кД) од транзиторен тип. Кај децата со хеморагичен цистит беше

потврдено присуство на аполипопротеин А-1 фракција (28 кД). Во групата со АФРИ без знаци и симптоми за УИ не беа регистрирани патолошки елефореграми.

Заклучок: SDS-ПАГЕ е корисна метода за сепарирање на уринарните протеини според молекуларната тежина. Постоење инкомплетна тубуларна протеинурија укажува на ренално потекло на фебрилноста. Детекција на аполипопротеин А-1 кај деца со хеморагичен цистит овозможува диференцијација во однос на гломеруларните причини за крварење. И покрај тоа, во литературата се среќаваат мал број трудови за вредноста на SDS-ПАГЕ во дијагнозата на различни бубрежни болести вкучително уринарните инфекции.

Клучни зборови: протеинурија, SDS-ПАГЕ, уринарна инфекција, респираторна инфекција, деца

INTRODUCTION

Urinary tract infections (UTI) are common pediatric problem after respiratory and gastrointestinal infections in childhood and represent a frequent health problem, especially in developing countries (1, 2). UTI in childhood occur more often in girls. They have a higher risk of UTI (8%) compared to 2% of the boys (3, 4).

Clinical signs are different based on the location of infection (distal, proximal) within the urinary tract. Fever may be the only symptom of UTI in young children (5). If the cause of fever cannot be otherwise identified, then the imperative is urine examination (6).

Proximal urinary infection-pyelonephritis acuta (PNA) generally develops rapidly; fever is variable, usually above 38 ˚C, flank or abdominal pain can also appear. Succusio renalis is positive in older children. Most often there is no dysuria unless it is a urinary infection that begins as a distal and later ascension to the proximal urinary tract.

Distal UTI was defined with normal or body temperature (T) < 38˚C. Dysuria (pain, discomfort, or burning when urinating) often is the first symptom suggesting distal urinary infection. It is necessary to emphasize that systemic symptoms may arise with kidney and urinary tract infections.

Most frequently UTI are caused by E. coli, Proteus, Klebsiella which are all Gram-negative bacteria (6, 7). Diagnosis of urinary infection is based on patient history, clinical findings, abnormal urine analysis and positive microbiological finding. Positive urine culture is the gold standard for diagnosis of UTI.

An interesting ethical and professional question arises: how to treat febrile children who previously received antibiotic therapy and have sterile urine culture in presence of pyuria (8, 9). Is that a pyelonephritis and are further invasive imaging studies needed.

OBJECTIVES

To analyze electrophoretic patterns of urinary proteins in children with documented and undocumented proximal UTI. To evaluate electrophoretic findings in distal UTI and pay special attention to children with hemorrhagic cystitis. To evaluate the value of SDS-PAGE of urinary proteins in children with acute febrile respiratory tract infections (AFRI) without signs and symptoms of UTI.

MATERIAL AND METHODS

The study was performed at the University Children's Hospital and Institute of Medical and Experimental Biochemistry, Faculty of Medicine in Skopje, Macedonia in 2016/2017. A total of 79 children aged 1-16 years were divided in four groups:

Group I. Fifteen patients with documented febrile upper UTI. Group II. Twenty-one children with undocumented proximal UTI. Group III consisted of twenty-three children with distal UTI. Group IV was composed of 20 children with AFRI without signs and symptoms of UTI.

Documented upper UTI (culture positive PNA) was defined as follows: high fever >38 ˚C, flank or abdominal pain, positive C reactive protein (CRP) >10 g/l, erythrocyte sedimentation rate (ERS) >20 mm/h, abnormal urinalysis (pyuria), positive nitrites/or leukocyte esterase and significant bacteriuria (> 100.000/ml). Succusio renalis was positive in older children (Table 1).

Table 1

	T(⁰C)	Flank/ abdominal pain	Dysuria	SR	CRP (g/l)	Pyuria	Nitrites	Le esterase	Urine culture >100.000/ml
PNA(c+)	> 38	+/-	-	+/-	>10	+	+/-	+	+
PNA(c-)	> 38	+/-	-	+/-	>10	+	-/+	+/-	-
Cystitis	< 38	-	+	-	<10	+	+/-	+	+
AFRI /v/ UTI	≤ 38	-	-	-	<10	-	-	-	-

Legends
PNA(c+) - Pyelonephritis acuta culture positive; PNA(c-) - Pyelonephritis acuta culture negative; AFRI/v/UTI - Acute febrile respiratory tract infections without signs and symptoms of UTI; SR - Sucussio renalis

Undocumented upper UTI (culture negative PNA) was defined with fever > 38°C, lack of any other cause of fever in patients who received antibiotics and had negative urine culture in presence of pyuria.

Distal UTI was characterized with normal body T or < 38°C, dysuria, (pain, burning or discomfort upon urination), CRP <10 g/l, ERS <20 mm/h, pyuria, positive nitrites/or leukocyte esterase and significant bacteriuria (> 100.000/ml).

In children with AFRI without symptoms of UTI, laboratory investigations indicated viral infection: CRP< 10 mg/l, ERS < 20 mm, Le< 12.0 x 109, urinalysis normal values and nitrite/ leucocyte esterase negative urine test.

Children aged less than one year were excluded from the study because of transitory immaturity of the glomerular filter and tubular system of the kidney.

In children older than 1 year urine samples were obtained by means of a bag technique and respectively midstream catch in children older than 3 years. The interpretation of urine cultures results was made according to Kass criteria (10). Bacterial colony counts equal to or greater than 100.000 colony forming units (CFU)/ml represented UTI. Urine cultures obtained by midstream catch or bag technique with 10.000 to less than 100.000 CFU/ml were interpreted as equivocal.

Separation of urinary proteins was performed by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) according to Gorg et al. (7). Urinary samples were neither diluted nor concentrated; 0.9 ml urine with 0.1 ml sample buffer was incubated for 3 minutes in boiling water. Standard prepared SDS-polyacrylamide gradient gels (4-22%) dimensions 195 x 250 x 0.5 mm. SDS-PAGE worked at 5oC for 2 hours on Multiphor II Unit, LKB (Brown, Sweden). Pharmacia LKB low-molecular weight calibration proteins were used for determination of molecular mass of separated protein fractions. After that gels were stained with Coomassie Blue R- 250 and prepared in stable preparations.

RESULTS

In group I, children with documented (culture positive) APN, 100 % (n=15) electrophoretograms of urinary proteins were characterized by the presence of incomplete tubular proteinuria which contained proteins of molecular weight range 24 to 67 kDa. The intensity of fractions was highest on first five days and decreased thereafter. (Figure 1).

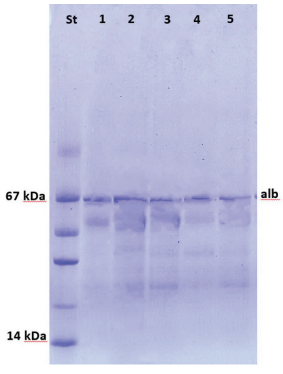

Figure 1. Initial electrophoretogram in boy with culture positive APN. A thin albumin band and incomplete tubular proteinuria is visible (molecular weight in the range 27-67 kDa).

All of the children with culture negative APN (group II; n=21) had the same electrophoretic pattern of incomplete tubular proteinuria (Figure 2).

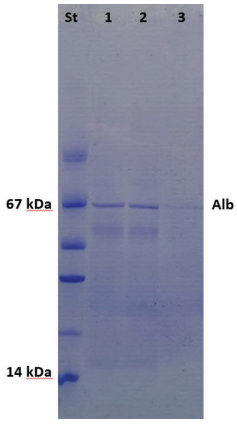

Figure 2. Incomplete tubular proteinuria in a child with culture negative APN in first three days.

Electrophoretograms in 16 children with cystitis (group III; n=23) were associated with presence of thin albumin band (67 kDa) (Figure 3).

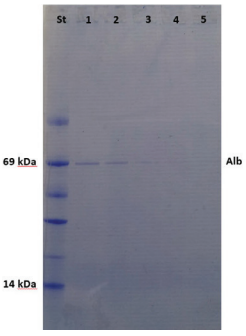

Figure 3. Electrophoretogram of a child with cystitis, presence of thin albumin band (67 kDa).

On the other hand, in seven children with hemorrhagic cystitis, electrophoretograms showed typical presence of 28 kDa band-apolipoprotein A-1 (Figure 4).

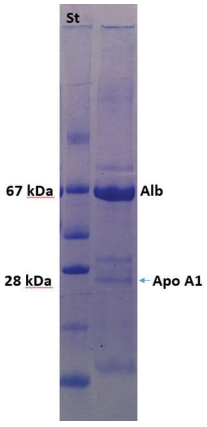

Figure 4. Electrophoretogram of a child with hemorrhagic cystitis, typical presence of 28 kDa band (apolipoprotein A-1).

In group IV (n=20), children with AFRI without signs and symptoms of UTI, there were no observed pathological electrophoretograms (Figure 5).

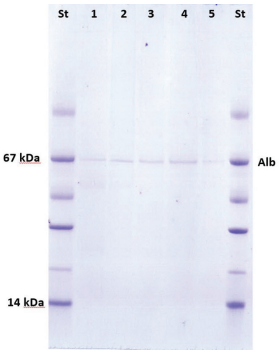

Figure 5. Electrophoretogram of a child with AFRI without signs and symptoms of UTI; only albumin band is visible.

DISCUSSION

SDS-PAGE is a method used to identify urinary proteins associated with various renal diseases including UTI. Urinary proteins with high molecular weight (> 69 kDa) are connected with glomerular damage, in comparison with the fact that low molecular weight proteins (12-60 kDa) indicate damage to the tubules. From the clinical point of view early diagnosis of APN in young children is very important, because of the risk of renal scaring.

Copp et al. in 2013 published results obtained from 28678 patients aged 1-18 years who were treated as outpatients UTI. They determined that urinalysis were performed in 76%, and urine culture in 57% of patients. Even 32% of children under the age of 2 years were treated with antibiotics without urinalysis and urine culture (11).

Creating diagnostic strategy for culture negative APN in children is still problem for many pediatricians, especially in invasive imaging studies: technetium-99m dimercaptosuccinic acid (Tc-99m DMSA) scan or computed tomography (CT) are indicated and widely used. The number of these patients are not too small; hence clinicians have to give them enough attention. Some authors suggest Tc-99m DMSA renal scan in pediatric patients with culture negative APN (12). In our opinion, in most patients with UTI, Tc-99m DMSA testing is not necessary as a part of the diagnostic process or to plan initial therapy. It is rather difficult to accept the fact of exposing children to Tc-99m DMSA scintigraphy or CT scan moderate radiation dose. On the other hand SDS-PAGE is a powerful diagnostic tool for detection of culture negative APN. It is non-invasive and absolute save investigation for the patients, cost-effective and may be repeated as often as is necessary.

A surprising announcement was reported by Rollino et al. that only 22.9% of their 52 patients with clinical pyelonephritis were properly culture documented (13).

Baer and Hjelm showed that over 90% of cystitis presented only a slight albumin band and no low molecular proteins; therefore, tubular involvement was excluded (14).

SDS-PAGE analysis in 50 patients with cystitis showed only presence of albumin band; on the contrary, patients with proximal UTI demonstrated tubular proteinuria and particularly in cases of vesicoureteric reflux albuminuria (15).

Various diseases of the kidneys and urinary tract (acute glomerulonephritis, UTI, urolithiasis, hypercalciuria, Alport syndrome, IgA nephropathy) may be the cause of hematuria. Differentiation of non-glomerular against glomerular hematuria is not always possible and many tests are recommended. Despite new investigations, 20-30% of hematuria cases are etiologically unclear. Sometimes a problem appears when hematuria clears within the same day and performing erythrocytes analysis is not possible the next day. The problem arises with the fact that only fresh urine is suitable for analysis. SDS-PAGE detect apolipoprotein A-1 which is a marker of postrenal hematuria and proteinuria and no fresh urine sample is needed. Apolipoprotein A-1 is present as a thin and shape fraction of 28 kDa in patients with hemorrhagic cystitis.

Schiwara and Spiller reported apolipoprotein A-1 as a useful tool in the differentiation of microhematurias and confirmed non-glomerular origin of the hematuria (16).

In our SDS-PAGE study of urinary proteins we found characteristic electrophoretic profiles for proximal (culture positive and negative APN), distal (cystitis and hemorrhagic cystitis) UTI and uncomplicated respiratory infections in children.

CONCLUSIONS

SDS-PAGE is a useful laboratory technique for separating proteins by their molecular size and detection of the origin of proteinuria, especially in children with undocumented febrile urinary tract infections. The presence of incomplete tubular proteinuria indicates the renal origin of the fever. Detection of apolipoprotein A-1 in children with hemorrhagic cystitis allows differentiation in terms of glomerular cause bleeding.

SDS-PAGE electrophoresis is a non-invasive, highly sensitive method that has a primary site in the urinary tract and precedes the invasive assessment methods. Despite these facts, in the literature there are few reports on SDS-PAGE in diagnosis of various renal diseases including urinary tract infections.

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Profesional paper

OBESITY AND ORAL HYGIENE

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ABSTRACT

Objective – The objective of this study is to present the relationship between obesity and oral cavity health, and to evaluate the correlation of oral heath motivation in improving oral health in obese subjects.

Material and Methods: Were recruited 83 subjects from age 5 to 11 years old. A study group of 44 subjects and a control group of 39 subjects were selected based on BMI. All subjects were given a questionnaire designed to analyze the lifestyle, nutrition habits and oral hygiene at home; an endoral visit was carried out to determine the amount of plaques, the index of bleeding and the index of caries. Each subject was instructed and motivated for oral hygiene at home and for balanced nutrition, and then re-evaluated after 21 days

RESULTS: Obese and overweight subjects showed that they had inflammation of the gingival tissue more severe than those with normal weight, supported by a larger amount of plaque. Caries' experience was the greatest in obese subjects, even if this difference is not statistically significant. After 21 days of motivation work, all patients reported improvement in plaque and bleeding indicators in the same way.

Key words: Obesity, caries, inflammation, periodontal swelling.

HYRJE

Përhapja e kulturës së parandalimit në botën stomatologjike ka përcaktuar një vëmëndje gjithmonë e më të madhe për studimin e faktorëve të riskut që ndikojnë në fillimin e patollogjive të kavitetit oral. Një nga faktorët më shumë të studiuar në vitet e fundit është obeziteti. Në fakt, nën dritën e studimeve të fundit mbi këtë temë, duket se obeziteti ndikon si në fillimin e sëmundjes karioze ashtu dhe të sëmundjeve paradontale.

Obeziteti është një patologji kronike e mirëfilltë me etiologji multifaktoriale që shkakton ulje të cilësisë dhe prespektivës së jetës së subjektit obez, duke qënë se është faktor kryesor risku për disa patollogji me karakter kroniko-degjenerativ si diabeti I tipit 2, disa forma tumorale, sëmundjet kardiovaskulare (infarkti dhe iktusi) dhe problemet muskuloskeletike.

Megjithëse obeziteti është një patollogji multifaktoriale, një rol të rëndësishëm në etiopatogjenezën e tij luan dieta hiperkalorike e shoqëruar me një stil sedentar jetese.

Sipas klasifikimit të OBSH përcaktohet mbipeshë një subjekt në të cilin indeksi i masës trupore (Body Mass Index - BMI) është ndërmjet 25.0 dhe 29.9 kg/m^2, dhe përcaktohet obez subjekti në të cilin indeksi I masës trupore (BMI) është mbi ose baraz me 30.0 kg/m^2.

Vlera të tilla të përdorura gjërësisht tek të rriturit kanë kufizime në popullatën pediatrike; tek fëmijët dhe adoleshentët, në fakt, përcaktimi I obezitetit është më kompleks në raport me atë të të rriturve meqënëse ndikohet nga mosha, nga një rritje shpesh jo sinkrone e peshës, e staturës dhe e sasisë së masës muskulare. Për të përcaktuar gjendjen e mbipeshës dhe/ose obezitetit te një fëmije, BMI duhet të vlerësohet në raport me seksin dhe moshën, duke patur parasysh tabelat e rritjes, që japin kurbat percentile të rritjes. Pesha është në normë kur BMI përputhet me percentilet 50 në tabelën e rritjes, ndërsa vlerat e BMI nën ose mbi 50 në tabelën e rritjes tregojnë gjendje të kequshqyerjes.

Ka tabela të ndryshme të rritjes, secila e taruar për popullata të ndryshme, prandaj është e vështirë të aplikohen për popullata të tjera dhe në nivel internacional. Për të pasur një përcaktim absolut të mbipeshës infantile në nivel internacional Task Forca Ndërkombëtare e Obezitetit ka propozuar tabelën e rritjes të Cole, e përftuar duke përdorur rezultatet e gjashtë studimeve trasversale mbi karakteristikat staturo-ponderale të disa grupeve të gjëra nacionale (Brazil, Angli, Hong Kong, Hollandë, Singapor dhe USA). Një e dhënë shqetësuese është rritja e vazhdueshme e obezitetit infantil në botë, sepse një fëmijë obez ka një rrezik të lartë të mbetet obez edhe kur arrin moshën madhore dhe të preket nga

sëmundje që lidhen me obezitetin dhe pasojat e tij që në moshë të re.

Lidhja ndërmjet obezitetit dhe sëmundjes karioze justifikohet me bashkëndarjen e disa faktorëve etiollogjikë, ndër të cilat janë disa zakone të gabuara të ushqyerit , në veçanti konsumi i lartë I ushqimeve të pasura me sheqer dhe marrja në sasi të tepruar e pijeve të sheqerosura acide. Këtu duhet të shtohet dhe gjendja e kserostomisë që gjendet në subjektet obezë. Në këto të fundit faktikisht konstatohet një pakësim I rrjedhjes salivare nga funksioni i dëmtuar i gjendrave të pështymës të shkaktuar probabilisht nga një çrregullim I aksit hipotalamo-hipofizo-surrenal ose nga një infiltrim masiv I makrofagëve në parenkimën salivare që dëmton funksionin.

Përsa I përket lidhjes ndërmjet obezitetit dhe sëmundjes paradontale, studimet e fundit në literaturë paraqesin një lidhje proporcionale të drejtpërdrejte ndërmjet BMI dhe humbjes së atakut klinik. Hipoteza më e besueshme sot është që inflamacioni kronik I gradës së ulur, që është në bazën e mekanizmit fiziopatollogjik të obezitetit, amplifikon fenomenet flogjistike nëpërmjet lëshimit në qarkullim nga ana e adipociteve të citokinave TNF-a, IL-6 e IL-8 duke rritur rrezikun e lindjes së patollogjive kronikodegjenerative, përfshirë dhe sëmundjen paradontale.

Ndërmjet citokinave të ndryshme të prodhuara, ajo që duket të luajë rolin kryesor në lidhjen ndërmjet obezitetit dhe sëmundjes parodontale është citokina TNF, e cila është citokina kryesore pro-inflamatore që përfshihet edhe në patogenezën e sëmundjes parodontale. Citokina TNF prodhohet nga makrofagët/monocitet që në fazat e para të përgjigjes inflamatore dhe është e aftë të shkaktojë riasorbimin kockor nëpërmjet diferencimit dhe aktivizimit të osteoklasteve. Studimet e fundit kanë treguar një rritje të nivelit të citokinës TNF në likidin krevikolar në subjektet obezë pa sëmundje parodontale, duke sugjeruar që rritja e TNF në likidin krevikolar e prodhuar nga indi adipoz mund të kontriboj në shkatërrimin më të madh të parodontit në mosha të avancuara. Faktorë të tjerë që mund të përfshihen në këtë korrelacion janë fluksi I pakësuar i gjakut dhe nje përgjigje imunitare e mangët. Fluksi i pakësuar i gjakut në nivelin e parodontit, I shkaktuar nga rritja në qarkullim I frenuesit të aktivizuesit të plazminogjenit, ndryshon reaktivitetin e indeve parodontale ndaj bakterieve parodontopatogjene. Disa studime kanë treguar një pakësim të nivelit të leptinave në xhepat parodontale të subjekteve obezë; nga momenti që kjo e fundit ka edhe funksion imunostimulues, një nivel I ulët mund të kompromentojë aftësinë mbrojtëse të sistemit imunitar ndaj bakterieve.

Studimi ynë u realizua me qëllim për të verifikuar egzistencën e një lidhjeje ndërmjet obezitetit dhe shëndetit oral në një kampion me fëmijë në moshë shkollore dhe më pas për të vlerësuar efektin e motivimit të higjenës orale dhe ushqyerjes në përmirësimin e shëndetit gingival në pacientët obezë.

MATERIALI DHE METODA

Morën pjesë në studim 83 persona, 38 femra dhe 45 meshkuj, në moshë 5 deri në 11 vjeç.

Pacientët u përzgjodhën në shkollën 9-vjeçare "Vasil Shanto" në Tiranë, duke u bazuar në kritere përjashtuese si më poshtë :

Pacientë të cilët i janë nënshtruar trajtimeve ortodontike.

Pacientë të prekur nga sëmundje sistemike që ndikojnë në shëndetin e paradontit.

Pacientë të prekur nga obeziteti sekondar.

Nga kampioni u zgjodh një grup studimi i përbërë nga 44 persona me BMI që tregon mbipeshë dhe/ose obezitet dhe një grup kontrolli me 39 persona me BMI që tregon peshë normale, në përputhje me tabelën e International Obesity Task Force.

ZAKONET E TË USHQYERIT			
Çfarë han zakonisht në mëngjes?			
Çfarë han zakonisht në drekë?			
Çfarë han zakonisht pasdite?			
Çfarë han zakonisht në darkë?			
Përdor përditë pije të gazuara?	☐po	☐ jo	
Han zemër (midis vakteve)?	☐po	☐ jo	
Zakonisht han çokollata?	☐po	☐jo	
Nëse po, sa herë në javë?	☐po	☐ jo	☐çdo ditë
Zakonisht han zarzavate?	☐po	☐ jo	
Nëse po, sa herë në javë?	☐po	☐ jo	☐çdo ditë
Han fruta?	☐po	☐ jo	
Nëse po, sa herë në javë?	☐po	☐ jo	☐çdo ditë
MENYRA e JETESES			
Praktikon sport?	☐po	☐ jo	
Nëse po, sa herë në javë?	☐një	☐tre	☐çdo ditë
Sa orë në ditë shef TV apo luan me kompjuter?	☐1 orë	☐3 orë	☐5 orë
HIGJENA E GOJES			
Sa herë herë në ditë e lan gojë?	☐kurrë	☐një	☐> se një
Koha që konsumon për larjen e gojës?	☐< se 1 min	☐> se 1 min	
Ke marrë ndonjëherë flor?	☐po	☐jo	

Për çdo pjesëmarrës në studim u plotësua një pyetësor mbi stilin e jetesës, zakonet e higjenës orale në shtëpi dhe lloji i ushqyerjes; u plotësua një kartelë klinike në të cilën u mblodhën të dhënat anagrafike të pacientit, anamneza patologjike, formula dentare, numri i dhëmbëve të kariuar, të mbushur dhe të humbur nga kariesi (DMFT), indexi i pllakës dhëmbore (FMPS), dhe indexi i gjakosjes gjatë sondimit (FMBS) i matur me sondën WHO.

Pacientët u udhëzuan dhe motivuan për teknikat e duhura të furçmit të dhëmbëve dhe për përdorimin e mjeteve të duhura sipas nevojave të tyre. Në takimin e dytë, pas 21 ditësh, u vlerësuan sërish indeksi i pllakës dhëmbore dhe indeksi i gjakosjes gjatë sondimit.

ANALIZA STATISTIKE

U realizua një analizë për të krahasuar të dhënat e marra nga përgjigjet e pyetësorit dhe nga vizita endorale në dy grupet.

Me qëllim vlerësimin e sinjifikancës statistikore u realizua testin chi-quadrat për të krahasuar të dhënat e sasisë së pllakës dhëmbore dhe gradës klinike të inflamacionit të indeve në grupin e studimit dhe në grupin e kontrollit, dhe testi T-student për të krahasuar indeksin DMFT mesatar në të dy grupet si në personat e modhës 5-6 vjeç ashtu dhe në personat mbi 7 vjeç.

Niveli i sinjifikancës (p-value) u vendos 0,05.

REZULTATET

Nga analiza e përgjigjeve të pyetësorit mbi zakonet ushqimore rezultoi se në grup-testin në një kampion me 44 fëmijë, 34 (77%) konsumonin merendina dhe çokollata çdo ditë dhe 10 fëmijë (23%) konsumonin vetëm njërën nga të dyja; ndërsa në grupin e kontrollit 25 fëmijë (64%) nga 39 konsumonin çdo ditë të dyja , 12 fëmijë (31%) vetëm njërën nga të dyja, 2 fëmijë (5%) asnjërën nga të dyja.

Në grupin e studimit 40 fëmijë (90%) konsumonin rregullisht pije me gaz, ndërsa në grupin e kontrollit 27 fëmijë (69%).

Për sa i përket stilit të jetësës, në grup-testin në një kampion me 44 fëmijë vetëm 9 (21%) praktikonin rregullisht aktivitet sportiv, ndërsa në grupin kontroll 14 nga 39 fëmijë (36%) praktikonin një sport rregullisht.

Në grup-testin 14 fëmijë (32%) kalonin mesatarisht 5 orë përpara televizorit ose në kompiuter, 25 fëmijë (57%) rreth 3 orë dhe 5 fëmijë (11%) rreth 1 orë; ndërsa në grupin e kontrollit 6 femijë (15 %) kalonin mesatarisht 5 orë, 24 fëmijë (62%) rreth 3 orë dhe 9 fëmijë (23%) vetëm 1 orë.

Përsa i përket zakoneve të higjenës orale në shtëpi në terma të frekuencës dhe kohës mesatare të furçimit, rezultoi se në grupin e studimit nga një kampion me 44 fëmijë 23 (61%) i lanin dhëmbët një herë në ditë, 15 (39%) dy herë në ditë dhe 3 fëmijë (7%) i lante sporadikisht; në grupin e kontrollit 24 fëmijë nga 39 (61%) i lanin dhëmbët dy herë në ditë dhe 15 fëmijë (39%) nje herë në ditë.

Në grup-testin 31 fëmijë (70%) harxhonin për të larë dhëmbët rreth një minutë, 11 fëmijë (25%) rreth dy minuta dhe 2 fëmijë (5%) nuk i lanin fare dhëmbët; ndërsa në grupin e kontrollit 22 fëmijë nga 39 (56%) i lanin dhëmbët për rreth një minutë dhe 17 fëmijë (44%) për rreth dy minuta.

Rezultatet statistikore, të përftuara nga të dhënat lidhur me indekset FMPS, FMBS dhe DMFT treguan se personat e grup-testit në krahasim me grupin e kontrollit: kanë inflamacion më të rëndë (FMBS 20-50% vs FMPS 0-20%) me një sinjifikancë statistikore p-value 0,013; dhe një numër eksperience kariesi më të madhe, edhe pse statitistikisht josinjifikative në grupmoshën 5-6 vjeç, më pas vlerat e DMFT barazohen për të dy grupe.

	Obeziteti 44	Kontrolli 39	Totali 83	P value
Mosha	8,25 (±1,76)	6,83 (±1,40	7,39 (± 1,73)	0.01
Seksi				0,62
Femër	21 (± 42%)	17 (± 50%)	38 (± 46%)	
Mashkull	22 (± 58%)	23 (± 50%)	45 (± 54%)	
Inflamacioni				0,008
I lehtë	11	30 (75%)	41	
I mesëm			38	
I rëndë			4	
Pllakëzat				
E lehtë			21	
E mesme			47	
E rëndë			15	
Shumë e rëndë			0	
DMFT				
≤ 6 vjeç				
≥ 7 vjeç				

Nga krahasimi i indeksit të pllakës dhëmbore dhe të gjakosjes gjatë sondimit nga vizita e parë në të dytën në dy grupet respektive rezultoi nje përmirësim i dukshëm i higjenës orale, si pasojë dhe e shëndetit të paradontit, në fakt u regjistrua një rënie e vlerave të indekseve FMBS dhe FMPS si në grup-testin ashtu dhe në grupin e kontrollit në të njëjtat shifra (Fig. 9,10, 11, 12).

DISKUTIMI

Rezultatet e studimit tonë konfirmojnë se fëmijët obezë kanë një rrezik më të madh për të zhvilluar sëmundje parodontale nëse janë të predispozuar, ndërkohë që duket që nuk ka asnjë lidhje ndërmjet obezitetit dhe kariesit dental, pasi kjo e fundit influencohet nga zakonet e këqija e të ushqyerit dhe nga zakone jo të mjaftueshme të higjenës së gojës. Nga analiza statistikore të përgjigjeve të pyetësorit nga prindërit e fëmijëve, rezulton se subjektet mbipeshë dhe/ose obezë kanë realisht një dietë të çekuilibruar në drejtim të konsumit të rritur të snacks, çokollatave, pijeve të gazuara etj përgjatë gjithë ditës, në krahasim me fëmijët me peshë normale. Përveç kësaj fëmijët që kanë një BMI ≥ 25 kg/m^2 praktikojnë më pak sport dhe përgjithësisht bëjnë një jetë më sedentare, duke harxhuar kohën më të madhe të ditës para televizorit. Ndërsa të dhënat mbi kohën dhe frekuencën ditore të furçimit rezultojnë të jenë thuajse njëlloj në të dy grupet.

Nga analiza statistikore e të dhënave të marra nga vizitat endorale në dy grupet rezulton se vlera mesatare e indeksit DMFT në pacientët obezë (grup-testi) është më i lartë se ai i pacientëve me peshë normale (kontrolli) në grupmoshën 5-6 vjeç, edhe pse një diferencë e tillë nuk rezultoi statistikisht sinjifikative; pas moshës 6 vjeç indeksi DMFT duket se barazohet për të dy grupet, ndoshta për arsye të rritjes së ekspozimit ndaj faktorëve të ndryshëm të riskut.

Për sa i përket inflamacionit gingival, i matur përmes indeksit të gjakosjes (FMBS), rezultoi të jetë më i lartë në pacientët mbipeshë dhe obezë (FMBS në vlerat 50-70%) krahasuar me ata në peshë normale (FMBS në vlerat 0-20%) për shkak të pranisë të një sasie më të madhe të pllakës. Diferenca e pllakës dhe gradës klinike të inflamacionit midis dy grupeve është statistikisht sinjifikative, prandaj fëmijët obezë kanë një risk më të lartë, krahasuar me ata në peshë normale, për tu prekur nga semundja parodontale nëse ekspozohen.

Një tjetër e dhënë sinjifikative e shfaqur nga studimi është një pakësim i dukshëm i pllakës dhëmbore dhe gjakosjes në të njejtët pacientë pas motivimit mbi higjenën orale. Fëmijët, si ata të grup testit ashtu dhe ata të grup kontrollit, pasi u informuan mbi teknikat e sakta të higjenës orale dhe u këshilluan mbi zgjidhjen ë mjeteve të duhura për këtë qëllim si furça, pasta dhëmbësh dhe shpëlarës me fluor, paraqiten në rivlerësim, 21 ditë pas vizitës së parë, vlera të ulura të FMPS dhe FMBS krahasuar me vizitën e parë. Përmirësimet në termat e uljes së sasisë së pllakës dhëmbore dhe gjakosjes në dy grupet rezultuan të njëjta, madje në grup-testin duke qënë së kishte një situatë fillestare më të rëndë, impakti i motivimit rezultoi më sinjifikativ.

KONKLUZIONET

Mund të konkludojmë se obeziteti mund të përbëjë një faktor rreziku për lindjen e sëmundjeve parodontale, por nëpërmjet programeve të përshtatëshme të parandalimit është e mundur të zvogëlohet graviteti. Megjithatë, kur bëhet fjalë për pacientë të moshës pediatrike, në rivlerësimin pas një periudhe të shkurtër kohore jo gjithmonë arrihet të kontrollohet mirë pllaka dhëmbore, prandaj janë të nevojshme masa të rritura për motivimin e fëmijëve për higjenën e gojës për të arritur përmirësimin e gjëndjes së indeve parodontale.

Përsa I përket lidhjes ndërmjet kariesit dentar dhe obezitetit, të dhënat nuk duket të mbështesin një lidhje të tillë në mospërputhje më atë që haset në literaturë.

Roli I higjenistit oral në lidhje më subjektet obezë është I dyfishtë: nga njëra anë duke nxitur një mënyrë jetese korrekte dhe një ushqyerje të ekuilibruar, sipas parimeve që pasqyrohen në protokollet e higjenës orale, dhe nga ana tjetër duke përdorur strategjitë e parandalimit të dëmtimeve të përgjithëshme të kavitetit të gojës ndaj të cilave subjekti obez është më I predispozuar.

Shtyllat kryesore për realizimin e një programi efikas të parandalimit stomatologjik janë përcaktuar, siç janë propozuar nga OBSH, në: vizita periodike kontrolli, motivimi për higjenën e gojës dhe një ushqyerje e saktë, fluoroprofilaksia në shtëpi dhe ajo profesionale.

Parandalimi duhet të realizohet nën një këndvështrim interdisiplinor, I karakterizuar nga bashkëpunimi I higjenistit, stomatologut, pediatrit dhe endokrinologut, pasi janë përcaktuar pacientët me rrezik të lartë për obezitet dhe pra, të predispozuar maksimalisht ndaj patologjive të zakonshme të kavitetit të gojës.

Një popullatë e tillë duhet të identifikohet sa më shpejt që të jetë e mundur me qëllim që të arrihet programimi i parandalimit të përzgjedhur nëpërmjet planeve të ndërhyrjes në objektiva të caktuara dhe të personalizuara. Një strategji e mirë parandaluese si ndaj sëmundjeve të kavitetit oral si dhe ndaj obezitetit dhe për pasojë dhe e sëmundjeve të lidhura me to, sigurisht do të pasqyrohet në pakësimin e kostos së shpenzimeve sanitare publike dhe në rritjen e nivelit të shëndetit të përgjithëshëm të popullatës.

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Profesional paper

ANGIOTENSIN II IS A NEGATIVE REGULATOR OF THE SEROTONIN LEVELS IN THE BRAIN

ANGIOTENSINA II SI RREGULLATOR NEGATIV I NIVELEVE TË SEROTONINËS NË INDIN TRUNOR

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ABSTRACT

The previous clinical extensive research of angiotensin converting enzyme inhibitors (ACEi) and angiotensin AT1 receptor antagonists (ARBs) as antihypertensive agents provided numerous examples of improvement of hypertension in diabetic nephropathy (DN). This research aims to determine the impact of ACEi perindopril and ARBs AT1 candesartan, used separately and in combination, on the level of serotonin in the brain tissue of Wistar rats with diabetic nephropathy induced by streptozotocin (STZ). The serotonin levels in the brain were measured with enzyme-linked immunosorbent assay (ELISA), in four experimental groups of animals: a control group with DN, a group with DN treated with perindopril, a group with DN treated with candesartan and a DN group treated with a combination of perindopril and candesartan. Perindopril (6 mg/kg/day), candesartan (5 mg/kg/day) and dual therapy with perindopril (3 mg/kg/day) and candesartan (2,5 mg/kg/day) was administered oraly every day during 8 weeks, starting 4 weeks after administration of STZ, while the control group received water alone. At the end of treatment, the rats were sacrificed and the brain tissue was taken for the measurement of serotonin levels. The results demonstrated that in all groups, the blockade of renin-angiotensin system (RAS), with perindopril, candesartan and their combination significantly increased the level of serotonin in the brain.

Key words: Renin-angiotensin system (RAS), serotonin, perindopril, candesartan, diabetic nephropathy.

ABSTRAKT

Hulumtimet e zgjeruara të deritanishme mbi enzimën konvertuese të angiotenzinës (ACEi) dhe bllokuesve të receptorëve AT1 të angiotenzinës (ARBs), si barna antihipertenzivë, siguruan shembuj të shumtë të përvojave në përmirësimin e hipertensionit tek nefropatia diabetike (DN). Ky hulumtim ka për qëllim ta determinojë ndikimin e ACEi perindopril dhe të ARBs AT1 kandesartan, të dhënë veçmas ose të kombinuar dhe ndikimin në vlerat e serotoninës në indin trunor të minjëve Wistar me DN të indukuar me streptozotocin (STZ). Nivelet e serotoninës në indin trunor u matën me metodën enzyme-linked immunosorbent assay (ELISA), në katër grupe eksperimentuese minjsh: grupi i kontrollit me DN, grupi me DN + perindopril, grupi me DN + kandesartan dhe grupi me DN në kombimin me perindopril + kandesartan. Perindorpil (6 mg/kg/ditë), kandesartan (5 mg/kg/ditë) dhe terapia e dyfishtë me perindopril (3 mg/kg/ditë) dhe kandesartan (2.5 mg/kg/ditë) ishte e dhënë per os çdo ditë për gjatë 8 javëve, duke filluar pas katër javëve nga dhënia e STZ, deri sa grupi i kontrollit pranonte vetëm tretësirë fiziologjike. Në fund të trajtimit minjtë u sakrifikuan dhe nga ata morëm indin trunor për hulumtim të niveleve të serotoninës. Rezultatet treguan që tek të gjithë tre grupet, bllokimi i sistemit renin-angiotensinë (RAS) me perindorpil, kandesartan dhe në kombimin të tyre, dukshëm e zvogëlojnë nivelin e serotoninës në indin trunor.

Fjalët kyçe: sistemi rennin-angiotenzinë (RAS), serotonina, perindoprili, kandesartani, nefropatia diabetike.

INTRODUCTION

A major advance in the field of neurophysiology was the discovery of the intrinsic and autonomous renin-angiotensin system (RAS) in the brain, which is regulated independently from the peripheral RAS (Ganten et al., 1971; Mendelsohn et al., 1984; Mendelsohn et al., 1988; Unger et al., 1988). In fact, it was discovered that all RAS components (angiotensionogen, renin, ACE, Ang II, Ang II receptors and their mRNA molecules) are present and are constitutively expressed in the adult nerve cells of the central nervous system (CNS). Even more interesting, various types of different research have shown that the central actions of angiotensins and RAS in CNS are not associated exclusively with their traditional functions, but they are also involved in cognition, behavior, learning and memory (Bonini et al., 2006), regulation of the autonomous system (Fink., 1997) and emotional responses (Haulica et al., 1999; Llorens and Mendelsohn, 2002).

Today, a vast number of scientific evidence suggests that besides its traditional role as a hormone, Ang II is also a neuropeptide that is produced by CNS and serves as modulator of neurotransmission and nerve cells excitability (Hermann et al., 1984; Li and Ferguson, 1993; Hauser et al., 1998; Kasparov and Paton, 1999; Barnes et al., 2003; Li et al., 2003). The histological and functional studies have shown that brain Ang II binds to AT_1 receptors in the presynaptic terminals and thus facilitates presynaptic release of dopamine (Mendelsohn, 1993; Brown, 1996), glutamate and GABA and it improves sympathetic neurotransmission by facilitating presynaptic noradrenaline release (Zimmerman et al., 1984; Szabo et al., 1990; Balt et al., 2001). In contrast, the present reference data regarding Ang II effects on serotonin and serotonergic transmission is quite poor and, very controversial.

In this context, a particular interest has attracted the literatute data according to which reduction of Ang II function has antidepressive and anxiolytic effects in CNS (Gard, 2002). There are known cases where the uses of particular antihypertensive drugs that block RAS have caused unexpected and anecdotal improvements in mood and cognition. Given these findings, we hypothesized that brain Ang II may also affect the brain serotonin system, acting as a negative modulator of the serotonergic transmission.

To test this hypothesis, we decided to investigate the serotonin levels in rat brain where Ang II effects are almost completely eliminated. A significant reduction of Ang II can be achieved using double RAS blockade, via combined treatment with ACE inhibitor (ACEi) and Ang II receptor blocker (ARB) that can cross the blood-brain barrier. This approach allowed blocking both the Ang II synthesis and its effect on CNS.

In particular, we used the antihypertensive drugs perindopril and candesartan because the combined treatment with these two is particularly common therapeutic strategy in the treatment of diabetic nephropathy (DN), due to its positive nephroprotective effects and the reduction of the present proteinuria in the affected individuals, which in turn reduce the progression of renal damage (Luno, 2005; Brewster and Perazella, 2004; Hilgers, 2004; Wade and Gleason, 2004; Nakao, 2004; Wolf and Ritz, 2005). However, if such a correlation exists between Ang II and serotonin concentration, there is a possibility for occurrence of side effects in CNS because these two pharmaceuticals cross the blood-brain barrier. Hence, in this study we investigated if the blockage of RAS would influence the serotonin levels in the brain tissue of Wistar rats. The secondary objective of this study was to reveal the possible therapeutic effects of these drugs and their interactions (used separately or in combination) on the brain serotonin system.

MATERIALS AND METHODS

Experimental design

For the purposes of the present study, the experimental rodent model of streptozotocin-induced diabetic nephropathy was used. One hundred normotensive Wistar rats, aging from 9 to 11 weeks, with approximately equal body weight from 200-300 g were housed under standard conditions (12 h light/dark cycle; 25±2°C ambient temperature; 55±10% relative humidity). Water and food were supplied ad libitum.

All rats received a single intraperitoneal injection of STZ (60 mg/kg), dissolved immediately before administration in 0.1 M citrate buffer (pH 4.5). Based on previous literature findings, this single dose of STZ was expected to induce hyperglycaemia after 72 hours and clearly expressed symptoms of DN after 4 weeks from the administration in most of the rats (Singh et al., 2006; Gojo et al., 2007; Al-Qattan et al., 2008. From: Balakumar et al., 2008). In our research, the diabetic state of the rats was confirmed 72 h after the treatment (initial blood glucose in all diabetic rats exceeded 300 mg/dl).

Four weeks after STZ dosing, when the kidneys had recovered from the acute mild nephrotoxic effects of STZ (Kraynak et al., 1995), the model rats were randomized into four groups, each group containing 25 animals. The first group was considered as a control diabetic group,

and these animas received sterilized 5% glucose solution without any medication. The second group was treated with 6 mg/kg Perindopril, while the third group was treated with 5 mg/кg Candesartan. The fourth group received concomitant treatment of 3 mg/kg Perindopril and 2,5 mg/kg Candesartan. All drugs were administrated orally via intragastric gavage, once daily for 8 weeks, dissolved in sterilized 5% glucose solution.

After the treatment, all rats were anesthetized deeply with sodium thiopenthal (50 mg/kg) and their whole brains were immediately removed from the skulls (usually within 1,5 min) on an ice chilled glass plate and stored at -80°C until further analysis.

Brain tissue homogenates preparation and quantitative detection of 5-HT

The present study was performed using a commercially available competitive ELISA Kit from Cusabio BIOTECH, for quantitative determination of rat serotonin concentrations in brain tissue homogenates.

Whole brain samples were weighed, homogenized in ice-cold 1X PBS preparing 10% tissue homogenates, and then stored overnight at -20°C. After two freeze - thaw cycles were performed to break the cell membranes, the homogenates were centrifuged for 5 minutes at 5000 g, 2-8°C. The supernatant was assayed and removed immediately. The assays were performed as per the manufacturer's instructions. The quantity of serotonin in brain homogenates was determined using a standard curve containing known amounts of serotonin.

STATISTICAL ANALYSIS

The data in the study were expressed as mean ± SEM. We used Two-Way Factorial ANOVA for Independent Samples to determine whether mean brain serotonin levels as determined by ELISA were significantly different in treated subjects, compared with the diabetic untreated controls.

In order to investigate the possibility for interaction between the two drugs, the results were organized in 2×2 scheme and analysed by Two-Way Factorial ANOVA for Independent Samples, using the statistical software package SPSS 11.

RESULTS

After 8 weeks of treatment with candesartan, the brain serotonin levels in the diabetic rats was increased significantly (P<0.05; Fig. 1), compared with that of the controls. The double blockade of RAS with candesartan and perindopril caused even more significant increase in the brain serotonin level compared with the diabetic controls (from 15.595 ± 2.78 to 26.722 ± 3.69, P<0.01; Fig. 1). In contrast, there was no significant increase in the brain serotonin level in the perindopril treated animals, compared with the diabetic controls.

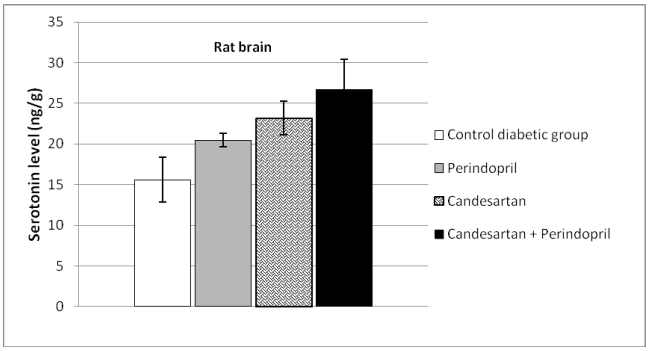
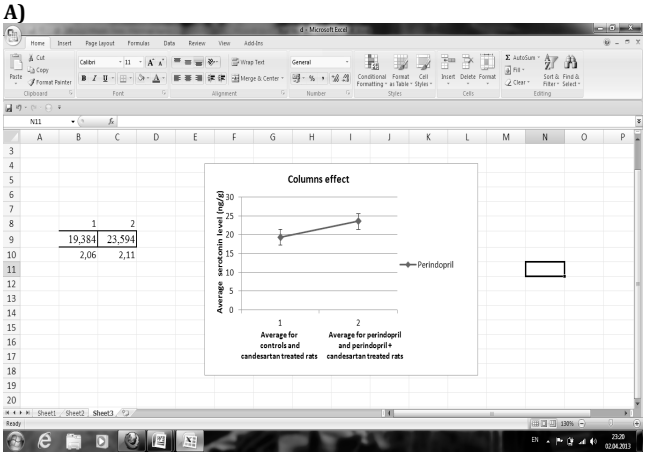


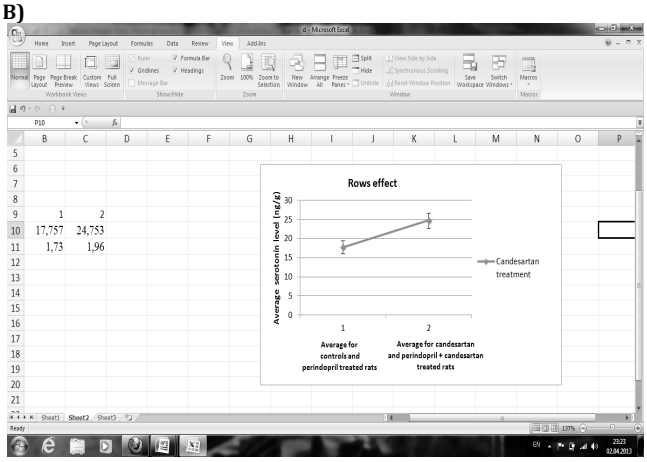
Figure 1: Effects of perindopril and candesartan on serotonin levels in rat brain.
All values are expressed as mean ± SEM, *P<0.05 as compared to the control diabetic group.

The results regarding the therapeutic effect and the effect of interaction between the drugs are shown in Figure 2. According to the 2×2 scheme, the statistical analysis for the columns effect (Fig. 2A), showed that the perindopril monotreatment did not increase the serotonin brain concentration significantly (P<0.1232), whereas the statistical analysis for the rows effect (Fig. 2B) showed that the candesartan monotreatment caused significant serotonin increase in the brain of the diabetic rats with induced DN (P<0.0159). The results also showed that there was no significant interaction between the drugs (P<0.7952). Considering that the trendlines for both of the effects are almost parallel (Fig. 2C), it is clear that the effect of the two drugs is simply additive.

A)



B)



C)

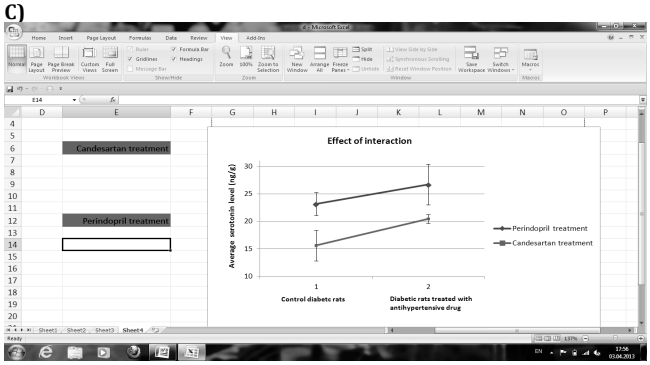


Figure 2: Therapeutic effect and effect of interaction between the drugs.
A) Columns effect. Effect of the perindopril monotreatment to the serotonin level. P<0.1232
B) Rows effect. Effect of the candesartan monotreatment to the serotonin level. P<0.0159
C) Effect of interaction between the two drugs. P<0.7952

DISCUSSION

The present research was aimed at determining the effects of the double RAS blockade on the serotonin brain levels in model Wistar rats with induced DN. Our results showed that the rat brain with heavily reduced Ang II effects via double RAS blockade had significantly increased serotonin levels, ie the decreased brain Ang II was in correlation with the increase of the brain serotonin concentrations.

As mentioned before, the literature findings regarding the Ang II effects on the serotonergic brain system are quite poor and contradicting. According to the study of Nahmod et al. (1978), Ang II causes serotonin release from neuron terminals and, it accelerates its synthesis. A similar positive correlation between brain Ang II and serotonin have been described by Haulicë et al. (1980), who found that intravenous infusion of Ang II induces an increase in the serotonin contents of the pineal gland, hypothalamus and brain stem in dogs.

The research using animal models for anxiety, such as elevated plus-maze and light/dark box, have shown that TGR(ASrAOGEN)680 rats characterized by reduced expression of angiotensinogen have more signs of anxiety compared to parental Sprague-Dawley rats (Voigt, 2005). In the same study, the authors have presented their results according to which the tissue content of 5-HT and its metabolite 5-HIAA is significantly lower in the hippocampus, frontal, and parietal cortex in TGR(ASrAOGEN)680 rats, compared with Sprague-Dawley ras. These findings suggest that low angiotensinogen level causes serotonin reduction in the brain, resulting in anxious phenotype.

More recently, the intracerebral microdialysis technique was used (Tanaka, 2003) in order to investigate whether Ang II affects the release of serotonin in the subfornical organ in freely moving rats. These results, on the other hand have shown that the extracellular 5-HT concentration and the concentration of its major metabolite, 5-hydroxyindoleacetic acid (5-HIAA), was significantly reduced in SFO after the Ang II microinjection. Moreover, the results of Jenkins (2008), point that the chronic candesartan infusion leads to improvement in mood and significant increase of the serotonin levels in the hippocampus, which is the exact opposite of Voigt's results and, in accordance with our results.

According to our results and the present literature data, we suggest that RAS affects the serotonergic system in a complex way, probably through several mechanisms. Thus, the decreased level or effect of Ang II is associated with increase in the brain serotonin level, which suggests that most probably Ang II is a negative modulator of the serotonergic transmission and the serotonin release. However, it is possible that the reduction of angiotensinogen has some influence on the serotonin decrease, but most probably this effect is not mediated via Ang II, but rather through some different mechanism or, via some of the other produced angiotensines.

In addition, the goal of this study was to determine the potential therapeutic effect of the perindopril monotherapy, the candesartan monotherapy and the tolerability of the combined treatment with ACEi and AT1 blocker on the brain serotonin system, in the treatment of STZ-induced DN. Our results showed that the monotherapy with candesartan caused an increase of the brain serotonin concentration. In contrast, the perindopril treatment did not cause significant change

in the brain serotonin level. The most significant change was observed with the concomitant treatment of both drugs, suggesting that in addition to the traditional antihypertensive effects, these two drugs in combination act as antidepressants and potential anxiolytics. Considering this, in individuals that apart from this antihypertensive therapy receive some antidepressants, such as selective serotonin reuptake inhibitors, this therapy may cause serotonin syndrome. However, future research is needed to investigate the interaction between these two and the drugs that act on the serotonergic system.

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Profesional paper

PSYCHOLOGICAL AND PHARMACOLOGICAL ASPECTS OF DEPRESSIVE SYMPTOMS IN PATIENTS WITH SCHIZOPHRENIA

ASPEKTET PSIKOLOGJIKE DHE FARMAKOLOGJIKE TË SIMPTOMEVE DEPRESIVE TE PACIENTËT ME SKIZOFRENI

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ABSTRACT

Introduction: The purpose of the study was to determine the differences in the level of depression in patients with schizophrenia before and after antidepressant therapy.

Material and Methods: The survey included 40 (20 male and 20 female) respondents between the ages of 25-45 who met the criteria for schizophrenic disorder to DSM-V treated in the psychiatric department at the Tetovo Clinical Hospital. All patients, in addition to regular neuroleptic therapy, were also treated with antidepressant therapy. The degree of depression was determined by the Beck-Beck Depression Inventory Depression Self-Assessment Scale (BDI) before and after treatment with antidepressants.

Results: During the study, we found that depressive mood was present in 37 (92.50%) patients with schizophrenia prior to initiating antidepressant therapy, and after depression, only 27 (67.50%) of patients with schizophrenia found the depressed mood after treatment. The Pearson correlation between the two groups is at a statistically significant level of 0.01.

Conclusion: During our longitudinal study, we found that regular antidepressant therapy in patients with schizophrenia results in the reduction of depression, which certainly affects their quality of life.

Key words: schizophrenia, personality, depression, self-assessment, antidepressant therapy.

ABSTRAKT

Hyrje: Qëllimi i strudimit ishte për të përcaktuar dallimet në nivelin e depresionit në pacientët me skizofreni para dhe pas terapisë me antidepresiv.

Materiali dhe Metoda: Studimi përfshiu 40 (20 meshkuj dhe 20 femra) të anketuar të moshës 25-45 vjeç, të cilët i plotësonin kriteret për çrregullim skicofreniforme sipas DSM-V trajtuar në repartin psikiatrik në Spitalin klinik në Tetovë. Të gjithë pacientët, përveç terapisë së rregullt neuroleptike, u trajtuan edhe me terapi antidepresive. Shkalla e depresionit është vlerësuar për shkallën e vetëvlerësimit të depresionit nga Beck -Beck Depresioni Inventari (BDI) para dhe pas trajtimit me barnat kundër depresionit.

Rezultatet: Gjatë studimit gjetëm se depresioni ishte i pranishëm në 37 (92.50%) te pacientët me skizofreni para fillimit të terapisë me antidepresiv, ndërsa pas trajtimit depresioni ishte vetëm te 27 (67.50%) të pacientëve me skizofreni. Korrelacioni Pearson midis dy grupeve është në një nivel statistikisht të rëndësishëm prej 0.01.

Përfundim: Në studimin tonë longitudinal është gjetur se futja e rregullt e terapisë antidepresive te pacientët me skizofreni sjell deri te ulja e depresionit, e cila natyrisht ndikon në cilësinë e jetës së tyre.

Fjalët kyçe: skizofrenia, personaliteti, depresioni, vetëvlerësimi, terapia kundër depresionit.

INTRODUCTION

Schizophrenia is a mental illness that occurs in about 1% of the population. Disease usually begins in the period of adolescence or in the young adult period, with equal representation between the two sexes (1). The term schizophrenia covers a heterogeneous group of the various clinical types of the disease. However, in most cases, schizophrenia is a chronic recurrent disease, characterized by a change in the acute episode and partial or complete remission. The prodromal stage, which may last for months, but for years, is usually present before the onset of the acute episode of the disease. Each new episode of the disease contributes to the further deterioration of the patient's condition, up to the late stages of the disease characterized by the dominance of the negative and cognitive symptoms (2, 3). This contributes to the appearance of certain psychopathological conditions in patients with schizophrenia, such as anxiety and depression.

Studies show that depressed mood is encountered in all types of mental disorders. Certain authors point out that the acute phase of schizophrenia can be a predictor of the occurrence of accompanying depressive symptoms (4, 5). However, they stress that depression can also occur in the post-psychotic phase of schizophrenia (post-psychotic depression). In a study conducted by Atcham and Moraine (2011), it was found that 50% of patients had depression after the first schizophrenic episode, and after a year of depression in only 35% of schizophrenic patients. The results they received could not explain whether depression in patients with schizophrenia is an integral part of the clinical picture of acute schizophrenia or is a self-comorbid disorder. It is characteristic that a larger number of patients suffering from schizophrenia have suicidal ideals and attempts that are associated with the presence of depressive symptoms and depressive moods, which significantly increase the risk of suicidal behavior. From this comes the conclusion that the successful prediction of depression in schizophrenic patients can help early diagnosis and successful treatment of depressive disorder, which prolongs the life span of schizophrenic patients and reduces the likelihood of suicidal behavior.

Modern psychology today seeks to integrate various psychological theories and concepts with contemporary neurophysiological discoveries. This is the basis for all attempts and tendencies to integrate various psychotherapy and pharmacotherapeutic inferences.

Certain researchers have observed that depression in schizophrenia correlates with antipsychotic treatment with the first generation of antipsychotics suggesting that depression is associated with anhedonia and mesolymbic dopaminergic dysfunction, which usually increases due to the dopaminergic blockade of the typical antipsychotics (7, 8, 9, 10). The second generation of antipsychotics have a major influence on the reduction of depressive symptoms, as well as on the positive and negative symptoms (11, 12, 13).

AIM OF STUDY

- To determine the degree of depression in patients with schizophrenia using certain psychological scales.
- Determine the percentage of patients with depressive symptoms among schizophrenic disorders.
- To determine the effect of antidepressant therapy in reducing depressed mood in patients with schizophrenic disorder.

MATERIAL AND METHODS

This study included: 40 examinees from both sexes, aged between 25 and 55 years, with a diagnosis of schizophrenic disorder with present depressive symptoms that were treated outpatient or hospitalized at the psychiatric department at the Clinical Hospital in Tetovo. The diagnosis of schizophrenic staging is based on the diagnostic criteria of DSM-V (Diagnostic and statistical manual of mental disorder, 2013). All patients, in addition to regular neuroleptic therapy (Olanzapine, Risperidone, Clozapine), were additionally receiving appropriate antidepressant therapy (Paroxetine, Sertraline, Venlafaxine). The scale for assessing the extent of depression symptoms was given twice: before starting with antidepressant therapy and at the end of the third month.

The examination was followed by the following structured test and clinical procedure (ie methods):

1. Standardized psychiatric clinical interview;

2. Psychiatric rating scale for clinical assessment of the symptomatology expression: 21-stage athletic scale for depression - BDI

3. Non-standardized questionnaire for socio-demographic and clinical data designed for the needs of the research.

Statistical analysis was made with the SPSS software package (Statistical Package for the Social Science, version 20). Database data processing was performed using standard descriptive and analytical methods. The attributive statistical series were analyzed by determining the ratio of ratios, proportions, rates, and by determining the statistical significance of the detected differences. Numerical series were analyzed with measures of central tendency and measures of dispersion of data. We examined the relationship between two numerical variables using the Pearson coefficient of correlation. The values of p <0.01 were considered statistically significant and significant.

RESULTS

In our sample of respondents who suffer from schizophrenia according to the results obtained on the Beck (BDI) self-assessment self-assessment scale, we obtained that depressed mood is not found only in three respondents, while in all 37 other (92.50%) patients it is found in all forms from mild to severe manifest depressive episode (Table 1, Diagram 1). Depressed mood, morning depression, early morning waking, feeling of guilt and weight loss are more pronounced in schizophrenic patients before starting with antidepressant therapy.

Table1. Prevalence of patients according to BDI scores before therapy with antidepressants

BDI	N	%
< 9	3	7.50
between 10--18	7	17.50
between 20 - 29	23	57.50
>30	7	17.50
Total	40.00	**100.00**

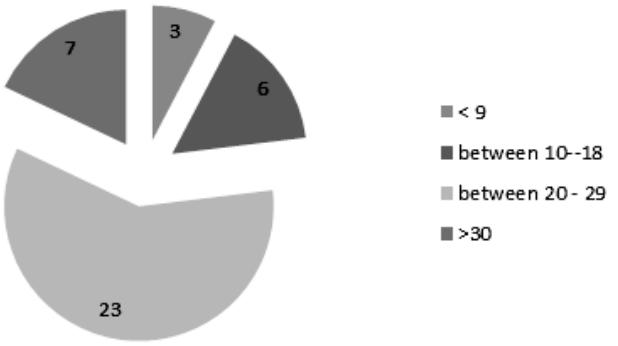

Figure1. Prevalence of patients according to BDI scores before therapy with antidepressants

The patients at the beginning of the treatment after the detection of depressive symptomatology were placed on appropriate antidepressant therapy. The therapy was received continuously for a certain period of time (at least three months) and was under regular psychiatric control. At the end of the treatment (after the 12th week), respondents were re-assigned to the self-assessment on the depression of Beck, in order to take a look at the effect of therapy on the degree of depression, and thus the improvement or deterioration under the effect of therapy. We find that the respondents after the applied therapy come to reduce depressive symptoms and reduce the depressed mood .. What 16 (40%) of the examinees we receive are depressed or have poorly depressed, while 24 (60%) have secondary to strongly depressed (Table 2, Chart 2)

Table2. Prevalence of patients according to BDI scores after therapy with antidepressants

BDI	N	%
< 9	13	32.50
between 10--18	3	7.50
between 20 - 29	19	46.50
>30	5	13.50
Total	40.00	**100.00**

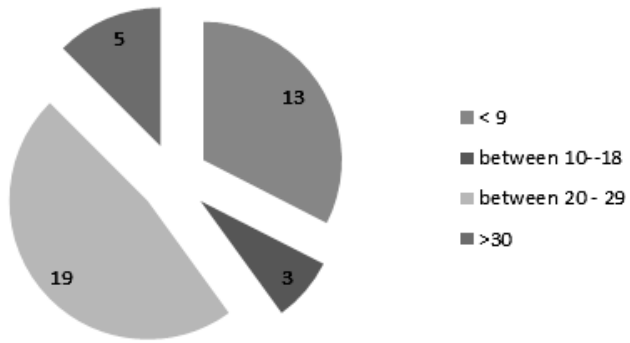

Figure2. Prevalence of patients according to BDI scores after therapy with antidepressants

The difference between the initial condition and the condition after 12 weeks of adequate psychopharmacological treatment with appropriate therapy is statistically significant at the level of 0.01 (Table 3, Graph 3). However, the decrease in the mark, the sensitivity on the worthlessness, the feeling of wine, the pulling, so that the positive affective experiences followed with joy, energy and enthusiasm gradually come to the expression.

Table3. Depression scores as measured with BDI for schizophrenic patients before and after therapy with antidepressants

Depression	Before therapy	After therapy
N	40	40
Mediana	25.55	10.42
S. D	8.47	4.94
Minimum	8	3
Maximum	47	26
Pearson Correlation	1	0,91**

** Correlation is significant at the 0.01 level

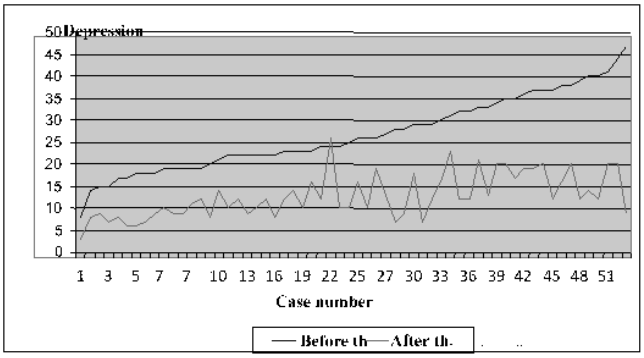

Figure3. Correlation between depression scores, schizophrenic patients and antidepressants

DISCUSSION

Schizophrenia is a chronic psychiatric disorder, a clinical syndrome with specific psychological symptoms, individual variations in the clinical picture, response to therapy and course of the disease, as well as a reduction in the functional capacities of the personality of all plans - personal, family, work and social . Previous research suggests that depressive symptoms are common in patients with schizophrenia (14, 15, 16).

Psychoanalytically-oriented authors consider that the basic and relatively constant symptom of all types of depression is the existence of a negative concept of the self. As a result, the mechanism of the onset of depression is always the same (whether it is a reactive, neurotic or psychotic depression), the aggressive attempts to obtain a gratification are added to the frustration, and when it does not succeed, the aggression turns to the Self. The consequence is the loss of self-esteem, as an expression of narcissistic conflict and the development of depression. Accordingly, the depression is the retroflection of aggression and the subsequent narcissistic problems of low self-respect. Low self-esteem in depression has its own expression in self-deception and worthless self-esteem, because it includes the Super-ego that "blames" the person for the loss and the bad behavior towards the object.

Our study showed the presence of depressive symptoms in almost all subjects with schizophrenic disorder before the increase in antidepressant therapy, and over time, depression decreased. Our results coincide with the Johnson Survey (2007) that concludes that 55% of patients had depressive symptoms with the first schizophrenic episode, while patients in the post-psychotic phase of schizophrenia had a lower incidence of depression (17).

Today's high frequency of depressive phenomena in mental disorders is believed to have its roots in many unsolved problems of our civilization, in the sense of personal insecurity of the modern man, which is influenced by a series of stressful and unfavorable psychosocial factors (18, 19) .

CONCLUSION

Modern psychiatry, both through theory and through therapy, tries to approach multidisciplinary schizophrenic disorders and explains it through an integrative approach. It is known that the internal representation of the personal space can be modified with the experience. Experience is modified not only through psychic perceptions, but also with brain functioning and brain architecture. All this together with the only genetic material, establishes the biological base of the personality. The biological basis generates our emotions, perceptions and behavior, but also the experience of current brain activities is reformed in the brain structure. Unlike previous knowledge, according to the latest, the structure of the brain is variable and flexible, and our mind is a complex, biological, historical, cultural and social phenomenon.

According to the most up-to-date psychological theories, psychic phenomena occurring in somatic and mental diseases are thought to be due to the disrupted self-regulation of personality. It is true that everything that happens inside us, our inner life, our emotions, our imaginations, govern us and influence our behavior. The inner life of man is a very rich and important source for his actions, reactions, and behavior. This concept corresponds to the latest findings, which even now includes development and better processing, based on evidence, which would give specific answers to the still-present enigma of interdependence and interaction between the supsychological and biological, somatic and cerebral, in the functioning , reaction and behavior of a person.

Until then, the clinician has his personal belief and knowledge, personal experience, interaction and ability to meet a person who has somatic or psychological symptoms, reaction and pathology and who rightly expects them to help.

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Profesional paper

РИЗИК ФАКТОРИ НА СКВАМОЗНИТЕ КЛЕТОЧНИ АБНОРМАЛНОСТИ НА ГРЛОТО НА МАТКАТА

RISK FACTORS FOR SQUAMOUS CELL ABNORMALITIES OF THE UTERINE CERVIX

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АПСТРАКТ

Вовед: Целта на нашата студија беше да ги детектираме најчестите ризик фактори на сквамозните интраепителни лезии и сквамозниот инвазивен карцином на грлото на матката.

Материјал и методи: Case-control студија, работена на 192 сексуално активни жени, на возраст од 20 до 59 години, поделени во две групи: испитувана и контролна, на Универзитетските клиники за гинекологија и акушерство и радиотерапија и онкологија во Скопје и на Институтот за јавно здравје на Република Македонија, во периодот од Јануари 2016 година до Јуни 2017 година. Кај сите жени се направи: анкета со специфичен прашалник, ХПВ ДНК тестирање, Nugent-ов скор систем, а по индикација, кај сите жени од испитуваната група и колпоскопска цервикална биопсија со ендоцервикална киретажа за хистопатолошка анализа.

Резултати: Анализата на податоците покажа асоцијација помеѓу ХПВ ДНК инфекцијата (хи квадрат тест=4.8204, p=0.028125, p<0.05), бактериската вагиноза (хи квадрат тест=4.1906, p=0.040649, p<0.05) и сквамозните клеточни абнормалности на грлото на матката. Нашата студија покажа дека пониското ниво на едукација за 2,29 пати (OR=2.29; 95%CI: 1.093-4.797) го зголемува ризикот за појава на сквамозни клеточни абнормалности на грлото на матката. Релативниот ризик за сквамозни клеточни абнормалности на грлото на матката, кај пациентките со понизок социјален статус беше 2,59 (OR=2.59; 95%CI: 1.137-5.503). Нашата студија покажа дека пушењето цигари за 2,45 пати го зголемува ризикот за појава на сквамозни клеточни абнормалности на грлото на матката (OR=2.45; 95%CI=1.3165-4.5762). Релативниот ризик за сквамозни клеточни абнормалности на грлото на матката, кај пациентките кои употребувале орални хормонски контрацептивни средства подолго од 5 години беше 3,00. Нашата студија покажа дека раниот прв сексуален однос пред 17 година од животот за 2,14 пати го зголемува ризикот за појава на сквамозните интраепителни лезии и сквамозниот инвазивен карцином на грлото на матката (OR=2.14; 95%CI: 1.0723-4.2821). Анализата на податоците од нашата студија покажа и асоцијација помеѓу сквамозните клеточни абнормалности на грлото на матката и диеталната исхрана (OR=2.11; 95%CI=1.0218-4.3832).

Заклучок: Анализата на податоците на нашата студија покажа асоцијација помеѓу сквамозните клеточни абнормалности на грлото на матката и ХПВ ДНК инфекцијата, бактериската вагиноза, нередовните гинеколошки контроли, честиот вагинален исцедок, раниот прв сексуален однос, пушењето цигари, долготрајната употреба на хормонски орални контрацептивни средства и диеталната исхрана.

Клучни зборови: ризик фактори, ХПВ ДНК инфекција, бактериска вагиноза, сквамозни клеточни абнормалности

ABCTRACT

Introduction: The purpose of our study was to detect the most common risk factors for squamous cell abnormalities of the uterine cervix.

Material and methods: Case-control study, performed on 192 sexually active women aged 20 to 59, divided into two groups: examination and control, at the University Clinics of Gynecology and Obstetrics and Radiotherapy and Oncology in Skopje and the Institute for Public Health of the Republic of Macedonia , in the period from January 2016 to June 2017. All women were made: a questionnaire, HPV DNA testing, Nugent score system, and by indication, in all women in the study group and colposcopic cervical biopsy with endocervical curettage for histopathological analysis.

Results: The analysis of the data showed an association between the presence of HPV DNA infection (chi square test = 4.8204, p = 0.028125, p <0.05), bacterial vaginosis (chi square test = 4.1906, p = 0.040649, p <0.05) and the occurrence of squamous intraepithelial lesions and squamous invasive carcinoma of the uterine cervix. Our study showed that the lower level of education for 2.29 times (OR = 2.29; 95% CI: 1.093-4.797) increased the risk of squamous cell abnormalities of the uterine cervix. The relative risk of squamous cell cervical abnormalities in patients with lower social status was 2.59 (OR = 2.59; 95% CI: 1.137-5.503). Our study showed that smoking cigarettes by 2.45 times increases the risk of squamous cell abnormalities of the uterine cervix (OR = 2.45; 95% CI: 1.3165-4.5762). The relative risk of squamous cell cervical abnormalities in patients who used oral hormone contraceptives for more than 5 years was 3.00. Our study showed that the first sexual intercourse before the age of 17 years of life for 2.14 times increases the risk of squamous intraepithelial lesions and squamous invasive cervical cancer (OR = 2.14; 95% CI: 1.0723-4.2821). The analysis of the data from our study also showed an association between squamous intraepithelial lesions and squamous invasive cervical cancer and dietary nutrition (OR = 2.11; 95% CI: 1.0218-4.3832).

Conclusion: The analysis of the data of our study showed an association between squamous intraepithelial lesions and squamous invasive cervix cancer and HPV DNA infection, bacterial vaginosis, irregular gynecological controls, frequent vaginal discharge, early first sexual intercourse, cigarette smoking, long-term use of hormonal oral contraceptives and dietary nutrition.

Key words: risk factors, HPV infection, bacterial vaginosis, squamous cell abnormalities

ВОВЕД

Карциномот на грлото на матката е четврт најчест карцином кај жените и седми воопште, со 527 624 нови случаи и со 265 672 смртни случаи во 2012 година, што е 7,5% од сите смртни случаи од карцином кај жените [1]. Скоро 9 од 10 (87%) смртни случаи од карцином на грлото на матката се случуваат во помалку економски развиените региони во светот. Со најголема проценета инциденца на карцином на грлото на матката од 80 на 100 000 е регионот Recife во Бразил, а со најмала од 3 до 4 на 100 000 е Израел [2]. Според последните податоци на GLOBOCAN, Македонија со проценета инциденца на карцином на грлото на матката од 12,4 на 100 000 се рангира на 17-то место во Европа, што е блиска до просечната европска, која изнесува 11,4 на 100 000 [3]. Карциномот на грлото на матката во Македонија е шести најчест карцином кај жените и десети воопшто, со 171 нови случаи во 2012 година [1]. Сквамозниот карцином на грлото на матката е најчест хистолошки подтип на карцином на грлото на матката. Околу 90% од случаевите на карцином на грлото на матката се сквамозен карцином, 10% се аденокарциноми и мал процент други видови. Макроскопски најчесто е егзофитичен, но може да расте и во ендоцервикалниот канал во ендофитична форма [4]. На појавата на карциномот на грлото на матката му претходат различни форми на интраепителни лезии кои опфаќаат низа прогресивни морфолошки промени [5], од продуктивна ХПВ инфекција-лесен степен на дисплазија па до in situ карцином [6]. Оваа фаза генерално е асимптоматска и се случува во период од 10 до 20 години [10].

Карциномот и интраепителните лезии на грлото на матката се асоцирани со неколку ризик фактори. Најчест ризик фактор е инфекција со Хуман Папилома Вирусот (ХПВ), особено со високо-ризичните ХПВ генотипови [8,9]. Истражувањата покажале позитивна корелација на карциномот на грлото на матката со: пушењето цигари, нискиот социо-економски статус, диетата, раниот прв сексуален однос, раната прва бременост, мултипаритетот, промискуитетот,

долготрајната употреба на оралните хормонски контрацептивни средства, имунокомпромитираниот статус, бактериската вагиноза и сексуално преносливите болести и позитивната фамилијарна историја за карцином на грлото на матката [10,11]. Овие ризик ко-фактори во основа ја зголемуваат веројатноста од изложување на високо-ризичен ХПВ генотип [12]. Целта на нашата студија беше да ги детектираме најчестите ризик фактори на сквамозните интраепителни лезии и сквамозниот инвазивен карцином на грлото на матката.

МАТЕРИЈАЛ И МЕТОДИ

Дизајн на студијата: Студијата претставува case-control студија.

Материјал: Материјал претставуваат 192 пациентки на возраст од 20 до 59 години, поделени во две групи: испитувана и контролна.

Испитувана група: Испитуваната група вклучи 128 сексуално активни жени со абнормален цервикален цитолошки наод, односно наод на ПАП тест, кој покажува постоење на сквамозна интраепителна лезија или сквамозен инвазивен карцином на грлото на матката.

Контролна група: Контролната група вклучи 64 сексуално активни жени со нормален цервикален цитолошки наод, односно ПАП тест.

Критериуми за исклучување: Во студијата не беа вклучени: бремени жени, жени со претходни операции на грлото на матката (конизации, јаглерод двооксид ласерски вапоризации и тотални хистеректомии), со претходни абнормални цитолошки и хистопатолошки наоди на грлото на матката, жени во тек на менструално крварење, жени кои последните шест недели биле или се под локална или системска антибиотска или антивирусна терапија и жени кои последните два дена имале сексуален однос или правеле вагинална тоалета.

Период на реализација: Студијата беше спроведена во периодот од јануари 2016 година до јуни 2017 година на Универзитетските клиники за гинекологија и акушерство и за радиотерапија и онкологија во Скопје и на Институтот за јавно здравје на Република Македонија во Скопје.

Методи: Кај сите жени се направени: анкета со специфичен прашалник, ХПВ ДНК тестирање, Nugent-ов скор систем, а по индикација, кај сите жени од испитуваната група и колпоскопска цервикална биопсија со ендоцервикална киретажа за хистопатолошка анализа.

Цитолошка анализа: Цитолошките резултати беа класифицирани според ревидираната Bethesda класификација [13,14], како: атипични сквамозни клетки со недетерминирано значење (ASC-US, Atypical Squamous Cells of Undetermined Significance); атипични сквамозни клетки кои не исклучуваат сквамозна интраепителна лезија од висок степен (ASC-H, Atypical Squamous Cells cannot exclude a High-grade squamous intraepithelial lesion); сквамозна интраепителна лезија од низок степен (LSIL, Low grade Squamous Intraepithelial Lesion, CIN 1, Cervical Intraepithelial Neoplasia Grade 1); сквамозна интраепителна лезија од висок степен (HSIL, High grade Squamous Intraepithelial Lesion, CIN 2, Cervical Intraepithelial Neoplasia grade 2, CIN 3, Cervical Intraepithelial Neoplasia grade 3, CIS, Carcinoma In Situ) и сквамозен инвазивен карцином.

Анкетен прашалник: Прашалникот беше слободно дизајниран и содржи прашања за демографските карактеристики на жените, социјалниот статус, економскиот статус, гинеколошката и репродуктивна историја, за сексуалниот статус и за ризик факторите.

Хистопатолошка анализа: Според морфологијата детерминирана во биоптичните примероци, цервикалните наоди беа карактеризирани како: нормален наод (неспецифичен цервицитис); сквамозна интраепителна лезија од низок степен (LSIL, Low grade Squamous Intraepithelial Lesion) - лесен степен на дисплазија, плоснат кондилом (flat condyloma), хронично вирусно воспаление на грлото на матката (cervicitis chronica virosa); сквамозна интраепителна лезија од висок степен (HSIL,High grade Squamous Intraepithelial Lesion) - умерен и тежок степен на дисплазија, in situ сквамозен карцином и инвазивен сквамозен карцином (Carcinoma planocellulare cervicis uteri invasivum) [15].

ХПВ ДНК тестирање: За детекција и типизација на ХПВ беа употребувани тестови кои ги користат методите на мултипна полимераза верижна реакција (Multiplex PCR, Polymerase Chain Reaction) и реверзна хибридизација. Резултатите од ХПВ ДНК тестот беа анализирани и прикажани врз основа на наодот на присуство или отсуство на ДНК од ХПВ и одредениот генотипот [16].

Nugent-ов скор систем: За изработка и интерпретација

на Nugent-овиот скор систем [17] беше направен препарат на предметно стакленце обоен по Грам и анализиран на светлосен микроскоп Olympus BH-2 (САД) на 1000 пати зголемување на видното поле. Се детектира присуство или отсуство на нормална бактериска вагинална флора, се детектираа најчестите бактериски морфотипови (Lactobacilli, Gardnerella vaginalis, Bacteroides, Mobiluncus, Prevotella) и се изработи Nugent-ов скор систем, врз база на кој беше дијагностицирана бактериската вагиноза. Интерпретацијата на Nugent-овиот скор одеше по следниот редослед: скор од 0-3, значи присуство на нормална вагинална флора (доминација на Lactobacilli-негативен за бактериска вагиноза); скор од 4-6, значи редукција на нормална вагинална флора (негативен за бактериска вагиноза) и скор од 7-10, во согласност со Nugent-овите критериуми, значи доминација на патогена вагинална флора (позитивен за бактериска вагиноза), "златен стандард" за постоење на бактериска вагиноза.

Статистичка анализа: Податоците беа внесени во стандарден софтвер за база на податоци (Excel). Статистичката анализа на формираните статистички серии беа спроведени со статистичкиот програм Статистички пакет за општествени науки (SPSS -, Statistical Package for Social Sciences), верзија 23.0. Структурата на статистичките серии со атрибутивни белези беше анализирана со одредување на пропорции и стапки. Структурата на нумеричките белези беше анализирана со одредување на мерки на централна тенденција и мерки на дисперзија. Проценатa на нормалноста на нумеричките серии се направи со помош на хи-квадрат тест. Аналитичката фаза се состои од следните постапки: анализа на односи (постоење на асоцијација) меѓу две серии со атрибутивни варијабли се направи со помош на хи-квадрат тест; анализа на односи меѓу две серии со нумерички варијабли (корелација) се направи со помош на регресиона анализа и коефициент на линеарна корелација. Тестирањето на разликите меѓу споредуваните групи (нивните дистрибуции, аритметички средини и пропорции) се направи со помош на Student-ов t-тест. Релативниот ризик од сквамозни интраепителни лезии и сквамозен инвазивен карцином на грлото на матката беше проценет со пресметување на соодносот на веројатности (OR, Odds Ratio) со 95% интервал на доверба (CI, Confidence Interval), користејќи логистичка регресија.

Статистички значајни се сметаа податоците кај кои p вредноста беше <0.05. Резултатите се прикажани табеларно и графички.

РЕЗУЛТАТИ

Табела 1. Дистрибуција на пациентките според возрасни групи

Возрасна група	Испитувана		Контролна	
	Број	(%)	Број	(%)
20-29	28	(21,87)	13	(20,31)
30-39	38	(29,69)	22	(34,38)
40-49	30	(23,44)	18	(28,12)
50-59	32	(25,00)	11	(17,19)
Вкупно	128	(100)	64	(100)

Просечната возраст на пациентките од испитуваната група беше 40,50±10,85 години, а просечната возраст на пациентките од контролната група беше 39,34±9,70 години. Според t-тестот процентуалната разликата помеѓу просечната возраст помеѓу двете групи е статистички несигнификантна за рё0.05 (p=0.4722, t=0.7204, 95%CI: -2.01-4.32) (Табела 1).

Цитопатолошки, имаше: 13 (10,16%) случаи на ASC-US, 7 (5,47%) случаи на ASC-H, 31 (24,22%) случај на LSIL, 56 (43,75%) случаи на HSIL и 21 (16,40%) случај на инвазивен сквамозен карцином на грлото на матката. Хистопатолошки, имаше: 9 (7,03%) случаи со нормален наод, 41 (32,03%) случај со LSIL, 54 (42,19%) случаи со HSIL и 24 (18,75%) случаи со инвазивен сквамозен карцином на грлото на матката.

ХПВ ДНК-инфекцијата беше детектирана кај 75.00% (96/128) од испитуваните пациентки. Анализата на податоците покажа асоцијација помеѓу присуството на ХПВ ДНК-инфекцијата и појавата на сквамозните клеточни абнормалности на грлото на матката (хи квадрат тест=4.8204, p=0.028125, p<0.05) (Табела 2).

Од вкупно 128 пациентки, бактериската вагиноза беше најдена кај 56 (43,75%) пациентки. Анализата на податоците покажа асоцијација помеѓу присуството на бактериската вагиноза и појавата на сквамозните клеточни абнормалности на грлото на матката (хи квадрат тест=4.1906, p=0.040649, p<0.05) (Табела 3).

Анализата на податоците покажа асоцијација помеѓу сквамозните клеточни абнормалности на грлото на матката и пациентките со завршено средно образование (хи-квадрат тест=4.9377, p=0,0262, p<0.05, со релативен ризик од 2,29), во однос на пациентките со виш/висок степен, како и асоцијација со пациентките со понизок социјален статус (работнички) (хи-квадрат

Табела 2. Дистрибуција на ХПВ ДНК-инфекцијата во однос на хистопатолошката дијагноза

ХПВ ДНК инфекција	Испитувана група Хистопатолошка дијагноза								
	Нормален наод (n=9)	LSIL (n=41)			HSIL (n=54)			Инвазивен сквамозен карцином (n=24)	Вкупно (n=128)
		Хроничен вирусен цервицитис (n=20)	Плоснат кондилом (n=2)	Лесна дисплазија (n=19)	Умерена дисплазија (n=15)	Тешка дисплазија (n=23)	In situ сквамозен карцином (n=16)		
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
ХПВ ДНК негативни	5(55,56)	7(35,00)	0(0)	8(42,10)	3(20,00)	4(17,39)	2(12,50)	3(12,50)	32(25,00)
ХПВ ДНК позитивни	4(44,44)	13(65,00)	2(100)	11(57,89)	12(20,00)	19(82,61)	14(87,50)	21(87,50)	96(75,00)

Легенда: n, број; LSIL, сквамозна интраепителна лезија од низок степен; HSIL, сквамозна интраепителна лезија од висок степен; ХПВ, хуман папилома вирус; ДНК, дезоксирибонуклеинска киселина

Табела 3. Дистрибуција на бактериската вагиноза во однос на хистопатолошката дијагноза

Бактериска вагиноза	Испитувана група Хистопатолошка дијагноза								
	Нормален наод (n=9)	LSIL (n=41)			HSIL (n=54)			Инвазивен сквамозен карцином (n=24)	Вкупно (n=128)
		Хроничен вирусен цервицитис (n=20)	Плоснат кондилом (n=2)	Лесна дисплазија (n=19)	Умерена дисплазија (n=15)	Тешка дисплазија (n=23)	In situ сквамозен карцином (n=16)		
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Присуство	1(11,11)	5(25,00)	1(50,00)	7(36,84)	7(46,67)	11(47,23)	9(56,25)	15(62,50)	56(43,75)
Отсуство	8(88,89)	15(75,00)	1(50,00)	12(63,16)	8(53,33)	12(52,77)	7(43,75)	9(37,50)	72(56,25)

Легенда: n, број; LSIL, сквамозна интраепителна лезија од низок степен; HSIL, сквамозна интраепителна лезија од висок степен

тест=5.2667, p=0.0127, p<0.05, со релативен ризик од 2,59), во однос на пациентките со повисок социјален статус (академско лице) (Табела 4).

Анализата на податоците покажа асоцијација помеѓу нередовните гинеколошки контроли (хи-квадрат тест=5.7351, p=0.0166, p<0.05, со релативен ризик од 2,18), честиот вагинален исцедок (хи-квадрат тест=17.0288, p=0.0001, p<0.05, со релативен ризик од 4,05), долготрајната (повеќе од 5 години) употреба на оралните хормонски контрацептивни средства (хи-квадрат тест=5.5385, p=0.0186, p<0.05 со релативен ризик од 3,00) и сквамозните клеточни абнормалности на грлото на матката (Табела 5).

Анализата на податоците покажа асоцијација помеѓу раниот (пред 17-та година) прв сексуален оснос (хи-квадрат тест=4.7643, p=0.0291, p<0.05, со релативен ризик од 2,14) и сквамозните клеточни абнормалности на грлото на матката (Табела 6).

Анализата на податоците покажа асоцијација помеѓу пушењето на цигари (хи-квадрат тест=8.1702, p=0.0043, pё0.05, со релативен ризик од 2,45), диеталната исхрана (хи-квадрат тест=4.1739, p=0.0411, pё0.05, со релативен ризик од 2,11) и сквамозните клеточни абнормалности на грлото на матката (Табела 7).

Табела 4. Демографски и социо-економски ризик фактори

	Испитува-на Група (n=128)	Контрол-на Група (n=64)	Вкупно (n=192)	Коефици-ент на сооднос –Odds Ratio (OR)	95% Интервал на доверба (CI-Confidence Interval)	p
	Број (%)	Број (%)	Број (%)			
Возраст 20-39 40-59	66 (51,56) 62 (48,44)	35 (54,69) 29 (45,31)	101 (5,.60) 91 (47,40)	0.88 1.00	0.483-1.610	0.6801
Образование основно средно вишо/високо	23 (17,97) 81 (63,28) 24 (18,75)	17 (26,56) 28 (43,75) 19 (29,69)	40 (20,83) 109(56,77) 43 (22,40)	1.07 2.29 1.00	0.449-2.554 1.093-4.797	0.8769 0.0262
Брачна состојба мажена немажена	110(85,94) 18 (14,06)	55 (85,94) 9 (14,06)	165(85,94) 27 (14,06)	1.00 1	0.422-2.371	1
Вероисповед христијанска муслиманска	104(81,25) 24 (18,75)	44 (68,75) 20 (31,25)	148(77,08) 44 (22,92)	0.51 1.00	0.255-1.012	0.0522
Социјални домаќинка работничка академско лице	55 (42,97) 51 (39,84) 22 (17,19)	28(43,75) 17(26,56) 19(29,69)	83 (43,23) 68 (35,42) 41 (21,35)	1.69 2.59 1.00	0.790-3.642 1.137-5.903	0.1737 0.0127
Економски вработена невработена	77 (60,16) 51 (39,84)	36 (56,25) 28 (43,75)	113(58,85) 79 (41,15)	1.00 0.85	0.464-1.563	0.6033

Табела 5. Гинеколошко-репродуктивни ризик фактори

	Испитува-на Група (n=128)	Контрол-на Група (n=64)	Вкупно (n=192)	Коефици-ент на сооднос – Odds Ratio (OR)	95% Интервал на доверба (CI-Confidence Interval)	p
	Број (%)	Број (%)	Број (%)			
Гинеколошки контроли да не	69 (53,90) 59 (46,10)	46(81,88) 18(28,12)	115 (59,90) 77 (40,10)	1.00 2.18	1.145-4.1704	0.0166
Чест вагинален исцедок да не	68 (53,13) 60 (46,87)	14(21,88) 50(78,12)	82 (42,71) 110 (57,29)	4.05 1.00	2.0366-8.0444	0.0001
Употреба на хормонски орални контра-цептивни средства да не	30 (23,44) 98 (76,56)	6 (9,37) 58 (90,63)	36 (18,75) 156 (81,25)	3.00 1.00	1.162-7.5358	0.0186
Фамилијарна анамнеза за карцином на грло на матка да не	10 (7,81) 118(92,19)	6 (9,38) 58(90,62)	16 (8,33) 176 (91,67)	0.82 1.00	0.2839-2.3641	0.7083
Родено деца ≤ 2 ≥ 3	102(79,69) 26 (20,31)	55 (85,94) 9 (14,06)	157 (81,77) 35 (18,23)	1.00 0.56	0.682-3.5578	0.2899
Родено прво дете пред 17 год. после 17 год.	21 (16,41) 107(83,59)	9 (14,06) 55(85,94)	30 (15,63) 162 (84,37)	1.20 1.00	0.5147-2.7146	0.6714

Табела 6. Сексуални ризик фактори

	Испитува-на Група (n=128)	Контрол-на Група (n=64)	Вкупно (n=192)	Коефици-ент на сооднос –Odds Ratio (OR)	95% Интервал на доверба (CI-Confidence Interval)	p
	Број (%)	Број (%)	Број (%)			
Прв сексуален однос пред 17-г. после 17-г.	48 (37,50) 80 (62,50)	14 (21,87) 50 (78,13)	62 (32,29) 130(67,71)	2.14 1.00	1.0723-4.2821	0.0291
Број на сексуални партнери 1 ë1	108(84,37) 20 (15,63)	59 (92,19) 5 (7,81)	167(86,98) 25 (13,02)	1.00 2.18	0.7801-6.1214	0.1294

Табела 7. Животни навики како ризик фактори

	Испитува-на Група (n=128)	Контрол-на Група (n=64)	Вкупно (n=192)	Коефициент на сооднос-Odds Ratio (OR)	95% Интервал на доверба (CI-Confidence Interval)	p
	Број (%)	Број (%)	Број (%)			
Пушење цигари да не	72 (56,25) 56 (43,75)	22 (34,37) 42 (65,63)	94 (48,96) 98 (5,.04)	2.45 1.00	1.3165-4.5762	0.0043
Пиење алкохол да не	11 (8,59) 117 (91,41)	5 (7,81) 59 (92,19)	16 (8,33) 176 (91,67)	1.11 1.00	0.3684-3.3412	0.8625
Употреба на лекови да не	25 (19,53) 103 (80,47)	11 (17,19) 53 (82,81)	36 (18,75) 156 (81,25)	1.17 1.00	0.5346-2.5581	0.6985
Диета да не	42 (32,81) 86 (67,19)	12 (18,75) 52 (81,25)	54 (28,13) 138 (71,87)	2.11 1.00	1.0218-4.3832	0.0411

ЗАКЛУЧОК

Анализата на податоците на нашата студија покажа асоцијација помеѓу сквамозните клеточни абнормалности на грлото на матката и ХПВ ДНК-инфекцијата, бактериската вагиноза, нередовните гинеколошки контроли, честиот вагинален исцедок, раниот прв сексуален однос, пушењето цигари, долготрајната употреба на хормонски орални контрацептивни средства и диеталната исхрана.

ДИСКУСИЈА

Перзистентните високо-ризични ХПВ-инфекции се најчести ризик фактори за појава на сквамозните интраепителни лезии и сквамозниот инвазивен карцином на грлото на матката. 75% од сексуално активната популација, во тек на својот живот, била во контакт со еден или повеќе ХПВ генотипови [18].

Во нашата студија ХПВ ДНК-инфекцијата беше детектирана кај 75,00% од пациентките со сквамозни клеточни абнормалности на грлото на матката. Овој релативно висок процент на ХПВ ДНК-инфекција кај пациентките со сквамозни клеточни абнормалности на грлото на матката кореспондира со некои претходно објавени студии [19-22]. Во нашата студија најдена е значајна поврзаност помеѓу присуството на ХПВ ДНК-инфекцијата и појавата на сквамозните клеточни абнормалности на грлото на матката (p=0.028125).

Бактериската вагиноза е чест вагинален синдром во репродуктивниот период на жената. Може да биде асоцирана со повеќе акушерски и гинеколошки компликации, како што се: предвремено породување, хориоамнионитис, ендометритис после царски рез, пелвична инфламаторна болест, постоперативни инфекции по хистеректомија и со абнормален наод на грлото на матката [23].

Во нашата студија бактериската вагиноза беше детектирана кај 43,75% од пациентките со сквамозни клеточни абнормалности на грлото на матката. Овој процент на бактериска вагиноза кај пациентките со сквамозни клеточни абнормалности на грлото на матката кореспондира со некои претходно објавени студии [24-26]. Асоцијација помеѓу бактериската вагиноза и сквамозните клеточни абнормалности на грлото на матката, како во нашата студија (p=0.040649), најдена е и во некои претходно објавени студии [26,27,28]. Во студијата на Антовска и сор., бактериската вагиноза е најдена повеќе кај подгрупата на жени со малигни лезии на грлото на матката (6.3%) отколку во подгрупата со бенигни лезии на грлото на матката (2.1%) [29].

Нашата студија покажа дека пониското ниво на едукција за 2,29 пати (OR=2.29; 95%CI: 1.093-4.797) го зголемува ризикот за појава на сквамозни клеточни абнормалности на грлото на матката. Асоцијација помеѓу интраепителните лезии и карциномот на грлото на матката и пониското ниво на едукација на жените покажана е и во турската студија на Sogukpmar и сор. од 2013 година, работена на 4319 жени [30]. Релативниот ризик за сквамозни клеточни абнормалности на грлото на матката, кај пациентките со понизок социјален статус беше 2,59 (OR=2.59; 95%CI: 1.137-5.503). Во египетската студија на El-Moselhy и сор. од 2016 година, релативниот ризик бил 3,42 (OR=3.42; 95%CI: 1.93-6.07) [31]. Идентичен релативен ризик е детектирана и во романската студијата на Irimie и сор. од 2011 година [32]. Пушењето цигари е еден од почестите ризик фактори за појава на сквамозните клеточни абнормалности на грлото на матката. Поврзаноста помеѓу катранот и карциномот на грлото на матката е покажана уште во 1950 година. Нашата студија покажа дека пушењето цигари за 2,45 пати го зголемува ризикот за појава на сквамозни клеточни абнормалности на грлото на матката (OR=2.45; 95%CI: 1.3165-4.5762). Асоцијација помеѓу сквамозните клеточни абнормалности на грлото на матката и пушењето цигари, детектирана е и во некои претходно објавени студии [33-35]. Релативниот ризик за сквамозни клеточни абнормалности на грлото на матката, кај пациентките кои употребувале орални хормонски контрацептивни средства подолго од 5 години беше 3,00. Во индиската студија на Geetha и Santhy од 2013 година, работена на 200 жени со сквамозен инвазивен карцином на грлото на матката, релативниот ризик бил 2,45 (OR=2.45; 95%CI: 1054-3.92) [36], додека пак во индонезиската студија на Paramita и сор. од 2010 година, релативниот ризик бил 4,21 (OR=4.21; 95%CI: 1.81-9.78) [37].

Нашата студија покажа дека раниот прв сексуален однос пред 17 година од животот за 2.14 пати го зголемува ризикот за појава на сквамозните интраепителни лезии и сквамозниот инвазивен карцином на грлото на матката (OR=2.14; 95%CI: 1.0723-4.2821). Асоцијација помеѓу сквамозните клеточни абнормалности на грлото на матката и раниот прв сексуален однос, детекрирана е и во турската студија на Reis и сор. од 2011 година (OR=58.07; 95%CI: 27.88-120.95) [38], како и во студијата на Utoo и сор. од 2017 година (OR=0.80; 95%CI: 0.30-2.70) [39]. Анализата на податоците од нашата студија покажа и асоцијација помеѓу сквамозните интраепителни лезии и сквамозниот инвазивен карцином на грлото на матката и дието (OR=2.11; 95%CI: 1.0218-4.3832), идентично како и во некои претходно објавени студии [40,41].

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NEPHROLITIAZA,INCIDENCA NE REGJIONIN E GOSTIVARIT

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RESUME

Introduction: Nephrolithiaza is an evolutive illness with multifaktorial ethyology which is characterized with forming stones in urinary tract. Objektive: The intention of this work is to shoë the quickness of nephrolithiazes in the region of Gostivar,it's localization of stones in UT; the frequency based on ages, gender, and the most frequent components of stones. The material: On retrospective study are analyzed statistic information's of 8000 examined patients in the Echosonography cabinet in the general hospital in Gostivar and the information taken from the healthy evidence in the period time from 1997-2002,and the information from the laboratory analysis for the consistence from the biochemistry lab."Benelu Internistika" in Gostivar,as well as from the Nuclear Medical Institute "Rugjer Boskovic" of Zagreb. Result: The results have shown that nephrolythiaza appears frequently in the population of Gostivar, covers both genders, all ages with the most frequent localization, in upper part of UT, and the most frequent components of Oxalate Ca salts. Conclusion: The nephrolythiaza is present in population of Gostivar. Based on the fact that we know the clinic,curing and the consequences of this illness.

REZYME

Hyrje: Nefrolitiaza është sëmundje evolutive me etiologji multifaktoriale që karakterzohet me formimin e gurëvenë traktin urinar.Qëllimi:Qëllimi I këtij punimi është të analizojmë shpeshtësinë e nefrolitiazës në regjionin e Gostivarit;lokalizimin e konkrementeve në traktin urinar;shpeshtësin sipas moshës,gjinisë dhe përbërjen kimike të gurëve.Materiali:Në studim retrospektiv janë analizuar të dhënat statistikore nga evidenca shëndetësore e 8000 pacientëve të ekzaminuar në Kabinetin e Ekosonografisë të spitalit të Gostivarit në periudhën kohore prej vitit 1997-2002 dhe të dhënat nga analizat laboratorike për përbërjën e gurëve në laboratorin biokimik"Benelu Internistika"dhe Institutin e Mjekësisë Nukleare "Rogjer Boshkovic"në Zagreb.Rezultatet:Rezultatet treguan se nefrolitiaza është e shpeshtë te popullata e Gostivarit,I prek të dy gjinitë,të gjitha moshat,lokalizohet më shpesh në pjesët e sipërmë të traktit urinar dhe me përbërje më të shpeshtë nga kripërat e oksalatit të kalciumit. Përfundimi: Nefrolitiaza është prezente te popullata e Gostivarit.

QËLLIMIMI I PUNIMIT

Qëllimi I këtij punimi është të analizojmë shpeshtësinë e nefrolitiazës në regjionin e Gostivarit;lokalizimin më të shpeshtë të konkrementeve në traktin urinar;shpeshtësin e saj sipas moshes,gjinisë dhe përbërjen kimike të gurrëve.

MATERIALI

Në këtë studim retrospektiv janë analizuar kartelat shëndetësore të 8000 pacientëveqë janë kontrolluar në Kabinetin e Ekosonografisë të spitalit të përgjithshëm në Gostivar,që janë mjekuar në periudhën kohore 1997-2002 vit.Nga gjithsej 8000 kontrollime ekosonografike,sëmundjet e traktit urinar janë diagnostikuar te 2301raste,kurse nefrolitiaza është gjetur te 920 të sëmurë.Analiza laboratorike e përbërjes kimike të gurrëve është kryer:në 8 kalkuluse në Laboratorin Biokomok "Benelu-Internistika"dhe në 100 kalkuluse në Institutin e Mjekësis Nukleare "Rugjer Boshkovic"në Zagreb.

Diagnoza e nefrolitiazës është bazuar në anamnezën, ekzaminimin objektiv,analizat laboratorike, radiografinë native dhe ultrasonografinë. Në raste të vecanta edhe me ekzaminime më të specializuara si:urografia intravenoze, pielografia retrograde, radiorendgenografia, tomografia e kompjuterizuar, angiografia e veshkëve, etj.

Për analizën statistikore të dhënat u shprehën në vlera absolute dhe përqindje, tabela dhe grafikone.

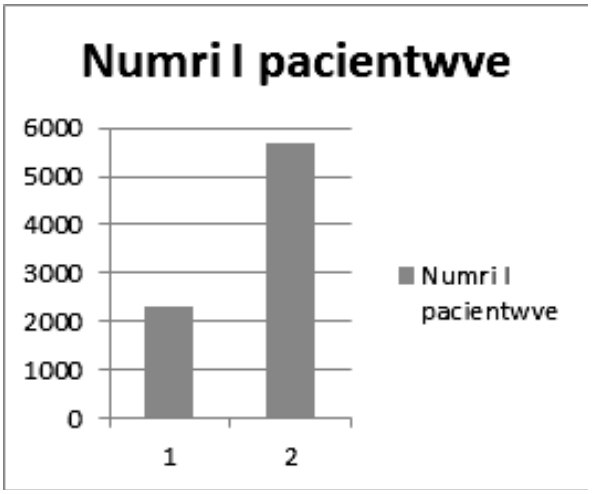
REZULTATET

Në Kabinetin e Ekosonografisë të spitalit të përgjithshëm në Gostivar, në periudhën kohore 1997-2002, janë ekzaminuar 8000 pacientë.

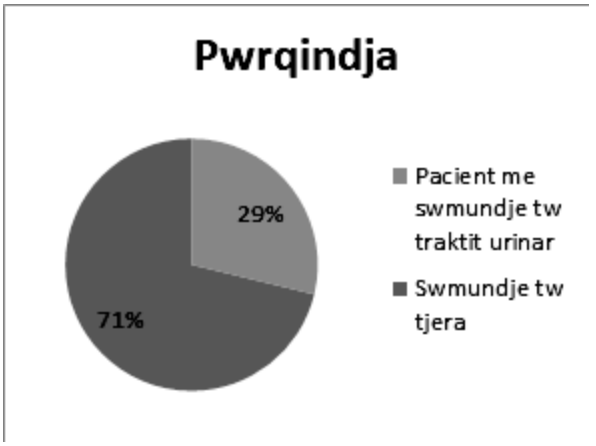
Tabela 1. Frekuenca e sëmundjeve të TU te pacientët e mjekuar në Kabinetin e Ekosonografisë në Spitalin e Përgjithshëm të Gostivarit në periudhën kohore 1997-2002

Sëmundjet e diagnostifikuara	Numri I pacientëve	**Përqindja**
Pacient me sëmundje të traktit urinar	2301	28,76%
Sëmundje të tjera	5699	71,23%
Gjithsej	8000	100%

Grafikoni 1



Grafikoni 2



Në tabelën 1 dhe në grafikonin 1 dhe 2 shihet se nga gjithsej 8000 pacientë të kontrolluar në Kabinetin e Ekosonografisë në Spitalin e Përgjithshëm në Gostivar në periudhen kohore 1997-2002, me sëmundje të traktit urinar kanë rezultuar 2301 ose 28.76% raste.

Tabela 2:Frekuenca e llojit të sëmundjeve të TU, të mjekuar në Kabinetin e Ekosonografisë në Spitalin e Përgjithshëm të Gostivarit në periudhën kohore 1997-2002.

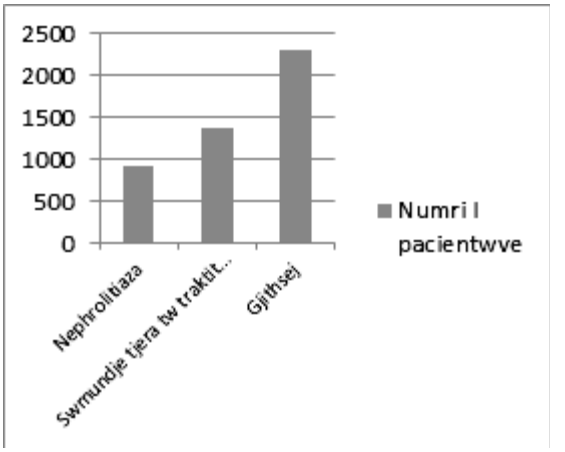
NR.	Sëmundja	Nr. i pacientëve	**Përqindja**
1.	Sëmundjet e trashëguara	241	10,5%
2.	Sëmundjet inflamatore, glomerulonefriti, pyelonefriti,TBC e veshkeve	509	22,1%
3.	Nephrolithiaza	920	40%
4.	Insuficienca kronike e veshkëve	203	8,8%
5.	Insuficienca acute e veshkeve	23	1%
6.	Sëmundjet e fshikzës urinare	138	6%
7.	Pacientë me nephrectomi	35	1,5%
8.	Sëmundje të prostatës	140	6,1%
9.	Veshkë cistike	92	4%
	Gjithsej	2301	100%

Në tabelën 2 shihet se nga gjithsej 2301 pacientë të diagnostikuar me sëmundje të TU, në Kabinetin e Ekosonografisë në Spitalin e Përgjithshëm në Gostivar me nefrolitiazë kanë rezultuar 920 ose 40%, me sëmundje inflamatore të vesgkëvë 509 ose 22.1%, me sëmundje të trashëguara 241 ose 10.5%, me insuficiencë kronike të veshkëve 203 ose 8.8%, me sëmundje të prostatës 140 ose 6.1%, me sëmundje të fshikzës urinare 138 ose 6%, me veshkë cistike 92 ose 4%, me nefrektomi 35 ose 1.5% dhe me insuficiencë acute të veshkëve 23 ose 1% te rasteve.

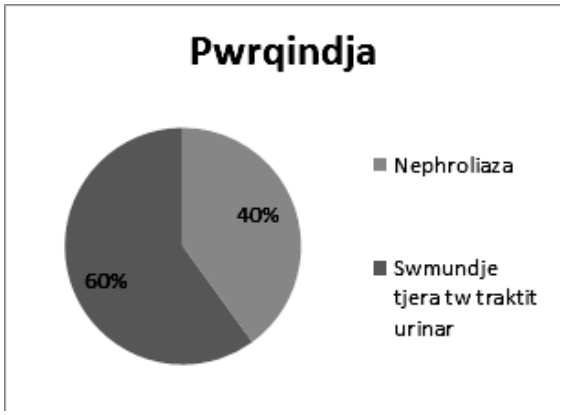
Tabela 3: Frekuenca e nefrolitiazës ndaj sëmundjeve tjera të TU, të diagnostikuara në Kabinetin e Ekosonografisë të Spitalit të Përgjithshëm të Gostivarit në periudhën kohore 1997-2002

Sëmundja	Numri I pacientëve	**Përqindja**
Nefrolitiaza	920	40%
Sëmundje tjera të traktit urinar	1381	60%
Gjithsej	2301	100%

Grafikoni 3



Grafikoni 4

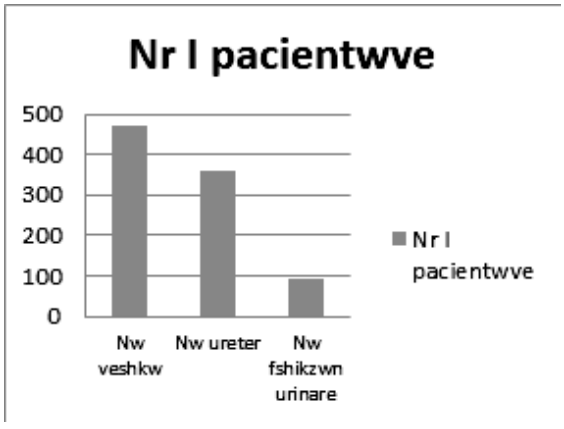


Në tabelën 3 dhe në grafikonet 3 dhe 4 shihet se nga gjithsej 2301 pacientë të diagnostikuar me sëmundje të TU, 920 ose 40% e tyre kanë rezultuar me nefrolitiazë dhe 1381 ose 60% me sëmundje tjera të TU.

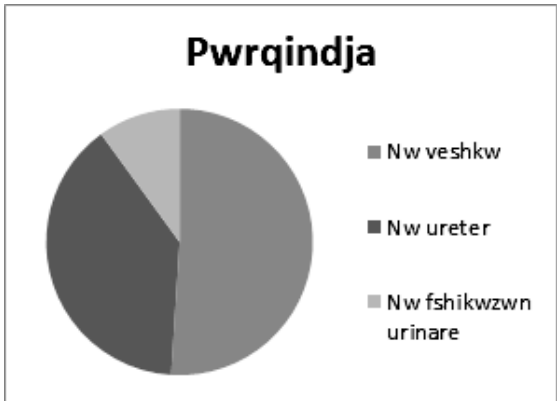
Tabela 4 Frekuenca e lokalizimit të gurëve në TU te pacientët e mjekuar në Kabinetin e Ekosonografisë të Spitalit të përgjithshëm të Gostivarit në periudhën kohore 1997-2002

Lokalizimi I kalkulusit në traktin urinar	Nr. I pacientëve	**Përqindja**
Në veshkë	469	51%
Në ureter	359	39%
Në fshikzën urinare	92	10%
Gjithsej	920	100%

Grafikoni 5



Grafikoni 6

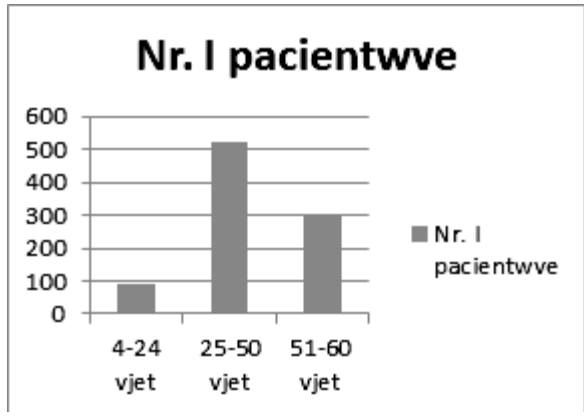


Në tabelën 4 dhe në grafikonet 5dhe 6 shihet se nga gjithsej 920 pacientë të diagnostikuar me nefrolitiazë në Kabinetin e Ekosonografisë në Spitalin e Përgjithsëm në Gostivar, në periudhën kohore 1997-2002 vit, 469 ose 51% kanë rezultuar me lokalizim të gurëve në veshkë, 359 ose 39% në ureter dhe 92 ose 10% të rasteve më fshikzën urinare.

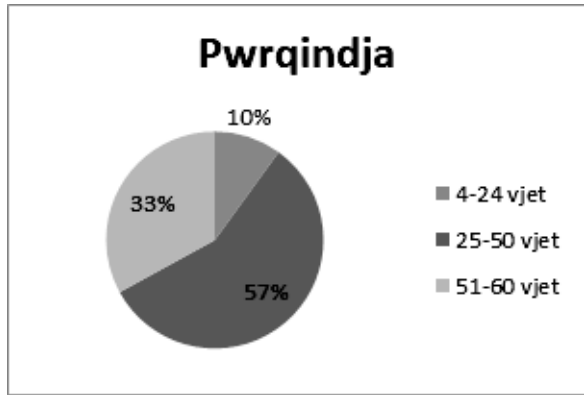
Tabela 5 Frekuenca e nefrolitiazës sipas moshës, te pacientët e mjekuar në Kabinetin e Ekosonografisë të Spitalit të Përgjithshëm të Gostivarit në periudhën 1997-2002

Mosha	Nr. I pacientëve	**Përqindja**
4-24 vjet	92	10%
25-50 vjet	524	57%
51-60 vjet	304	33%
Gjithsej	920	100%

Grafikoni 7



Grafikoni 8

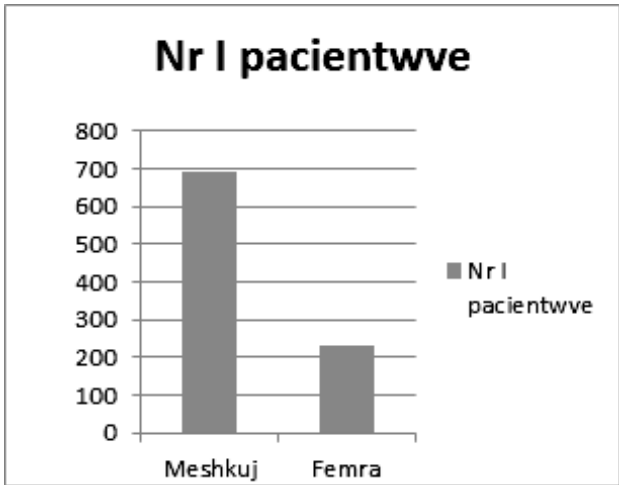


Në tabelen 5 dhe në grafikonet 7 dhe 8 shihet se nga gjithsej 920 raste me nefrolitiazë të egzaminuar në Kabinetin e Ekosonografise në Spitalin e Përgjithshëm në Gostivar, në periudhën kohore 1997-2002 vit, 524 ose 57% kanë qenë të grupmoshës 25-50 vjeç, 304 ose 33% të grupmoshës mbi 51 vjeç dhe 92 ose 10% të grupmoshës nen 25 vjet.

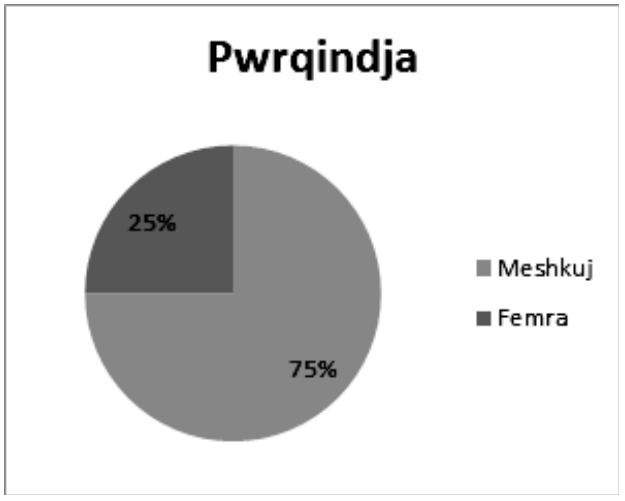
Tabela 6 Frekuenca e nefrolitiazës sipas gjinisë, te pacientët e ekzaminuar në Kabinetin e Ekosonografisë të Spitalit të Pergjithshëm të Gostivarit në periudhën kohore

Gjinia	Nr. i pacientëve	**Përqindja**
Meshkuj	690	75%
Femra	230	25%
Gjithsej	920	100%

Grafikoni 9



Grafikoni 10

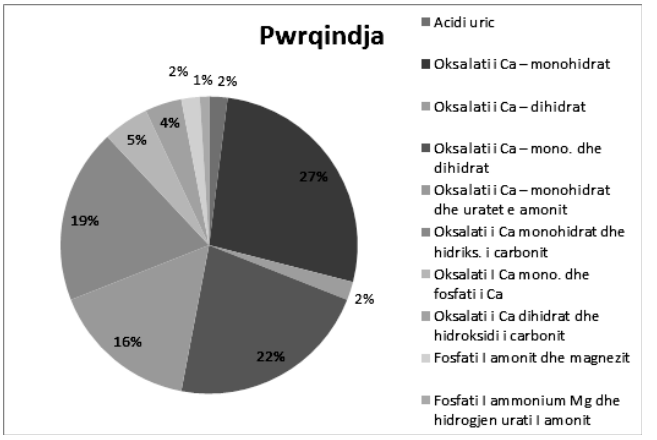


Në tabelën 6 dhe në grafikonet 9 dhe 10 shihet se nga gjithsej 920 raste me nefrolitiazë që jane mjekuar në Kabinetin e Ekosonografisë në Spitalin e Përgjithshëm në Gostivar, në periudhën kohore 1997-2002 vit, 690 ose 75% kanë qenë meshkuj, kurse 230 ose 25% femra.

Tabela 7 Frekuenca e përbërjes të 100 konkrementeve të analizuar në Institutin e Mjekësisë Nukleare "rugjer Boshkovic" në Zagreb

Përbërja kimike	Meshkuj	Femra	Gjith.	**Përqin.**
Acidi uric	2	0	2	2%
Oksalati i Ca – monohidrat	11	16	27	27%
Oksalati i Ca – dihidrat	2	0	2	2%
Oksalati i Ca – mono. dhe dihidrat	13	9	22	22%
Oksalati i Ca – monohidrat dhe uratet e amonit	10	6	16	16%
Oksalati i Ca monohidrat dhe hidriks. i carbonit	6	11	19	19%
Oksalati I Ca mono. dhe fosfati i Ca	3	2	5	5%
Oksalati i Ca dihidrat dhe hidroksidi i carbonit	2	2	4	4%
Fosfati I amonit dhe magnezit	1	1	2	2%
Fosfati I ammonium Mg dhe hidrogjen urati I amonit	0	1	1	1%
Gjithsej	50	50	100	100%

Grafikoni 11



Në tabelën 7 dhe grafikonin 11 shihet se nga 100 konkrementet, (të 50 meshkujve dhe 50 femrave), të analizuar në Institutin e Mjekësis Nukleare "Rugjer Boshkovic" në Zagreb, 27% kanë qenë të përbërë prej kripërave të oksalatit të Ca monohidrat, 22% prej oksalatit të Ca monohidrat dhe dihidrat, 19% prej oksalatit të Ca monohidrat dhe hidroksidi i karbonit, 16% prej oksalatit të Ca monohidrat dhe urateve të amonit, 5% prej oksalatit të Ca monohidrat dhe fosfatit të Ca, 4% prej oksalatit të Ca dihidrat dhe hidroksidi i karbonit, 2% prej acidit uric, 2% prej oksalatit të Ca dihidrat, 2% prej fosfatit të amoniumit dhe magnezit dhe 1% prej fosfatit të ammonium magnezit dhe hidrogjen uratit te amoniumit.

DISKUTIMI

Në bazë të rezultateve tona në Kabinetin e Ekosonografisë të Spitalit të Përgjithshëm në Gostivar, në periudhën kohore 1997-2002 vit, me sëmundje të traktit urinarë janë mjekuar 28.76% ose 2301 nga gjithsej 8000 pacientë. Nga gjithsej 2301 rast me sëmundje të TU nefrolitiaza është diagnostikuar te 40% ose 920 pacientë. Nëse e analizojmë numrin e konkrementeve në raport me numrin e përgjithshëm të popullatës në komunën e Gostivarit del se 1.3% e tyre kanë gurë në TU. Kjo përqindje prej 1.3% korrespodon me vlerat e shpeshtësisë së gurëve në nivel botëror ku ajo sillet prej 1-3 % (1,2,3,4).

Sa i përket lokalizimit të guëve në TU, kemi gjetur se te 51% ato janë në veshkë, 39% në ureter dhe 10% në fshikzën urinare; Pra, 90% e gurve gjinden në veshkë dhe ureter dhe 10% në fshikzën urinare (1,2).

Kur është fjala për moshën, të dhënat tona tregojnë se në Komunën e Gostivarit nefrolitiaza i prek të gjitha moshat, prej 4-60 vje ç. Më tepër është e prekur grupmosha 25-50 vje ç me 57%, pra, mosha më reproduktive e njeriut, që përputhet me rezultatet e autorëve tjerë. Poashtu, kemi vërejtur se janë prekur edhe moshat nën 24 vjeç me 10% të rasteve (1,2,3,4).

Sa i përket gjinisë, në ekzemplarin tonë, kemi gjetur se konkrementet në Komunën e Gostivarit më shpesh formohen te meshkujt se sa te femrat, në raport 3:1 (1,2,3,4). Ne supozojmë se shkaku i kësaj dukurie qëndron në kushtet e jetesës, të punës, mënyrën e ushqimit, dhe veseve që favorizojnë paraqitjen e nefrolitiazes. Sipas rezultateve laboratorike për përbërjen e kalkuluseve të marra nga dy laboratorë të ndryshëm kemi konstatuar se 60-84 % e gurëve janë të përbërë nga kripërat e oksalatit të kalciumit, 10-15 % nga fosfati i kalciumit, 3% magnesium ammonium fosfatit, 2% nga uratet dhe 1% nga përbërës të tjerë: 60-70 % oksalati i kalciumit, 15 % fosfati i kalciumit, 10% magnesium ammonium fosfati, uratet 2-5 % (1,2,3). Pra, kemi gjetur se në regjionin e Gostivarit kalkuluset në shumicën e rasteve dërrmuese janë të përbërë nga oksalati i kalciumit, që mund të lidhet me pozitën gjeografike, mënyrën e ushqimit, përdorimi i lakrës, spinaqit, domatet, kafeja, kakao, etj., të pasura me kripëra të oksalatit të kalciumit, pastaj me faktorët klimatik: vera të nxehta dhe të thata, të gjithë këto faktorë favorizues të nefrolitiazës.

PËRFUNDIM

Në bazë të rezultateve tona mund të përfundojmë se:

- Në Komunën e Gostivarit nga nefrolitiazaështë prekur 1.3% e popullatës;
- Grupmosha më e prekur është 25-50 vjeç me 57% të rasteve;
- Sëmundja më shpesh e prek gjininë mashkullore se sa atë femërore në raport 3:1;
- Gurët në 90% të rasteve janë të lokalizuar në veshkë dhe ureter;
- Konkrementet më shpesh janë të përbërë nga kriprat e oksalatit të kalciumit, te gjithsej 60-84 % të rasteve;

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ASSOCIATION OF THE MUTATION IN BRAF GENE (V600E) WITH THE CLINICAL PROGRESSION OF DISEASE IN PATIENTS WITH METASTATIC SKIN MELANOMA

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ABSTRACT

Malignant melanoma is the most aggressive form of skin neoplasm characterized by very rapid clinical progression and high mortality. Current studies indicates that progression, treatment response and prognosis of metastatic melanoma depends on the molecular-genetic abnormalities and their specific combinations in malignant melanocytes. In malignant melanoma, somatic mutations in BRAF gene are most frequent at nucleotide position 1799, where most common transition substitution T>A results in valine being substituted with glutamine (p.Val600Glu or abbreviated as V600E) at amino acid position 600 of the B-Raf protein product. BRAF V600E mutation has been found frequently in patients with metastatic melanoma of the skin.

The main goal of this study is to determine the correlation of BRAF V600E mutation presence with the survival of patients with metastatic melanoma of the skin.

In the preliminary phase of this observational prospective study, the presence of BRAF V600E mutation was determined in 16 patients with histopathologically confirmed metastatic melanoma of the skin.

The results of the analyses performed thus far indicates the presence of correlation of BRAF V600E mutation with the clinical progression of the disease, particularly with the survival during the 12-months evaluation period in patients with metastatic melanoma of the skin.

Keywords: metastatic melanoma, disease progression, BRAF gene, V600E mutation

INTRODUCTION

The incidence of malignant skin melanoma in the recent years has increased at a global level. According to the World Health Organization reports, the malignant skin melanoma takes the third place in mortality from malignant diseases. If diagnosed early, melanoma is a disease that can be treated with good results; however, in advanced stage of the disease, melanoma is the most aggressive form of skin carcinoma. Published results from completed studies of metastatic malignant melanoma show that the average survival period is 6-9 months (1).

Genetic abnormalities during the malignant transformation and melanoma development, including epigenetic changes, cytogenetic aberrations, and genome instability are only partially known, despite the extensive research. The malignant melanoma pathogenesis involves mutations, deletions, amplifications, and other abnormalities of the genes: NRAS, KRAS, NRAS, BRAF, PTEN, KIT, CDKN2A, PTEN, MET, ERB2, and others. Many molecular abnormalities have been identified that take part in the melanoma tumorogenesis and influence the regulation of cell proliferation, survival and invasion, including the intracellular signal pathways: RAS-RAF-ERK, PI3K-AKT, and p16INK4/CDK4/RB (2,3). There are many studies that prove that the RAS-RAF-ERK (MAPK) pathway has a key role in the malignant melanoma development (4).

According to some authors, the microarray analyses results, which observe differences in the expression of big number of genes at the same time, direct to a finding that malignant melanoma is not an individual entity, but it can be split to at least 4 normal types (5). It seems that

each of these molecular subtypes is different according to the clinical progression, therapy response, and the prognosis of the disease. The mutation profile, i.e. the determination of mutations at the same time in a selected gene group is important in the clinical studies, too, in order to examine the genotype-driven therapy efficiency in malignant melanoma (6).

In spite of the many gene abnormalities studied in malignant melanoma, especially in metastatic forms, in the recent years molecular analyses have been performed on a number of other genes related to certain clinical and pathological characteristics of this neoplasm, even genes that are less examined, but potentially relevant from applicational and scientific aspects.

The BRAF gene is a proto-oncogene located at the chromosomal locus 7q34, which encodes the serine/treonin-protein kinasa B-Raf, involved in the intracellular transduction of mitogenic signals from the superficial cell receptor to the effector genes in the nucleus.

In malignant neoplasms, the somatic mutations in the BRAF gene are most common at the nucelotid position 1799, where the most common transition substitution T>A results in replacement of the aminoacid valin by glutamin acid (marked as p.Val600Glu, or abbreviated as V600E) at position 600 of the B-Raf protein product. This results in 10 times higher enzyme activity in terms of the unmutatetd form, and in this case, RAS-mediated membrane translocation is not necessary to activate the enzyme (7). The activation of the mutated B-Raf protein is a result from conformational changes in the protein structure (8).

The V600E mutation transforms the proto-oncogene BRAF into an active oncogene that over-stimulates the signal pathway and takes part in an uncontrolled cell proliferation (9).

Depending on the studies, the BRAF V600E mutation is found in 37-50% of all malignant skin melanoma cases (10). An interesting fact is that this mutation appears in almost 80% of benign nevuses, and absent in uveal melanomas (11).

The importance of this mutation in malignant melanoma, especially in more advanced stages of the disease, is essential in the selection of patients for targeted therapy with BRAF and/or MEK-kinasa inhibitors, mentioned above (12).

Although this mutation is present in almost 80% of bening nevuses, the issues of malign transformation in these benign forms is still not resolved. Yu et al. in their study point out that the MAPK cascade is not sufficient for the malignant melanoma tumorogenesis (13).

In malignant melanoma, the BRAF V600E mutation is involved in various mechanisms of tumour progression (14). It is considered that the mutated protein product is the proliferation inductor and leads to hyperactivation of the MAPK-signaling cascade, which induces cell division and promotionally acts on the tumour development (15). It has been proven that the BRAF V600E mutation affects the production of interleukin 8, a proinflammatory chemokin and autocrine factor, and the vascular endothelial growth factor (VEGF). These factors, consequentially, act promotionally, support the tumour growth, and the neoangiogenesis (16).

The malignant cells, helped by the BRAF V600E mutation, avoid the apoptosis and maturity processes, which further results in an uncontrolled potential for cell replication. Furthermore, it is considered that this develops tumor progression in terms of local tissue invasion and metastasizing, which is a complex process where several proteins are included that control the cell signalization, migration, invasions and contractility. Additionally, there are data that show that the melanoma cells with BRAF V600E mutation avoid the immune response of the body (14).

The research on the BRAF V600E mutation is expected to contribute to the establishment of bio-markers that can be used in diagnostics (especially in the clinical and pathological classification), for therapy choice (the targeted therapy being in focus), as well as in the prognosis and further evaluation of patients with metastatic malignant skin melanoma.

AIM

The aim of our study is to determine the correlation between the BRAF gene mutation presence and certain clinical and demographic data, especially the survival of patients with metastatic malignant skin melanoma during the 12-month evaluation period.

MATERIALS AND METHODS

This prospective, observational, genetic-associative study analysed the demographic, clinical, and molecular-genetic data of patients with metastatic skin melanoma at

the Public Health Institution University Clinic of Plastic and Reconstructive Surgery in Skopje, with prior signed patients' consents and aproved by the Ethical Committee at the Medical Faculty in Skopje.

After collecting samples from patients' metastatic lymph nodes, the was a clinical follow-up of 12 months.

During the resection of the metastatic lymph nodes, in cooperation with a pathologist, tissue fragment was taken, weighing less than 0.2 g. The histopathological sample from the rest of the same lymph node was separately evaluated in order to confirm the presence of at least 70% malign cells.

The selection of patients was made according to determined eligibility criteria (histopathologically tested metastatic deposits on skin malignant melanoma in the lymph nodes or the skin, handwritten consent by the patient, accessibility of appropriate clinical data and others), as well as study exclusion criteria (clinically confirmed autoimmune diseases, chronic corticosteroid or immuno-suppressive therapy, pregnant patients, inappropriate histopathological confirmation of metastatic deposit in the lymph node or percentage of presence of malign cells in the resection lower than 70%, insufficient number of clinical parameters, unsatisfactory quality of isolated DNA and RNA from the sample, etc.).

The determination of the site of taking tissue fragments from the material was in consultation with pathologists of the Pathological Anatomy Institute at the Medical Faculty in Skopje. The clinical part of the study was conducted at the Clinic of Plastic and Reconstructive Surgery in Skopje. The molecular-genetic and statistical analyses were performed at the Molecular Biology Laboratory at the Science and Mathematics Faculty. The isolation of genome DNA from tissues was performed by standard extraction with phenol-chloroform and consequential ethanol precipitation.

The detection of the mutation c.1799 T>A in the BRAF gene (i.e. V600E at protein product level) was done using the method of gene typization using pair of TaqMan-oligonucleotide probes: for the wild-type allele marked by fluorescent VIC marker, for the mutated allele by FAM, while both probes were connected by the NFQ fader. The nucleotide sequences of the pair of oligonucleotide primers for amplification of a BRAF gene region, and the two TaqMan probes were used according to the study of George et al.(17).

The mutation presence was determined by the fluorescent signal detected by the Real-Time PCR system (StepOne Real-Time PCR, Applied Biosistems). The received data were analyzed using the Applied Biosistems software, an integral part of the Real Time-PCR system.

The statistical calculations were made by comparison of the V600E mutation presence in the BRAF gene to the appropriate demographic and clinical parameters, using the XLSTAT 2016 and Microsoft Excel 2016 software systems. The relation of the clinical and pathological data to the molecular ones from the patients was calculated using the Student t-тест in parameter values with normal distribution, i.e. using the Mann-Whitney U-test in case of deviation from the normal distribution of values of the appropriate parameter. Values at $p<0.05$ were considered to be statistically significant.

RESULTS

Demographic and Clinical Characteristics

This research used data collected and samples analyzed from extracted metastatic lymph nodes where presence of metastatic deposits of malignant melanoma was histopathologically confirmed.

The basic demographic and analyzed clinical data for total of 16 patients with metastatic skin melanoma in this study, are shown in table 1.

Table 1. Data on the metastatic melanoma patients

Parameter			
Age	Median value ± SD (minimum-maximum)	63.00 ± 11.40 (41-81)	
		n	%
Gender	Male	11	68.75
	Female	5	31.25
	Total	16	100.00
Fitzpatrick scale	II	8	50.00
	III	7	43.75
	IV	1	6.25
	Total	16	100.00
Clinical stage	IIb	8	50.00
	IIIa	1	6.25
	IIIc	7	43.75
	Total	16	100.00
Location	reg. axillae	10	62.50
	reg. inguinalis	6	37.50
	Total	16	100.00
Survival	Live	11	68.75
	Deseased	5	31.25
	Total	16	100.00

SD = standard deviation

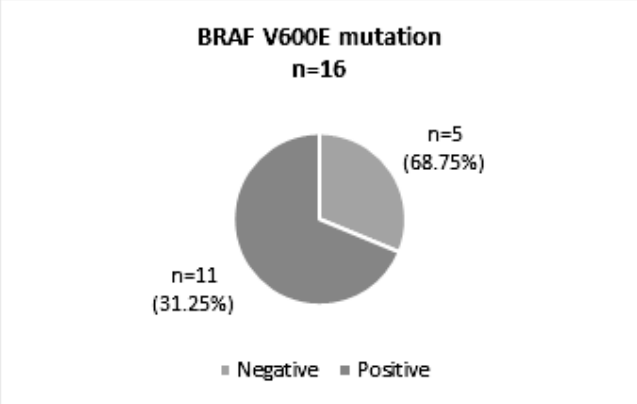
Presence of V600E mutation in the BRAF gene

The presence of the V600E mutation in the BRAF gene was determined in DNA samples isolated from a surgically removed metastatic lymph nodes from 16 patients with skin melanoma.

As shown in table 2, and graph 1, the mutation was found in 11 out of 16 patients, i.e. in 68.75% of patients.

Table 2. Presence of V600E mutation in the BRAF gene

Presence of BRAF V600E mutation	n	%
Negative	5	31.25
Positive	11	68.75
Total	16	100.00



Graph 1: Graphical chart of the mutation V600E presence in the BRAF gene

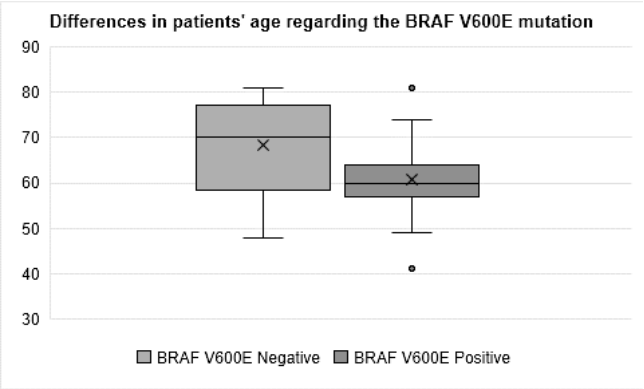
Presence of V600E mutation in the BRAF gene in terms of patients' age

The processing of compiled data shows that the presence of V600E mutation presence in the BRAF gene varies with patient's age.

Namely, the median value of age in the subgroup of patients with metastatic melanoma, positive on V600E mutation presence in the BRAF gene, is lower than the median value of age of the sbgroup of patients who are negative on this mutation, for approx. 8 years (table 3 and graph 2).

Table 3. Differences in the V600E mutation presence in the BRAF gene in terms of the age of patients with metastatic melanoma

Age (years)	Negative on BRAF V600E	Positive on BRAF V600E
Average	68.20	60.64
Standard deviation	12.24	10.74
Minimum	48	41
Maximum	81	81



Graph 2: Graphic chart of the V600E mutation presence in the BRAF gene in terms of the age of patients with metastatic melanoma. Values show patients' age

Legend for interpretation of the box-and-whiskers charts:

The lower end of each rectangular structure relates to the first quartile (25. percentile), while the upper end of the third quartile (75. percentile) to the values, and encompasses the median 50% of all measurements. The horizontal line of each rectangular structure shows the median (geometric environment), while the symbol X shows the average (arithmetic median). The vertical positive and negative intercepts refer to the distribution of the extreme maximum and minimum deviations in measurements corrected by the third and first quartiles, respectively. The uncorrected deviations (outliners) are shown by circles.

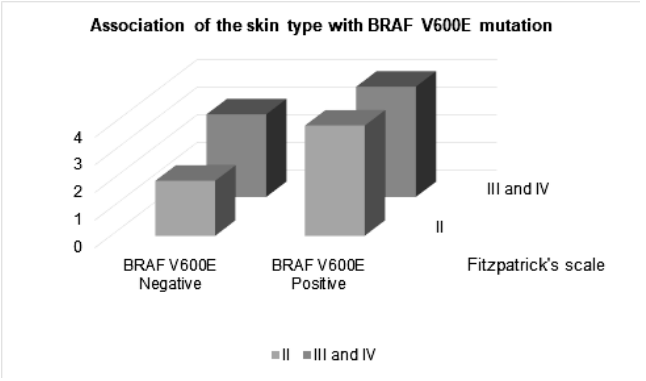
Presence of V600E mutation in the BRAF gene in terms of the patients' skin type according to the Fitzpatrick scale

Our study shows differences in the V600E mutation presence in the BRAF gene depending on the skin type of patients with metastatic skin melanoma, according to the Fitzpatrick scale (table 4 and graph 3).

Table 4. Differences in the V600 mutation presence in the BRAF gene according to the skin type of patients with metastatic melanoma according to the Fitzpatrick scale

Skin Type (Fitzpatrick scale)	Negative on BRAF V600E n (%) **	Positive on BRAF V600E n (%) **	Total n (%) **
Type II	2 (25.00)	6 (75.00)	8 (100.00)
Type III and IV *	3 (37.50)	5 (62.50)	8 (100.00)

* due to small number of patients, types III and IV are combined in one group
** the percentage is calculated based on both groups and their skin types

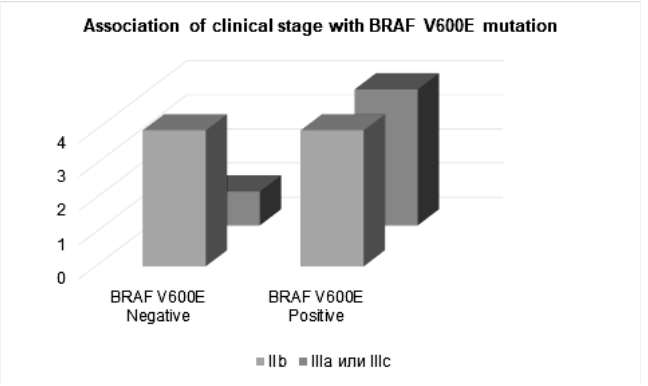


Graph 3: 3D-graphic chart on V600E mutation presence in the BRAF gene in terms of the skin type by the Fitzpatrick scale in patients with metastatic melanoma. The values show the number of patients

Table 5. Differences in the presence of V600E mutation in the BRAF gene in terms of the clinical stage of the patients' primary melanoma

Clinical stage of primary melanoma	Negative on BRAF V600E mutation n (%) **	Positive on BRAF V600E mutation n (%) **
Iib	4 (80.00)	4 (36.36)
IIIa or IIIc	1 (20.00)	7 (63.64)
Total	5 (100.00)	11 (100.00)

* due to small number of patients, stage IIIa and IIIc are combined
** the percentage is calculated based on the presence of mutation in patients



Graph. 4: 3D-graphic chart of presence of V600E mutation in the BRAF gene in terms of clinical stage of primary melanoma in patients. Values show the number of patients.

Presence of V600E mutation in the BRAF gene in terms of clinical stage of the patients' primary melanoma

The presence of the V600E mutation in the BRAF gene differentiates between the subgroup of patients with clinical stage of primary melanoma without invasion in the deeper skin layers and without metastases in the lymph nodes (stage IIb) compared to the stages where there is deeper invasion of melanoma in the skin structures and subskin tissue, as well as presence of metastatic lymph nodes (in stages IIIa and IIIc).

These data are shown in table 5 and graph 4.

Presence of V600E mutation in the BRAF gene in terms of survival of patients

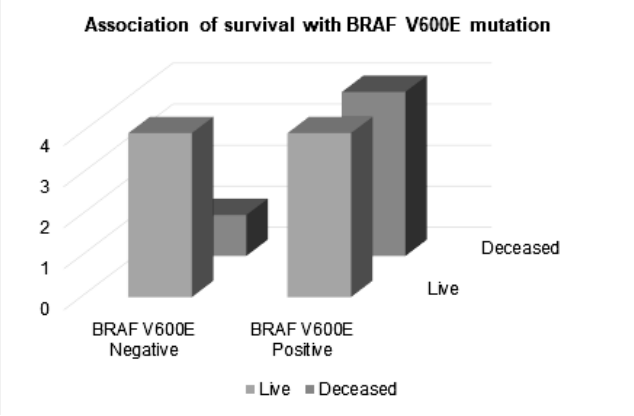
This study shows differences in the presence of the V600E mutation in the BRAF gene in terms of survival during a 12-month-evaluation period (table 6 and graph 5).

As can be seen from the data, the presence of the V600E mutation in the BRAF gene is higher by approx. 23% in the subgroup of deceased patients during the evaluation, compared to the survivors.

Table 6. Differences in the presence of the V600E mutation in the BRAF gene in terms of survival of patients

Survival	Negative on BRAF V600E mutation n (%) *	Positive on BRAF V600E mutation n (%) *	Total n (%) *
Living	4 (36.36)	7 (63.64)	11 (100.00)
Deceased	1 (20.00)	4 (80.00)	5 (100.00)

* the percentage is calculated in terms of the presence of both subgroups of patients according to the survival



Graph 5: 3D-graphic chart of the presence of the V600E mutation in the BRAF gene in terms of survival of patients Values show the number of patients

DISCUSSION

This pilot study shows the preliminary results of a research conducted on the presence of the V600E mutation in the BRAF gene in patients with metastatic skin melanoma. Data have been processed for 16 patients out of the planned 50 patients in the doctoral dissertation submission.

The processing of the preliminary research data show certain differences that can be observed in terms of values; however, the small number of patients does not allow application of statistical analyses (n<20). Therefore, the descriptive analysis of data and their table and chart forms provide a basic idea on the structure of patients with metastatic skin melanoma, as well as on the initial trend in terms of the differences in distribution of patients, negative or positive, on the presence of the V600E mutation in the BRAF gene

This mutation is found in approx. two thirds (68.75%) of the examined patients, while the rest of 31.25% are negative on its presence. This percentage is a bit higher than approx. 50% of the examinees, as is the prevalence in most of the published studies, although the presence has shown variations in literature (14). These variations may be due to various factors, including ethnical differences, various criteria on inclusion in studies, methodology on detection of mutations, which specially affects the sensitivity. The use of the Real-Time PCR is one of the most sensitive accessible methods for detection of mutations of individual nucleotides, as the V600E mutation in the BRAF gene, which can determine the presence of mutant allele even if there is less than 1% of malignant cells of the sample, as opposed to the sequencing, where minimum 20% of the tissue sample cells must contain the mutant allele (18).

In our study, the presence of the V600E mutation in the BRAF gene show differences also in the age of patients with metastatic skin melanoma. The arithmetic median value of the age of patients with metastatic melanoma positive on this mutation presence is lower by approx. 8 years than the median value of age in patients negative on the mutation. The standard deviation values and the minimum, i.e. maximum age are very similar between these two subgroups of patients, which is in favour of this observation. Otherwise, the tendency of younger patients with malignant skin melanoma having more frequent presence of this mutation has already been noted in literature and can have direct negative implications on the further clinical progression of the disease, but also the choice of postoperative therapy (19).

We found differences in the presence of V600E mutation in the BRAF gene in terms of skin type according to the Fitzpatrick scale in the examined group of patients with metastatic skin melanoma. The comparison was done in two subgroups of patients: with lighter skin complexion (type II by the Fitzpatrick scale), and with darker complexion (type II and IV by the Fitzpatrick scale, combined, due to small number of patients). The V600E mutation in the BRAF gene was found in 75% of patients with lighter complexion, against 62.5% in patients with darker. This prevalence of mutation according to the skin type, has also been noted in the conducted studies; it is considered to be due to better UV-protection that the pigment melanin provides in darker complexion, as opposed to the lighter, i.e. the skin of lower type according to the Fitzpatrick scale (20).

The analysis of the compiled data in our research also showed differences in the V600E mutation presence in the BRAF gene between the subgroup of patients with clinical stage of primary melanoma with no invasion in

the deeper skin layers and no metastases in the lymph nodes (stage IIb), as opposed to the subgroup with both stages found, where there is deeper invasion of melanoma in the skin structure and subcutaneous tissue, as well as presence of metastatic lymph nodes (stages IIIa and IIIc). 80% of the subgroup of patients negative on this mutation are the ones with confirmed clinical stage IIb, while only 20% have advanced stages of IIIa or IIIc.

Our study has also found differences in the presence of the examined mutation in terms of survival during the 12-month-evaluation period. The V600E mutation was found in 80% of the subgroup of deceased patients during the evaluation, compared to 20% of the survivors, i.e. the prevalence mutation differs by approx. 23%.

The poor prognosis in advanced stage of melanoma is the reason to conduct more studies in order to determine the factors that cause failure of targeted therapy, the decreased percentage of response to certain therapy, and recurrence of the disease. Shinozaki in his study examines the prognostic effect of the BRAF V600E mutation (21). The study results showed that the presence of the mutated BRAF was significantly related to smaller survival period of 13 months compared to 30.6% in patients who did not have mutated BRAF. Another study by Ardekani et al. showed similar results and proved that the BRAF expression was related to significantly lower survival period (22).

Although the number of published papers is small, the prognostic significance of the BRAF V600E mutation in patients with metastatic melanoma is confirmed from several published studies (23). Results from two studies with 105 patients classified as clinical stage III of melanoma showed that the mutations BRAF V600E and V600K and the number of positive lymph nodes were independent prognostic factors for determining the survival period (24,25). For the newly diagnosed patients with melanoma stage IV, Long et al point out that the BRAF V600E mutation is poor prognostic factor, but they do not find and relation between the time of metastases appearance compared to the time of the primary melanoma excision (26). Despite the fact that all of these results from the conducted studies agree with the fact that the BRAF gene mutations are associated to the progression of the primary melanoma, there are no larger studies to date of patients with malignant skin melanoma stages I-III and therefore it is difficult to draw conslusions on the importance of mutations in this group of patients (27).

From the above, we can conclude that the preliminary results from the analyses of this study are in favour of the correlation between the V600E mutation presence in the BRAF gene and the disease progression, especially in terms of survival during the 12-month-evaluation period in patients with metastatic skin melanoma.

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IMPLANT TREATMENT IN FRONTAL MAXILLA IN A PATIENT WITH CONGENITALLY MISSING LATERAL INCISORS (CASE REPORT)

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ABSTRACT

Tooth agenesis is one of the most common developmental dental anomalies in humans. The aim of this study is to offer a solution in cases of anterior agenesis with dental restoration with osseointegrated implants as the most conservative treatment. The main reason for this treatment option is to avoid preparation of the adjacent teeth. This is particularly very important element in planning the therapeutic approach since most of the patients are at young age. Following orthodontic treatment, the most common problems relate to less than ideal locations of teeth adjacent to the edentulous area and relapse of the orthodontic treatment outcomes. The problems created by the proximity of the roots of teeth to an edentulous area as a consequence of orthodontic treatment are difficult to manage. A case of a 22-year old patient with missing of lateral incisors in maxilla with previously completed orthodontic treatment is presented. The clinical and paraclinical examination showed that the available edentulous spaces were marginally acceptable for implant supported restorations. Bilateral single-tooth implant supported metal-ceramic prosthetic crowns were constructed six months after osseointegration.

Keywords: lateral incisors, agenesis, orthodontic treatment, dental implants, crowns

INTRODUCTION

The most common missing teeth in the population of European ancestry are the wisdom teeth (2535%), followed with the lower second premolars (3%) and permanent upper lateral incisors (2%)[1]. Interdisciplinary cooperation between orthodontists, oral surgeons and prosthodontists became especially apparent and important when treating tooth-bounded gaps resulting from hypodontia [2, 3]. Agenesis of lateral incisors usually is treated with one of the following options: simple isolated orthodontic treatment, in which the canines are positioned in the place of lateral incisors; multidisciplinary orthodontic-prosthetic approach with fixed crowns which restore the empty spaces; and multidisciplinary orthodontic- implantologic- prosthetic option, in which after creating a sufficient bone segment in maxilla for implant treatment, single prosthetic crowns are fabricated and then fixed to the implants [4].

To make the final decision, if a patient is suitable for the orthodontic approach and to participate if additional restorations may be necessary, the authors strongly suggest a carefully executed treatment plan. This treatment plan should include full radiographic work-up, cephalometric analysis, full esthetic work-up (esthetic evaluation form), model analysis for Angle classification and Bolton discrepancies, model set-up, including the recontoured canine to predict the esthetic and functional result, as well as the amount of reduction (width, labial convexity, incisal and lingual eminence), which are necessary to achieve the desired results [5]. If carefully planned and executed, the orthodontic approach is the most conservative approach. Long-term esthetic results, superior esthetic outcome compared with implants and Maryland bridge, psychological comfort that the patient

has no missing teeth are the main advantages, while the disadvantages of the orthodontic treatment refer to the possibility of a new restorative treatment and bleaching of the canine if it appears too dark [6].

Another approach to congenitally missing lateral incisors is the restorative approach. The restorative approach may be categorized as (1) resin-bonded bridge, (2) conventional bridge, and (3) cantilever bridge. The advantages of restorative approach are the occlusal and esthetic adjustments that can be done within the restoration (full-coverage fixed partial dentures) and the fast approach if no orthodontic treatment needed. However, the restorative approach is the least conservative one, additional orthodontic treatment may be needed, it has to be changed over lifetime and additional preparation of the adjacent teeth may be necessary [7].

The third recommended approach is the implant supported one. Several criteria have to be considered before placing a single tooth implant in adolescents: time of implant placement, development of a proper implant site, enough space coronally and apically, sufficient height of gingival and space retention before implant placement.

Advantages of orthodontic-implantological treatment are: ideal intercuspidation of canines with physiological occlusion and function, better physiognomy and aesthetics in frontal region because the teeth are maintaining the proper position in the dental arch and the permanent teeth are maintaining their natural shape and form and orthodontic treatment is significantly shorter [8, 9]. Disadvantages are: complete physiological osseal jaw growth must be definitive; during the time of implant osseointegration, a retaining of the space between central incisors and canines must be effective to prevent the inclination of adjusting teeth; a final couture of soft and hard tissue around the implants cannot be always predictable in aesthetic aspect; and finally, financial cost is always higher compared to the other approaches [10, 11].

The case described here suffers from aplasia of the upper lateral incisors. After the orthodontic treatment, the gaps were kept open, implant-supported restorations were placed later on. As the orthodontist, oral surgeon, prosthodontist and dental technician had been working together consistently, the outcome of aesthetics will be considered really satisfactory.

CASE REPORT

Twenty two-year-old male patient referred to our clinic with bilateral missing of lateral maxillary incisors. Taking into consideration all the conditions and after a consult with orthodontist, a multidisciplinary approach was planned. All the necessary examination methods mentioned above were performed. The orthodontic treatment included fixed orthodontic appliances in order to move the canines distally, to ensure contact between the central incisors and to maintain the space between central incisors and canines (Figure 1). After completed orthodontic treatment, all the necessary measurements were made for the implant phase. Therefore, two endooseal dental implants were inserted in the missing teeth regions (12 and 22) following the standard surgical and implant protocols and principles (Figures 2 and 3). Single tooth implant-supported metalceramic crowns were constructed and fixed six months after definitive implant osseointegration (Figures 4 and 5). The patient was evaluated by an orthodontist, an oral surgeon and a proshtodontist; the aeshtetic and functional results were considered as very satisfactory.

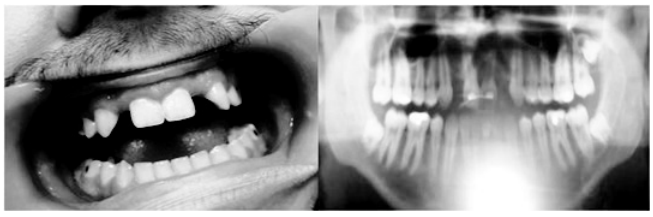

Figure 1. Clinical and radiological condition after completed orthodontic treatment.

he retainer placed on the central incisors is also visible here.

Figure 2. Intraoperative view of implant placement.

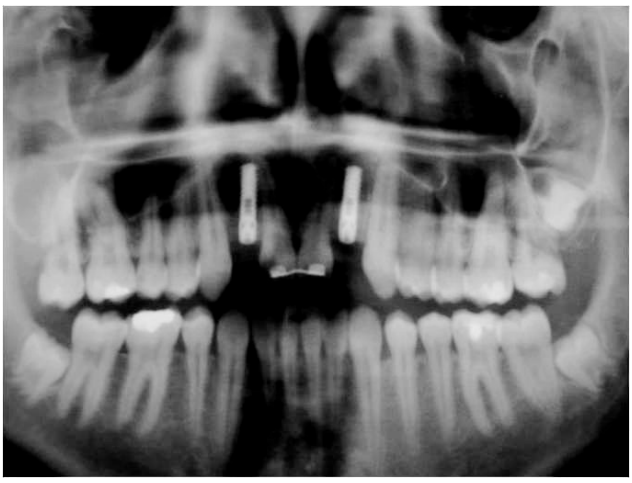

Figure 3. X-ray image, six months after implant placement.

Figure 4. Definitive position of fixed single tooth abatments.

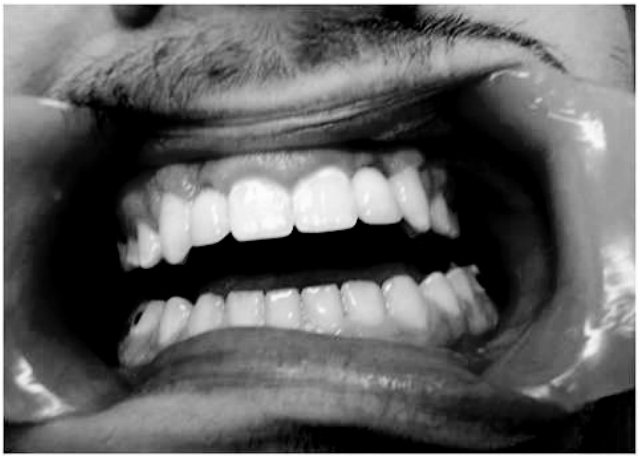

Figure 5. Definitive position of fabricated and fixed single-tooth metal-ceramic crowns over the implants .

DISCUSSION

The maxillary anterior buccal crestal bone thickness can be very thin and deficient in vertical and buccolingual dimensions, much less than 2 mm. In fact, similar to findings in cadaver and clinical studies, a recent cone-beam study [12] revealed that facial bone thickness of 2 mm at levels 1, 2, 3, 4, and 5 mm from the bone crest was present in 0%, 1.5%, 2.0%, 3.0%, and 2.5% of patients, respectively. After removal of teeth, blood supply to this predominantly thin facial bone overlying maxillary anterior teeth can be disrupted, leading to detrimental bone loss or soft-tissue recession [13, 14]. Therefore, atraumatic procedures, use of alternative implant sites with adequate bone volume, and delayed placement of implants are recommended until enough bone volume is generated at the implant site by performing bone grafting, socket preservation techniques, or orthodontic bone regeneration.

The orthodontic extrusion of nonrestorable or periodontally compromised teeth increases the hard and soft tissue volume in the future implant site [14] and may eliminate the vertical bone volume deficiencies. Alveolar ridge augmentation techniques are more predictable in restoring the width of an alveolar ridge than its height [15]; nonetheless, orthodontic extrusion is one of the most reliable means of gaining vertical bone augmentation. This is particularly true in the maxillary anterior region, where vertical bone augmentation is difficult. Good plaque control, the existence of at least one-third to one-fourth of the apical attachment, and a sufficient stabilization period are necessary for a successful forced eruption. [16] The orthodontic extrusion is done at a rate of 1 mm per week, and a stabilization period of 1 month for each millimeter extruded has been recommended. When a periodontally compromised tooth is extruded, torquing and tipping of the tooth toward an angular bone defect increase the alveolar bone volume in the future implant site. With this strategy, some improvement of the interproximal papillary height can be expected.

With congenitally missing teeth, adjacent or opposing teeth may tip, drift, or overerupt, leaving edentulous spaces that are not favorable to replacement of missing teeth. Collectively, this affects the space and bone volume required for implant placement or the implant-supported restoration. The staged orthodontic treatment and some orthodontic strategies, such as the orthodontic extrusion, delayed orthodontic space opening, and the orthodontic implant site- switching technique, can preserve or augment the future implant site.

When it comes to treatment planning, x-ray imaging, 3D imaging and CT scan are necessary along with Bolton analysis and studio models. Establishing adequate proportion and optimal aestetitics in frontal maxilla are very significant clinical aspects. Objective orthodontic considerations in restorative management with endosseous implants are: short and retrognathic maxilla, prognathic mandible, and shorter lower anterior facial

height, which sometimes need orthognathic correction as part of the complete treatment. Dental problems vary and include bimaxillary retroclination of incisors, spacing, centerline discrepancies, microdontia, hypoplastic enamels, ankylosis of the retained primary teeth, overeruptions, and volume deficiencies of alveolar ridges. The mentioned challenges, as well as the bone volume deficiencies, compromise the successful placement of implants. Orthodontic strategies and techniques, such as uprighting mechanics, extrusion/intrusion, delayed space opening, and orthodontic implant site-switching, can be used to create, preserve, or augment the implant site. After orthodontic site development, the final planned position of the teeth should be maintained with a rigid bonded retainer; overlooking this stage may compromise the implant site and require orthodontic retreatment.

Creating a sufficient space for dental implants requires minimal mesio-distal dimension of 5.5 to 8.0 mm and the optimal dimension for clinical crown needs to be at least 6.3 mm. Interradicular dimension should be at least 5.7mm, and there should be a 1.5 mm distance from adjusting roots of natural teeth.

Careful attention has to be paid to the distance of the apical roots between central incisor and canine [17]. A minimum of 5 mm is required generally to provide sufficient space for a 3.5-mm implant. This space has to be provided by an orthodontist, who controls the mesiodistal root angulation when creating space for an implant. During this process of creating space, the mesiodistal space coronally is achieved earlier due to a socalled tipping movement, followed by a change of the mesiodistal angulation of the roots. It is crucial not to rely on the appearance of the mesiodistal distance of the coronal aspect, which is achieved earlier than the proper mesiodistal distance of the roots. Not paying attention to this aspect leads to too early removal of the orthodontic appliances and, therefore, insufficient space between the roots. To prevent this mistake, radiographs of this particular area should be made to make sure that sufficient interradicular space is created before removal of orthodontic appliances.

CONCLUSION

The concern for esthetics is an ever-growing demand and goal in today's dental treatment plans provided to patients. In the past, function, biology, and structure were more important; esthetics had to follow. Today, it should be the goal to start with the best esthetic outcome in mind and then work out the treatment plan according to it. That does not mean that function, biology, and structure are less important than before; it just means that the esthetic goal should be set first, not at the end of the treatment.

As discussed previously, many instances need a team play of several specialties to reach the optimal esthetic result for individuals. It is important that every member of the team is exactly aware of what he or she has to do; otherwise, the result may become compromised or even disastrous. Such complications may be avoided by systematically designing a multidisciplinary treatment plan in which individual responsibilities are detailed in chronologic order, so that everybody has a clear picture of what to do and what the team players have to do.

Specifically, for missing congenitally lateral incisors there are several treatment options, which all can lead to a good result if patients are properly selected for an ideal treatment. Canine substitution can be a good treatment solution, if certain criteria are met. Nevertheless, team play with a restorative dentist is often required to reach an optimal esthetic outcome. Also, the restorative option can be used to meet a patient's high esthetic demands, if used in the right situation; hence, requiring an interdisciplinary treatment approach is often necessary to get the best result

Implants are probably the most favorable treatment alternative for many dentists for replacing missing anterior teeth. The implant approach in the anterior region is a delicate situation, which can be challenging esthetically, especially in the long term. In this scenario, it is necessary to work as a team to have ideal conditions before and after implant placement. Autotransplantation can be a good alternative in growing patients. It is not suitable for nongrowing adults. As in all the other treatment options, an interdisciplinary approach between oral surgeon, periodontist, orthodontist, and restorative dentist is crucial. This may be the most important take-home message in today's world: with the high demand for esthetics, it is not possible for a dentist who tries to work alone to achieve an optimal esthetic result, especially in challenging cases. Furthermore, it is imperative to have the best people in every specialty working together to satisfy patients' esthetic needs. More importantly, there should not be a scenario where several specialists are working on a case but one where all these specialists are working together on a case. This ideal equilibrium between all the different specialists defines

the interdisciplinary team approach, which will lead to the best esthetic outcome possible.

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FEATURES THAT OPTIC NEURITIS PRESENT AT PEDIATRIC AGE (TO 14 YEARS)

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ABSTRACT

Purpose: To present all the clinical, diagnostic and laboratory features of the optic neuritis in children population.

Methods and patients: The study included all children who presented monosimptomatic optic neuritis, either with viral or neurological etiology and who were consulted in ophthalmopediatry unit of "Mother Teresa" university clinic Tirana. The study included an overall number of 12 cases with optic neuritis with a follow up of a 4 years period from the moment of the first episode. From these subjects, 6 were females and 6 males.

Results: The most frequent cases were encountered in the period April-June, but one case was also recorded in August and two others in November. Only two cases were presented as retro bulbar neuritis: a 13 years old girl who had a Herpes Zoster associated with a skin marks and a 12 years old boy. The visual sharpness varied from 0.1-0.4, and was returned to normal soon after the treatment. Diplopia is almost unusual in children. Only 2 cases were with Dissociated Nistagmus and a 6 months old boy was presented with Intranuclear Ophtalmoplegy

Keywords: papillaedema,optic neuritis,demyelinizant desease,multiple sklerosis,visual acuity.

Optic Neuritis (ON) is an inflammatory and demyelinating disease of the optic nerve. The most of the cases are monosympthomatic, either bilateral or unilateral. Approximately 75%[1] of patients may progress to Multiple Sclerosis. The entity affects mainly the group age 20-50 years old[2], but it can be seen in children in rare cases. The disease is always associated with an acute loss of the vision, color perception damages, injuries mainly visual field cekocekale and the altidunale.

In about 25% of cases[3], we found some damage of the pupillary reflect in the affected eye, were found 70% appear in the form of retro bulbar neuritis (without papillary edema), 28% of cases occur with papillary edema (papillitis) without retinal hemorrhage, 1%[4] with diplopia and the others with different clinical symptoms like nistagmus etc. MRI of the head, (not in all cases shows the demyelinating of the nerve fibers process the optic nerve. The immediate treatment consists of the high doses of methylprednizolon for 3 days, followed by prednisone 1mg/kg/day per 11 days.[5]

The purpose of the study was to present all the clinical, diagnostic and laboratory features of the optic neuritis in a children population.

METHODS AND PATIENTS

The study included all the children who presented monosimptomatic neuritis, either with viral or a neurological etiology, who were examined in the Ophthalmopediatry Cabinet of "Mother Teresa" University Hospital Center, in the Pediatric Department.

The study included 12 cases with optic neuritis, and covered a 4 years period from the moment the first episode.

The youngest child diagnosed with optic neuritis was 5,5 years old girl, after an influenza attack and the oldest child was a 14 years old boy who was diagnosed with Multiple Sclerosis. From these children, 6 were females and 6 males.

For the first two years the follow up was done every 3 months. All patients performed a CT scan, a MRI of the head, the color perception test and a direct and indirect

ophthalmoscopy. 7of them underwent a lumbar puncture, 9 performed the visual field testing, 7 performed PEV and 8 underwent to Angiophluoroscheinography.

The diagnostic criteria for an optic neuritis were: a) Decrease of the visual acuity, b) Pupillary defects, c) Direct and indirect Ophthalmoscopy, d) Defects in the visual field, e) Defects in the perception of colors, f) Changes in P.E.V, g) Imagery findings

RESULTS:

In the study, were included 12 subjects, aged from 5 to 15 years old, from which 6 males and six females. The most frequent cases were encountered in the period April-June, but were recorded also one case in August and two others in November.[6]

Only two cases were presented as retro bulbar neuritis:[7] a 13 years old girl who had a Herpes Zoster associated with a skin marks and a 12 years old boy. The visual sharpness varied from 0.1-0.4, and was returned to normal[8] soon after the treatment. These finding are presented in the table ... and the figure 1.

Diplopia is almost unusual in children[9]. Only 2 cases were with dissociated nistagmus and a 6 months old boy was presented with Intranuclear Ophtalmoplegy.

a) The defects in the visual field; On the examination of visual field with Goldman Perimeter, we found 4 cases with central scotome, 2 cases with Para central scotome associated with peripheral defects, 2 cases with ceko-cecale scotome (Papillo-macular node) and the last 4 cases had no changes in the visual field (fig.2.)
b) The changes in the color perception: Only in 5 cases was discovered a Central Dicromatopsi and the defects in the red-green axis. In two of these cases, there was a hereditary factor, as they both had family members with Multiple Sclerosis. The most common findings were HLA-A3 and HLA-A9
c) Visual evoked potentials (VEP): In 5 out of 12 cases there were noticed minor changes, three of which were normalized within a 1-2 years time.

The treatment consisted of Sol Methyl Prednisolone[10] i / v the first 3 days followed with Prednisolone 1 mg / kg tapering down every five days. This therapy protects the patient for about 3-5 years from the recurrence of disease and reaches almost full improvement of vision.

DISCUSSION AND CONCLUSIONS:

The finding of the optic neuritis in early childhood has been neglected earlier. The authors were of the opinion that cases with optic neuritis in infants related to post-viral infections (Para infections Optic Neuritis). In these cases, about 1% was accompanied by a serious condition such as an encephalitis and often the diagnose of a neuritis was lost, as its clinical features were hidden among other symptoms. Furthermore, around 30% -35% of the subjects had also other neurological phenomena.

The involvement of the optic nerve in children is almost always bilateral, with a time lag of several hours up to a 1-week. The entity is considered to be a demyelinating benign disease, because the demyelinating process is always present and on the 90% of cases, the vision recovers completely. This recover of vision that occurs in children in these cases, it is thought to be due to the fact that the vision most probably is influenced by conductor block conductivity than from the formation of the demyelinating plaque. The latter is a characteristic features of the adult form.

A retro bulbar pain usually precedes the clinic of the disease, especially when the child sighting moves the eyes. It lasts 1-2 days and when the pain stops, an immediate decrease in /vision is established. In the fundus examination there are mainly light papillitis or associated with papillae edema. Later in time, this associates with a slight dimness of the optic disc (pallor). In children periflebitis are not seen. Rare appeared with retro bulbar neuritis.

The authors are of the opinion that cases with optic neuritis in infants relate to post-viral infections (Para infections Optic Neuritis). In these cases about 1% was accompanied by a serious condition of encephalitis and often loses of neuritis, as they were hidden under clinical framework. About 30% -35% have also got neurological phenomena. Regarding the rapid recovery of vision that occurs in children in these cases, it is thought that here we have to do more with a conductor block conductivity than the formation of demyelinate plaque that really happens in adults.

CONCLUSIONS:

1. ON. it is not a rarity in children under age 14.
2. It is a benign form of S.M.
3. It is almost bilateral.

4. The clinic is varied and quite atypical sometimes.
5. It isn't associated with Periflebitis and diplopia.
6. Over 90% of cases the recover full vision.
7. Even two years after regaining the appearance PEV are abnormal.
8. The hereditary is present in the family.
9. The majority of cases are caused by different viruses but with a demyelinate process.
10. Treatment consists in the use of Methylprednizolon i/v and corticotherapy holder.

Fig.1. The recovery of the visual acuity. Total recovery-partial recovery.

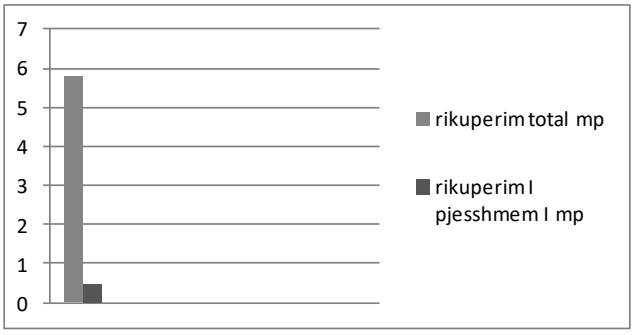
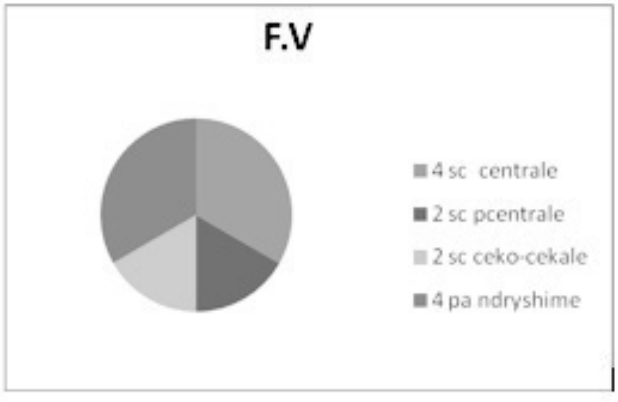


Fig.2.



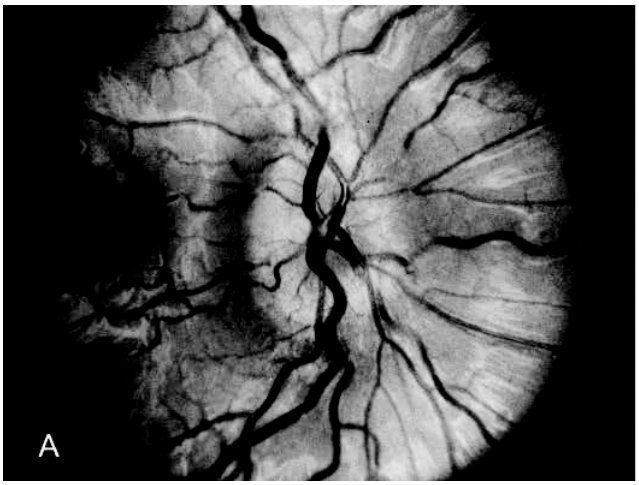
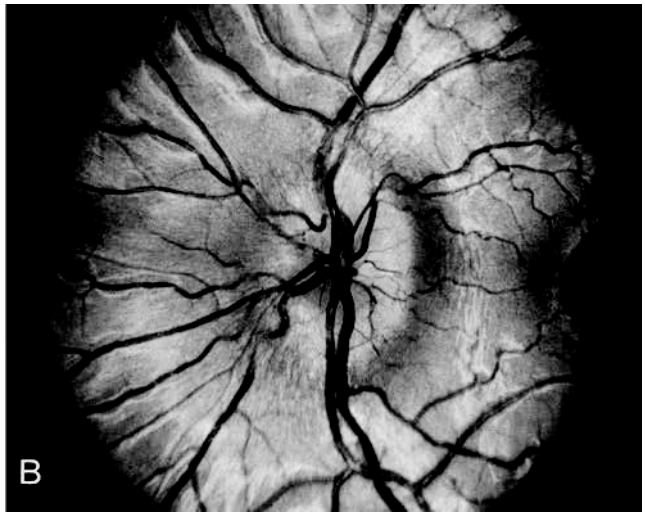


Fig.3. A: Papillaedema right eye



B: Papillaedema left eye

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SUCCESSFUL PREGNANCY OUTCOME IN SYMPTOMATIC PATIENT WITH WILSON DISEASE IN HUOG "KOCO GLIOZHENI"

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ABSTRACT

Background: Wilson's disease (WD) is an metabolic and genetic disorder that leads to copper accumulation in organs and tissues, including the liver and CNS. Untreated WD is accompanied with poor outcome of pregnancy . Excess copper from maternal circulation transported through placenta is followed by spontaneous abortion or intrauterine fetal death.

Objective: The aim of our study was to analyze clinical presentations, diagnostic tests, the complex treatment of patient with WD in pregnancy, and to evaluate the fetal outcome.

Results: 28 years old patient was admitted in hospital, with her first pregnancy with gestational age 33 weeks, diagnosed with preeclampsia. She complained headache, visual disturbances, blood pressure was 220/100 mmHg and generalized edema. The patient referred that she had discontinued the D-penicilamine treatment in the beginning of the pregnancy. After 1 week the clinical situation was worsening, with hepatic insufficiency, severe preeclampsia and was decided for emergency cesarean section. Fetal outcome was good, after one week at NICU, the baby was transferred at her mother, and both were discharged in good health conditions.

Conclusion: Despite several reports of successful pregnancy outcomes after appropriate medical treatment, pregnant patients with WD still need careful management. Patients with WD require lifelong medication. However, they often stop taking medication before or during pregnancy for fear of teratogenicity. Cessation of medication can lead to progression of the disease and involvement of major organs, which can be fatal for both mother and fetus.

INTRODUCTION

Wilson's disease (WD) is an inherited disease of copper transport caused by loss of function of the ATP7B copper-binding protein[1] [2] [3].It is characterized by copper accumulation in the liver, brain and other vital organs[4] This results in the development of characteristic liver disease and neuropsychiatric symptoms [5]. The prevalence of Wilson disease is 1 per 30 000 individuals. [6] The highest prevalence of WD is reported in a small village of Crete where six out of 90 births were diagnosed as WD patients. [7]

The age of presenting symptoms varies widely from age three years to older than 50 years[8], even though most patients develop symptoms in adolescence to early adulthood. [9] The first manifestation of Wilson's disease affects the central nervous system in 40% of the patients. hepatic symptoms in 40% of patients, psychiatric onset in 20% of them.[10, 4]The diagnosis of Wilson disease cannot be made by a single test alone: a combination of tests is always required [8]

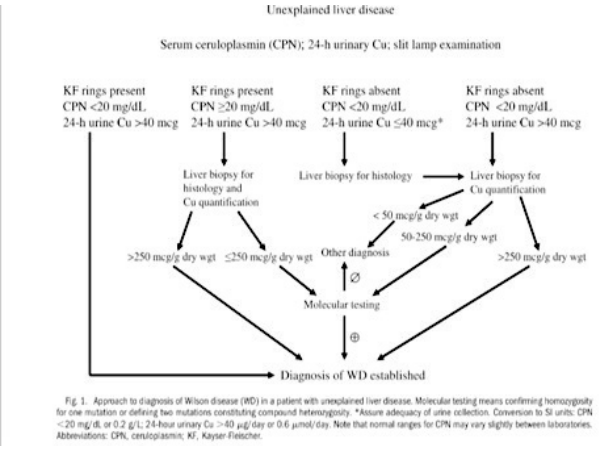

Fig. 1. Approach to diagnosis of Wilson disease (WD) in a patient with unexplained liver disease. Molecular testing means confirming homozygosity for one mutation or defining two mutations constituting compound heterozygosity. *Assure adequacy of urine collection. Conversion to SI units: CPN <20 mg/dL or 0.2 g/L; 24-hour urinary Cu >40 µg/day or 0.6 µmol/day. Note that normal ranges for CPN may vary slightly between laboratories. Abbreviations: CPN, ceruloplasmin; KF, Kayser-Fleischer.

Fig.1[11]

Untreated WD inevitably leads to hepatic, neurologic or psychiatric problems, or their various combinations. [12] Once the symptoms of Wilson disease have improved and tests show that a person's copper levels have been lowered to a safe level, maintenance treatment begins. [13] Treatment is based on the removal of copper excess by chelating agents such as D-penicillamine, trientine, or tetrathiomolybdate or by blocking the intestinal copper absorption with zinc salts.[14] The initial dosage of D-penicillamine is 250-500 mg/d, with an increase of 250 mg every 4-7 days until reaching the maximum dosage 1000-1500 mg/d in 2-4 doses . The recommended maintenance dosage is 750-1000 mg/d .[15]Typical dosages of trientine are 900–2700 mg/day in two or three divided doses, with 900–1500 mg/day used for maintenance therapy. [16]Different zinc salts (sulphate, acetate, gluconate) are used.Larger children and adults require 150 mg/day in three divided doses and smaller children require 75 mg/day. [17] The liver transplant is lifesaving for those with advanced disease refractory to medical therapy or with fulminant hepatic failure. [18] A low-copper diet may also be recommended. Foods to avoid include: Chocolate, dried fruit, liver, mushrooms, nuts, shellfish.[19]

Wilson disease in pregnancy

Treatment must be continued during pregnancy because interrupting therapy has been associated with fulminant hepatic failure, irreversible neurologic deterioration and maternal death.[4,20]Dose reduction of chelating medications is recommended in the range of 25%-50% until the delivery because of concern for teratogenicity.[21, 17]Studies in pregnancy have not demostrated that zinc increases the risk of fetal abnormalities. [22]

Untreated, WD may lead also to early pregnancy complications (miscarriages), infertility, pregnancy induced hypertension, placental abruption, thrombocytopenia and deranged coagulation[23]

Patients with WD and cirrhosis may be at increased risk for obstetrical complications such as intrauterine growth restriction and preeklamsia, and they should be referred to a maternal-fetal specialist. [20]Treated patients have a high probability of getting pregnant and giving birth to a child.[24]

CASE REPORT

The 28 years old patient, B.Z. in her first pregnancy was hospitalized in our hospital with the diagnosis "33-34 weeks pregnancy, preeclamsia". She complained headache, visual disturbances. On the physical examination was noticed: blood pressure 220/100 mmHg, general edema (her actual weight was 70 kg, her weight before pregnancy was 57 kg).

The blood tests on the first day of hospitation were:

Complete blood count:

WBC 6700/mm^3,

RBC 3,78milion/mm^3,

HGB 11,7 g/dl,

HCT 38%,

PLT 118 000/mm^3.*

Biochemical analysis:

Glucose 86 mg/dl,

Urea 35 mg/dl,

Creatinine 0,90 mg/dl ,

Ac uric 3,8 mg/dl,

Total protein 6,9 mg/dl,

Total bilirubine 0,84 mg/dl,

ALT 32 v/dl,

AST 64 v/dl,

Fibrinogen 195 mg/dl,

PT 77%,

INR 1,2

(the red values are abnormal)

The first ultrasound examination concluded a unic fetus, cephalic, vivo, with a weight of 1600-1700 gr (percentile 5). Amniotic fluid was normal. Fetal heart beating and fetal movements were normal. Arterial Umbilical Doppler was also normal.

Also it was concluded free fluid in moderate amount in maternal abdomen.

The patient started the therapy with Methyl-Dopa 0,25g: 4x2 tab/po,

Nifedipine 0,01g: 3x1 tab/po. Also it was administrated 2 doses of Betamethasone 12mg IM.

The blood tests in the few coming days:

Complete blood count:

RBC 3,23milion/mm^3,

HGB 9,9 g/dl,

HCT 32,6 %,

PLT 90 000/mm3,

HT 2 min + 15 sec, KT 4 min + 30 sec

Biochemical analysis:

Total bilirubine 0,51 mg/dl,

ALT 30 v/dl,

AST 36 v/m,

Fibrinogjen 135 mg/dl,

PT 49 %,

INR 1,95

The second ultrasound examination resulted: the fetus with the weight on the percentile of 1.3, cephalic. Amniotic fluid was normal. Fetal heart beating and fetal movements were normal. The Doppler fetal was normal, CPR ratio was 1.6.

Also it was concluded free fluid in moderate amount in maternal abdomen and at the level of two hypochondriac region.

The patient was explained the blood test deterioration compared to the first day. Taking into account the situation, she told that she was diagnosed from Wilson Disease. She referred that she had discontinued the D-penicilamine treatment herself in the beginning of the pregnancy because of fearing the teratogenicity and had hidden her disease from usbecause of fearing the possibility of restarting D-penicilamine in the pregnancy. The patient made a gastro-hepatologist consultant where the doctor conluded the diagnosis “hepatic cirrhosis because of Morbus Wilson”. The future mother was applied only Rh(D) isogroup plasma, albumin (human), vitamin K, zinc sufphate 100 mg in two divided doses.

After 1 week the clinical situation was worsening, with hepatic insufficiency, severe preeclampsia and was decided for emergency cesarean section. The baby weight was 1660 g, tha Apgar score at 1 minute was 7 and at 5 minute was 8. After one week at NICU, the baby was transferred at her mother, and both were discharged in good health conditions.

DISCUSSION

Woman with Wilson’s disease may have severe oligomenorrhea or amenorrhea, menstrual irregularities, infertility due to diffusion of copper from plasma to ovarian tissues.[25] UntreatedWD is accompanied with poor outcome of pregnancy.[26, 27]Excess copper from maternal circulation transported through placenta is followed by spontaneous abortion or intrauterine fetal death.[26] Even through some cases of successful pregnancy outcomes in patients diagnosed with Wilson’s disease who receive regular treatment and remain asymptomatic, however, these pregnancies should be considered high risk and merit regular surveillance. [27] Patients require life long treatment, however, they often stop taking medication before or during pregnancy for fear of teratogenicity. Cessation of medication can lead to progression of the disease and involvement of major organs. [28]This might be fatal for both mother and fetus.[29] Although considered to be a safe choice in pregnancy, in a small number of cases D-penicillamine has been reported to cause congenital malformations of the fetus, including fragile blood vessels, low positioned ears, micrognathia and hyperflexy hips and joints.[24,30]Zinc is an effective therapeutic option and can be safely used in managing patients with Wilson’s disease throughout the pregnancy. [23]The optimal mode of delivery depends on the physical status of the patient. In well-controlled asymptomatic women, vaginal delivery should be considered the first choice. Cesarean section should be reserved for obstetric indications or for when other complications are present.[27] In our case the pregnancy was terminated in the 34 week of pregnancy because of the mother complications. Breast feeding under chelation therapy is not recommended, although there are reports that children breast fed by mother on D-penicillame show no abnormalities. [31]

CONCLUSIONS

Patients with Wilson’s disease should take lifelong medication.

Excess copper can cause preeclamsia, IUGR, placental abruption and fetal neurologic damages.

Even through some cases of successful pregnancy outcomes in patients who receive medication, careful and multidisciplinary management is required, including: the gasto-hepathologist, the hematologist, the neurologist.

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LONG TERM OUTCOME OF A PATIENT WITH DENT-2 DISEASE

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ABSTRACT

Dent-2 disease a relatively new entity described in 2005 which characterize with low molecular weight proteinuria, hypercalciuria, nephrocalcinosis and progression to chronic kidney disease and in some cases to end stage renal diseases. The molecular basis is mutation in OCRL1 gene which is known to cause oculocerebrorenal syndrome of Lowe. The prognosis of Dent disease is unfavorable, with slow progression to end stage renal failure. There are no clear guidelines about the best therapeutic options for patients with Dent disease. Treatment of hypercalciuria with thiazide diuretics is recommended as well potassium citrate in order to prevent nephrolithiasis and nephrocakcinosis. Our patient fulfilled the clinical, biochemical and genetic criteria for Dent-2 disease. He had been lost for regular follow up for many years without any medical treatment. Interestingly, despite massive proteinuria (including glomerular component) and severe hypercalciuria there was no worsening of the renal function neither ultrasound changes in his kidneys.

Key words: Dent-2 disease, low molecular weight proteinuria, hypercalciuria, SDS-PAGE, outcome

INTRODUCTION

Dent-2 disease a relatively new entity described in 2005 which characterize with low molecular weight proteinuria, hypercalciuria, nephrocalcinosis and progression to chronic kidney disease and in some cases to end stage renal diseases [1]. The molecular basis is mutation in OCRL1 gene which is known to cause oculocerebrorenal syndrome of Lowe 2,3,4,5]. In this report we describe long term outcome of a patient with Dent disease who presented with massive (nephrotic range) proteinuria and severe hypercalciuria, but did not show worsening of renal function during the follow up.

CASE REPORT

A 3 year old boy presented with asymptomatic proteinuria and was referred for clinical investigations. On admission he was edema free, his blood pressure was 80/55 mmHg and there was no gross hematuria. Renal biopsy was done and showed minimal change disease on light microscopy and normal immunofluorescent finding. SDS-PAG electrophoresis showed typical low molecular proteinuria. Urinary excretion of calcium was also increased. The clinical diagnosis of Dent disease was established and detailed clinical and laboratory data of this patients were presented elsewhere [4,6]. The molecular study confirmed the mutation in the OCRL1 gene [1]. In our patient, mutation was located in the 5th exon [4-base deletion; del259-262 (TGTT)]. After establishing the diagnosis of Dent-2 disease the patient was appointed for long term follow up at out-patient nephrology Clinics. Since he had high urinary excretion of calcium (11.2 mg/kg/ day; normal < 4.0) treatment with low dose hydrochlorthiazide was advised. After one year regular follow up the family moved to Italy and the boy was lost for follow up for the next 10 years.

At the age of 26 the patient was reevaluated at the out-patient Clinic. He showed normal adult growth, normal blood pressure (TA 110/75 mmHg). There was no edema. The rest of physical examination was unremarkable. Laboratory investigations were as follows: Complete blood count within referent values. Urinalysis: protein 2+, sachar 1+, pH 6, ketones negative, Specific gravity, 1010, blood 1+, leukocyte esterase negative, nitrite negative, biliribine negative, urobilinogene negative. Serum biochemistry showed normal values for degradation products (urea 6.5 mmol/l, creatinine 67 umol/l, uric acid 223 umol/l). Serum proteins and albumin were 81g/l and 43 g/l respectively. There was mild increase in creatrine

kinase (445 U/L) and LDH (665 U/l) while AST, ALT, GGT were within referent values. His proteinuria was elevated at 4.5 g/d. SDS-PAGE electrophoresis revealed mixed glomerulo-tubular pattern with dominant low molecular fractions (10-67 kD)(Figure 1). His urinary Beta2-microiglobulin was 33 mg/l (normal <0.25). Mild generalized hyperaminaicduria was detected. In addition urinary calcium excretion was assessed on several occasions ranging between 6.7-11 mg/kg/d (normal < 4.0). Ultrasound examination showed two normal seized kidneys without stones neither nephrocalcinosis (Figure 2) .

DISCUSSION

Usually Dent disease is detected in asympotmatic patients during regular examination for isolated proteinuria. Rarely patients may present with colicky pain, haematuria, nephrolithiasis or nephrocalcinosis. In Japanese series majority of patients presented with isolated low molecular weight proteinuria [7]. Hypecalciuria was not mandatory finding and was found in 51% of the patients.

Dent-2 disease was reported for the first time in 2005 [1]. Five patients with the phenotype of Dent disease who were found negative for mutation in ClCN5 gene underwent testing for candidate genes. Interestingly, all were found to carry mutations in ORCL1 gene, which was known to cause multisystem disorder oculocerebrorenal syndrome of Lowe. During clinical reevaluation no cataracts neither neurolgic deficits were found. Mild intellectual disability was the only abnormal physical finding. Moderately increased serum levels of creatine phosphokinase and lactic dehydrogenase were evidenced [1.2.3.4]. This entity was termed Dent-2 disease, while those patients carrying CLNC5 mutations were designed as Dent-1 disease,

Our patient is one of the first five who got the diagnosis of Dent-2 disease. The later reports revealed that mild intellectual disability and peripheral cataracts may be seen among Dent-2 patients.

The prognosis of Dent disease is unfavorable, with slow progression to chronic kidney disease and ultimately renal failure [5]. There is no recurrence of the disease in the transplanted kidney. There are no clear guidelines about the best therapeutic options for patients with Dent disease. Treatment of hypercalciuria with thiazides is recommended as well potassium citrate in order to prevent nephrolithiasis and nephrocalcinosis [8].

Also the treatment with ACE inhibitors is questionable, since the proteinuria is typically of low molecular weight. In the case of associated glomerular proteinuria and histology of focal global glomerulosclerosis there is indication for ACE inhibitors administration [9,10].

Our patient is interesting since he had been lost for medical treatment for many years, but besides massive proteinuria (including glomerular component) and severe hypercalciuria there was no worsening of the renal function neither ultrasound changes in his kidneys.

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FIBROTHECOMA OF THE OVARY

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ABSTRACT

Fibrothecoma ovarii, is a benign ovari stromal tumors. Fibrothecomas represent 4 % of all ovarian neoplasms. Fibrothecomas can occur in pre and post menopausal women and are the most common of the sex cord- stromal tumors. We describe here a case of a 67 -year-old women with an ovarian fibrothecoma that was diagnosed as a solid tumor in the pelvic cavity, before surgery. The patient successfully underwent surgical removal. The histopathological evaluation showed fibrothecoma of the ovary.

Key words: fibrothecomas; ovarian neoplasms; solid tumor; surgical removal

INTRODUCTION

Fibrothecomas are benign sex cord-stromal tumors of the ovary, composed of various proportions of fibromas and lipid-rich, estrogenic thecomas. Fibrothecomas can occur in pre and post menopausal women and they are most frequent during middle age, rare in children.

On grosspathological inspectionnthey are firm and white or tan. On microscopic examination, there are intersecting bundles of spindle cells, produsing collagen with thecomatous areas.

Fibrothecomas tend to be asymptomatic, but usualy pelvic pain is the main simptom, also there is the risk of torsion and possibly the development of symptoms.

The risk of ovarian cancer is increased in the association of ovarian tumor, ascites and hydrothorax with the significant elevated tumor marker Ca-125. However, this association can be observed in a rare clinical and benign pathological entity, that is Demons-Meigs syndrom.

The primary treatment is surgical extirpation of the primary lesion.

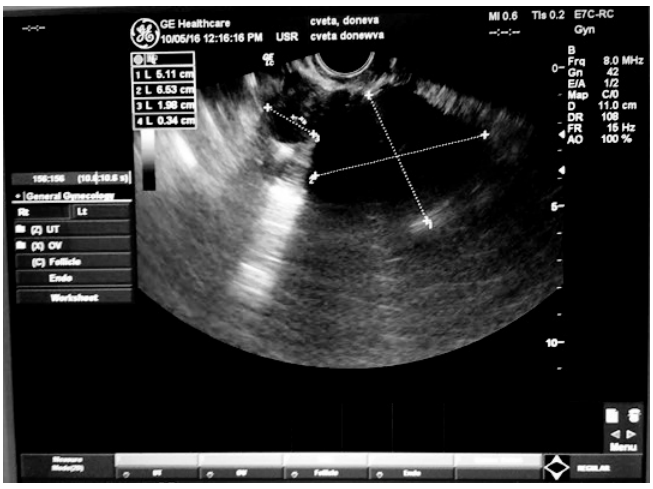
In this report, we describe the treatment of a 67-years old woman with an ovarian mass. The lesion was diagnosed as a solid tumor in pelvic cavity, before surgery. After surgery, the tumor was diagnosed as a fibrothecoma of the ovarii.

CASE REPORT

Patient D. C, age 67-years-old, was hospitalized on October 2016 to the Department of Gynaecology at University Clinic of Obstetrics and Gynecology- Skopje with complaints of pelvic pain for about 3 months. The pain was primarly located in the lower part of the abdomen, but worse in the right portion. This patient had menarche when she was 12 years old. From her reproductive history she was gravida 4, para 3 and 1 artificial abortions. Her last menstruation was 22years ago. The patient for many years is with controled hypertenssio arterialis and with DM tip II. Tumor markers were in a refferent values and also the full blood test. Initially the patient was diagnosed with solid tumor in the pelvic cavity.

The vaginal examination showed order rear of vaginal fornix filled with solid tumor mass, mobile and free from environment. Results from PAP tes trevealed only atrophy with inflamatory process.

Transvaginal sonography performed at our hospital showed that the uterus was in AVFL, measuring 23mm, endometrial lining, behind the uterus to right tumor mass measured 66x54mm in size, with unclear limited environmental.



The patient underwent surgical treatment on October 12, 2016. Total hysterectomy with a bilateral oophoro-salpingectomy were performed. Intraoperative finding correlated with ultrasonography. A histopathological analysis showed the benign nature of tumor fibrothecoma ovarii lateris dextri. Polypus endometrii senilis.

The patient recovered from surgery and was discharged from the hospital six days after surgery, in satisfactory condition and did not receive any additional treatment beyond regular checkups.

DISCUSSION

Fibrothecomas are benign ovarian stromal tumors, usually unilateral account for only 4% of all ovarian neoplasms but represent the most common solid primary ovarian tumors in asymptomatic woman in their 50s during perimenopause (transition to menopause) or postmenopause.

Fibrothecomas are benign neoplasm that can mimik malignant ovarian tumors because they present as solid adnexal masses, sometimes associated with ascites and pleural effusions. Ovarian fibromas and fibrothecomas presented with pleural effusions or ascites, known as the Demons-Meigs syndrome. In 28% of fibrothecomas showed elevated levels of Ca-125.

Fibromas and fibrothecomas may also associated with the basal cell nevus Gollin-Goltz syndrome, which consist of bilateral large multinodular ovarian fibromas, multiple basal cell carcinomas of the skin, adontogenic keratocysts and other abnormalities.

Ofen, fibrothecomas do not cause symptoms, but they sometimes can cause pelvic pain or discomfort-especially if they are associated with ovarian torsion(twisting). In some cases ovarian fibrothecoma can be part of Meig Syndrome (a triad of ovarian fibrothecoma, ascites and pleural effusion).

Diagnosis is usually made by ultrasonography showing a solid ovarian lesion, or on some occasionas, mixed tumors with solid and cystic components, computed tomography (CT), magnetic resonance imaging (MRI). Sometimes, they are initially detected during palpation (feeling with fingers or hand) performed as part of a pelvic examination. Ultrasonography is generally used as the first-line imaging technique for the evaluation of ovarian pathologic abnormalties. However, ultrasound features of fibromas and fibrothecomas are usually nonspecific and MRI is often needed for further differentiation of fibrothecomas, from other solid ovarian mases with fibrous components (fibroma, cystadenofibroma and Brenner tumor) especialy differential considerations include uterine leiomyomata. The presence of interface vessels betwen the uterus and the adnexal mass can help differentiate a uterine leiomyoma from an ovarian fibromous tumor.

Usually the lesion is surgically removed. Primarly, there is a cancern that the lesion identified in a patient could be cancerous, but there is also the risk of torsion and possibly the development of symptoms. However in younger patients unilateral salpingo-oophorectomia is adequate, but in older patients hysterectomy with bilateral salpingo-oophorectomy. In the case of Meigs Syndrome, removal of fibrothecomas generally resolves the other aspects of the condition as well.

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III. Faqja e tretë dhe të tjerat – *teksti i plotë i artikullit*: Teksti i plotë I artikujve hulumtues ose vrojtues normalisht, por jo domosdoshmërisht, duhet të jetë i ndarë në paragraf me këta nëntituj: hyrja, metodat dhe materialet, rezultatet dhe diskutimi.

1. Hyrja: Krijoni një kontekst apo prapavijë(trualli) të studimit (që në fakt është natyra e problemit dhe rëndësia e tij). Për të bërë këtë duhet të bëni një hulumtim të literaturës – duke kërkuar, gjetur dhe lexuar punimet përkatëse, që duhet të jenë si referencë në dorëshkrimin tuaj. Sqaroni hipotezat tuaja dhe planifikoni t'i testoni ato, si dhe përshkruani qëllimet tuaja. Kini qëndrim të qartë se çka prisni të gjeni dhe arsyet që ju udhëhoqën tek hipotezat që keni krijuar. Objekti i hulumtimit më së shpeshti fokusohet kur parashtrohet si pyetje. Mos përfshini të dhëna apo rezultate nga puna që do të raportohet.

2. Metodat & Materialet: Ky paragraf duhet të përfshijë atë informacion që ishte në dispozicion në kohën që plani apo protokoli i studimit po shkruhej. Të gjitha informacionet e marra gjatë studimit i takojnë paragrafit të Rezultateve.

Përshkruani përzgjedhjen tuaj të pjesëmarrësve së vrojtimit ose eksperimentit (pacientët ose kafshët laboratorike, përfshirë kontrollat) qartë, duke përfshirë kriteret e përshtatshme (inkluzive) dhe përjashtuese (ekskluzive).

Parimi udhëheqës duhet të jetë i qartë se si dhe pse studimi është bërë në një mënyrë të caktuar. Jepni detaje të mjaftueshme për metodat, mjetet dhe materialet (jepni emrin dhe adresën e prodhuesit në kllapa), dhe procedurat për të lejuar të tjerët të kuptojnë dhe riprodhojnë rezultatet tuaja.

Nëse një metodë e caktuar që është përdorur është e njohur, atëherë nuk është e nevojshme të jepet përshkrim komplet i saj. Mund t'i referoheni punimit në të cilin së pari herë është përshkruar dhe të përmendni ndonjë modifikim/ndryshim që keni bërë. Jepni arsyet për përdorimin e tyre dhe vlerësoni kufizimet e tyre. Në fund, përshkruani se si i keni analizuar të dhënat tuaja, duke përfshirë metodat statistikore dhe pakon programore që keni përdorur.

Autorët e dorëshkrimeve të rishqyrtuara duhet të përfshijnë një paragraf që përshkruajnë metodat që kanë përdorur për lokalizimin, përzgjedhjen, ekstrahimin dhe sintetizimin e të dhënave. Përdorni formën joveprore të foljes, në vetën e tretë,

Additional Information for Authors

I. First page - *front page*: It should contain: (a) title of paper, a short, but informative; (b) the first name, initials of middle name and last name of each author; (c) the institution; (d) the name of the department that is attributable to the scientific work; (e) the name and address of the author with whom to correspond about the manuscript (f) source/support in the form of grants, equipment, drugs, or all.

II. Second page - *abstract and keywords*: The abstract should be written with a maximum of 150 words for unstructured abstracts and 250 words for structured abstracts (containing parts: objective(s) of study or research, basic procedures, such as selection of subjects or laboratory animals, observational and analytical methods, then, the main findings/results (data and their statistical significance, if possible), and the main conclusions. Emphasize the new and important aspects of the study or observation.

Below the abstract identify and write the keywords: 35 words or short phrases that will assist in indexing the paper and publication of the abstract.

Use terms from the list of Index Medicus for Medical Sub-Headings (MeSH); if there is no appropriate MeSH term for some newly introduced terms, we can use the given terms.

III. Third and further pages – *full text of the article*: The full text of research or observational articles should normally be, but not necessarily, divided into sections with the following headings: introduction, material and methods, results and discussion.

1. Introduction: Provide a context or background for the study (that is, the nature of the problem and its significance). To do this you must complete a literature review – searching for, finding and reading relevant papers, which must be referenced in your manuscript. Explain your hypotheses and the plan to test them, and describe your aims. Clearly state what you expect to find and the reasoning that led you to the hypotheses that you have made. The research objective is often more sharply focused when stated as a question. Do not include data or conclusions from the work being reported.

2. Methods & Material: This section should include only information that was available at the time the plan or protocol for the study was being written. All information obtained during the study belongs in the Results section.

Describe your selection of the observational or experimental participants (patients or laboratory animals, including controls) clearly, including eligibility and exclusion criteria. The guiding principle should be clarity about how and why a study was done in a particular way.

Give sufficient details of the methods, apparatus and materials (give the manufacturer's name and address in parentheses), and procedures to allow others to understand and reproduce your results.

If a particular method used is well known then there is no need to give a complete description. You can reference the paper in which it was first described and mentioned any modifications you have made. Give the reasons for using them, and evaluate their limitations. Finally,, describe how you analysed your data, including the statistical methods and software package used.

Authors submitting review manuscripts should include a section describing the methods used for locating, selecting, extracting, and synthesizing data.

kur dokumentoni metodat, gjë që do të fokusonte vëmendjen e lexuesit tek puna që është bërë e jo tek hulumtuesi (P.sh. Janë marrë, janë realizuar, janë prezantuar etj.)

2. a) **Statistikat:** Përshkruani metodat statistikore me detaje të mjaftueshme për t'ia mundësuar një lexuesi me njohje në atë fushë t'i qaset të dhënave origjinale për të verifikuar rezultatet e raportuara. Kur është e mundur, përcaktoni sasinë e zbulimeve dhe prezantoni ato me indikatorë përkatës të gabimeve në matje apo pasiguri (siç janë inter-valet e besueshmërisë). Evitoni mbështetjen vetëm në testet statistikore të hipotezave, siç janë vlerat p, që dështojnë të transmetojnë informacion të rëndësishëm mbi madhësinë e efektit. Jepni detaje rreth përzgjedhjes së rasteve (randomizimi) dhe përshkruani metodat dhe sukseset e vro¬jtimit gjatë realizimit të studimeve të verbuara. Definoni termet statis¬tikore, shkurtesat dhe më së shumti simbolet. Specifikoni programin kompjuterik që është përdorur.

3. Rezultatet: Ky paragraf duhet t'i bëjë gjetjet tuaja të qarta. Prezantoni rezultatet tuaja në rend logjik në tekst, tabela dhe ilustrime, duke dhënë së pari rezultatet kryesore ose më të rëndësishme. Mos i përsërisni të gjitha të dhënat në tabela apo ilustrime, në tekst. Nënvizoni ose përm-bledhni shkurtimisht vetëm vrojtimet më të rëndësishme.

Kur të dhënat përmblidhen në paragrafin e Rezultateve, jepni rezultate numerike jo vetëm si derivate (për shembull, përqindja) por gjithashtu si numra absolut nga të cilët derivatet janë llogaritur, dhe specifikoni metodat statistikore që janë përdorur për t'i analizuar ato.

Kufizoni tabelat dhe figurat në aq sa janë të nevojshme për të sqaruar argumentin e punimit dhe për të vlerësuar të dhënat ndihmëse. Duke përdorur grafikonet për të reprezentuar të dhënat tuaja si alternativë e tabelave, do të rrisë kuptueshmërinë e lexuesit. Mos i dyfishoni të dhënat në grafikone dhe tabela. Duhet të jeni të qartë se cili lloj i grafikoneve është i përshtatshëm për informacionet tuaja. Për shembull, për të reprezentuar korelimin mes dy ndryshoreve, preferohet grafiku vijëzor, krahasuar me grafikun rrethor apo në formë shtyllash.

Sa i përket të gjitha paragrafeve, qartësia dhe të qënit i thuktë është kyçe. Mos prezantoni të njëjtat të dhëna më shumë se një herë. Kufizojeni veten në të dhënat që ndihmojnë në adresimin e hipotezave tuaja. Kjo është e rëndësishme edhe nëse të dhënat i aprovojnë ose nuk i pranojnë ato. Nëse keni bërë analiza statistikore, duhet të jepni vlerën e proba¬bilitetit (p) dhe të tregoni se është shprehës (sinjig në nivelin që ju po testoni. Varësisht nga analizat e përdorura, gjithashtu mund të jetë e rëndësishme të jepni intervalet e besueshmërisë së rezultateve (Confidence Interval – CI), ose parametrat statistikorë si proporcionet e rastit (odds ratio). Bëni përshkrimin tek secila figurë duke bërë të qartë domethënien e përgjithshme pa referencë në tekstin kryesorë, por mos diskutoni rezultatet në të. Lëreni lexuesin të vendosë vetë se çfarë men-don për të dhënat. Mundësia juaj për të thënë se çfarë mendoni, është në vazhdim, tek diskutimi.

3. Tabelat: Secila tabelë duhet të vendoset në vendin e tekstit ku duhet të vihet logjikisht, e plotësuar me të njëjtat rregulla sikur teksti i plotë. Mos i dërgoni tabelat si fotografi. Secila tabelë duhet të citohet në tekst. Tabelat duhet të jenë me numra ashtu që të jenë në koordinim me refer-encat e cituara në tekst. Shkruani një përshkrim të shkurtë të tabelës nën titullin. Çdo sqarim shtesë, legjendë ose sqarim i shkurtesave jostan¬darde, duhet të vendoset menjëherë poshtë tabelës.

4. Diskutimi: Ky paragraf është pjesa ku ju mund të interpretoni të dhë-nat tuaja dhe të diskutoni duke ballafaquar dhe krahasuar gjetjet tuaja me ato të hulumtuesve të mëparshëm. Rishikoni referencat e literaturës dhe shihni nëse mund të

Use the third person passive voice when documenting methods which would focus the readers' attention on the work rather than the investigator.(e.g. Were taken, was performed, were presented itd.)

2. a) **Statistics:** Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as p values, which fail to convey important information about effect size. Give details about the ran- domization and describe the methods and success of observations while using blinded trials. Define statistical terms, abbreviations, and most symbols. Specify the computer software used.

3. Results: This section should make your findings clear. Present your results in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat all the data in the tables or illustrations in the text. Emphasize or summarize only the most important observations.

When data are summarized in the Results section, give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical methods used to analyze them.

Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Using graphs to represent your data as an alternative to tables will improve the reader's understanding. Do not duplicate data in graphs and tables. You need to be clear what type of graphs is suitable for your information. For example, to represent the correlation between two variables, a line graph is preferred to a pie chart or a bar chart.

As with all sections, clarity and conciseness is vital. Don't present the same data more than once. Restrict yourself to the data that helps to address your hypotheses. This is important whether the data supports or disproves them. If you have carried out a statistical analysis, you should give the probability (P) value and state it is significant at the level you are testing. Depending on the analysis used, it may also be important to give the confidence intervals of the results, or the statistical parameters such as the odds ratios. Provide a caption for each figure making the gen¬eral meaning clear without reference to the main text, but don't discuss the results. Let the readers decide for themselves what they think of the data. Your chance to say what you think comes next, in the discussion.

3. Tables: Each table should be inserted at the point of the text where they have to be placed logically, typed by the same rules as for the full text. Do not send tables as photographs. Each table should be cited in the text.Tables should be numbered so that they will be in sequence with references cited in the text. Provide a brief explanation of the table below the title. Any additional explanations, legends or explanations of non¬standard abbreviations, should be placed immediately below the table.

4. Discussion: This section is where you interpret your data and discuss how your findings compare with those of previous researchers. Go over the references of your literature review and see if you can determine how your data fits with what you have found.

You also need to account for the results, focusing on the mechanisms be¬hind the observation. Discuss whether or not your results support your original hypotheses. Negative

përfundoni se si të dhënat tuaja përkojnë me atë që keni gjetur.

Ju gjithashtu duhet të llogarisni rezultatet, duke u fokusuar në mekaniz¬mat në prapavij të vrojtimit. Diskutoni nëse rezultatet tuaja mbështesin hipotezat tuaja origjinale. Gjetjet negative janë aq të rëndësishme në zhvillimin e ideve të ardhshme sikur gjetjet pozitive.

E rëndësishme është se, nuk ka rezultate të këqija. Shkenca nuk të bëjë me të drejtën dhe të gabuarën, por merret me zgjerimin e njohjeve të reja.

Diskutoni si janë paraqitur gabimet në studimin tuaj dhe çfarë hapa keni ndërmarrë për të minimizuar ato, kështu duke treguar se ju çmoni ku¬fizimet e punës tuaj dhe fuqinë e përfundimeve tuaja. Duhet gjithashtu të merrni në konsideratë ndërlikimet e gjetjeve për hulumtimet në të ardhmen dhe për praktikën klinike. Lidhni përfundimet me qëllimet e studimit, por evitoni qëndrimet dhe përfundimet e pakualifikuara, që nuk mbështeten në mënyrë adekuate nga të dhënat. Shmangni prioritetet deklarative apo të aludoni në punën që nuk është krahasuar.

5. Referencimi: Referencat janë baza mbi të cilën është ndërtuar raporti juaj. Shqyrtimi i literaturës dhe leximi i referencave gjithmonë duhet të jetë pikë fillestare e projektit tuaj. Ky paragraf duhet të jetë i saktë dhe të përfshijë të gjitha burimet e informacionit që keni përdorur.

Në formatin " Vancouver" , referencat numërohen një nga një, sikur që shfaqen në tekst dhe identifikohen me numra në bibliografi..

Shënoni të gjithë autorët kur janë gjashtë e më pak; kur janë shtatë ose më tepër, shënoni tre të parët, pastaj shtoni "et. al." Pas emrave të autorëve shkruhet titulli i artikullit; emri i revistës i shkurtuar sipas mënyrës së Index Medicus; viti i botimit; numri i vëllimit; dhe numri i faqes së parë dhe të fundit.

Referencat e librave duhet të jepen sipas emrit të autorit, titulli i librit (mund të citohet edhe titulli i kapitullit para titullit), vendi i botimit, botuesi dhe viti.

Në tekst, numrat e referencave jepen me indeks të sipërm. Vëreni se çështja e numrave neglizhohet nëse ka numërtim të vazhdueshëm përg¬jatë gjithë vëllimit, ka hapësirë mes numrit të vëllimit dhe numrit të faqes, numrat e faqeve janë në këtë formë: 51-4 në vend të 51-54, dhe emri i revistës ose librit është në italic. Në vazhdim është një shembull i referencës:

Artikujt e revistave:

1. Lahita R, Kluger J, Drayer DE, Koffler D, Reidenberg MM. Antibod- ies to nuclear antigens in patients treated with procainamide or acetylpro¬cainamide. *N Engl J Med* 1979;301:1382-5.
2. Nantulya V, Reich M. The neglected epidemic: road traffic inju- ries in developing countries. *BMJ* 2002;324: 1139.
3. Murray C, Lopez A. Alternative projections of mortality and dis- ability by cause 1990-2020: global burden of disease study. *Lan- cet* 1997;349: 1498-504.

Librat dhe tekste tjera:

4. Colson JH, Tamour NJJ. Sports in juries and their treatment. 2nd ed. London: S. Paul, 2006.
5. Department of Health. *National service framework for coronary heart disease*. London: DoH, 2000. www.doh.gov.uk/nsf/coronary.htm (accessed 6 Jun 2003).

findings are just as important to the de¬velopment of future ideas as the positive ones.

Importantly, there are not bad results. Science is not about right or wrong but about the continuing development of knowledge.

Discuss how errors may have been introduced into your study and what steps you took to minimise them, thus showing that you appreciate the limitations of your work and the strength of your conclusions. You should also consider the implications of the findings for future research and for clinical practice. Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. Avoid claiming priority or alluding to work that has not been compared.

5. Referencing: The references are the foundation on which your report is built. Literature searches and reading of references should always be the starting point of your project. This section must be accurate and in¬clude all the sources of information you used.

In the Vancouver format, references are numbered consecutively as they appear in the text and are identified in the bibliography by numerals.

List all authors when there are six or fewer; when there are seven or more, list the first three, then add "et al." The authors' namer are fol-lowed by the title of the article; the title of the journal abbreviated ac-cording to the style of Index Medicus; the year of publication; the volume number; and the first and last page numbers.

References to books should give the names of any editors, place of publication, editor, and year.

In the text, reference numbers are given in superscript. Notice that issue number is omitted if there is continuous pagination through¬out a volume, there is space between volume number and page numbers, page numbers are in elided form (51-4 rather than 51-54) and the name of journal or book is in italics.The following is a sample reference:

Journal articles:

1. Lahita R, Kluger J, Drayer DE, Koffler D, Reidenberg MM. Antibod- ies to nuclear antigens in patients treated with procainamide or acetylpro¬cainamide. *N Engl J Med* 1979;301:1382-5.
2. Nantulya V, Reich M. The neglected epidemic: road traffic inju- ries in developing countries. *BMJ* 2002;324: 1139.
3. Murray C, Lopez A. Alternative projections of mortality and dis- ability by cause 1990-2020: global burden of disease study. Lan- cet 1997;349: 1498-504.

Books and other monographs:

4. Colson JH, Tamour NJJ. Sports in juries and their treatment. 2nd ed. London: S. Paul, 2006.
5. Department of Health. *National service framework for coronary heart disease*. London: DoH, 2000. www.doh.gov.uk/nsf/coronary.htm (accessed 6 Jun 2003).
6. Osler AG. *Complement: mechanisms and functions*. Englewood Cliffs: Prentice-Hall, 1976.

Avoid using as references abstracts; "unpublished data" and "personal communications". References to accepted but yet unpublished articles are allowed to be made, only if you note "in press".

6. Kamberi A, Kondili A, Goda A, dhe bp; *Udhërrëfyes i shkurtër i Shoqatës Shqiptare të Kardiologjisë për parandalimin e Sëmundjes Aterosklerotike Kardiovaskulare në praktikën klinike,* Tiranë, 2006

7. Azemi M, Shala M, dhe bp. *Pediatria sociale dhe mbrojtja shënde- tësore e fëmijëve dhe nënave*. Pediatria, Prishtinë 2010; 9-25

Shmangni përdorimin e abstrakteve si referenca; "të dhëna të papub-likuara" dhe "komunikime personale". Referencat e pranueshme, por ende të papublikuara lejohet të merren, vetëm nëse shënoni se janë "në shtyp".

6. Mirënjohjet: Ju mund të keni dëshirë të falënderoni njerëzit që ju kanë ndihmuar. Këto mund të rangohen prej atyre që ju kanë përkrahur me teknika eksperimentale deri tek ata që ju kanë këshilluar deri në bër¬jen e dorëshkrimit final.

7. Formati i fajllit të të dhënave për **ilustrimet** (**figurat**): JPG

Nëse përdoren fotografitë e pacientëve, qoftë subjekti, qoftë fotografitë e tyre nuk duhet të jenë të identifikuara, ato duhet të shoqërohen me lejen e shkruar nga ta për përdorimin e figurës. Format e lejuara janë në dispozicion nga redaksia.

Nëse fajllet e të dhënave janë shumë të mëdha për t'u dërguar me e-mail, rekomandohet dërgimi me CD në adresën tonë.

8. Legjendat për Ilustrimet (Figurat)

Legjenda e tabelës duhet të vendoset mbi tabelë. Referenca e një tabeleje, e cila është marrë nga ndonjë publikim tjetër, duhet të vendoset poshtë tabelës. (Është përgjegjësi e autorit të sigurojë lejen e ribotimit nga botuesit e atij botimi) Legjenda e figurës duhet të vendoset në fund të faqes. Referenca e figurës e marrë nga ndonjë tjetër publikim vendoset në fund të legjendës. (Leja e ribotimit duhet të sigurohet nga botuesi i këtij botimi).

6. Acknowledgements: You may wish to acknowledge people who have helped you. These can range from those who supported you with exper¬imental techniques to those who read or offered advice on your final manuscript.

7. Data file format for **illustrations** (**figures**): JPG

If photographs of patients are used, either the subjects should not be identifiable or their pictures must be accompanied by written permis-sion to use the figure. Permission forms are available from the Editor.

If data files are too big for transmission as an Email attachment submis¬sion of a CD to our address is recommended.

8. Legends for Illustrations (Figures)

The legend of a table has to be placed above the table. The reference of a table, which has been taken from another publication, must be placed below the table. (It is the author's responsibility to obtain the permission of reproduction from the publishers of the publication.) Figure legends are to be placed at the end of the paper. The reference of a figure taken from another publication stands at the end of the legend. (Permission of reproduction must be obtained from the publishers of this publication).