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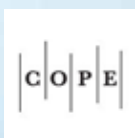
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## ORIGINAL PAPER

# Cancer Antigen (CEA and CA 19-9) as an Markers of Advanced Stage of Colorectal Carcinoma

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**Introduction:** CEA and CA 19-9 are the most common tumor associated antigens used in the staging of patients with rectal cancer and other parts of the colon. **Goal** of this study was to evaluate the value of CEA and CA 19-9 in the serum of patients with colon cancer and prove its place in the diagnostic staging. **Material and Methods:** The study was retrospective-prospective performed at the Gastroenterohepatology Clinic, Clinical Center of Sarajevo University. The study included 91 hospitalized patients who had histologically confirmed diagnosis of adenocarcinoma of the colon in 98% of cases. All patients underwent colonoscopy, targeted biopsy and all determination of CEA concentrations and CA 19-9 levels. All of them underwent abdominal CT and MRI of the pelvis in case of rectal cancer. **Results:** The study analyzed 58 men and 33 women, mean age 66.6 years, with the youngest patient at age of 35 and the oldest at age of 89 years. The largest number of patients was aged 56-75 years. According to localization 77 patients had carcinoma located in the area of the rectum and sigma 37.4 and 37.4 in the rectostigmoid area and sigma. In 37 patients metastasis was present especially in the liver and liver and lungs at 22 and 5 cases. CEA and CA 19-9 were determined in all cases but patients with metastases have had extremely high values with fact that in the two cases of cecoascendent colon cancer we found values that were extremely high (1789ng/ml and 10780U/ml). Values of CA19-9 were significantly higher ( $p<0.05$ ). CEA mean values were highest in patients aged over 75 years. In case of CA 19-9 high mean values have been recorded in patients aged over 75 years with statistically significant differences between the age groups ( $p<0.05$ ). **Conclusion:** CEA and CA19-9 are cancer antigens that are late markers of carcinogenesis, with significantly elevated serum concentrations in case of colon cancer with already developed metastases. Older age group of patient has significantly elevated levels of both antigens. Cancer was more common in men than women and 2:1. **Key words,** adenocarcinoma of the colon, CEA, CA 19-9, metastases

corresponding

## 1. INTRODUCTION

Colon cancer is the human tumor which equally affects both men and women. It belongs to common, solid tumors and is the third most common in men. By mortality it ranks as fourth after lung, stomach and liver. The highest frequency is recorded in the highly industrialized countries, such as coun-

tries of North America, Australia and New Zealand. Mean incidence of this tumor is noticeable in the countries of Europe and it was noted that the population that migrates from regions with lower rates, in a higher percentage is affected in high-risk regions by colorectal cancer (1). Statistical data from our country of Bosnia and Her-

zegovina does not exist, because we do not possess unique statistical data at the state level.

Many years of research of the available world data show that carcinogenesis is associated with lifestyle, type of diet, smoking, as well as the influence of the environment in which man lives and works. Sedentary work, inadequate nutrition, low in fiber and vitamins as well as stress, significantly impacting the development of the disease. Carcinogenesis is a long, complex and gradual process. Epithelial cells affected by the abnormal proliferation under genetic influence, leading to the creation of new clones, unrecognized by suppressor genes that probably are so damaged that they are unable to recognize the changes at the level of DNA, so that now new, different cells produce new cells that will be used to form tumor. Histological analysis of the tissue sample from the upper third of the crypt, see enhanced proliferation activity in neoplastic lesions (2).

Thanks to distal endoscopy as gold standard in the diagnosis of colorectal cancer it is diagnosed in time, located, target biopsy is made and histopathological analysis. Endoscopic ultrasound, CT and MRI with complete clinical evaluation, enable abdominal surgeon



the choice of therapeutic treatments as surgical as well as oncological.

Carcinoma embryonic antigen (CEA) is an oncofetal tumor marker discovered 1965 by Gold and Freedman. In 70% of cases is significant in the diagnosis of colorectal cancer. According to units of measurement that we use, values up to 5ng/ml are considered as normal antigen concentration in serum. It has been observed that these values in smokers, in case of ulcer colitis, liver cirrhosis and chronic bronchitis can be increased up to 10 ng/ml. Well differentiated adenocarcinoma is accompanied with higher CEA serum concentration. Increase of its concentration for a period of few months after the surgery is speaking in favor of recurrence. Its concentration is also correlated with the tumor size. Thus, tumors of smaller size have normal serum concentrations of CEA antigen. Only tumors greater than 3 cm are accompanied with high concentration of CEA antigen (3).

Carbohydrate antigen (CA19-9) is a cancer antigen whose elevated serum concentration is detected also in case of colorectal cancer. It is a tumor marker that is observed in elevated serum concentration with metastatic colon cancer.

## 2. GOALS

The goal of our study was to determine serum levels of CEA and CA19-9 in patients with colorectal cancer. To correlate serum levels of antigen with size and location of the tumor. Correlate CEA and CA19-9 with metastases as well as possible complications. Perform colonoscopy to visualize the tumor lesion and perform targeted biopsy in order to obtain histopathological confirmation of colon cancer.

## 3. MATERIAL AND METHODS

The study was of prospective – retrospective type, which included 91 patients hospitalized at the Clinic of gastroenterohepatology in the period from 2010-2013, with the diagnosis of colon cancer.

All patients underwent colonoscopy, targeted biopsy, so we visualized tumor infiltrative lesions in a specific segment of the colon. Patients also underwent targeted biopsy.

Histopathologic examination of tissue samples was performed at the Institute of pathology of the Clinical Center of Sarajevo University. Tissue samples of tumor infiltrate were sent stained in formalin to Institute for pathology where they were cut, stained and analyzed histologically, so we could get the histological confirmation of our clinical diagnosis.

All patients have determined serum concentrations of CEA and CA19-9 antigen. These analyzes were carried out at the Institute of Biochemistry-CCU Sarajevo.

The data are presented in tables (and charts) by the number of cases, percentage, mean, standard deviation and ranges of values. To test the significance of the differences were used Chi-square test, Student's t-test and one-way analysis of variance ANOVA with a significance level of  $p < 0.05$  which was considered statistically significant or at the 95% confidence level. The analysis was conducted using statistical software for biomedical research Med Calc v12.7.

## 4. RESULTS

The research was conducted at the Clinic of gastroenterohepatology and the research included 91 patients. Of these, 58 were men and 33 women. By the analysis of gender structure we get that in the total sample were over-represented men with 58 or 63.7% of cases compared to women with 33 or 36.3% of cases.

The average age of the patients was  $66.6 \pm 11.6$  years with a median of 69 years and ranged from 35 years to 89 years in the oldest patients. For ease of comparison according to the levels of tumor markers patients were divided into age groups of 10 years, among which dominated the older age groups

Localization		
	%	N
Colon ascendants	8	8.8
Colon cecoascendent	2	2.2
Colon descendent	9	9.9
Colon transverse	4	4.4
Rectum	34	37.4
Rectostigmoid	9	9.9
Sigma	25	27.5
Total	91	100.0

Table 1. Tumor localization

Metastases		
	%	N
No	54	59.3
Liver	22	24.2
Liver and lungs	5	5.5
Lymph nodes	9	9.9
Adipose tissue	1	1.1
Total	91	100.0

Table 2. Presence of metastases

56-65 years (29 or 31.9%) and 66-75 years (33 or 36.3%).

The most common localization was rectally or in 34 or 37.4% of cases, followed by sigma with 25 or 27.5% of cases, while the least was observed localization in cecoascendent colon in only in 2 cases or 2.2%.

According to the type of tumors most present was adenocarcinoma in 89 or 97.8% of the cases followed by one case (1.1%) of intraepithelial and squamous cell carcinoma type.

Within the total sample metastases were observed in 37 cases or 40.7%, of which dominate metastases in lymph nodes in 32 or 35.2% of cases, of which 9 patients had only affected lymph nodes. Followed metastases in the liver in 22 or 24.2% of cases, 5 or 5.5% in the liver and lungs and 1 in adipose tissue.

Analysis of the average value of CEA shows that the it was higher in males ( $1063.4 \pm 2718.2$ ; range 0.24 to 12.0) than women ( $142.2 \pm 446.7$ ; range 0.56

	Comparison by gender					
	Mean	SD	SEM	Min.	Max.	
CEA F=4.485 p=0.006	Male	1063.4	2718.1	388.3	.24	12000.00
	Female	142.1	446.6	80.2	.56	2073.00
	Total	706.4	2183.7	244.1	.24	12000.00
CA19-9 F=0.077 p=0.782	Male	1865.4	8229.6	1226.8	1.90	54883.90
	Female	2453.2	9663.1	1826.1	1.90	50319.00
	Total	2090.8	8745.7	1023.6	1.90	54883.90

Table 3. Comparison of mean CEA and CA19-9 values by gender

	Comparison by age					
	Mean	SD	SEM	Min.	Max.	
CEA F=0.186; p=0.945	< 45 yrs.	449.4	1073.0	405.6	.24	2876.39
	46-55 yrs.	.9	.3	.2	.70	1.26
	56-65 yrs.	827.9	1886.2	377.2	1.57	7426.16
	66-75 yrs.	603.2	2257.6	412.2	.34	12000.00
	<75 yrs.	971.5	3081.6	795.6	1.43	11840.34
	Total	706.4	2183.8	244.2	.24	12000.00
CA19-9 F=2.546; p=0.047	< 45 yrs.	13619.1	24544.0	12272.0	2.00	50319.00
	46-55 yrs.	10.6	10.9	6.3	2.39	22.93
	56-65 yrs.	475.9	1531.6	312.6	1.90	7429.18
	66-75 yrs.	980.5	2478.9	460.3	1.90	12000.00
	<75 yrs.	4482.4	15156.3	4203.6	1.90	54883.90
	Total	2090.9	8745.7	1023.6	1.90	54883.90

Table 4. Comparison of mean CEA and CA19-9 values by age groups

	Comparison according to localization					
	Mean	SD	SEM	Min.	Max.	
CEA F=0.627 p=0.708	Colon ascendants	287.1	587.1	239.7	.34	1478.79
	Colon coascendant	1314.8	1857.1	1313.1	1.67	2628.00
	Colon descendants	821.6	1953.7	690.7	1.43	5645.00
	Colon transverse	8.2	14.1	7.0	.56	29.40
	Recti	1225.4	3253.8	594.0	.24	12000.00
	Rectostigmoid	653.6	1257.9	444.7	1.50	3356.90
	Sigma	162.0	627.3	133.7	.60	2960.04
	Total	706.4	2183.7	244.1	.24	12000.00
CA19-9 F=0.118 p=0.994	Colon ascendants	931.3	1306.7	533.4	1.90	3349.00
	Colon coascendant	1070.7	1507.3	1065.8	4.95	2136.60
	Colon descendants	2015.2	4151.6	1467.8	1.90	12000.00
	Colon transverse	184.7	358.8	179.4	1.90	723.00
	Recti	2717.6	10771.1	2112.4	1.90	54883.90
	Rectostigmoid	688.2	1889.8	668.1	1.90	5365.08
	Sigma	2730.4	11526.1	2644.2	1.90	50319.00
	Total	2090.8	8745.7	1023.6	1.90	54883.90

Table 5. Comparison of mean CEA and CA19-9 values by tumor localization

to 2073) but with the extreme values in one case it was not possible to confirm a statistically significant difference ( $p>0.05$ ). Average values of CA19-9 were higher in women ( $2453.2\pm9663.1$ ; range 1.9 to 50319) compared to males ( $1865.4\pm8229.7$ ; range 1.9 to 54883.9) without significant difference between genders ( $p>0.05$ ).

Average values of CEA were highest in patients aged over 75 years ( $971.5\pm3081.6$ ) and lowest in patients aged 46-55 years ( $0.96\pm0.28$ ) without

statistically significant differences between age groups ( $p>0.05$ ). In case of CA19-9 the highest average values have been reported in patients aged over 75 years ( $4482.4\pm15156.3$ ) and lowest in patients aged 46-55 years ( $10.6\pm10.9$ ) with statistically significant differences between age groups ( $p<0.05$ ).

Average values of CEA were highest in tumor process located in cecoascendant colon ( $1314.8\pm1857.1$ ) and lowest in the localization in colon transverse ( $8.3\pm14.1$ ) without statistical differences

between localizations ( $p>0.05$ ). In the case of CA19-9 the highest average values were observed in the localization at sigma ( $2730.4\pm11526.1$ ), and lowest in the localization in colon transverse ( $184.7\pm358.9$ ) with no statistically significant differences between localization ( $p>0.05$ ).

Analysis of the average value of CEA shows that it has been highest in the case of intraepithelial tumor ( $1789.4\pm3945.6$ ) compared to adenocarcinoma ( $559.6\pm1810.6$ ), but given the extreme values in one case it was not possible to confirm a statistically significant difference ( $p>0.05$ ). Average values of CA19-9 were higher in the case of intraepithelial tumor ( $10779.9\pm22074.0$ ) compared to adenocarcinoma ( $2009.8\pm722.9$ ) with significant differences according to the type of cancer ( $p<0.05$ ).

Average values of CEA were highest in patients with metastases in the liver and lungs ( $2098.7\pm2727.4$ ) and lowest in case of metastases in regional adipose tissue ( $1.66\pm0$ ) without statistically significant difference ( $p>0.05$ ). In the case of CA19-9 the highest average values were observed in case of liver metastases ( $4061.4\pm12998.9$ ) and lowest in case of metastasis in adipose tissue ( $1.9\pm0$ ) without statistically significant differences ( $p>0.05$ ).

Analysis of the presence of metastases according to the side shows that the metastases were more frequent in case of tumor process localization in the right hemicolon (8 or 57.1%) compared to the localization at the left hemicolon (29 or 37.7%). Statistical analysis by the Fisher exact test shows that there is no statistically significant difference in the presence of metastases in relation to the side of a tumor process ( $\chi^2=1.863$ ;  $p=0.143$ ).

## 5. DISCUSSION

Cancer embryonic antigen (CEA) and carbohydrate antigen (CA19-9) are well-known tumor markers that are used in the diagnosis of colorectal cancer. They are also used in preoperative staging and postoperative follow-up of patients, especially patients who are treated with chemotherapy. The appearance of elevated levels of these markers in the serum is in most cases a sign of recurrence or metastatic lesions in near

	Comparison according to tumor type					
	Mean	SD	SEM	Min.	Max.	
CEA F=1.453 p=0.240	Adenocarcinoma	559.5	1810.6	217.9	.34	12000.00
	Intraepithelial	1789.4	3945.6	1247.7	.24	11840.34
	Squamous	8.9	.	.	8.93	8.93
	Total	706.4	2183.7	244.1	.24	12000.00
CA19-9 F=6.615 p=0.002	Adenocarcinoma	722.9	2009.8	255.2	1.90	12000.00
	Intraepithelial	10779.9	22074.0	6980.4	1.90	54883.90
	Squamous	13.5	.	.	13.54	13.54
	Total	2090.8	8745.7	1023.6	1.90	54883.90

Table 6. Comparison of mean CEA and CA19-9 values by tumor type

	Comparison according to metastases					
	Mean	SD	SEM	Min.	Max.	
CEA F=0.991 p=0.429	No	445.6	2079.5	309.9	.24	12000.00
	Liver	1276.6	2727.4	609.8	1.75	11840.34
	Liver and lungs	2098.2	2311.7	1033.8	13.79	5645.00
	Lymph nodes	53.8	128.6	45.4	.34	371.78
	Adipose tissue	1.6	.	.	1.66	1.66
	Total	706.4	2183.7	244.1	.24	12000.00
CA19-9 F=0.291 p=0.916	No	1658.0	8001.3	1265.1	1.90	50319.00
	Liver	4061.3	12998.9	3063.8	1.90	54883.90
	Liver and lungs	2421.7	2224.7	994.9	78.56	5365.08
	Lymph nodes	136.9	318.2	112.5	1.90	922.02
	Adipose tissue	1.9	.	.	1.90	1.90
	Total	2090.8	8745.7	1023.6	1.90	54883.90

Table 7. Comparison of mean CEA and CA19-9 values by presence of metastases

environment of the tumor as well as remote ones (1).

Colonoscopy with macroscopic visualization of tumor lesions, followed by targeted biopsy are now considered invasive methods, but we have to admit that these are the methods of choice in the diagnosis of colorectal cancer.

CEA and CA19-9 are used in clinical practice, but we have to accept the reality that they are not specific for early detection of colon cancer, meaning they cannot be used in the diagnosis of carcinoma in situ (1).

Nakatani H. and associates in their research from 2012 provided the data that the colon cancer located in the region of sigma had extremely high concentrations of CEA and CA19-9. CT could not detect metastases. Otherwise it was a case of well differentiated adenocarcinoma or elevated concentrations without metastases (2). When we

compare our results we must say that in our study colon cancer had markedly elevated levels of CEA and CA19-9 with metastasis and with the radiation in lymph nodes. Mean CEA values were highest in patients with liver and metastases in the lungs (2098±2727.4) and the lowest in case of metastases in regional adipose tissue (1.66±0) without statistically significant difference (p>0.05). In case of CA19-9 the highest average values were observed in case of

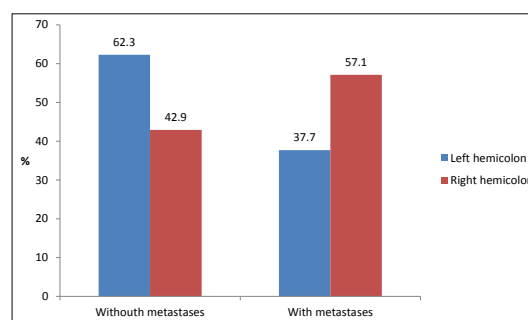


Figure 1. Presence of metastases according to tumor side

liver metastases (4061.4±12998.9) and lowest in metastasis in adipose tissue (1.9±0) without statistically significant difference. Average values of CEA and CA19-9 were higher in patients without complications. Compared with study by Ochiai H. and associates who in his study did not find significantly higher CEA and CA19-9 levels in patients who had recorded metastases into lymph nodes (4). According to our research, we found in 9 patients (9.9%) metastases in the lymph nodes but without significantly increased levels of these markers. What we found by exploring the colon cancer is that they were extremely higher CEA and CA 19-9 values in patients who have had cancer in the right hemicolon.

According to the localization the largest number of patients had colon cancer in the rectum area 34 (37.4%), followed by sigma in 25 cases (27.5%) and rectostigmoid area 9 cases (9.9%) with the presence in the descending colon in 9 cases (9.9%). It means that dominated was localization in right hemicolon in 74% of cases. Bin Jin and associates published that they have found 44 cancers in the rectum region and 68 cancers in other regions of the colon (5). According to our research, we can conclude that there are no major differences between these studies, because it was given that in the largest number of cases cancer was located in the area of the rectum and sigmoid, because we have 91 patients suffering from colon cancer of which 34 cancers was in the area of the rectum and 25 in the region of sigma.

Analysis of the gender structure showed that in the total number of patients with a higher percentage was man 58 or 63.7% compared to women who were present in 33 or 36.3% of cases. According Selcubicik E. and associates in their study was also more present men than women (7).

The population in our sample was older with the average age of patients of 66.6±11.6 years, with a median that ranged from 35 years to 89 years. Otherwise, in our research were most dominant older age groups of 56-65 years (29 or 31.9%) and 66-75 years (33 or 36.3%). El-

derly population was observed also in the studies of other authors (6,7).

Analysis of the average value of CEA shows that it was higher in males ( $1063.4 \pm 2718.2$ ; range 0.24 to 12,000) than women ( $142.2 \pm 446.7$ ; range 0.56 to 2073) but due to the extreme values in one case it was not possible to confirm a statistically significant difference ( $p > 0.05$ ).

Average values of CA19-9 were higher in women ( $2453.2 \pm 9663.1$ ; range 1.9 to 50.319) compared to men ( $1865.4 \pm 8229.7$ ; range 1.9 to 54883.9), without statistically significant differences by gender ( $p > 0.05$ ) (7).

Average values of CEA were found in patients aged over 75 and the lowest in patients aged 46-55 years. Statistically significant differences was not found between age groups ( $p > 0.05$ ).

In the case of CA19-9 the highest average values were recorded in patients aged 75 years and the lowest in patients aged 46-55 years. There is a statistically significant difference between age groups and ( $p < 0.05$ ). Other researchers (8), the results were similar to ours.

## 6. CONCLUSION

By an insight into the complete study it can be concluded that significantly more were represented by histological type adenocarcinoma of the

colon and the localization of most of them was in the left hemicolon with the highest number in the area of rectum and sigma. Increased serum CEA and CA 19-9 levels were followed by cancer with metastases because we had only one patient with high value of cancer antigen but without proven metastasis. According to this, these are late markers in the detection of colorectal cancer. Disease that occurs in old age and is more common in men. Metastases were present at the first visit to a doctor and were mostly in the liver and combined both in the liver and lungs. Extremely elevated CA 19-9 concentrations were found in case of cecoascendent adenocarcinomas of the colon. According to all of the above, we can conclude this is now a human tumor that dominates human pathology, it is detected late because patients come mostly due to developed complications in form of anemia, malignant stenosis and intestinal obstruction.

**CONFLICT OF INTEREST: NONE DECLARED**

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## ORIGINAL PAPER

# The Prevalence of Helicobacter Pylori Infection in Patients with Reflux Esophagitis – Our Experience

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**Introduction and aim:** The role of Helicobacter pylori in esophageal disease has not been clearly defined. To clarify this issue, we analyzed 120 patients with histologically confirmed esophageal disease. **Material and methods:** In this prospective study, 120 patients who underwent upper endoscopy examination were included; among them 70 patients with clinically, endoscopically and histologically confirmed GERD, and 50 patients with BE. This investigation was performed in the Clinic of Gastrohepatology in Prishtina, during the period: June 2009–December 2011. Each patient was investigated for *H. pylori* infection, by performing biopsy for HUT test. **Results:** In BE group, *H. pylori* infection was present in 16.0% of patients. In GERD group, *H. pylori* infection was present in 42.9%, and in patients of the control group, in 52.0% of cases. So, in BE group, the prevalence of *H. pylori* infection showed less significant difference, compared to the control group ( $P = 0.003$ ) and in GERD group ( $P = 0.0035$ ). Between GERD group and the control group there was no significant difference (GERD vs. G control.  $P = 0.421$ ). **Conclusion:** The prevalence of *H. pylori* infection in patients with BE (16%) was lower in comparison with patients with GERD (42.9%) and with control group ( $p < 0.01$ ). The prevalence of *H. pylori* infection in patients with BE, especially those with LSBE (9.1%) was very low, which indicates a possible protective role of this microorganism. **Key words:** Barrett's esophagus, gastroesophageal reflux disease (GERD), *H. pylori* infection, biopsy, HUT-test

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## 1. INTRODUCTION

*Helicobacter pylori* (*H. pylori*) causes a long-term infection of the human gastric and duodenal mucosa (1). Mucosal colonisation predisposes for peptic ulcer disease, atrophic gastritis and distal (antral) stomach cancer (2), with various effects on gastric acid secretion. Genetic variability of *H. pylori* is high (3). Several genes have been identified that may play a role in the pathogenicity (4,5). Most important is the cytotoxin-associated gene A (*CagA*), which is associated with peptic ulcer disease (6), and intestinal type adenocarcinoma of the stomach (7). Patients with duodenal ulcer often have high basal gastrin levels, high peak acid output and high

24-hour intragastric acidity (8-10). In contrast, patients with *H. pylori*-associated gastric ulcer often have hypochlorhydria (11).

Several reports suggest that the prevalence of *H. pylori* and especially the most pathogenic form—*CagA* might be lower in patients with gastroesophageal reflux disease (GERD), including Barrett's oesophagus (BE) than in the rest of the population (12, 13). One explanation for the negative association between mucosal colonisation with *H. pylori* and GERD is the effect of *H. pylori* on acid production, since extensive gastritis involving the corpus may lower acid secretion by impairing parietal function.

The aim of this study was to determine the prevalence of *H. pylori* infection and its possible protective role in the appearance of GERD and its progression to BE.

## 2. MATERIAL AND METHODS

This investigation was performed on the Clinic of gastroenterohepatology. The time of investigation was June 2009–December 2011.

In this prospective study, from 120 patients, 70 patients were with GERD, and 50 patients with BE. All the patients were interviewed for their age, sex, reflux symptoms, chronicity, medications used, the presence of *H. pylori* infection, weight, family history, smoking. Upper endoscopy was performed by using the Videogastroscope GIF type Q 145 series. Endoscopic reflux changes was performed, according to Los Angeles (LA) classification (14,15,16). Diagnosis of infection with *H. pylori* was making by biopsy for HUT test (Astra Zeneca GmbH). Histological processing was performed in the Institute of Pathology in Prishtina and Skopje. During the recognition of intestinal metaplasia by biopsy, especially goblet cells can facilitate the use of alcian blue stain of pH 2.5 (17,18,19). Dysplasia is categorized as: low and high based on cytological and histological architectural abnormalities (20,21,22,23,24,25,26,27).

The study included patients with positive anamnestic data, endoscopic findings positive for the presence of erosive gastroesophageal disease, which

last month did not receive any PPI treatment, or nonsteroidal anti-inflammatory drugs.

The study excluded patients who did not have typical anamnestic data for gastroesophageal reflux disease, those who have gastroesophageal erosive changes during endoscopy, and patients with pre-existing histopathological proven esophageal adenocarcinoma

The results were processed by modern statistical methods. Data processing is performed with InStat 3 statistical package. The difference was considered significant if  $P < 0.05$ .

### 3. RESULTS

This study included 50 patients with BE, 70 patients with GERD and 50 healthy persons or persons with ulcer of the duodenum, as a control group. The average age of patients in BE group was 52.4 years. (SD  $\pm$  10.8 yr.) In the GERD group average age was 40.8 years. (SD  $\pm$  13.5 yr.), whereas in control group average age was 42.1 years. (SD  $\pm$  12.7 yr.). The age difference between groups was significant (One Way ANOVA  $F = 13.91$ ,  $P < 0.001$ ). Among patients with BE, the most represented age group was 50-59 years, in the GERD-group the most represented age group was from 40-49 years.

In all groups included in this study, men were more represented than women. In the group with BE 78.0% were men, in the group with GERD 64.3%, and in the control group 60.0%. However, the difference was not statistically significant ( $\chi^2$ -test = 4.08,  $p = 0.130$ ). Average body height of respondents in Group BE was 174,8 cm (SD  $\pm$  8,2 cm), in the GERD group it was 168,5 cm (SD  $\pm$  8,9 cm) and among patients of the control group it was 170, 4 cm (SD  $\pm$  9,5 cm). The difference was statistically significant (One Way ANOVA  $F = 7.45$ ,  $P < 0.001$ ). Patients in Group BE were higher than those of group GERD (BE vs GERD  $P < 0,001$ ), and also higher than the control group (BE vs control group:  $P < 0,05$ ), and between the average heights of GERD group and the control group, the difference was not statistically significant (GERD vs. g Control.  $P > 0.05$ ).

Patients in group BE smoked larger number of cigarettes (60%) than patients in the group with GERD (37,1%),

as well as comparing to patients of the control group (50.0%). The difference was statistically significant ( $\chi^2 = 6.26$ ,  $SS = 2$ ,  $P = 0.044$ ). Regarding alcohol consumption, the difference was not significant ( $\chi^2 = 0.316$ ,  $SS = 2$ ,  $P = 0.854$ ). As for the level of education, the difference was significant ( $\chi^2 = 6.48$ ,  $SS = 2$ ,  $P = 0.039$ ) and the family history showed a significant difference ( $\chi^2 = 9.44$ ,  $SS = 2$ ,  $P = 0.009$ ). Patients in BE group (4.0%) received less medications than patients in the GERD group (5.7%), as well as comparing to the control group (14.0%). Acid reflux by night was more expressed in patients with Barrett-esophagus.

Patients in BE group and GERD group had higher BMI, in comparison with patients of the control group; One Way ANOVA obtained a significant difference (One Way ANOVA  $F = 23,27$ ,  $P < 0.001$ ). Also in patients from BE group, average value of BMI was higher than in patients of GERD group (BE vs. GERD.,  $P < 0.001$ ), and in both groups BMI was higher than in patients of the control group (BE vs Control g.  $P < 0.001$ , GERD vs. g Control.  $P < 0.01$ ).

The difference between the duration of symptoms was significant (One Way ANOVA  $F = 161.5$ ,  $P < 0.001$ ; BE vs. GERD  $P < 0.001$ , BE vs. G control.  $P < 0.001$ , GERD vs. G control.  $P < 0.001$ ). The duration of symptoms in BE group was 27.8 years. (SD  $\pm$  2.16 yrs) In GERD group it was 15.2 years. (SD  $\pm$  1.57 yrs) and in control group 4.4 yr. (SD  $\pm$  1.85 yrs). In BE group there were 40 patients (or 80.0%) with hiatal hernia. In GERD group there were 30 patients (42.9%) with hiatus hernia. It was concluded that hiatal hernia was more common in the group with BE, with a statistically significant difference ( $\chi^2$ -Test = 15.1,  $P < 0.001$ ).

In patients included in the study, the prevalence of infection with *H.pylori* was also analyzed. In BE group, *H. pylori* infection was present in 16.0% of patients. In GERD group, *H. pylori* infection was present in 42.9%, and in patients of the control group, in 52.0% of cases. So, in BE group, the prevalence

Groups		HP+	HP-	Total
BE	N	8	42	50
	%	16.0	84.0	100.0
GERD	N	30	40	70
	%	42.9	57.1	100.0
Control gr.	N	26	24	50
	%	52.0	48.0	100.0

BE vs. control gr.  $\chi^2$ -test = 12.87,  $P=0.003$   
 GERD vs control gr.  $\chi^2$ -test = 0.64,  $P=0.421$   
 BE vs GERD;  $\chi^2$ -test = 8.52,  $P=0.0035$

Table 1. Prevalence of infection with *H. pylori* in patients with BE and GERD

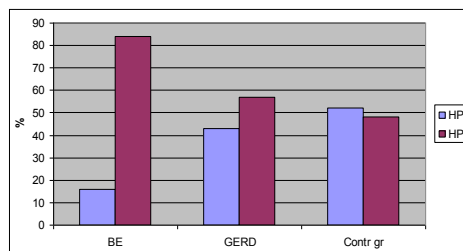


Figure 1. The prevalence of infection with *H. pylori* in patients with BE vs. patients with GERD

Typus of BE		HP+	HP-	Total
SSBE	N	7	32	39
	%	17.9	82.1	100.0
LSBE	N	1	10	11
	%	9.1	90.9	100.0
Total	N	8	42	50
	%	16.0	84.0	100.0

Fisher Exact Test  $P=0.665$

Table 2. Presence of infection with *H. pylori* by endoscopic type BE

of *H. pylori* infection showed less significant difference, compared to the control group (BE vs. control group,  $\chi^2$ -Test = 12.87,  $P = 0.003$ ) and in GERD group (BE vs. GERD;  $\chi^2$ -Test = 8.52,  $P = 0.0035$ ). Between GERD group and the control group there was no significant difference (GERD vs. G control.  $\chi^2$ -Test = 0.64,  $P = 0.421$ , (Table 1, Figure 1).

Regarding endoscopic type of BE and the presence of infection with *H. pylori*, there was no significant difference (Fisher Exact Test,  $P = 0.665$ ). Infection with *H. pylori* was present in 17.9% of patients with SSBE and 9.1% of patients with LSBE

### 4. DISCUSSION

The management of GERD and BE remains a challenging problem and this is partly due to a limited knowledge of its natural history. The relation-

ship between GERD, BE and *H. pylori* is very complex (1). There might also be connection between prolonged proton pump inhibition and the rate of progression to atrophic gastritis, leading to hypochlorhydria (12-14).

*H. pylori*, in contrary to overweight and hiatal hernia, may interact with the risk of BE rather in physiological aspect, than anatomically. *H. pylori* can reduce the risk for BE by possible reduction of acidity in the stomach by the action of urease. The fact that *H. pylori* may protect against BE is contrary to the established status of risk factors for peptic ulcer and gastritis.

*H. pylori* infection was present in 16.0% of patients in BE group, comparing to 42.9% of patients in the group with GERD, and to 52.0% of cases in the control group.

Results from one study (28) showed low prevalence of *H. pylori* infection in patients with BE (12%). Data from the literature also showed low prevalence of *H. pylori* infection in these patients. In the same study, of 251 patients who underwent endoscopy, *cagA* + *H. pylori* was present in 44% of examinations, 36% of 36 patients with GERD, 20% of 10 patients with SSBE, and in 0% of 18 patients with LSBE. A limitation in our study was lacking of the laboratory method for determination of *cagA* + types of *H. pylori*.

*H. pylori* infection has also been implicated in the pathogenesis of GERD.

*H. pylori* infection may be associated with increased acid secretion, but in contrast with achlorhydria resulting in atrophic gastritis, depending on the bacterial species and the inflammatory response that causes it. Studies showing that *H. pylori* negative patients have more severe esophagitis compared with *H. pylori* positive, suggesting that this bacterium may have a protective role in patients with GERD. In fact, infection with *H. Pylori* can induce atrophy and thus reduction of acidic secretion, which ultimately results in reduced risk of developing GERD. In contrast, the eradication of *H. pylori* infection may result in normal acid production and exacerbation of GERD. However, recent clinical studies can not provide strong enough evidence for a possible role of *H. pylori* infection in the devel-

opment of GERD and erosive esophagitis. In clinical practice, since *H. Pylori* infection is associated with an increased risk of peptic ulcer and gastric cancer, existing guidelines recommend its eradication, regardless of the potential effect on GERD (28,29).

*H. pylori*, in particular the *CagA* phenotype, through gastritis and associated hypochlorhydria might be a protective factor against GERD and its complications (30). In recent years it has become clear that a significant number of patients will develop reflux oesophagitis after apparently successful eradication (30).

The findings are consistent with the hypothesis that the declining infection rates of *H. pylori* in the general population have led to a rise in the occurrence of GERD and associated oesophageal adenocarcinoma [28]. The prevalence of *CagA* phenotype was also lower in patients with complicated GERD (such as BE), than in the rest of population (31).

## 5. CONCLUSION

\* The prevalence of *H. pylori* infection in patients with BE was lower in comparison with patients with GERD and with control group ( $p < 0.01$ ).

\* The prevalence of *H. pylori* infection in patients with BE, especially those with LSBE was very low, which indicates the possible protective role of this microorganism.

*H. pylori* infection was present in 17.9% of patients with SSBE and in 9.1% of patients with LSBE,  $P = 0.665$ ).

CONFLICT OF INTEREST: NONE DECLARED

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ORIGINAL PAPER

# The Relationship of Chronic Renal Failure and Body Mass Index in Patients without Diabetes

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**Introduction:** Chronic renal failure (CRF) represents a serious medical problem. Numerous studies have shown that increased body mass index (BMI) as an independent risk factor when it comes to the occurrence and development of CRF. **Material and methods:** The sample in our prospective study presents a total of 150 patients: 30 for each CRF stage (stages I-IV) and 30 patients in the control group. This study did not include patients in the terminal stage of chronic renal failure (stage V), as well as patients with newly diagnosed diabetes. Body mass index–BMI was calculated using the formula  $BMI = \text{weight}/\text{height}^2$  ( $\text{kg}/\text{m}^2$ ). In accordance with the K/DOQI guidelines patients were divided into four CRF stages. **Results:** In our study there is a predominance of female patients. The mean age of patients was 55.43 years. Most of the patients had a BMI between 25 and 30  $\text{kg}/\text{m}^2$ . We did not find significant correlation between BMI and the development or CRF. **Conclusions:** We did not find correlation between increased body mass index (BMI) and the occurrence or development of CRF in persons without diabetes. **Key words:** body mass index – BMI, chronic renal failure (CRF).

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## 1. INTRODUCTION

Chronic renal failure (CRF) represent an important public health problem due to the strikingly high incidence and prevalence of this disease in the world (1,2). Together with an increased incidence of the disease also has increased the number of other pathological conditions caused by CRF including renal failure, cardiovascular diseases and lethal outcome. For a long time the evaluation and treatment of renal diseases were focused on the diagnosis and treatment of each identified renal disease. Studies conducted in the past 10 years have shown that adverse CRF outcomes can prevent or delay by reduction of risk factors and the inclusion of adequate therapy even in the early stages of renal failure, not taking into account the causes that led to the CRF (3). Results of researches and epidemiological studies suggest that increased

body mass index is an independent risk factor when it comes to the occurrence and development of CRF (4).

## 2. MATERIAL AND METHODS

One-year prospective clinical study (January 2011 to January 2012) conducted at the Clinical Center University of Sarajevo, Bosnia and Herzegovina, included 150 patients who were in various stages of chronic renal failure (stage I to IV). Each study group consisted of 30 patients, also with the control group of 30 healthy individuals. The study included all the information about age, complete laboratory analysis of patients with chronic renal failure and 30 individuals who does not have chronic renal failure. Patients who are excluded from the study were as follows: patients in the terminal stage of chronic renal insufficiency (stage V), patients with kidney transplant, patients with

unstable renal function, patients with newly diagnosed diabetes, polycystic kidney disease, hydronephrosis, renal anomalies, renal tumors and accompanying decompensating disease.

In the study, we used the medical records of patients that contained the necessary clinical, laboratory and demographic data. At admission to each patient were taken demographic and anthropometric data (gender, age, height and weight) as well as possible comorbidity. Estimate of creatinine clearance was performed using Cockcroft-Gault formula (5). BMI is calculated using the formula:  $BMI = \text{weight}/\text{height}^2$  ( $\text{kg}/\text{m}^2$ ). According to the classification of nutritional status based on BMI, proposed by the World Health Organization (WHO), the subjects of the study were classified into different groups of the nutritional status (6). The classification of patients according to stages of chronic renal insufficiency was performed in accordance with the criteria of Kidney Disease Outcomes Quality Initiative (K/DOQI) (1).

Results of the study were analyzed using descriptive statistics which includes determining the mean, standard deviation and standard error. Pearson correlation was used to assess the correlation. Statistically significant was considered values of the test with  $p < 0.05$ .

## 3. RESULTS

Of the total number of subjects (N=150) 71 were male and 79 female. The mean age of patients was 55.43 years, and the age structure of the sub-



jects of the study are shown in Table 1.

The mean BMI of the respondents by nutritional status according to the WHO classification is shown in Table 2.

Analysis of the average values of BMI through various stages of CRF showed a slight decrease in this parameter in accordance with the higher stages of renal disease (Table 3). Statistical analysis shows that there is a statistically significant difference in mean BMI values between the study groups ( $p < 0.05$ ).

Analysis of the relationship between the nutritional status according to BMI and CRF stage is shown in Table 4

Statistical analysis of the body mass index–BMI in relation to the stage of renal failure indicates that there is no statistically significant difference or correlation ( $p > 0.05$ ).

#### 4. DISCUSSION

When it comes to gender representation of patients in the study there is evident predominance of women corresponding data from the literature (7). The obtained results showed that age of our subjects clearly indicates a link between older age of patients and pro-

	Age					
	N	Mean	SD	SEM	Minimum	Maximum
Control	30	45.63	15.062	2.750	20	75
I stage	30	48.43	12.800	2.337	20	67
II stage	30	59.07	10.712	1.956	32	80
III stage	30	61.03	14.327	2.616	19	81
IV stage	30	63.00	15.872	2.898	27	83
Total	150	55.43	15.397	1.257	19	83

Table 1. Mean age of patients involved in the study by each group.  $U=9.616$ ;  $DF = 4$ ;  $p=0.0001$

	BMI	
	N	%
<20 underweight	2	1.7
20-25 normal weight	39	32.5
25-30 overweight	53	44.2
>30 obesity	26	21.7
Total	120	100.0

Table 2. BMI of the patients

	BMI					
	N	Mean	SD	SEM	Minimum	Maximum
Control	30	28.3728	4.05049	.73952	17.87	38.10
I stage	30	28.4321	4.35902	.79584	18.94	35.16
II stage	30	26.4039	3.55907	.64979	20.52	33.41
III stage	30	26.8390	4.58154	.83647	17.21	37.25
IV stage	30	25.7256	3.16379	.57763	20.76	34.34
Total	150	27.1547	4.06969	.33229	17.21	38.10

Table 3. Mean BMI of patients in each group  $U=2.761$ ;  $DF = 4$ ;  $p = 0.030$

gression of chronic renal failure, which also corresponds to the literature data, according to which the prevalence of chronic renal failure varies significantly with age and was higher in the elderly (8).

The mean BMI of our patients was 27.1547 kg/m<sup>2</sup>, values range from 17.21 to 38.10 kg/m<sup>2</sup>. In our study, we concluded that the BMI values decrease with the development of chronic renal insufficiency. Review of the available

literature revealed that many authors suggest that there is a clear correlation between obesity and the development of chronic renal failure and that obesity is a risk factor for development of chronic renal failure, which can directly or indirectly lead to renal failure (9). In our study, we did not demonstrated a correlation between increased BMI and the occurrence of renal failure nor have we found significant correlation between increased BMI and the progression of chronic renal failure, which corresponds to the study by Brown et al (10). Results obtained in our study may be explained by the fact that obesity is commonly associated with diabetes, the most common cause of chronic renal failure, since our study did not include patients with diabetes.

#### 5. CONCLUSION

We did not demonstrate significant correlation between increased body mass index and the occurrence or development of renal failure in patients who do not have diabetes.

CONFLICT OF INTEREST: NONE DECLARED

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		Group * BMI					
		BMI					Total
		<20 underweight	20-25 normal weight	25-30 overweight	>30 obesity		
Group	Control	N	1	6	12	11	30
		%	50.0	15.4	22.6	42.3	25,0
	I stage	N	0	11	15	4	30
		%	.0	28.2	28.3	15.4	25,0
	II stage	N	1	10	11	8	30
		%	50.0	25.6	20.8	30.8	25,0
	III stage	N	0	12	15	3	30
		%	.0	30.8	28.3	11.5	25,0
	IV stage	N	1	6	12	11	30
		%	50.0	15.4	22.6	42.3	25,0
	Total	N	2	39	53	26	120
		%	1,7	32.5	44.2	21.7	100.0

Table 4. Relationship between BMI and stage of CRF.  $\chi^2=11.398$ ;  $DF = 12$ ;  $p=0.249$ .  $Rho=-0.166$ ;  $p=0.070$

## ORIGINAL PAPER

# Influence of Remifentanil/Propofol Anesthesia on Ventilator-associated Pneumonia Occurrence After Major Cardiac Surgery

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The study is designed to evaluate the influence of remifentanil/propofol anesthesia on ventilator-associated pneumonia (VAP) occurrence and respiratory support (RS) time after major cardiac surgery. In retrospective-prospective study we investigated the respiratory support time and VAP occurrence in group of 47 patients with remifentanil/propofol and 35 patients with fentanyl/midazolam anesthesia after major cardiac surgery in period June 2009–December 2011. Groups are divided in subgroups depending of who underwent cardiac surgery with or without cardiopulmonary by pass (CPB). The time of respiratory support (RS) was the shortest in remifentanil group without CPB (R/Off 63min ± 44.3 vs R/On 94min ± 49.2 p=0,22), but was longer in fentanyl group (F/Off 142 min ± 102.2 vs F/On 212 min ± 102.2 p=0.0014). The duration of RS of ON pump remifentanil group was shorter than in ON pump fentanyl group (R/On 94 min vs F/On 212 min p=0.0011). The time of RS of OFF pump remifentanil group was lower than in Off pump entangle group (R/Off 63min ± 44,3 vs F/Off 142min ± 102.2 p=0,021) with statistically significance. Ventilator-associated pneumonia was detected in 7 patients (8.5 %). Six patients (17.1%) were from entangle group and one patient (2.1%) from remifentanil group. The most common isolates were *Pseudomonas aeruginosa* in all patients and both *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* in one patients. Conclusion: The remifentanil anesthesia regimen in cardiac surgery decreases length of respiratory support duration and can prevent development of VAP. The role of remifentanil anesthesia in preventing VAP, as one of the most important risk factor for in-hospital mortality after cardiac surgery is still incompletely understood and should be investigated further. **Key words:** remifentanil/propofol anesthesia, ventilator-associated pneumonia, cardiac surgery.

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## 1. INTRODUCTION

We investigated the influence of remifentanil anesthesia on the time of RS and ventilator associated pneumonia (VAP) occurrence after cardiac surgery. Most cases of VAP are caused by bacterial pathogens that normally colonize the oropharynx and gut, or that are acquired via transmission by health-care workers from environmental surface or from other patients (1). VAP is the main infectious complication in

cardiac surgery patients and associated with an important increase in morbidity and mortality (2). VAP incidence in patients with RS increases with its duration. Incidence of VAP when patient is with RS is about 50% in first four days (3). VAP mortality range according literature is from 33% to 50%, and VAP patients have two times bigger mortality rate rather than the similar patients without VAP (4,5).

Extended and long lasting cardio surgical procedures demand prolonged intubation and respiratory support especially in patients who underwent cardiopulmonary by-pass, postoperative bleeding, massive blood transfusion and inotrope treatment (6). So, the VAP in early postoperative period may reduce operative benefits. The remifentanil anesthesia regimen in cardiac surgery decreases length of respiratory support, staying in ICU and hospital and can prevent VAP development (7).

## 2. PATIENTS AND METHODS

We investigate the time of respiratory support and VAP occurrence in retrospective-prospective study of 35 consecutive patients who underwent major cardiac surgery with fentanyl anesthesia in Clinic for Cardiovascular Disease, University Clinical Center Tuzla, and 47 patients who underwent major cardiac surgery with remifentanil anesthesia in Clinical Hospital Mostar in period June 2009- December 2011.

Patients were divided in two groups. In the first fentanyl (F) group induction agents were: fentanyl (20-50 mcg/kg), midazolam (0.1-0.3mg/kg), pancuronium (0,04-0,08 mg/kg). Support agent for F group were: midazolam (3-4 mg /kg /h), fentanyl 120-150 mcg/h, pancuronium 2 mg/h, and sevofluran MAC do 2 vol%. Remifentanil (R) group induction agents were the same

as in F group, but support agent was propofol (50-100 mcg/kg/min) and remifentanyl (0,1-2 mcg/kg/min). The group R of patients had 5mg diazepam iv and 5mg metamizol iv in ICU at admitting time. All patients were under standard pre-operative procedure with central vena cava catheter. Samples of arterial blood gas analysis were taken from a catheter placed in the radial artery by Seldingers technique. All patients had non-complicated intubation and ICU extubation.

We divided groups in two subgroups according to the using of CPB (Remifentanyl On pump group and Fentanyl On pump group) and two groups without using CPB (Remifentanyl Off pump group and Fentanyl Off pump group). In all groups we followed up the duration of respiratory support and noted microbiology verified VAP in early postoperative period. We excluded patients with ejection fraction under 40%, candidates for emergency surgery and patients who had preoperative inotrope therapy and blood transfusion.

### 3. RESULTS

The study included 82 adults (47 patients in remifentanyl and 35 patient in fentanyl group). The two groups were similar with indication for surgery and duration anesthesia. There were 23 female patients (28%), 13 in remifentanyl group and 10 in fentanyl group, and 59 male patients (71.9 %), 34 (72.3%) from R group and 25 (71.4%) from F group. Mean age of male patients was 53.35±9.92 (range 45-74) and of female patients was 59,20±10.07 (range 54-75) with overall mean age 57.45±10.07 and range 45-75 years. The time of respiratory support (RS) was the shortest in remifentanyl group without CPB (R/Off 63 min ± 44,3 vs R/On 94min ± 49,2, p=0,22), but was longer in fentanyl group (F/Off 142 min ± 102,2 vs F/On 212 min ± 102,2 p=0,0014). The duration of RS of ON pump remifentanyl group was shorter than in ON pump fentanyl group (R/On 94 min vs F/On 212 min, p=0.0011). The time of RS of OFF pump remifentanyl group was

On pump	94min ± 49	212 min ± 102.2	p= 0.0014
Off pump	63 min ± 44.3	142 min ± 102.2	p= 0.021
	p=0.22	p=0.0014	

Table 1. R-group F-group

R/ n= 47 2.7±1.22	n=31 2.96±1.42	n=16 2.25±0.44	p=0.056
F/ n= 35 3.8±2.52	n=20 4.65±3.06	n=15 2.66±0.61	p=0.019
N=82 p=0.0128	p=0.0053	p=0.01	

Table 2. On pump Off pump

lower than in Off pump fentanyl group (R/Off 63 min ± 44,3 vs F/Off 142 min ± 102,2, p=0,021) with statistically significance. All patients underwent CPB were longer time on respiratory support than patients without CPB. The results are showed in table 1.

Two (4.7 %) patients from R group and 4(11.4 %) patients from F group had inotrope therapy. Ventilator-associated pneumonia were detected in 7 patients (8.5 %) after cardiac surgery, 6 patients (17.1%) from F (fentanyl) group and 1 patient (2,1%) from R (Remifentanyl) group. All of them were male. The most common isolates were *Pseudomonas aeruginosa* in all patients and both *Pseudomonas aeruginosa* and *Klebsiella pneumonia* in one patients. All patients with VAP received blood transfusion after surgery. There was no significance of CPB duration between Remifentanyl and fentanyl group (F 93.8 min± 6.53 vs R 89.6 min ± 7,9, p= 0,38). The time in ICU for Remifentanyl group was 2.7±1.22 day and 3.8 ±2.52 for Fentanyl group with significance (p=0.0128). Patients from Remifentanyl On pump group were 2.96±1,42 days, and patients from Remifentanyl Off pump group were 2.25±0.22 days in ICU with no significance (p=0.056). The results are showed in Table 2.

### 4. DISCUSSION

VAP is leading cause for nosocomial mortality and morbidity (8). Patients undergoing heart surgery have higher frequency of developing VAP, especially in patients that require more than 48 hours of mechanical ventilation and is associated with high in-hospital mortality (7). Remifentanyl may be beneficial in patients undergoing cardiac surgery because of provided safe and stable operating conditions and earlier tracheal extubation (9). Shorter time of respiratory support decreases risk for VAP occurrence.

CPB using in heart surgery increases intubation period and length of stay in ICU, but remifentanyl decreases that periods. VAP incidence increases with longer period of respiratory support. Process of intubation, alone, is risk factor, but VAP incidence in noninvasive treatments is significantly lower. Perioperative and postoperative transfusion, reintubation and prolonged mechanical ventilation are independent risk factors for VAP in patients following cardiac surgery (10). Cardiac surgery without CPB decreases postoperative blood transfusion necessity. VAP patients have two time's bigger mortality rate rather than the similar patients without VAP. The average ICU and in hospital time is longer for VAP patients about 4 to 13 days (4). One of the ways to decrease respiratory support time is using short-acting anesthetics to enable fast postoperative recovery. Remifentanyl is ultra-short acting opioid and postoperative pain management should be planned carefully.

### 5. CONCLUSION

Remifentanyl/propofol anesthesia using in major cardiac surgery decreases respiratory support time and risk of VAP occurrence. We showed that risk factors for VAP occurrence are longer respiratory support time and cardiac surgery with CPB. Blood transfusion has important role and should be considered. The shortest length of stay in ICU had patients who underwent remifentanyl anesthesia regimen in major cardiac surgery without CPB.

CONFLICT OF INTEREST: NONE DECLARED

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## ORIGINAL PAPER

# Prevalence and Pharmacologic Treatment of Patients with Low Back Pain Treated at the Kosovo Energetic Corporation

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**Introduction:** Low back pain (LBP) is a common complaint among the general population with a subgroup developing chronic and disabling symptoms generating large societal costs. Recurrences and functional limitations can be minimized with appropriate conservative management, including medications, physical therapy modalities, exercise and patient education. **Objectives:** The purpose of this study was to determine the prevalence of low back complaints in industrial workers, to investigate whether individual risk factors involved in the occurrence of LBP, and to determine the most frequent used drug in LBP treatment. **Materials and Methods:** Data for this study were provided from Kosovo Energetic Corporation. A cross-sectional study design was utilized. Self-administered questionnaires were distributed among 228 industrial workers. Patient with LBP underwent a comprehensive clinical, radiological and biochemical evaluation. **Results:** showed that LBP occurred in 63.5% of workers. Individual factors didn't show significant associations with LBP. Age (OR=0.99/95% CI 0.95-1.03), weight (OR=1.13/95% CI 0.99-1.06), height (OR=0.97/95% CI 0.91-1.02), and work experience (OR=1.01/95% CI 0.97-1.05) increase odds for LBP but not significantly. The most frequently used drugs on patients included in this study are NSAIDs. On 33 (55.0%) patients for the treatment of LBP two types of drugs are administered. **Conclusion:** With increased physical activity, health promotion, reduced body weight can prevent morbidity from LBP. A continuous consultation with the Clinical Pharmacist demonstrates effective way of dosage and drug re-evaluation for the patients with LBP. **Key words:** LBP, prevalence, drug, treatment.

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## 1. INTRODUCTION

Low back pain (LBP) is a common complaint among the general population with a subgroup developing chronic and disabling symptoms generating large societal costs (1). Associations between physical workload and LBP have been reported in numerous studies (2). Although much research effort has been spent and several risk factors such as heavy lifting, lifestyle and psychosocial factors identified, the etiology of LBP is still unclear (3).

Most research has attempted to determine causal factors to predict and

prevent work-related LBP. Common factors included sex, age, work postures and type of work (4, 5).

Recurrences and functional limitations can be minimized with appropriate conservative management, including medications, physical therapy, exercise and patient education (6).

Symptomatic drug therapy aims to achieve analgesic and anti-inflammatory effect. Emotionally unstable patients are given sedatives and myorelaxants. And it is also important paravertebral infiltration on the level of com-

pressed spinal root, combined with local anesthetics and glucocorticoids (7).

Initial therapy with acetaminophen, a nonsteroidal anti-inflammatory drug (NSAID), or a cyclo-oxygenase-2-specific inhibitor is recommended. Muscle relaxants can be effective when there is significant muscle spasm present, but benefits must be balanced with their sedative properties (8).

Long-term use of drugs has not shown to be effective and poses serious risk, sometimes with fatal effects (NSAID), toxicity (paracetamol), and drug dependency (muscular relaxant and opioid) (9).

Acute LBP drug therapy leads to short-term pain reduction, but in patients with chronic LBP any benefits would be rare (10).

The mainstay of pharmacologic therapy for acute LBP is acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). If no medical contraindications are present, a two- to four-week course of medication at anti-inflammatory levels is suggested. Pharmacological treatments of chronic LBP include analgesics, anti-inflammatory drugs and muscular relaxants, but the evidence on their efficacy is not convincing.

For relief of acute pain, short-term use of a narcotic therapy should prompt a reevaluation of the etiology of a patient's back pain (6).

## 2. OBJECTIVES

The purpose of this study was to determine the prevalence of low back complaints in industrial workers, to investigate whether individual risk factors involved in the occurrence of LBP, and to determine the most frequent used drug in LBP treatment.

## 3. MATERIAL AND METHODS

### 3.1. Study design and data collection

A cross-sectional study design was utilized. Self-administered questionnaires were distributed among industrial workers. They answered to questions under the observation and guidance of the research assistants.

### 3.2. Study population

Subjects from the power plant company were identified as follows: welders, maintenance technicians, electricians, thermal technicians, mechanical field technicians, drivers/crane operators, mining technicians, transmission technicians, firefighters. The principal tasks of workers are: drilling, blasting, mucking/loading, tramming, rock-breaking, supervisory, and engineering. These occupations are directly related to the production and are therefore involved in prolonged standing, twisting and turning, lifting of heavy loads.

### 3.3. Questionnaire survey

The participants completed a self-administered questionnaire at the Institute of Occupational Medicine–Department of Physical Medicine and Rehabilitation in Obiliq. The questionnaire contained questions on individual data including age, gender, height, weight, level of education, job title, and occurrence of LBP in the previous 12 months (1- year prevalence). The main point of interest in the questionnaire was experience of LBP within the past 12 months, and whether or not it was work related. During the past year have you experienced low back problems (backache, pain, and discomfort) where LBP was defined as a pain localized in the lower back without specific underlying cause, between the lower angle of the scapulae and above the buttocks (ICD-9).<sup>[11]</sup> If the answer was no, no further questions were needed. If the answer was yes, the physician asked another questions: did you take medications, what kind of medications did you

take and how many kinds of medications did you take?

Patient with LBP underwent a comprehensive clinical, radiological and biochemical (blood analysis) evaluation. They had LBP presenting herniated disc (n=49), lumbar spondylosis n= (60), or facet joint pain, n= (36), diagnosed through clinical and radiographic examination by a physiatrist.

### 3.4. Eligibility criteria

Inclusion criteria are age from 18-65 years, willing and able to give informed consent. Workers with occupational or non-occupational accidents affecting the lower back were excluded from the study.

### 3.5. Ethical clearance

The study had been approved by the Regional Ethical Board at the Institute of Occupational Medicine and by the Research Ethics Committee, University of Prishtina, Kosovo.

### 3.6. STATISTICAL ANALYSIS

All statistical analyses were performed using the Statistical Package for Social Science R. In the statistical analysis differences between normally distributed continuous variables were tested with the Student t-test and differences between categorical variables with the chi-square test ( $\chi^2$ ). Multiple logistic regression model were used to compute adjusted odds ratios (OR) and their 95% confidence intervals (95% CI) for the various symptoms and causes of with LBP as the dependent variable. Wald statistics were used to estimate

Sex	LBP (yes)		LBP (no)	
	N	%	N	%
Men	135	93.1	79	95.1
Women	10	6.9	4	4.8
Total	145	100	83	100

Table 1. Presence or absence of LBP based on gender

the 95% confidence intervals around the odds ratio. Level of statistical significance was set to  $p < 0.05$ .

## 4. RESULTS

During the two months of data collection, 289 workers were interviewed and 61 refused to participate. So 228 questionnaires were completed. The response rate of the questionnaire was 78.9 %.

Table 1 summarizes the prevalence of LBP among workers who participated in the study. Of the 228 workers evaluated, 145 (63.5%) presented with LBP, male patients are 135 or 93.1%, whereas 10 female subjects or 6.9 %. At the same time, 83 (36.4%) did not have LBP; male subjects were 79 or 95.1%, while female subjects were 4 or 4.8%.

Results from Multiple Logistic Regression analysis as related to risk factors are reported in Table 2. Among workers age (OR=0.99/95% CI 0.95-1.03), weight (OR=1.13/95% CI 0.99-1.06), height (OR=0.97/95% CI 0.91-1.02), and work experience (OR=1.01/95% CI 0.97-1.05) increase odds for LBP but not significantly.

Among 49 or 33.8% of patients terminal diagnosis was Disc Hernia, along with 60 or 41.4% Spondylosis lumbalis, and at 36 or 24.8% Facet Joint Pain with-

Parameters	B	S.E.	Wald	Sig.	O.R.	95.0 % CI for O.R.	
						Lower	Upper
Age	-0.01	0.02	0.27	0.6	0.99	0.95	1.03
Weight	0.03	0.02	3.51	0.06	1.13	0.99	1.06
Height	-0.04	0.03	1.67	0.2	0.97	0.91	1.02
Work experience	0.01	0.02	0.13	0.72	1.01	0.97	1.05

Table 2. Determination of the impact between individual parameters and occurrence of LBP

		Sex		Total	P-value
		M	F		
N (%)		135 (93.1%)	10 (36.7%)	145 (100.0%)	P=0.039
Diagnosis	Facet joint pain	35 (26.3%)	1 (13.6%)	36 (24.8%)	P=0.196
	Spondylosis lumbalis	57 (42.1%)	3 (31.8%)	60 (41.4%)	
	Hernia discii	43 (31.6%)	6 (54.5%)	49 (33.8%)	

Table 3. Diagnosis of the subjects based on gender

Drugs	Diagnosis			Total N (%)
	Facet joint pain N (%)	Spondylosis lumbalis N (%)	Hernia disci N (%)	
Total	36 (100.0)	60 (100.0)	49 (100.0)	145 (100.0)
NSAID	33 (92.3)	57 (95.7)	43 (87.5)	133 (91.7)
Sedative	11 (30.8)	13 (21.7)	27 (54.2)	51 (35.1)
Corticosteroide	8 (23.1)	8 (13.0)	14 (29.2)	30 (20.6)
Narcotic opioid	-	-	37 (75.0)	37 (25.5)
Myorelaxant	6 (15.4)	39 (65.2)	20 (41.7)	65 (45.0)

Table 4. Drugs used in concordance with diagnosis

Drugs	Diagnosis			Total N (%)
	Facet joint pain N (%)	Spondylosis lumbalis N (%)	Hernia discii N (%)	
One drug	14 (38.5)	3 (4.3)	-	17 (10.0)
Two drugs	22 (61.5)	57 (95.7)	6 (12.5)	85 (55.0)
Three drugs	-	-	43 (87.5)	43 (35.0)
Total	36 (100.0)	60 (100.0)	49 (100.0)	145 (100.0)

Table 5. Number of drugs used based on diagnosis

out significant gender difference, ( $P>0.05$ ). (Table 3).

On three dominant diagnoses the most used drugs are NSAIDs, whereas sedatives and opioid narcotics are frequently used during the treatment of Disc Herniation (Table 4).

The most frequently used drugs on patients included in this study are NSAID with 91.7% followed by myorelaxant drugs 45%, sedatives 35.1%, opioid narcotics 25.5% and corticosteroids 20.6% (Figure 1).

On 85 or 55.0% of patients dual medicine treatment is administered, on 43 patients or 35.0% triple medication treatment is administered and on 17 patients or 10.0% single medication was administered. Only on patients suffering from Herniated Disc triple drug treatment is administered. At subjects going through Lumbar Spondylitis (95.7%) dual drug treatment is administered, and meanwhile, Facet Joint Pain was treated with single drug administration (Table 5).

## 5. DISCUSSION

This cross-sectional investigation attempted to examine the prevalence of LBP among power plant workers. The hypothesis that was considered in this study was that the prevalence of LBP in power plant workers would be high since they comprise a unique

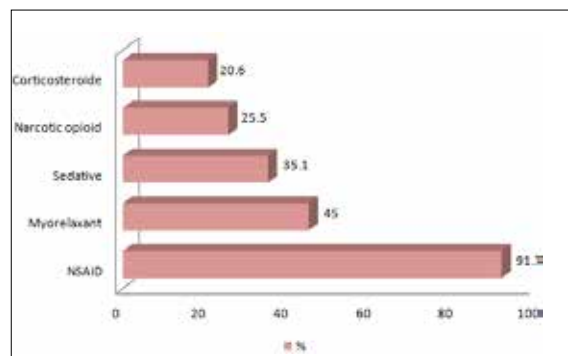


Figure 1. The range of used drugs

occupational group characterized by heavy physical labor with high levels of force being exerted. The LBP prevalence among power plant workers was 63.5%. The findings of this study agree with previous studies on the prevalence of LBP in working populations being between 60–85% (12, 14).

According to the literature, the main predictors of back pain include physical stress (e.g., prolonged lifting, driving, forceful or repetitive movements involving the back), psychosocial stress (e.g., high perceived workload and time pressure, low control and lack of social support at work), personal characteristics (e.g., psychological status and tobacco use), and physical characteristics (e.g., obesity and height) (15, 16). Male and female workers subjected to heavy physical demands showed an earlier onset of LBP in comparison with the general population (13).

No association was found between weight and height and the prevalence

rate of LBP. This is in agreement with the findings of other researchers (17). Individual characteristics such as age, height, weight, duration of employment, were not predictive for low back complaints leading to absence from work (18, 19).

There is conflicting evidence regarding the effectiveness of different types of treatment for reducing pain and disability in patients with LBP. One systematic review and two subsequent RCTs found that advice to stay active reduced sick leave and chronic disability compared with no advice or traditional medical treatment (including analgetics as required and advice to rest) (20).

Recent studies suggest that acupuncture is more effective than no treatment or sham treatment, is as effective as other medical interventions of questionable value (for example, TENS and NSAID for chronic back pain), but is less effective than massage (21).

The evidence that NSAID relieve pain better than placebo is strong. Muscle relaxants relieve pain more than placebo, strong evidence also shows, but side effects such as drowsiness may occur (22).

In our study 97.1% of subjects are treated with NSAID, whereas 30% with opioid analgesic. In the study of Sadhra et al [20] 85% of the miners reportedly used strong oral analgesics, 11% received parenteral (injectable) analgesic, with 3% and just 1% using mild and topical analgesics respectively.

Moreover, there is conflicting evidence about whether NSAIDs are superior to other drug treatments (paracetamol, opioids, muscle relaxants) for treatment of LBP. One systematic review found no significant difference among NSAIDs or between NSAIDs and other drug treatments in pain relief. Three small RCTs identified by a systematic review found no significant difference in symptoms or return to work between an opioid analgesic, paracetamol (acetaminophen), and NSAIDs (20). Acetaminophen is recommended dosages (i.e., up to 4 g per day in patients without liver problems) can be a helpful adjunct and avoids the renal and gastrointestinal toxicities of NSAIDs.

One systematic review of 51 randomized controlled trials comparing



NSAIDs with placebo found strong evidence that NSAIDs significantly improved pain control. There is strong evidence that various NSAIDs are equally effective. Opioids should be considered a second- or third-line analgesic option and should be used only for a short period for most patients. Several small studies have shown no significant advantage of opioid use in symptoms relief or return to work when compared with NSAIDs or acetaminophen (24).

As reported in other studies (25, 27), this study also found that patients that received more than one drug in the treatment of severe pain have had better improvement rate compared with the others that have received only one drug. A randomized paper concluded that in patients suffering with chronic LBP the use of NSAID in combination with Vitamin B is far more effective for pain reduction than the sole use of NSAID (25).

Further, two meta-analyses provide strong evidence that muscle relaxants are helpful in the treatment of nonspecific acute LBP (26, 27). For example, patients receiving cyclobenzaprine (Flexeril) were significantly more likely to report improvement in LBP symptoms at two weeks than patients receiving placebo. Muscular relaxants can reduce pain to a moderate degree. The review (2 higher-quality RCTs, 222 people) reported that tetrazepam 50 mg three times daily significantly reduced pain and increased overall improvement compared with placebo after 10 to 14 days (27).

The findings from the present study are in the agreement with the results of two RCT (28, 29) that epidural steroid injections may be helpful in patients with radicular symptoms that do not respond to two to six weeks of conservative therapy, while they found no clinically important results about epidural corticosteroid injections in people with chronic back pain without sciatica. Randomized trials have demonstrated short-term (i.e., weeks to months) but not long-term improvement in pain and disability with epidural steroid injections (30).

## 6. CONCLUSION

It was concluded that LBP occurred at a high rate in this company. The most administered drugs are NSAIDs. Majority of workers with LBP used two types of drugs.

With increased physical activity, health promotion, reduced body weight can prevent morbidity from LBP. A continuous consultation with the Clinical Pharmacist demonstrates effective way of dosage and drug re-evaluation for the patients with LBP.

**CONFLICT OF INTEREST: NONE DECLARED**

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## ORIGINAL PAPER

# Impact of Complications and Bladder Cancer Stage on Quality of Life in Patients with Different Types of Urinary Diversions

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**Goal:** Determine correlation between complications and stage of the disease and their impact on quality of life in patients with different types of ileal urinary derivation after radical cystectomy, and upon estimation of acquired results, to suggest the most acceptable type of urinary diversion. **Patients and methods:** In five year period a prospective clinical study was performed on 106 patients, to whom a radical cystectomy was performed due to bladder cancer. Patients were divided into two groups, 66 patients with ileal conduit derivation and 40 patients with orthotopic derivation, whereby in each group a comparison between reflux and anti-reflux technique of orthotopic bladder was made. All patients from both groups filled the Sickness Impact Profile score six months after the operation. All patients had CT urography or Intravenous urography performed, as well as standard laboratory, vitamin B12 blood values, in order to evaluate early (ileus or subileus, wound dehiscence, bladder fistula, rupture of orthotopic bladder, urine extravazation) and late complications (VUR, urethral stricture, ureter stenosis, metabolic acidosis, mineral dis-balance, hypovitaminosis of vitamin B12, increased resorption of bone calcium, urinary infection, kidney damage, relapse of primary disease), so as disease stage and it's impact on quality of life. **Results:** From gained results we observe that each category of SIP score correlates with different rate of correlation with the type of operation, group, T, N, and R grade, except work category. Average value of SIP score rises depending on the type of operation and T stage. It is notable that there is no difference in T1 stage, no matter the type of operation. So the average value of SIP score in T1 stage for conduit was 20.3, for Abol-Enein and Ghoneim 17.25 and Hautmann 18.75 respectively. Average value of SIP score in T2 stage for conduit was 31, for Abol-Enein and Ghoneim 19.1 and Hautmann 17.8. Average value of SIP score in T3 stage for conduit was 38.03, for Abol-Enein and Ghoneim 18.75 and Hautmann 19.5. SIP score for T4 was present only in patients with conduit performed and average value of SIP score was 40.42. There is a high level of correlation of late complications and psychosocial and physical dimension with their parameters, while for an independent dimension of correlation is not significant. Early complications have insignificant correlation in all categories of SIP score. **Conclusion:** Upon analyzing quality of life and morbidity, significant advantage is given to orthotopic derivations, especially Hautmann derivation with Chimney modification, unless there are no absolute contraindications for performing this type of operation. Factors which mostly influence quality of life are cancer stage, type of derivation, late complications and patient age. SIP score, as a well validated questionnaire, are applicable in this kind of research. **Key words:** QOL, SIP score, radical cystectomy, complications, stage.

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## 1. INTRODUCTION

Although the post-operative morbidity analysis is simple for evaluation,

the measuring of the quality of life still represents an issue. Quality of life has been a subject of medical research for

over twenty years and now numerous authorities agree that measuring quality of life is the key measuring in clinical research. The main problem in all researchers within this field is the lack of universal accordance upon definition of the quality of life term. The WHO concept defines the quality of life of an individual as an individual perception of their position in life in the context of the culture and assessment of the system in which they live and in relations towards their goals, expectation, standards and worries. It's generally leveled concept deeply influenced by physical health of the person, his psychological status, the level of independence, social relations and their relation towards main characteristics of their environment (1). Quality of life describes and measures influence of different conditions of everyday life and activities, taking into consideration emotional and social functions, as well as purely physical (2). Radical cystectomy implies simultaneous surgery of urinary tract, digestive tract and lymph nodes, therefore complications occur often upon such extensive surgical treatment. In accordance with current literature, incidence of this secondary condition varies a lot (19%-64%) (3,4), most likely because of very different definitions of morbidity. Current literature is not consistent regarding assessing quality of life of cutaneous forms of urinary derivation com-

pared to continent forms. The problem is in the fact that this kind of disorders influencing the quality of life there are no specific instruments which would quantify and objectify the level of disorder of quality of life.

Furthermore, is the quality of life influenced uniquely by the type of derivation or by other factors as well? In the lack of specific questionnaire on quality of life for urinary derivation after radical cystectomy, we mostly use general questionnaires, such as Sickness Impact Profile (SIP score).

SIP score represents one of the most comprehensive instruments for assessing quality of life, and it's function is to show quality of life disorder through behavior disorder of the patient, as a consequence of the disease or therapy (5).

## 2. MATERIAL AND METHODS

In this prospective study, 106 patients were evaluated who were suffering from invasive bladder cancer, and were divided in two groups. In both groups all patients had transitional cell cancer (TCC) and no distant metastases were found or local recurrence.

**Group A:** This group consisted of 40 patients with orthotopic derivation, 20 patients with Hautmann derivation and Chimney modification of ureterointestinal anastomosis, and in other 20 patients a supravescical derivation by Ghoneim was performed. In both types of orthotopic derivation 40 cm of terminal ileum was used. In early postoperative period, early postoperative complications were followed: ileus or subileus, wound dehiscence, bladder fistula, rupture of orthotopic bladder, urine leak. Six months after surgery, a control evaluation was performed, and all patients from these groups have filled the SIP score in order to assess and grade quality of life, so the following laboratory tests were performed: minerals, urea, creatinine, ABS status, blood count, vitamin B-12 and alkaline phosphatase and urine culture. We also determined the level of residual urine for these patients using ultrasound, and we also performed a CT urography and cystoscopy in order to verify eventual late postoperative complications: vesico-ureteral reflux, urethral stricture, ure-

ter stenosis, metabolic acidosis, mineral disbalance, hypovitaminosis of vitamin B12, increased re-absorption of bone calcium, urinary infection, kidney damage or recurrence of primary disease. We also gained data related to incontinence and erectile dysfunction.

**Group B:** This group consisted of 66 patients to whom after radical cystectomy, ileal conduit derivation was per-

formed. In early postoperative stage in this group early postoperative complications were followed: ileus or subileus, wound dehiscence. Six months after operational treatment, a control study was conducted and all patients from this group filled the SIP score in order to assess and grade quality of life, so the following laboratory tests were performed: minerals, urea, creatinine, ABS

Correlations coefficients SIP score according to group, operation, T and G stage							
		Skupina	Tip operacije	T stadij	N stadij	R stadij	Gradus
Sum %	Ro	.816**	-.790**	.750**	.433**	.349**	-.359**
	P	.000	.000	.000	.000	.000	.000
	N	106	106	106	106	106	106
Body care and movement	Ro	.825**	-.809**	.737**	.497**	.329**	-.359**
	P	.000	.000	.000	.000	.001	.000
	N	106	106	106	106	106	106
Mobility	Ro	.10**	-.793**	.754**	.435**	.319**	-.324**
	P	.000	.000	.000	.000	.001	.001
	N	106	106	106	106	106	106
Ambulation	Ro	.820**	-.799**	.771**	.387**	.306**	-.355**
	P	.000	.000	.000	.000	.001	.000
	N	106	106	106	106	106	106
Physical dimension	Ro	.821**	-.800**	.789**	.459**	.291**	-.335**
	P	.000	.000	.000	.000	.002	.000
	N	106	106	106	106	106	106
Sleep and rest	Ro	.434**	-.413**	.690**	.430**	.282**	-.374**
	P	.000	.000	.000	.000	.003	.000
	N	106	106	106	106	106	106
Home management	Ro	.695**	-.676**	.755**	.449**	.308**	-.361**
	P	.000	.000	.000	.000	.001	.000
	N	106	106	106	106	106	106
Work	Ro	.701**	-.691**	.389**	.293**	.221**	-.328**
	P	.000	.000	.000	.002	.023	.001
	N	106	106	106	106	106	106
Recreation	Ro	.321**	-.314**	.736**	.399**	.255**	-.222**
	P	.001	.001	.000	.000	.008	.022
	N	106	106	106	106	106	106
Eating	Ro	.428**	-.412**	.585**	.367**	.312**	-.327**
	P	.000	.000	.000	.000	.001	.001
	N	106	106	106	106	106	106
Independent dimension	Ro	.663**	-.650**	.766**	.502**	.302**	-.385**
	P	.000	.000	.000	.000	.002	.000
	N	106	106	106	106	106	106
Emotional behavior	Ro	.757**	-.743**	.747**	.513**	.333**	-.265**
	P	.000	.000	.000	.000	.000	.006
	N	106	106	106	106	106	106
Alterness behavior	Ro	.746**	-.720**	.781**	.443**	.404**	-.306**
	P	.000	.000	.000	.000	.000	.001
	N	106	106	106	106	106	106
Social interaction	Ro	.774**	-.767**	.714**	.423**	.386**	-.304**
	P	.000	.000	.000	.000	.000	.002
	N	106	106	106	106	106	106
Communication	Ro	.804**	-.778**	.802**	.436**	.364**	-.339**
	P	.000	.000	.000	.000	.000	.000
	N	106	106	106	106	106	106
Psychosocial dimension	Ro	.769**	-.748**	.788**	.452**	.390**	-.286**
	P	.000	.000	.000	.000	.000	.003
	N	106	106	106	106	106	106

Table 1. Correlations of all categories of SIP score by group, operation or disease stage.

status, blood count, vitamin B-12 and alkaline phosphatase and urine culture. We also performed intravenous urography or CT urography or MR urography, and by physical examination or by anamnesis data, we determined eventual complications related to ileostomy. All these examinations were performed in order to verify eventual late postoperative complications: vesicoureteral reflux, ureter stenosis, metabolic acidosis, mineral disbalance, hypovitaminosis of vitamin B12, increased reabsorption of bone calcium, urinary and stomal infection, asymptomatic bacteriuria, kidney damage, functional or cutaneous complications with ileostomy or recurrence of primary disease.

### 3. RESULTS

This is a tabular overview of all SIP parameters by type of operation, examined group and stage and grade of disease. Here we should notice that group 1 represents orthotopic derivation and group 2 derivation with ileal conduit. It is notable that each category of SIP score correlates with different rate of correlation, group, T, N, R and grade. Except the category work.

In the upper table it is notable that there is a high level of correlation of late complications and psychosocial and physical dimension with their parameters, while in independent dimension correlation is not significant. Early complications have not significant correlation with all categories of SIP score.

Average value of SIP score rises depending on the type of operation and T stage. It is notable that there are no differences in T1 stage, no matter the operation. So the average SIP score value in T1 stage for conduit was 20,3, for Abol-Enein and Ghoneim 17,25 and Hautmann 18,75. Average value of SIP score in T2 stage for conduit 31, for Abol-Enein and Ghoneim 19,1 and Hautmann 17,8, Average value in SIP score T3 stage for conduit was 38,03, for Abol-Enein and Ghoneim 18,75 and Hautmann 19,5. SIP score for T4 stage was present only in patients with conduit performed and average value of SIP score being 40,42.

Upper table represents that patient who had ileal conduit performed who will have higher percentage of disability

compared to patient with Gonheim or Hautmann. The same goes for grade, meaning that patient with HG will have higher score of disability compared to patients with LG, patients with higher T stage higher rate of disability. Last statistically significant variable or factor which influences quality of life is late complications for all three types of derivations (their number) which means that patients with more complications will have higher disability. So, the regression analysis is showing that the T stage is the most influential regarding the change of quality of life (decrease/disability or however is labeled), followed by the type of operation, tumor grade and late complications are characteristic for all three types of operational procedures. Other variables show certain influence but of no significant importance.

### 4. DISCUSSION

Radical cystectomy with lymphadenectomy represents the only secure way of treating organ limited invasive bladder cancer, which allows not only tumor control, but also enable a positive functional result, especially regarding urinary derivation. During past several decades different types of urinary derivations have been developed. They are divided in three basic forms: conduit diversions, usually ileal conduit, orthotopic neobladders and pouches, which could be catheterized. The purpose of urinary diversions upon cystectomy have improved from simple diversion and protection of upper urinary tract to functional and anatomic restoration of lower urinary tract, by imitating as much as possible preoperative condition. Main purpose of urinary derivation is to be

Correlations coefficients complications according to SIP score			
		Late complication	Early complication
Sum %	Ro	.649**	.465**
	p	.000	.000
	N	106	106
Body care and movement	Ro	.686**	.424**
	p	.000	.000
	N	106	106
Mobility	Ro	.677**	.526**
	p	.000	.000
	N	106	106
Ambulation	Ro	.627**	.464**
	p	.000	.000
	N	106	106
Physical dimension	Ro	.660**	.508**
	p	.000	.000
	N	106	106
Sleep and rest	Ro	.456**	.445**
	p	.000	.000
	N	106	106
Home management	Ro	.577**	.363**
	p	.000	.000
	N	106	106
Work	Ro	.424**	.192*
	p	.000	.049
	N	106	106
Recreation	Ro	.470**	.514**
	p	.000	.000
	N	106	106
Eating	Ro	.385**	.402**
	p	.000	.000
	N	106	106
Independent dimension	Ro	.548**	.429**
	p	.000	.000
	N	106	106
Emotional behavior	Ro	.555**	.409**
	p	.000	.000
	N	106	106
Social interaction	Ro	.601**	.475**
	p	.000	.000
	N	106	106
Alterness behavior	Ro	.649**	.458**
	p	.000	.000
	N	106	106
Communication	Ro	.647**	.496**
	p	.000	.000
	N	106	106
Psychosocial dimension	Ro	.617**	.480**
	p	.000	.000
	N	106	106

Table 2. Correlations of SIP score with overall early and late complications. \*\*. Coorelation significant on level  $p < 0,01$   
\*. Coorelation significant on level  $p < 0,05$

the safest in tumor control, has minimal complications in early and late postoperative period and to be adaptable to patient's life habits, in order to ensure best quality of life (6).

Using evidence based on current medical literature related to quality

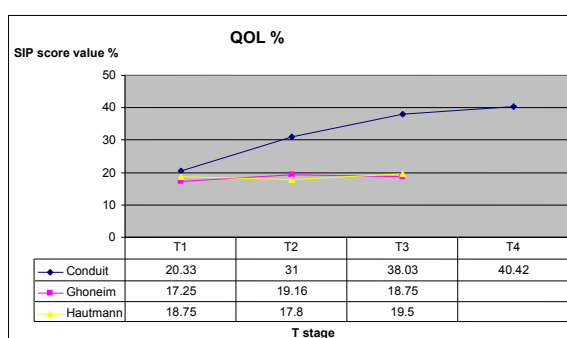
Model	Coefficients						
	Non standardized coefficients		Standardized coefficients	t	p	95.0% CI for B	
	B	SE	Beta			Min	Max
(Constant)	27.839	4.406		6.318	.000	19.092	36.585
T stage	1.851	0.274	0.508	6.759	0	1.307	2.395
Operation	-5.157	0.676	-0.438	-7.627	0	-6.499	-3.815
Age	4.891	.835	.498	5.859	.000	8.811	19.198
Grade	-2.461	1.196	-0.095	-2.058	0.042	-4.835	-0.087
Late complication	1.454	0.664	-0.148	-2.19	0.033	-2.772	-0.136
Early complication	-1.135	0.603	0.108	1.884	0.061	-0.061	2.332
N stage	0.897	0.579	0.077	1.548	0.125	-0.253	2.047
Late complication Bricker	0.442	1.119	0.021	0.395	0.044	-1.78	2.664
R stage	0.435	1.375	0.016	0.317	0.752	-2.295	3.165
Sex	0.401	1.009	0.018	0.397	0.692	-1.602	2.404
Late complication Hautmann and Ghoneim	-0.007	0.007	-0.048	-1.002	0.319	-0.02	0.007

a. Dependent variable: Sum %

Table 3. Results of multivariate regression of SIP score

of life, authors cannot state with certainty that patients with continent forms of derivation have better quality of life. Porter and Penson in 2005 performed a systematic examination (meta-analysis) of literature regarding quality of life. They used MEDLINE as data source and searched for all articles regarding quality of life published in 1996-2004 period. Inclusive criteria was that patient was a grownup, suffering from bladder cancer, comparative studies, original examination, primary study of outcome related to quality of life, using a good and validated questionnaire of quality of life. Only studies which were comparing neobladder, continent reservoirs or conduit diversions were included. Authors concluded that current literature was not sufficient to deduct which type of urinary derivation provides better outcome regarding quality of life. (7).

Sickness Impact Profile (SIP) score which was used in this study to evaluate patient's health condition with different types of urine derivation (ileal conduit and orthotopic continent bladder), is designed to measure the level of dysfunction of behavior related to disease and disease impact on patient's behavior and to reflect subjective perception of possibilities to perform certain activities. By using this questionnaire, we can evaluate physical, social and mental status of patient in everyday life, to evaluate results of different type of treatments and to measure progress of



Graph 1. Values of total SIP score by operation and T stage

patient in longitudinal studies for specific disease categories and/or disability as a consequence of different diseases, traumas and treatments.

Upon searching for correlations, using Spearman correlation index, we observed that there is a correlation between SIP score and all patients form examined groups, with disease stage, N and R stage and grade, that there is a correlation of late complications and psychosocial and physical dimension with their parameters, while for independent dimension correlation was not significant. Early complications have no significant correlations with all categories of SIP score. If we divide types of derivation, we observe that there are significant positive and negative correlations of all categories of SIP score with late complications in ileal conduit group, while there is no correlation between early complication and orthotopic derivation group.

By using multi-variant regression analysis it is proven that T stage, group of operation and age have high level of influence on general quality of life, while grade and early complications

influence is not significant. Other parameters like late complications of orthotopic derivation, N stage, R stage and gender do not have any influence on quality of life.

Although all these facts speak in favor of choosing orthotopic bladder as method of choice, we should also take into consideration that patients with ileal conduit are ten years older with all of their comorbidity, that most of them suffered from advanced disease (T3 and T4 and positive lymph nodes) or higher values of creatinine and urethral invasion were contra indications for continent bladder. Nonetheless, higher morbidity due to primary disease, 6 months upon surgery, was not or only partially manifest. In this study, we noticed that quality of life rises proportionally to disease stage, so patients with T1 tumor in both groups have almost the same percentage of quality of life (18% v.s. 20%). The reason lies in the fact that the chance for advancing disease with all of its complications influences significantly quality of life no matter the derivation, which could be proved by using HRQOL questionnaire which covers all aspects of life. This specimen is very small to draw any conclusions, but it could be a good base for further research, especially because all statistical researches in this field point the fact that it all starts without disease stage. It is necessary to point out that this study covers patients aging from 38 to 82, and that there is a significant difference in quality of life estimation. It is caused by the fact that there could be significant differences in categories such as work, social interaction (question of decreased sexual function was elaborated) and recreation between examined groups. Although, in this study, in none patient a local recurrence of disease was verified 6 months upon surgery, it is obvious that T stage influences significantly quality of life. Accordingly, SIP questionnaire with its results in assessing overall quality of life, could be used as a predictor for a doctor for minimal changes, such as pain or micro metastasis, which could not be discovered by using radiology or biochemistry procedures, but deteriorate basic physiological processes, which reflect subsequently as an impaired quality of



life. In such cases, frequent check-ups or well-timed treatments would be a relief to the patient, but in the same time, will give the family a chance to prepare and accept the facts.

In the end, we could say that SIP score represents an optimal instrument of evaluation in patients with ileal urinary derivation performed upon radical cystectomy. Due to lack of quality of life questionnaire for urinary derivations, being well validated also, SIP score as a general questionnaire on impact of disease on quality of life represents a good alternative for a targeted questionnaire for urine derivation. Eventual new questionnaire should also include a disease stage as one of necessary parameters which should be evaluated. Having in mind that the patient's condition is a dynamic process, which depends on experience and habits, accurate results of quality of life should be acquired one year or more after surgery, in order to determine with certainty which type of derivation is less troublesome for patient.

## 5. CONCLUSION

By using SIP score it has been proven that T stage, group of operation, late complication in ileal conduit and age have high level of influence to overall quality of life, while early complications influence is not significant. Other parameters like late complications of orthotopic derivations, N stage, R stage and gender do not influence quality of life at all. Quality of life rises proportionally with disease stage, so patients with T1 stage of tumor in both groups have practically the same percentage of quality of life (18% v. s. 20%). As a result of this research, a question of T stage of disease importance as a parameter is raised in relation to type of urinary derivation, for the purpose of determining quality of life. Still, this specimen is not sufficient to acquire relevant answers, but can be good basis for further researches.

**CONFLICT OF INTEREST: NONE DECLARED**

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## ORIGINAL PAPER

# Features of Postmenopausal Uterine Haemorrhage

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**Introduction:** Postmenopausal uterine bleeding is a „cancer until proven otherwise“. Endometrial cancer is a typical disease among postmenopausal woman, because every bleeding in this age etiology associated with endometrial cancer (10-30%). The lifespan of women today has been extended and post menopause today last one third of a woman's life. Early diagnosis of endometrial cancer has a very high cure rate. Screening for this cancer has limits in practice and is necessary given the definition of high-risk groups would be subject to primary and secondary prevention. **Goal:** Primary to evaluate the leading causes of postmenopausal uterine bleeding among patients at risk for endometrial cancer (diabetes, obesity, nulliparity, late menopause (after 55 years) and compared them with the causes of postmenopausal uterine bleeding patients without this risk. **Material and methods:** A retrospective, descriptive study with a targeted sample of 50 consecutive patients who had registered postmenopausal uterine bleeding in high-risk groups (cohorts) and the same number of patients with postmenopausal uterine bleeding that does not belong to the risk group (control group). Each patient underwent clinical examination, then fractionated curettages and its histopathological verification and assessment of treated clinical stage of disease with PH analysis of the resected specimens. **Results:** The patients of the studied risk group were significantly affected by endometrial cancer compared with the control group (RR=2.45, 95% CI 1.2-4.6, p=0.005). Endocervical pathology did not differ between groups. Clinical forms of bleeding: for those that are profuse bleeding cancer was present in 54.6% of cases. With intermittent bleeding cancer is verified in the 33.3% of patients. Risk patient groups with cancer frequently suffer from clinically more advanced stages of histologically aggressive endometrial cancer (serous adenocarcinoma—type II, low differentiated cancer). **Key words:** postmenopausal bleeding, endometrial cancer, risk factors, clinical forms of bleeding.

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## 1. INTRODUCTION

Menopause is the last physiological bleeding from the uterus. Postmenopause is according to the definition of the World Health Organization (WHO) defined as the time from the end of the menstrual period onwards. It is divided into early and late—senium (after 70 years). Both of these conditions establish retrograde if the period from the last day of bleeding was one year ago (1,2,3). Improving living conditions, socioeconomic status, women today spend nearly a third of life in post-

menopausal period. Casuistry morbidity in this age group dominates the prevention, early detection and treatment of malignant diseases. WHO estimates that until 2030 approximately 1.2 billion of women will be aged over 50 years. Due to these facts, each country invited to the health needs of women in menopause incorporated as an essential item in health research and public health programs (1,3).

### 1.1. Postmenopausal uterine bleeding

Postmenopause uterine bleeding is etiologically associated with endo-

metrial cancer in 10 to 30% of cases (4,5,6,7). Other causes of these hemorrhages are hyperplasia with atypia as premalignant changes and atrophy of the endometrium (8,9,10).

### 1.2. Endometrial cancer

It is estimated that every woman in postmenopause before of 75 years has 2-3% chance of developing endometrial cancer. Endometrial cancer in Europe and the United States is the most common cancer of female genital tract (11,12,13). In our country, according to the frequency it is behind cervical cancer.

### 1.3. Risk factors for endometrial cancer

There are multiple risk factors for endometrial cancer. These are situations when there is chronic exposure of endometrium to neoplastic (pro-gesterone) action of endogenous or exogenous estrogen source (6), then older age, nulliparity, obesity (21,22), diabetes, late onset of menopause, reduced physical activity (23). Therapeutic use of selective estrogen receptor modulators (SERMs tamoxifen) and others at high risk of endometrial cancer are women who are carriers of mutations associated with hereditary nonpolyposis colon cancer (HNPCC) (24).

### 1.4. The diagnosis of endometrial cancer

Fractional explorative curettage is currently the most reliable diagnostic procedure in premalignant and malignant diseases with symptoms of endometrial uterine bleeding after meno-

pause (4,7). Unexpected risk of endometrial cancer was significantly lower among women who underwent fractionated curettage (D&C), compared to those who had a biopsy of the endometrium (33).

Transvaginal sonography is the method of choice to assess the state of the endometrium. Endometrium thickness in women with bleeding in postmenopause is 4 mm with 96% sensitivity and 68% specificity according to the largest clinical study, so called Nordial study (33)

## 2. GOAL

- Analyze the leading causes of uterine bleeding among postmenopause woman which belong to risk groups (with diabetes, obesity, nulliparous, with late onset of menopause) and compare them with the causes of uterine bleeding among postmenopausal women without these risk factors (control group);
- Compare the incidence of malignant endometrial diseases among these groups of patients;
- Compare results abrasdata cavum uterus in both groups of patients;
- Compare the results of the findings of endocervical abrasdata of these patients;
- For those diagnosed with endometrial malignancy compare clinical stage, degree of tumor differentiation, the degree of infiltration of the uterine wall;
- Determine whether risk groups get histologically more aggressive types of endometrial cancer and less differentiated form of endometrial cancer compared to the control group.

## 3. MATERIAL AND METHODS

Study was performed on consecutive and retrospective sample of patients hospitalized at the Gynecology Ward of the General Hospital „Prim . Dr. Abdulah Nakas“ in Sarajevo and Department of Obstetrics, Gynecology and Perinatology of Cantonal Hospital Zenica admitted with diagnosis of postmenopause bleeding. The sample consisted of 45 consecutive patients with anamnesis and clinically confirmed

presence of risk factors (with diabetes, obese patients, nulliparous, in late menopause, with confirmed hypertension) as a risk group and 45 consecutive patients admitted with diagnosis of postmenopausal bleeding without risk factors, as a control group. In all patients was taken history, they underwent gynecological and ultrasound examination, exploration curettage (D&C) or possibly hysteroscopy sample. Women with diagnosed premalignant or malignant endometrial disease underwent surgery and PH verification of resected specimens.

The definition and selection of patients was performed in the following groups of patients (categorical variables): Risk and control group; Nulliparous and multiparous; Nutritional status: normal BMI (20 to 25.9), excessive weight (26-30) and obese (over 30); The menopause onset: early (under 40 years) and late (over 55 years); Early (<70 years) and late (> 70 years) Clinical forms of bleeding: abundant, poorly, intermittent, spotting.

The parameters of the research were obtained from the case history of patients in successive order, retrospectively, then reports on the histological processing of material from cavum and endocervical or an operative samples. The key test characteristics (variables) were:

- Endometrial malignancy, histological type and stage;
- Premalignant disease-endometrial hyperplasia with and without atypia;
- Endometrial cancer confirmed-clinical stage (FIGO) (degree of infiltration of endometrial cancer histologic type, degree of differentiation);
- Malignant or premalignant endocervical disease (mucosa).

Collecting of investigated parameters was performed using the survey which defined population characteristics and variables that are being investigated. Questionnaires were encrypted to protect privacy of each patient.

Statistical analysis and presentation of results:

The characteristics examined were: endometrial cancer, endometrial premalignant disease, clinical stage, degree

of myometrial infiltration, histological type of the cancer, the degree of differentiation of the tumor, the presence or absence of tumor vascular lesions.

The outputs of the research were:

a) absolute risk (probability of disease in the study group); b) Relative risk (risk ratio compared to the control group); c) Attributable risk (the difference between two groups); d) OR (odd ratio-risk ratio); e) Diagnostic accuracy (sensitivity, specificity, PPV +/-); f) Incidence of studied characteristics in a defined population.

Given the high perceived etiologic association of postmenopausal uterine bleeding with premalignant and malignant diseases of the endometrium, or high prevalence of the studied characteristics of defined population in general (bleeding in postmenopausal women) the study included 90 subjects (45 with and 45 without the risk) as risk and the control group

Statistical evaluation of the results (categorical variables) was conducted by chi-square test. Level of statistical significance was determined by calculating the p-value with the accepted significance level of 95% ( $p < 0.05$ ). Statistical analysis is complemented by the so-called assessment of confidence interval of 95% (CI-confidence interval).

## 4. RESULTS

Results of the research are presented in tabular form in accordance with the tested categorical variables.

### The incidence of endometrial cancer in risk group

Endometrial cancer	
Risk group	30
Control group	12.2
Both groups	21.1

Table 1. The incidence of endometrial cancer

The incidence of endometrial cancer in the risk group was 30% and in the control group 12.2%, compared with 21.1% in both groups

The relative risk for occurrence of endometrial cancer in risk group compared to the control RR=2.45, 95% CI 1.2-4.6; P=0.005. Risk ratio is OR=3.07, 95% CI 1.41 to 6.68 ( $p=0.0045$ , Chi-square=8.54,  $p=0.0035$ ). Respondents from risk group more often suffer from endometrial cancer.

	NORMAL FINDING	HYPERPLASIA SIMPLEX TIPYCA	HYPERPLASIA COMPLEX TIPYCA	HYPERPLASIA COMPLEX ATIPYCA	ENDOMETRIAL CANCER	SARCOMA UTERI	ENDOMETRIA ATROPHY	POLYP
Risk group	5	5	3	1	15	1	8	7
Control group	14	11	2	2	6	0	5	3

Table 2. Curettements of the uterus

	NORMAL FINDING	HYPERPLASIA SIMPLEX TIPYCA	HYPERPLASIA COMPLEX TIPYCA	HYPERPLASIA COMPLEX ATIPYCA	ENDOMETRIAL CANCER	SARCOMA UTERI	ENDOMETRIA ATROPHY	POLYP
Risk group	3	5	3	1	15	1	10	8
Control group	15	15	2	5	5	0	5	3

Table 3. Risk group –Diabetes mellitus

	NORMAL FINDING	HYPERPLASIA SIMPLEX TIPYCA	HYPERPLASIA COMPLEX TIPYCA	HYPERPLASIA COMPLEX ATIPYCA	ENDOMETRIAL CANCER	SARCOMA UTERI	ENDOMETRIA ATROPHY	POLYP
Risk group	8	5	3	1	15	1	10	2
Control group	10	12	5	2	6	0	8	2

Table 4. Risk group – obese patients

%	NORMAL FINDING	HYPERPLASIA SIMPLEX TIPYCA	HYPERPLASIA COMPLEX TIPYCA	HYPERPLASIA COMPLEX ATIPYCA	ENDOMETRIAL CANCER	SARCOMA UTERI	ENDOMETRIA ATROPHY	POLYP
Risk group	19%	11%	5%	2%	30%	1%	17%	5%
Control group	37%	24%	4%	3%	12%	0	11%	8%
Baseline	28%	18%	5%	3%	21%	0	14%	11%

Table 5. Hyperplasia with and without atypia

**Curettements of the uterus both groups**

The indicators were: OR=3.07 95%; CI 1.41 to 6.08 (p=0.0045), Chi Square test = 8.54, p= 0.0035). Patients fro, risk group had statistically significantly higher incidence of endometrial cancer. The incidence of endometrial cancer in both groups was 23.0%.

**Risk group –Diabetes mellitus**

RR=2.45, 95% CI 1.18 to 5.0;p=0.015. Patients with diabetes and have postmenopausal bleeding was significantly had higher incidence of endometrial cancer.

**Risk group – obese patients**

RR 2.41, 95% CI 1.07 to 4.30, p=0.031, Chi square test p=0.0275

Obese patients with uterine bleeding in postmenopause had significantly higher incidence of endometrial cancer. The incidence of endometrial cancer in obese patients is 26.23%.

**Premalignant changes in endometrial hyperplasia with and without atypia**

Endometrial complex hyperplasia with atypia: there was no statistically significant difference between the risk and the control group–(RR 0.66, 95% CI 0.114-3.89, p=0.65). Complex Endometrial hyperplasia without atypia: no statistical significant difference compared

PH	Normal finding	Metaplasia planocellularis	AdenoCa Endo cervicis	Ca endometrii (Figo II/III)	Polypus Canalis cervicis	Other
Risk group	30%	6%	5%	1%	1%	2%
Control group	29%	8%	4%	1%	1%	2%

Table 6. Endocervical pathology

to the control group–(RR 1.25, 95% CI 0.3 to 4.5, p=0733, OR 1.26). Endometrial hyperplasia simplex significantly more occurred in the control group (the lowest level of premalignant potential)–(RR 0.45, 95% CI 0.22-0.9, p=0.02, OR 0.38). Overall prevalence of premalignant lesions in both groups was 25.5%.

**Endocervical pathology**

There was no statistically significant difference in the incidence of malignant and premalignant endocervical pathology between groups: a) adenocarcinoma of the cervix (RR 0.54, 95% CI 0.5-5.95, p = 0.62), b) Adenocarcinoma of the cervix and endometrium cancer (FIGO II)–(RR 2.0, 95% CI 0.62 to 6.4, p=024 R = 2.09). The total incidence of adenocarcinoma in both groups was 1.66%. Normal findings of endocervical abrasdata found in risk group 66.6% in the control virtually the same–65.5%.

**Clinical stage (FIGO) in verified cancer**

Patients of risk group with endometrial cancer more frequently had the

more advanced clinical stage (FIGO)–(RR 1.22, 95% CI 0.40 to 3.68, p = 0.72).

**Clinical cancer: degree of infiltration**

Infiltration of myometrium showed no statistically significant difference between the risk and the control group (RR 1.12, 95% CI 0.74 to 1.67, p = 0.58, R = 1.65.)

**Histologic types of endometrial cancer**

Respondents from risk group more often suffer from histologically aggressive form of endometrial cancer compared to the control group (RR =2.85, 95% CI = 0.39 to 20.54, p = 0.298)

Of the total number of confirmed endometrial cancer of well differentiated (grade I) we found 30% (8) of moderately differentiated (grade II) 55% (15), and poorly differentiated (grade III) 40 cases. Within the control group, there has never been a case of poorly differentiated cancer. We conclude that the risk group had significantly higher histological immature tumors with potentially greater malignancy (p = 0.35). The



study attributes vascular invasion of cancer did not find significant differences in the incidence of vascular invasion and lymph vessels in both groups.

## 5. DISCUSSION

In our sample among patients of both groups we get a relatively high incidence of endometrial cancer of 21%. Analyzing the impact of risk factors on the incidence of endometrial cancer, we came to the conclusion that the patients exposed to known risk (diabetes and obesity) are significantly more often affected than those in the control group ( $p = 0.005$ ). Diabetic patients in the risk group had the highest risk ( $p = 0.015$ ), followed by obese patients ( $p = 0.031$ ). Thus, a significant correlation between the analyzed risk factors with the incidence in this study leads to the conclusion that prevention of diabetes, lifestyle changes, reduction of obesity and physical activity can significantly reduce the risk of the emergence of this disease. Patients exposed to the analyzed risk factors are put in the focus of attention in the primary and secondary prevention of endometrial cancer.

Patients from risk group with confirmed endometrial cancer were more likely to have clinically severe stages of the disease. There were no significant differences in the extent and frequency of infiltration of the wall of the uterus. There is an apparent high incidence of infiltration of the wall of the uterus in both groups (78%) as an indicator of late detection of endometrial cancer. In our sample in both groups, cancer was detected in the first stage in 60% of cases, in the second stage in 32% and the third in 8% of cases.

All cases of poorly differentiated endometrial cancer (biologically potent) are found in the risk group. There was no significant difference in the incidence of lymph-vascular invasion in both groups.

Subjects exposed to the risk factors have higher prevalence of aggressive histologic types of endometrial cancer.

By analyzing the frequency of endocervical pathology the histologic evaluations did not show any significant

Stage	Ia	Ib	Ic	Ila	Ilb	III	IV
Risk group	3	4	2	3	2	2	0
Control group	1	2	1	0	1	0	0

Table 7. Clinical stage of cancer

Degree	25%	50%	>75%
Risk group	26%	36%	38%
Control group	30%	34%	36%

Table 8. The degree of infiltration of the uterus wall

Types	Adeno Ca	Serous adeno Ca	Bright cells Ca	Other
Risk group	67%	22%	4%	7%
Control group	81%	9%	0	10%

Table 9. Types of endometrial cancer

differences between the two groups. These results coincide with the data of other authors.

Results of studies by other authors, meta-analysis, cohort and case-control association studies of diabetes and risk of endometrial cancer showed statistically significant results (15,16).

Obesity as a public health problem increases the risk of developing endometrial cancer (2,4,18). Research shows that obesity, especially abdominal obesity (waist circumference over 80 cm) in symptomatic postmenopausal women carries a high risk for endometrial cancer. Burbos N, Mosunda P. et al. in their research, developed a clinical predictive methods and models to assess the risk of endometrial cancer in post-menopausal period. It is a triad (FAD 31), where F is the frequency of bleeding, A = age, D = Diabetes and 31 is the cut off BMI score (14,15).

## 6. CONCLUSIONS

By the analysis of the results we have come to the following conclusions:

Patients from risk group (diabetes, obesity) in our sample were significantly more often affected by endometrial cancer compared to the control group (post-menopausal bleeding in patients without risk); Patients with uterine bleeding in postmenopause suffering from diabetes mellitus and obese patients (BMI > 31) were significantly more likely to have endometrial cancer compared to the control group; There was no significant difference in the incidence of endometrial complex hyperplasia with and without atypia in risk group than in the control group;

There was no significant difference in the incidence of endocervical pre-malignant and malignant pathology between groups; Patients from risk group with endometrial cancer were significantly more affected by histologically aggressive form of cancer, as they more frequently had the disease in clinically more advanced stages; Infiltration of the wall of the uterus was present in 80% of patients with confirmed endometrial cancer in both groups, indicating a late detection.

CONFLICT OF INTEREST: NONE DECLARED

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- Eating soya improves human memory. *Psychopharmacology (Berl)* 157: 430-436.

## ORIGINAL PAPER

# Frequency of Vaginal Birth After Cesarean Section at Thr Clinic of Gynecology and Obstetric in Sarajevo

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**A**t the Clinic of Gynecology and Obstetrics, Clinical Center University of Sarajevo there is a trend of increasing number of cesarean deliveries in the last 15 years. During the 2012 percentage of Caesarean sections was 35 %, which represents a true pandemic in obstetrics profession and all scientific postulates are threatened by these practices. Of the total number of vaginal births only 48 deliveries were after previous cesarean section. Of the total number of subjects in which the delivery is completed vaginally after a previous cesarean delivery in 5 (10.42 %) was used vacuum extraction, forceps was not used, while manual exploration of the uterus in order to check the condition of the scar of a previous cesarean section was performed in 32 (66.67%) cases. The largest number of respondents who were surveyed were at age from 31 – 35 years (n=25), followed by group between 26-30 years (39.58%). The analysis of complications of vaginal birth after Caesarean delivery revealed that 93.75 % of the patients did not have any complications, at 4.17 % occurred postpartum hemorrhage and in one patient febrile condition. Birth after cesarean delivery can be successfully completed vaginally, with a careful application of prostaglandins, with a good estimate of an experienced obstetrician, and adequate conditions to complete delivery by cesarean section if a vaginal birth is not going in the right direction and as planned. **Keywords:** cesarean section, vaginal birth.

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## 1. INTRODUCTION

Obstetric practice is witness of the world trend of increasing rates in caesarean sections during the past few years. Australia and the United States have the highest rate of caesarean sections in the developed world of 28.5% and 29.1% (1). Similar trends of increasing rates of caesarean sections occur in Latin America, especially in Mexico, 25.7% and Brazil 27.9%, as well as other developing countries, such as India (State of Kerala) 21.4% (2). Although „optimal rate“ of caesarean sections remains debate, the World Health Organization proposed optimal rate of 15% (2). At the Clinic of Obstetrics, Clini-

cal Center University of Sarajevo, there is also a increasing trend of births completed by cesarean section in the last 15 years. During the 2012 there was 35% Caesarean sections from total number of deliveries, which represents a true pandemic in obstetrics profession and all scientific postulates are threatened by these practices.

## 2. GOAL

The goal of this study was to demonstrate the possible occurrence of complications after vaginal delivery following cesariona section at the Clinic of Gynecology and Obstetrics in Sarajevo.

## 3. MATERIAL AND METHODS

This study included pregnant women which had one or more previous deliveries completed by caesarean section in the 2012. All the subjects are treated in relation to parity and age, interval between births, gestational age, mode of onset of the delivery, method of completing childbirth, complications in childbirth, incidence of complications and birth weight. As criteria for inclusion in the study was weight of the infants greater than 500 g and the length of gestation over 25 weeks. Qualitative variables were statistically analyzed by chi square test and quantitative by ANOVA. The level of significance was set to  $p < 0.05$ .

## 4. RESULTS

In the study period of one year at the Clinic of Obstetrics there was 3216 (100%) births. Of the total number of births there was 2101 (63.8%) vaginally completed and 1115 (34.7%) by cesarean section (Table 1). Of the total number of vaginal births only 48 deliveries were after previous cesarean section.

	N	%
Cesarian section	1115	34.70%
Vaginal delivery	2053	63.80%
Vaginalni delivery after cesarian section	48	1.50%
Total	3216	100.00%

Table 1. Method of delivery

During the 2012 in 75 cases women started a vaginal birth after a previous

cesarean section. Of the total number of respondents, in 36% the labor was not successfully completed vaginally, but the repeated cesarean section was needed, while in 64% of patients vaginal delivery was successfully completed (Table 2).

Vaginalni delivery after cesarian section	N	%
Sucesfully completed	48	64%
Unsucsessfull	27	36%
Total	75	100%

Table 2. The success of vaginal births after cesarean section

From the total number of cases in which the delivery was completed vaginally after a previous cesarean delivery in 5 (10.42%) vacuum extraction of the child was needed, forceps was not used in any case, while manual exploration of the uterus in order to check the condition of the scar from the previous cesarean section was performed in 32 (66.67%) respondents. Chi square test showed a statistically significant difference in the incidence of obstetric surgical procedures during and after childbirth, from which was usually made exploration of the uterus to check for a scar from a previous cesarean section,  $\chi^2 = 48.054$ ,  $df = 2$ ,  $p < 0.05$  (table 3).

	YES	NO
Vacuum extraction	5 (10.42%)	43 (89.58%)
Forceps	0 (0%)	48 (100%)
Exloparatio cavi uteri manualis (scar check)	32 (66.67%)	16 (33.33%)

Table 3. Obstetric surgical procedured during and after childbirth

The largest number of respondents who were surveyed were between the age of 31-35 years ( $n=25$ ), followed by those at age between 26-30 years (39.58%). In 47.92% of the women delivery was between the 35<sup>th</sup> and 38<sup>th</sup> gestation week, while in 33.33% of cases between 31<sup>st</sup> and 34<sup>th</sup> gestation week. Of the total number of vaginal birth after cesarean section, the interval between the last two births was most often between 3 and 4 years or in 68.75% of cases, while 75% of infants had birth weight between 2600 and 3500 grams.

The analysis of complications of vaginal birth after Caesarean delivery revealed that 93.75% of the patients did not have any complications, at 4.17%

	N	%
Age	<25 yrs.	1 2.08%
	26-30 yrs.	19 39.58%
	31-35 yrs.	25 52.08%
	36-40 yrs.	3 6.25%
	>41 yrs.	0 0.00%
	$\chi^2=55.74$ ; $df=4$ ; $p<0.05$	
Gestational age	26-30 weeks	7 14.58%
	31-34 weeks	16 33.33%
	35-38. weeks	23 47.92%
	>39 weeks	2 4.17%
	$\chi^2=21.883$ ; $df=3$ ; $p<0.05$	
Interval izme u porododa	<2 yrs.	10 20.83%
	3-4. yrs.	33 68.75%
	>5 yrs.	5 10.42%
	$\chi^2=27.885$ ; $df=2$ ; $p<0.05$	
Tjelesna težina novoro en eta	up to 2500g	4 8.33%
	2600g-3500g	36 75.00%
	>3600g	8 16.67%
	$\chi^2=45.5$ ; $df=2$ ; $p<0.05$	

Table 4. The analysis of the parameters that affect the childbirth outcome

postpartum hemorrhage occurred and in one case febrile condition. It is important to note that there were no cases with uterine rupture at the place of the scar from a previous cesarean section and there were no uterine atony. This all leads to very low risk ratio for complication of  $RR=0.07$ ;  $CI=0.262$  to  $0.1978$  or less than 1%.

	N	Percent
Postpartum hemorrhage	2	4.17%
Rupture of the uterus in the scar area	0	0%
Uterine atony	0	0%
Febrilis puerperialis	1	2.08%
Without complications	45	93.75%
Total	48	100%

Table 5. The incidence of vaginal birth complications after Caesarean delivery

### 5. DISCUSSION

The old postulate: "Once cesarea, always cesarean" leads to repeated caesarean sections in women who have had previous cesarian section, so are more frequent cases with 2 and 3 cesarean sections (3,4,5). There are many studies about natural birth after previous cesarean section. Women after giving birth by caesarean section are more reluctant for a new pregnancy-birth. According to some studies it occurs in 43.8 % of cases. If we know that most of caesarean sections are done in nulliparous women, it is clear that large numbers of women with cesarean section remains with one child (withouth attempts for further pregnancies) (6,7,8).

The biggest complication in women who have had previous cesarean section is the rupture of the uterus at the place of the previous section. Birth protocol in these cases depends on the ultrasound thickness estimation of the LUS (lower uterine segment) and Bishop's cervical score (9,10). Women older than 35 years are more likely to have a failed attempt of a test birth (11). Also, postpartum complications after elective cesarean section are not higher than after vaginal delivery (12) .

At the Clinic of Obstetrics, Clinical Center University of Sarajevo there is a pandemic of caesarean sections in the last 15 years. The increasing trend has reached a percentage of 34.7% performed caesarean sections in the 2012. Real indications for cesarean section are often contradictory with obstetrics findings, and as there is no option for caesarean section on personal request, sometimes arouse doubt. However, when from the total number are ruled out such cases, still remains a large number of the performed caesarean sections among nulliparous and iterative in pluriparous. In order to put an end to such practices there are attempts to get those women whom underwent cesarean section in a previous pregnancy to give birth during second pregnancy vaginally if there are conditions for it from the mother and fetus. In our study, which covered the 2012, 75 vaginal births was attempted after previous cesarean section. Success rate is 64%. Mankuta and colleagues (13) reported attempted vaginal birth after cesarean section in 50 %, Lyndon-Roche and associates in 60% (14) and Haller and associates in 83.5% of cases. Succesfull vaginal birth after cesarean Mankuta and Associates found in 50% (13), Brattele and associates in 65.6% (15), Haller et al in 30.7% (16) . In our study, only five deliveries was completed with use of vacuum extractor, while in 32 deliveries was made manuel exploration to verify the scar of a previous ce-

sarean section. It is important to note that the interval between the two births was between 3-4 years in most cases, while in 93.75% women completed vaginal childbirth without complications. Pregnant women with attempted vaginal birth after cesarean section have a high risk of uterine rupture. The risk is particularly high if the labor is induced by prostaglandins. However, there are authors who believe that the careful application of Sintocin at birth after caesarean section does not increase the incidence of uterine rupture. Pregnant women with spontaneous vaginal delivery after cesarean section have a low risk of uterine rupture and febrile conditions, as we showed in our study.

## 6. CONCLUSIONS

Birth after cesarean delivery can be successfully completed vaginally, with a careful application of prostaglandin, with a good estimate of an experienced obstetrician and adequate conditions to complete the delivery by caesarean section if a vaginal birth is not progressing in the right direction and as planned.

**CONFLICT OF INTEREST: NONE DECLARED**

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## ORIGINAL PAPER

# Correlation of the Body Mass Index and Calcium Nephrolithiasis in Adult Population

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**Introduction:** Prevalence of the kidney stones (renal calculi) has been on the increase in several countries, in parallel with the increase of overweight, diabetes (type 2 diabetes) and hypertension. **Goal:** The goal of our research was to evaluate the connection between the calcium nephrolithiasis and overweight, as quantified using the Body Mass Index (BMI) of the adult population, with a particular reflection on the age groups within it. **Material and methods:** The research was prospective and it was implemented at the Clinical Center of Banja Luka, at the Urology Clinic in the period from 1<sup>st</sup> April 2012 to 1<sup>st</sup> January 2013. The trial encompassed 120 patients with calcium nephrolithiasis of the upper part of the urinary tract and 120 patients without nephrolithiasis. A group of patients with the calcium nephrolithiasis presented a working group, while a group of patients without nephrolithiasis presented a control group. The BMI obtained on the basis of bodily weight and height of the patient, where the age and sex of specific reference values of the BMI were developed by the Center for Disease Control and Prevention (CDC) were not used in the calculation of the BMI. **Results:** Analyzing the values of the BMI in relation to age groups, where there was a statistically significant difference in the working group, whereas in the control group there was a statistically high significant difference, testing of statistical significance of the average value of the BMI was done by observed age groups of working and control group, as well as to the total sample of work and control group using the Chi-Square test and T-test for independent samples. Having observed the age group of 20-40 years, statistically significant differences have been noted at the level of risk of 10%, which confirms that there is a connection between the categories of the BMI and the group, which the patient comes from (Chi-Square test  $p=0.05$ ), that is, T-test has shown that the values are different at the level of 10%, i.e.  $p<0.1$  ( $p=0.073$ ). Having observed the age group 40-60, there was no dependency between the category of the BMI and the group, that is, the differences are not statistically significant,  $p>0.05$  (t-test  $p=0.314$ ). In addition to this, the average BMI values are not significantly different,  $p>0.05$  (t-test  $p=0.871$ ). Having observed the age group of the older than 60, there was no dependency between the category of the BMI and the group, that is, the differences are not statistically significant,  $p>0.05$  (Chi-square test  $p=0.167$ ). Having observed the total sample of the working and control group, there was no dependency of the category of the BMI and the group (or urolithiasis),  $p>0.05$  (Chi-Square test  $p=1.208$ ), whereas the results of the T-test showed that there was no statistically significant difference of the arithmetic mean values of the BMI working group and control group,  $p>0.05$  (t-test  $p=0.620$ ). **Conclusion:** Overweight in younger age groups of adult population may be connected to the occurrence of calcium nephrolithiasis, thus we suggest that urolithiasis should be considered with them, as part of overweight, by which a change of living habits and the manner of food consumption could prevent this disease. **Key words:** urolithiasis, calcium kidney stone (renal calculi), overweight, Body Mass Index.

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## 1. INTRODUCTION

Urolithiasis is a multi-factorial disease, the presence of which in daily urology practice is with the incidence of 0.5% in Europe and the United States of America, whose prevalence has been on a constant increase (1). Prevalence of symptomatic kidney stones amounts to 5-10%, generally in the total population, with a slight predominance in males (2, 3). Prevalence of the kidney stones in the United States of America has increased by 37% in the period from 1976-1980 to 1988-1994 for both males and females (1). The biggest number of the kidney stones are calcium stones, than acid uric making about 9%, struvite (magnesium ammonium phosphate hexahydrate) making approximately about 10% and the rest of 1% is presented by all the other stones (cystine, drug stones, ammonium acid urate) (4). Reference books data show that there is an increase of prevalence of calcium phosphate stones (Calcium phosphate-CaP) in the last two decades, predominantly with women (5, 6). Prevalence of kidney stones has been on the increase in several countries, in parallel with the increase in overweight and diabetes (type 2 diabetes) and hypertension (1, 7, 8, 9) Iba A and associates have shown that the metabolic syndrome, under which overweight is classified, causes changes in urinary constituents, leading to the increased risk of occurrence of urate and calcium kidney stones (uric

acid stone and calcium stone) (10). In the last 10 years, the incidence of the kidney stone has been on the increase in the pediatric population and this increase has gone in parallel with a significant increase of pediatric overweight in the USA (11). The correlation between overweight and kidney stones has been documented for the adult population as well. Body Mass Index (BMI) presents a useful tool in overweight screening. The goal of our research was to evaluate correlation between calcium nephrolithiasis and overweight, quantified using Body Mass Index (BMI) with adult population, with a particular overview of the age sub-groups within it.

## 2. MATERIAL AND METHODS

The research included 120 patients with calcium lithiasis of the upper part of the urinary tract and 120 patients without lithiasis. The group of patients with the calcium nephrolithiasis presented a **working group**, while the group of patients without nephrolithiasis presented a **control group**. The research was prospective and it was implemented at the Clinical Center of Banja Luka, at the Urology Clinic in the period from 1<sup>st</sup> April 2012 to 1<sup>st</sup> January 2013. Diagnosis of the calcium lithiasis of the upper part of the urinary tract was determined on the basis of ultrasonography of the urinary tract, which was initially performed on all the patients of both working and control group, as well as native urography of the urinary tract/intravenous urography and chemical analysis of the stone of the patients, who have later had a spontaneous emission of the stones or after some of the methods for active removal of the stones, with the patients of the working group. Excluding factors were chronic immobilization, anatomic and functional disturbance of the urinary tract, which, as a consequence, cause obstructive uropathy, hyperparathyroidism, history of malignancy as well as other comorbidities, medications or diets that could result in secondary hypercalciuria.

The BMI was obtained on the basis of bodily weight and height of the patients, using the following formula:

$$BMI = \frac{mass (kg)}{(height (m))^2}$$

N	Valid	120
	Missing	0
Mean	50.19	
Median	52	
Mode	59	
Std. Deviation	15.60	
Minimum	21	
Maximum	86	

Table 1. Demographic characteristics of the total working group sample.

Age group		Patient sex		Total	
		Male	Female		
Age group	20 to 40	No.	21	19	40
		%	52.5%	47.5%	100,0%
	40 to 60	No.	20	20	40
		%	50.0%	50.0%	100,0%
	above 60	No.	22	18	40
		%	55.0%	45.0%	100,0%
Total	No.	63	57	120	
	%	52,5%	47.5%	100.0%	

Table 3. Sex structure of the total sample of the working group by the age categories

Categorization of the BMI was as follows: the values of the BMI 18.5 – 25 presented normal weight, the values below 18.5 signified underweight, the values of 25-30 overweight and the values above 30 signified that the individuals are obese. The age and sex specified reference values of the BMI developed by the Centers for Disease Control and Prevention (CDC) were not used in the calculation of the BMI.

## 3. RESULTS

Demographically speaking, the samples of working and control group of 120 patients included 40 persons in the following three age categories: 20-40, 40-60 and above 60 years.

The average age of the **working group** amounted to 50.19 years with the standard deviation of 15.60. The basic descriptive characteristics of the age structure of the total working group sample are given in Table 1.

According to the age categories of the working group sample, descriptive characteristics are shown in the following manner (Table 2).

	N	Mean	Std. Deviation	Minimum	Maximum
20 to 40	40	31.5250	5.11402	21.00	40.00
40 to 60	40	52.2250	4.98967	41.00	59.00
Above 60	40	66.8250	6.78946	59.00	86.00
Total	120	50.1917	15.59966	21.00	86.00

Table 2. Demographic characteristics of the working group sample by the age categories.

N	Valid	120
	Missing	0
Mean	48.68	
Median	49.00	
Mode	23.00	
Std. Deviation	17.03	
Minimum	19.00	
Maximum	79.00	

Table 4. Demographic characteristics of the total sample of the control group

	N	Mean	Std. Deviation	Minimum	Maximum
20 to 40	40	28.9750	6.26953	19.00	38.00
40 to 60	40	49.3500	6.25751	40.00	59.00
above 60	40	67.7250	5.96566	59.00	79.00
Total	120	48.6833	17.02839	19.00	79.00

Table 5. Demographic characteristics of the control group sample by the age categories

Age group		Patients' sex		Total	
		Male	Female		
Age group	20 to 40	No.	21	19	40
		%	52.5%	47.5%	100.0%
	40 to 60	No.	15	25	40
		%	37.5%	62.5%	100.0%
	above 60	No.	12	28	40
		%	30.0%	70.0%	100.0%
Total	No.	48	72	120	
	%	40,0%	60.0%	100.0%	

Table 6. Sex structure of the total control group sample by the age categories.

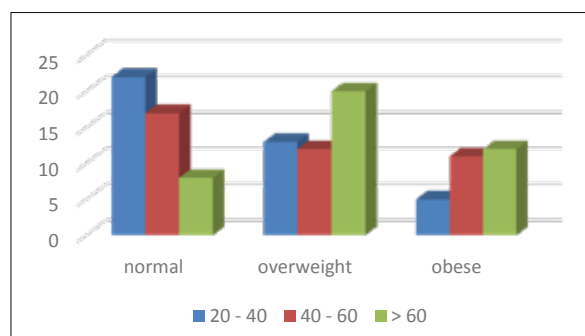


Figure 1. Overweight (expressed through the BMI) by age groups of the working group

Sex structure of the sample was not completely balanced, as the sample contained 52.2% men and 47.5% women (Table 3).

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	12.030	4	.017
Likelihood Ratio	12.798	4	.012
Linear-by-Linear Association	9.112	1	.003
N of Valid Cases	120		

Table 7. Chi-Square test (connection of the BMI and age group) of the working group.

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	2.205	2	.332
Likelihood Ratio	2.232	2	.328
Linear-by-Linear Association	1.972	1	.160
N of Valid Cases	120		

Table 8 – Chi-Svadrat test (connection of the BMI and sex) of the working group

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	16.135	6	0.013
Likelihood Ratio	17.118	6	0.009
Linear-by-Linear Association	9.918	1	0.002
N of Valid Cases	120		

Table 9. Chi-Square test (connection of the BMI and age group) of the control group.

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	5.780 <sup>a</sup>	3	.123
Likelihood Ratio	6.328	3	.097
Linear-by-Linear Association	1.915	1	.166
N of Valid Cases	120		

Table 10. Chi-Square test (connection of the BMI and sex) of the control group.

The average age of the **control group** amounted to 48.68 years with the standard deviation of 17.03. The basic descriptive characteristics of the total sample of the control group are given in Table 4.

According to the age categories of the working group sample, descriptive characteristics are shown in the following manner (Table 5).

Sex structure of the sample of the control group was not completely balanced, as the sample included 40% men and 60% women (Table 6).

Having analyzed the BMI category per age group of the **working group**, the trial showed that with the youngest age category there was the smallest share of overweight and obese patients (Figure 1). In the total sample of the working group there were no underweight patients.

Analysis of the BMI **according to age categories of the working group** has showed that there is statistical dependency between the BMI and age group. Table 7 shows that the differences were statistically significant

	Group name	Number	Average	Standard deviation	Standard error
BMI	Working	40	24.8993	3.55042	.56137
	Control	40	23.5347	3.16431	.50032

Table 11. – Arithmetic mean of the BMI in the age group of 20-40 years of the working and control group.

	Group name	Number	Average	Standard deviation	Standard error
BMI	Working	40	27.1675	4.70839	.74446
	Control	40	27.3153	3.23616	.51168

Table 12. – Arithmetic mean of the BMI in the age group of 40-60 of the working and control group.

	Group name	Number	Average	Standard deviation	Standard error
BMI	Working	40	28.2250	3.35305	0.53016
	Control	40	30.2570	3.77271	0.59652

Table 13. – Arithmetic mean of the age group >60 years of the working and control group.

	Group name	Number	Average	Standard deviation	Standard error
BMI	Working	120	26.7639	4.12582	.37663
	Control	120	27.0357	4.36035	.39804

Table 14. – Arithmetic mean BMI on the total sample of working and control group.

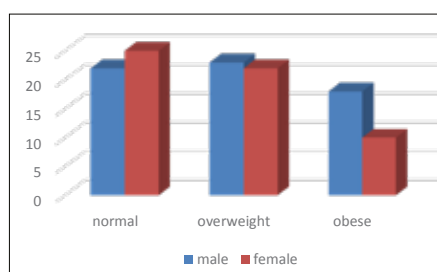


Figure 2 – Structure of patients of the working group by sex in terms of overweight

( $p < 0.05$ ) ( $p$ -values are in the last column).

On the other side, the value of the BMI working group was not related to sex, that is, the differences that occurred (men got worse results) are not statistically significant, which was confirmed by the Chi-Square test ( $p > 0.05$ ). This is shown by Figure 2 and Table 8.

In the **control group** of patients, as well as in the working group, there is a connection between overweight and age group, but not between the overweight and patients' sex. The following Figure 3 shows the structure of the patients' control group according to the BMI categories in relation to the age group. It is clearly seen that in the youngest age group, there is a smaller share of the overweight in relation to the older groups. Table 9 shows that differences

in percentages (%) of the BMI per age structures of the control group are statistically highly significant ( $p < 0.01$ ). In the total control group sample, there was one underweight patient.

Values of the BMI control group were not connected to sex, that is, the differences that existed are not statistically significant, which is confirmed by the Chi-Square test ( $p > 0.05$ ). This is shown by Figure 4 and Table 10. It is noted that in each of these categories, from the point of view of being overweight, there is a bigger number of women, which is the result of domination of this sex in the control group sample.

Analyzing the values of the BMI in terms of age groups, where in the working group there was a statistically significant difference, whereas the control group had a statistically highly significant difference, **testing of the statistical significance of the average BMI value was done by the observed age groups of working and control group, as well as in the total sample of the working and control group using the Chi-Square test and T-test for independent samples** (Tables 11, 12, 13, 14 and 15). Having observed the age group 20-40 years, statistically significant differences were observed at the level of risk of 10%, which implies that there is a connection between the categories of the BMI and the group, which the patient comes from (Chi-Square test

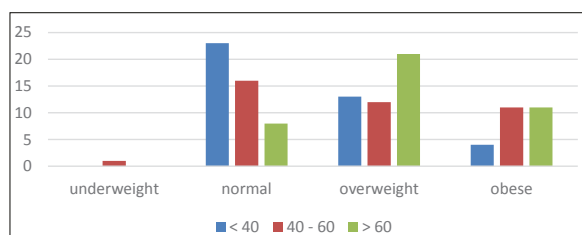


Figure 3. Overweight (expressed through the BMI) by age groups of the control group

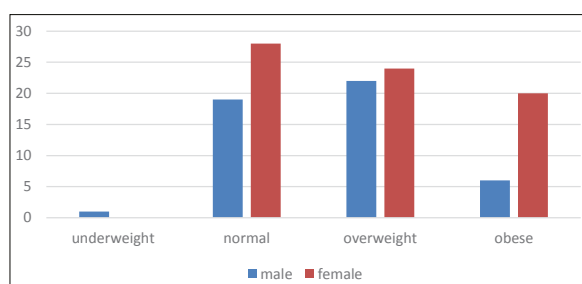


Figure 4. Structure of the control group patients by sex in terms of being overweight



	Chi-Square test (CORRELATION BETWEEN PHENOMENA)			T - test (EQUALITY OF ARITHMETIC MEAN)		
	Value	P	Conclusion	Value	P	Conclusion
20 – 40	6.008	0.050	0.05<p<0.10	1.815	0.073	0.05<p<0.10
40 – 60	3.554	0.314	p>0.05	-0.164	0.871	p>0.05
60 +	3.583	0.167	p>0.05	-2.546	0.013	p<0.05
Total	1.208	0.751	p>0.05	-0.496	0.620	p>0.05

Table 15 – Testing of the statistical significance using the Chi-Square test and T-test for independent samples

p<0.05) and T-test have shown that the values are different at the level of 10%, i.e.  $p<0.1$  ( $p=0.073$ ). Specifically, the difference between the average BMI values (working 24.9 and control 23.5) is not significant with a general reliability of 95% (risk of 5%), but it is significant with a somewhat higher risk degree. When observed for the age group of 40-60, there was no dependency between the category of the BMI and the group, that is, the differences are not statistically significant,  $p>0.05$  (Chi-Square test  $p=0.314$ ). In addition to this, the average values of the BMI are not statistically different,  $p>0.05$  (t-test  $p=0.871$ ). Having observed the age group of older than 60 years old, there was no dependency between the category of the BMI and the group, that is, the differences are not statistically different,  $p>0.05$  (Chi-Square test  $p=0.167$ ). Results of the T-test have shown that there is a significantly higher average value of the BMI in the control group, when compared to the working group of  $p<0.05$  ( $p=0.013$ ). When observed at the total sample of the working and control group, there was no dependency of the category of the BMI and the group (or urolithiasis),  $p>0.05$  (Chi-Square test  $p=1.208$ ) and the results of the T-test have showed that there was no statistically significant difference of the arithmetic mean values of the BMI of the working and control group,  $p>0.05$  (t-test  $p=0.620$ )

#### 4. DISCUSSION

Numerous epidemiological studies have shown that there is an evident growth of the urolithiasis together with the increase of the BMI. It is known that the metabolic changes in the sense of "morbid overweight" lead to an increase of the risk of occurrence of urolithiasis. With an increase of the BMI, the patients get into a soft metabolic acidosis, which results with an increase of

acid excretion (decline of pH of urine) and decline of citrate excretion, a significant increase of urinary excretion of calcium and uric acid, which may lead to the occurrence of the calcium and uric acid stones (10, 14, 15, 16). Other studies have also shown that the metabolic syndrome has been associated with an increased risk of occurrence of uric and calcium stones, due to lower values of pH urine and increase of acid uric excretion, which is a cause of occurrence of uric acid stone, as well as decrease of citrate excretion and increase of excretion of acid uric and calcium, which leads to occurrence of calcium stones (10). Metabolic syndrome, which has been defined by existence of increased BMI, hypertension, insulin resistance and dislipidemia, in any case, shows more abnormality which are in correlation with increased risk of occurrence of urolithiasis. Dr Dean Assimos, at AUA Annual Meeting in 2011, presented in detail the way of metabolic syndrome and concluded that diabetes, hypertension, coronary artery disease and increased BMI have been associated with an increased risk of occurrence of kidney stones (17). The correlation between overweight and kidney stones has been documented for both adult as well as pediatric population. It is completely clearly defined what the overweight patients should do in the sense of decreasing the risk of occurrence of kidney stones. First, the bodily weight should be reduced, as much as possible, as with a significant loss of surplus kilograms the risk of occurrence of urolithiasis will decrease. Second, with or without reduction of the bodily weight, there are also steps that could lead to decrease of the risk for occurrence of the kidney stones. Namely, adequate intake of liquid is necessary to provide adequate dilution of urine, supplementation of citrate, as an inhibitor

of occurrence of the calcium lithiasis, decreased level of proteins, in order to decrease acidosis they lead to, as well as decreased intake of salts, which may also decrease the calcium excretion.

The results of our study have shown that, by the usage of Chi-Square test and T-test for independent samples, that there was a connection between the overweight and age group, in the sense that the overweight was statistically significantly more present in the older age sub-groups of both groups of the patients, with and without urolithiasis, as well as that there was no dependence between overweight and patients sex. The results of our study have shown that in the age group (20-40 years) there was a statistically significant difference at the risk level of 10%, which says that there was a correlation between the categories of the BMI and the group from which the patient comes (Chi-Square test,  $p<0.05$ ) and T-test have shown that the values are different at the level of 10%, i.e.  $p<0.1$  ( $p=0.073$ ). Specifically, the difference between the average values of the BMI (working 24.9 and control 23.5) was not significant with an usual reliability of 95% (5% risk), but it has been significant with a big higher degree of risk. When observed at the total level of the working and control group, there was no dependence of the BMI category and group (or urolithiasis),  $p>0.05$  (Chi-Square test  $p=1.208$ ), and the results of T-test have shown that there was no statistically significant difference of arithmetic mean values of the BMI of working and control group,  $p>0.05$  (T-test  $p=0.620$ ). There were no statistically significant differences at the level of older age sub-groups (40-60 years, >60g). Partial deviation of the results of our study, from the results of other authors who have unambiguously shown the correlation of overweight as a part of metabolic syndrome with the occurrence of kidney lithiasis, may be caused by the fact that the sample of our research, from the point of view of overweight would contain a much lower number of overweight patients ( $BMI>30$ ) in relation to the remaining number of patients in the sample from the point of view of other categories of the BMI ( $BMI>30$ ), with a conclusion that, still, in the age group



of 20-40 years of age, there was correlation of overweight with urolithiasis.

## 5. CONCLUSION

Overweight in the younger age group of adult population may be connected to the occurrence of calcium nephrolithiasis, which is why we suggest that the urolithiasis should be considered with the same ones as a part of overweight, by which the change of living habits and manner of nutrition could prevent this disease.

**CONFLICT OF INTEREST: NONE DECLARED**

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## ORIGINAL PAPER

# Cervical Syndrome – the Effectiveness of Physical Therapy Interventions

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**Introduction:** The cervical syndrome refers to a set of disorders caused by the changes in the cervical spine and the soft-tissue surrounding it, with pain as the predominant symptom. Sore neck has been a common problem among a large section of today's population. The factors contributing to this issue include the modern lifestyle, prolonged sitting and incorrect, fixed or constrained working postures. The root of these difficulties is found in the mechanical disorders of the cervical spine structures, poor body posture and jerky body movements. In the Scandinavian countries neck pain is considered to be a public health problem. **Methods:** The study evaluated 25 patients with an established diagnosis of cervical syndrome. The research was conducted at the PI Institute of Occupational and Sports Medicine of Zenica–Doboj Canton. Each patient received twenty physical therapy treatment sessions. **Results and conclusions:** The study included 25 patients suffering from the cervical syndrome. The statistical analysis of gender distribution indicated that 36% of the patients were male, while 64% were female. The mean age of study participants was 46.76±4.23. The patients ranged in age from 39 to 54 years, with no statistically significant difference in the mean age of male and female patients,  $p=0.691$ . Analysing the types of occupational activities performed by the patients, the study found a positive relation between neck pain and prolonged sitting at work. The patients who performed office work made up 76% of the total number. Each method of physical therapy applied in the treatment of neck pain patients proved useful. However, the combination of electrotherapy, kinesiotherapy and manual massage proved to be most effective. **Conclusion:** The cervical syndrome is a common medical condition primarily affecting adult population, with prevalence being higher among women and office workers. The condition places a considerable socioeconomic burden on the afflicted. Cervical pain ranges greatly in severity – from moderate to unbearable, thus leading to high levels of work absence as well as to a decrease in the quality of life. Proper physical therapy program can help the patients with neck pain return to their normal everyday activities, improve their quality of life, as well as reduce the absence from work. **Key words:** cervical syndrome, physical therapy, neck pain (NP)

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## 1. INTRODUCTION

The cervical syndrome refers to a set of disorders caused by the changes in the cervical spine and the soft-tissue surrounding it, with pain as the predominant symptom. Sore neck has been a common problem among a large section of today's population. The factors contributing to this issue include the

modern lifestyle, prolonged sitting and incorrect, fixed or constrained working postures. The root of these difficulties is found in the mechanical disorders of the cervical spine structures, poor body posture and jerky body movements.

In the Scandinavian countries neck pain is considered to be a public health problem. In the 1-year study Fejer and

et al. reported the Scandinavian countries to have more neck pain patients than the rest of Europe and Asia. Also, women reported more neck pain than men. (1)

Two thirds of the world population experience NP (neck pain) at some point during lifetime, the highest prevalence being among the middle-aged. (2) NP is a common symptom affecting the western countries. According to the research conducted in Canada, approximately 67% of adults have experienced NP during their lifetime. (3) The survey of Takala and al. estimated lifetime prevalence of NP at 18% for women and

16% for men, while 10% of all patients had pain radiating from neck to the upper extremities. (4) The Mini Finland Health Survey, conducted on a population sample of 8000 Finns aged 30 or more, reported chronic neck syndrome in 9,5% of the men and 13,5% of the women (5). In recent years, a significant body of research has proved a high prevalence of NP among adolescents – ranging between 20 and 60% in the developed countries, which is associated with the advance of technology and reduced activity. (6)

The most common causes of NP are the degenerative changes within the cervical spine, occurring in even 90% of the cases. The degenerative changes develop in the intervertebral joints, costovertebral joints, uncovertebral joints and intervertebral discs, the disc herniation. (7) The annual incidence of

cervical disc herniations is estimated at 5.5 per 100.000 population, occurring most frequently between the ages of 45 and 54 years (according to Kondo et al.) (4) Apart from the degenerative processes, NP can result from a variety of causes, including trauma (fractures, contusions, distortions and ligament tears), inflammatory processes (rheumatoid and infective), as well as metabolic changes, and tumors. (7)

The main symptom is pain. Cervical spine pain can radiate to the shoulder, down one or both arms and to the back. The sensation of soreness comprises increased muscle tension in the back of the neck, palpable neck stiffness, reduced neck movement and vegetative disturbances in the region of the head and the upper extremities (ear buzzing, blurred vision, headache, dizziness, fatigue). (8) NP disorders affect both physical and psychological function and can have negative impact on everyday life activities in terms of limiting functional mobility, thus reducing the quality of life. (3)

The NP syndrom represents a frequently occurring problem today, and is greatly related to the modern lifestyle. Namely, the number of people who maintain prolonged sitting positions either at home (watching TV) or at work (sitting at a computer desk) has grossly increased. The excessive and incorrect loading of the spine leads to poor posture. (9, 10) Due to the forced work-related body posture, the cervical spine (as well as the neck and the shoulder muscles) undergoes great stress. Many studies have confirmed the relation between neck/arm pain and inadequate work-related body posture. (11, 12)

## 2. OBJECTIVE

The purpose of this study is to demonstrate the gender and age distribution of patients with cervical syndrome, their daily work-related activities, and to report assessment of pain before and after physical treatment. An additional aim is identify the physical therapy method that offers the most effective pain relief.

## 3. METHODS

The study evaluated 25 patients with an established diagnosis of cervical syn-

	Frequency	Percent	Valid Percent	Cumulative Percent
Male	9	36.0	36.0	36.0
Female	16	64.0	64.0	100.0
Total	25	100.0	100.0	

Table 1. Gender Distribution

Age	N	Mean	SD	SEM	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Male	9	47.22	4.65	1.55	43.64	50.80	39.00	54.00
Female	16	46.50	4.11	1.02	44.30	48.69	40.00	54.00
Total	25	46.76	4.23	0.84	45.01	48.50	39.00	54.00

Table 2. Age Distribution

drome. The research was conducted at the PI *Institute of Occupational and Sports Medicine* of Zenica–Doboj Canton. Each patient received twenty physical therapy treatment sessions. The examiners assessed the degree of pain before and after the treatment. Pain intensity was measured using the visual analogue scale (VAS), with eleven categories, ranging from 0 – 10, where 0 represents – no pain, 1, 2, 3 points – mild pain, 4, 5, 6 points – moderate pain, 7, 8, 9 points – severe pain, and 10 points – worst possible pain. Pain assessment was conducted on the 1<sup>st</sup> and the 20<sup>th</sup> day of the treatment. A detailed and accurate medical history was recorded, including basic patient information. After the collection of the data a statistical analysis was performed, with the results presented in tables and graphs. The level of significance was  $p < 0.05$ . The ANOVA test was employed.

## 4. RESULTS

The study included 25 patients suffering from the cervical syndrome – 9 (36%) men and 16 (64%) women. The descriptive data demonstrates the prevalence of women patients, giving the male:female frequency ratio of 1:1.77.

Age distribution analysis revealed the mean age of the patients included in the study to be  $46.76 \pm 4.23$  years. The mean age of the male participants was  $47.22 \pm 4.65$  years, while that of

the female participants was  $46.50 \pm 4.11$  years. The ANOVA test demonstrated no particularly significant statistical difference to be present in the mean age of the patients in relation to

gender,  $F=0.162$ ;  $df=1$ ;  $p=0.691$ .

Most patients included in the study had been performing office-related jobs – 19 (76%), while 6 (24%) of the patients had been involved in physical type of work. The chi-square test revealed a significant statistical difference in the frequency of the type of work the pa-

	Frequency	Percent	Valid Percent	Cumulative Percent
Office work	19	76.0	76.0	76.0
Physical work	6	24.0	24.0	100.0
Total	25	100.0	100.0	

Table 3. Types of occupational activities performed by the patients participating in the study

Pain	Frequency	Percent	Valid Percent	Cumulative Percent
Mild	4	16.0	16.0	16.0
Moderate	6	24.0	24.0	40.0
Severe	13	52.0	52.0	92.0
Worst possible	2	8.0	8.0	100.0
Total	25	100.0	100.0	

Table 4. Patient groups according to the intensity of NP

	Frequency	Percent	Valid Percent	Cumulative Percent
Acute phase	22	88.0	88.0	88.0
Chronic phase	3	12.0	12.0	100.0
Total	25	100.0	100.0	

Table 5. Phases of the condition at baseline

Pain	Frequency	Percent	Valid Percent	Cumulative Percent
Electrotherapy	16	64.0	64.0	64.0
Kinesiotherapy	5	20.0	20.0	84.0
Manual massage	4	16.0	16.0	100.0
Total	25	100.0	100.0	

Table 6. Physical therapy methods for the treatment of patients with cervical syndrome

tients performed, with those involved in office-related activities representing the larger group,  $\chi^2=6.760$ ;  $df=1$ ;  $p=0.009$ .

Overall, mild neck pain was experienced by 4 (16%), moderate pain by 6 (24%), and worst possible pain by 2 (8%) patients. Severe pain affected the largest group – 13 (52%) patients. There was a significant statistical difference in the frequency of patients regarding the degree of pain, with the predominance of those afflicted by severe pain. The findings were confirmed by the chi-square test,  $\chi^2=11.00$ ;  $df=1$ ;  $p=0.012$ .

Table 5 represents the analysis of the phases of the condition at baseline. Most patients were in the acute phase of the condition 22 (88%), while only 3 (12%) of them were in the chronic phase of it.

Electrotherapy, the commonly used physical therapy method for the treatment of patients with cervical syndrome, was employed for 16 (64%) patients; 5 (20%) patients performed kinesiotherapy, while manual massage was applied with 4 (16%) patients.

## 5. DISCUSSION

The cervical syndrome is a common medical problem today, affecting women more than men of the same age.

This study included 25 patients. According to the statistical analysis of gender distribution, 36% of the patients were male, and 64% were female.

The study conducted in the USA in 2004 involved 537 patients with neck pain – 42% were man and 58% were women. (8) Another study was carried out in Salt Lake City in 2007, including 274 neck pain patients – 74% women and 26% men. (13) Anderson's study, encompassing 990 patients, also had more women than men – 570 women versus 420 men. (14)

The mean age of the patients included in this study was  $46.76 \pm 4.23$  years. The patients ranged in age from 39 to 54 years. Also, there was no statistically significant difference in the mean age of male and female patients,  $p=0.691$ .



Graph 1. Average pain intensity score before and after the treatment depending on the type of physical therapy intervention

In the study conducted in the USA by Xuemei L. et al., the mean age of the neck pain patients was 54.15 years. (8) In his study that included 990 patients with neck pain, Anderson reported the mean age of the female patients to be 44 years, while the mean age of the male patients was 49 years. (14) Although neck pain affects both younger and older population groups, most studies show greater frequency among people aged 35 to 49, which matches the results of this study. (15)

Analyzing the types of occupational activities performed by the patients, this study found a positive relation between neck pain and prolonged sitting at work. The patients who performed office work made up 76% of the total number.

Ariëns et al. have reported an increased risk of developing neck pain in workers who sit for more than 95% of the working time compared to those who rarely sit at work. (16)

The cervical syndrome may progress from acute to subacute and chronic stages. In the acute phase, the pain may be present from a couple of days to a couple of weeks. If the pain lingers for a few weeks or longer, it is considered to be chronic (affecting around 10% of the patients). (2)

A detailed analysis of the clinical phase of the condition revealed that 88% of the neck pain patients participating in this study were in the acute stage while 12% were in the chronic stage. Assessing the posttherapeutic effects of certain physical treatments on the patients' functional status, a statistical conclusion on the electrotherapy being the most effective method in improving the NP patients' functional status was drawn. Each method of physical therapy applied in the treatment of

NP patients proved useful. However, the combination of electrotherapy, kinesiotherapy and manual massage proved to be most effective.

Ivanković Prokić assessed the effectiveness of physical therapy interventions for cervical syndrome in a study including a group of 31 patients. The study tracked pain intensity measured with a VAS and the cervical spine movement, from baseline to end of therapy. The physical therapy procedures employed in the treatment were ultrasound (93,54% patients), DDC (70,69%), TENS (32,25%), IFC (22,58%), GC (22,58%), Novocaine electrophoresis (9,67%) and magnetotherapy (6,45%). The results that were based on the VAS scoring system and the increase in the cervical spine range of motion demonstrated a significant improvement in the group, hence confirming the significant clinical effectiveness of physical therapy in the treatment of neck pain, which matches the outcome of this study. (17)

## 6. CONCLUSION

The cervical syndrome is a common medical condition primarily affecting adult population, with prevalence being higher among women and office workers. The condition places a considerable socioeconomic burden on the afflicted. Cervical pain ranges greatly in severity – from moderate to unbearable, thus leading to high levels of work absence as well as to a decrease in the quality of life. Proper physical therapy program can help the patients with neck pain return to their normal everyday activities, improve their quality of life, as well as reduce the absence from work.

CONFLICT OF INTEREST: NONE DECLARED

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## ORIGINAL PAPER

# Clinical Characteristics of Aerobic Vaginitis and Its Association to Vaginal Candidiasis, trichomonas Vaginitis and Bacterial Vaginosis

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**Aim of the work:** Examine clinical characteristics of aerobic vaginitis and mixed infection for the purpose of better diagnostic accuracy and treatment efficiency. **Materials and methods:** Prospective research has been conducted at Clinic for Gynecology and Obstetricity, Department for microbiology and pathology at Polyclinic for laboratory diagnostic and Gynecology and Obstetricity Department at Health Center Sapna. Examination included 100 examinees with the signs of vaginitis. Examination consisted of: anamnesis, clinical, gynecological and microbiological examination of vaginal smear. **Results:** The average age of the examinees was 32,62±2,6. Examining vaginal smears of the examinees with signs of vaginitis in 96% (N-96) different microorganisms have been isolated, while in 4% (N-4) findings were normal. AV has been found in 51% (N-51) of the examinees, *Candida albicans* in 17% (N-17), BV in 15% (N-15), *Trichomonas vaginalis* in 13% (N-13). In 21% (N-21) AV was diagnosed alone while associated with other agents in 30% (N-30). Most common causes of AV are *E. coli* (N-55) and *E. faecalis* (N-52). AV and *Candida albicans* have been found in (13/30, 43%), *Trichomonas vaginalis* in (9/30, 30%) and BV (8/30, 26%). Vaginal secretion is in 70,05% (N-36) yellow coloured, red vagina wall is recorded in 31,13% (N-16) and pruritus in 72,54% (N-37). Increased pH value of vagina is in 94,10% (N-48). The average pH value of vaginal environment was 5,15±0,54 and in associated presence of AV and VVC, TV and BV was 5,29±0,56 which is higher value considering presence of AV alone but that is not statistically significant difference ( $p>0,05$ ). Amino-odor test was positive in 29,94% (N-15) of associated infections. Lactobacilli are absent, while leukocytes are increased in 100% (N-51) of the examinees with AV. **Conclusion:** AV is vaginal infection similar to other vaginal infections. It is important to be careful while diagnosing because the treatment of AV differentiates from treatment of other vaginitis. **Key words:** Aerobic vaginitis, vaginal infections, diagnosis.

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## 1. INTRODUCTION

Ecosystem of vagina is a complex and dynamic system of flora of various microorganisms in different quantity and ratio. Clinical future and treatment of some of the vaginitis, such as trichomonas vaginitis (TV), vulvovaginal candidiasis (VVC) and bacterial

vaginosis (BV) are well defined, while other abnormal vaginal conditions are yet to be defined. In 2002, Donders and ass. (1) suggested term aerobic vaginitis (AV) based on bacteriological, immunological and clinical characteristics. This study has been conducted for better understanding of frequency and clinical

characteristics of AV, where symptoms, signs and laboratory tests (pH and amino-odor test) have been analyzed in patients diagnosed with one or mixed infections. These results should help in clinical determination of the causes for vaginal symptoms and more accurate diagnosis and treatment of AV.

## 2. AIM OF THE WORK

Examine clinical characteristics of aerobic vaginitis and mixed infection for the purpose of better diagnostic accuracy and treatment efficiency.

## 3. MATERIALS AND METHODS

Prospective research has been conducted at Clinic for Gynecology and Obstetricity, Department for microbiology and pathology at Polyclinic for laboratory diagnostic and Gynecology and Obstetricity Department at Health Center Sapna in period from May 2007 till January 2008. The study included 100 examinees aged 18 to 45.

The examinees with clinical signs of vaginitis had some of the stated symptoms (increased vaginal secretion, changed colour of secretion, changed colour of vaginal walls, subjective problems, changed pH value of vaginal environment and positive amino-odor test).

Examination programme consisted of three parts:

- taking anamnesis data (interview)
- clinical gynecological examination
- microbiological examination of vaginal and cervical smear

Interview consisted of the following data: age of the examinee, marital status, number of deliveries, number of miscarriages and symptoms which indicated presence or absence of vaginitis.

Gynecological examination was performed by gynecologist in gynecological clinic. Gynecological examination was performed with speculum and bimanually. Speculum examination showed clinical characteristics of vaginal wall: redness, presence of vaginal secretion and change in its quality. Presence of 3 or more clinical characteristics are considered to be positive for diagnosis of vaginitis.

Gynecological examination also determined pH value of vaginal environment in all of the examinees. Determination of pH value of vaginal environment was performed with indicator tape with span from 0 to 14. Colour indicator tape was put on lateral arch of vagina and results showed on the tape within 30-60 seconds. pH value above 4,0 was considered significant in vaginitis diagnosis. After determining pH value of vaginal environment, all the examinees had amino-odor test. Test included putting vaginal secretion on the glass and pouring 2-3 drops of 10% KOH. Release of fish-like smell was recorded as positive result. After that, vaginal and cervical smears were taken for microbiological analysis of aerobic and anaerobic microorganisms and antibiogram. Smear that was taken for the microbiological analysis has been examined with standard microbiological methods: examination of the preparation coloured by Gram and cultivated on standard microbiological bases such as blood and endo agar and identification of increase with biochemical methods. Examination to resistance has been done by disc-diffuse method on Müller-Hinton base.

Analysis of vaginal flora was performed under the microscope with 400 times magnification where presence and absence of lactobacilli, change

of flora considering presence of coccus bacterial flora or short curved sticks and combinations, presence of clue cells and presence of parasites and fungi were recorded. Leukocyte finding was graded by number of leukocytes found under the 400 times magnification in the field of view: result with less than 10 leukocytes in the field of view and result with more than 10 leukocytes in the field of view.

BV is defined with findings that have 3 out of 4 possible criterion: liquid homogenous grey secretion, presence of clue cells, pH value higher than 4,0 and positive aminoodor test.

AV was determined based on criterion by Donders: enhanced yellow secretion, pH value  $\geq 5$ , negative aminoodor test, increased number of leukocytes  $>10$ , absence of lactobacilli and microbologically isolated microorganisms: *Escherichia coli* (*E. coli*), *Staphylococcus aureus*, group B streptococcus and enterococci.

Findings were processed by methods of descriptive statistics, student t-test,  $X^2$  test. Differences for values  $p < 0,05$  were considered statistically significant and differences for values  $p < 0,01$  statistically highly significant.

#### 4. RESULTS

The examined group of women N-100 were in reproductive period with average age of  $32,62 \pm 2,6$ , and married in 85% (N-85). Examining vaginal smears of the examinees with signs of vaginitis in 96% (N-96) different microorganisms which belong to aerobic and anaerobic bacteria, protozoa and fungi have been isolated, while in 4% (N-4) findings were normal. AV has been found in 51% (N-51) of the examinees, *Candida albicans* in 17% (N-17), BV in 15% (N-15), *Trichomonas vaginalis* in 13% (N-13) and 4% (N-4) of the examinees didn't have microbiological cause of vaginitis.

Characteristics	Value
Age	32,62±2,6a
Married (N)	85
Single(N)	15
Number of deliveries	3,53±0,5a
Number of miscarriages	2,40±0,2a

Table 1. Characteristics of the examinees with the signs of vaginitis. Legend: a-arithmetic mean + standard tolerance

Characteristics of vaginal secretion	AV (N-51)	AV+TV+BV (N-30)	%
<b>Colour</b>			
Yellow	16	20	70,05
White	2	5	13,72
Grey white	1	3	7,84
Green	2	2	7,84
<b>Consistency</b>			
Rare	7	13	40,38
Thick	14	17	61,53
<b>Smell</b>			
Unpleasant	2	13	29,94
Without smell	19	17	70,58
<b>Colour of vagina wall</b>			
Red	7	9	31,13
Normal	18	17	68,62
<b>Pruritis</b>			
Present	15	20	72,54
Absent	4	10	27,45
<b>pH value of vaginal environment</b>			
4	1	2	5,88
5	13	24	72,54
6	7	4	21,56
<b>Amino-odor test</b>			
Positive	1	15	29,94
Negative	20	15	68,62

Table 2. Traits of vaginal secretion, clinical and biochemical characteristics of the examinees with signs of AV

In 21% (N-21) of the examinees AV was diagnosed alone while associated with other agents in 30% (N-30). Most common causes of AV are *E. coli* (N-55) and *E. faecalis* (N-52). AV and *Candida albicans* have been found in (13/30, 43%), *Trichomonas vaginalis* in (9/30, 30%) and BV (8/30, 26%). Examining clinical characteristics of AV and associated infections of AV and VVC, TV and BV, enhanced secretion has been recorded in 100% (N-51) of the examinees with different characteristics of vaginal secretion (Table 1.) Vaginal secretion is in 70,05% (N-36) yellow co-

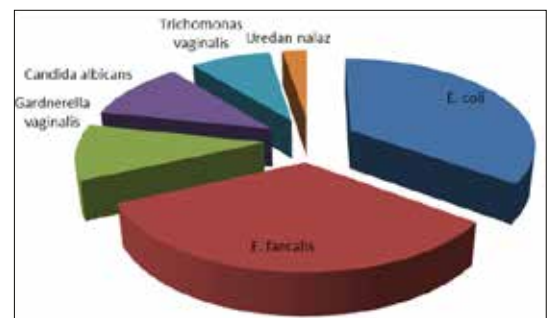


Figure 1. Results of microbiological examination of the examinees with signs of vaginitis

loured, secretion of thick consistency is in 61,53% (N-31) and changed smell of secretion is in 29,94% (N-15) of the examinees with AV. Colour of vagina wall changed into red is recorded in 31,13% (N-16) and pruritis or itching in genital area had 72,54% (N-37) of the examinees with AV. Increased pH value of vagina has been found in 94,10% (N-48) and normal in 5,88% (N-3). pH value 5 in 72,54% (N-37) and pH value 6 in 21,56% (N-11).

Most of the examinees had pH value 5. The average pH value of vaginal environment in the examinees with AV was  $5,15 \pm 0,54$  and in associated presence of AV and VVC, TV and BV was  $5,29 \pm 0,56$  which is higher value considering presence of AV alone but that is not statistically significant difference ( $p > 0,05$ ). Amino-odor test was negative in the examinees with AV, while with associated infections it was positive in 29,94% (N-15). Microbiological examination hasn't recorded presence of lactobacilli in vaginal secretion while leukocytes have been elevated in all of the examinees with AV in 100% (N-51).

## 5. DISCUSSION

In 1990 Helen McDonald warned that women with the risk of preterm labor had two types of abnormal vaginal secretion, first is BV and second are other aerobic microorganisms such as E.coli and Klebsiella (2,3). In 80-90% of cases enhanced vaginal secretion is associated with microbiological cause which can be identified and most of the vaginal infections are consequence of the infection with synergistic bacteria (bacterial vaginosis and nonspecific vaginitis), fungi (vulvovaginal candidiasis) and protozoa (trichomoniasis). It is considered that approximately 50% of infections are caused by bacteria and 50% by fungi and parasite (4). In this research aerobic bacteria play significant role in ethiology of vaginitis and they are often associated with two or more causes which indicates to polymicrobe ethiology of vaginitis (5). AV has been found in 51% (N-51), alone in 21% (N-21) and associated in 30% (N-30). It is most commonly associated with *Candida albicans* in (13/30, 43%), *Trichomonas vaginalis* in (9/30, 30%) and BV in (8/30, 26%). In similar studies of AV Fan founds AV as the main cause of vag-

initis in one study in 14,7% and in other in 23,74%. In 58% AV is mixed with another causes such as VVC in 30%, TV in 25% and BV in 45% (6,7). Percentage of representation of AV in our research is higher in relation to the quoted one but the percentage of association with other types is the same. Although many studies state that the frequency of AV is still unknown (8), the frequency in pregnant women is in 25%. AV is mostly caused by E.coli and E.faecalis while other causes haven't been found in this research, although Donders states that causes of AV are: E. coli, enterococi, *Staphylococcus* sp. and group B of streptococcus (9). E.coli is cited as one of the most common causes of this vaginitis and sometimes is isolated alone. The role of E.coli in vaginitis is very controversial and this microorganism is one of the main causes of neonatal sepsis and chorioamnionitis (10). Enhanced and changed vaginal secretion has been found in all of the examinees with AV, that is with yellow coloured secretion in 70,05% (N-36) which is similar to Fan research who found yellow vaginal secretion in 63% of the examinees with AV. Thick consistence of secretion was in 61,53% (N-31). Red colour of vagina walls has been recorded in 31,13% (N-16) and pruritus or itching in 72,54% (N-37) of the examinees with AV. Elevated pH value of vaginal environment has been found in 94,10% (N-48), while in similar study pH higher than 4,5 has been found in 84% of the examinees with AV (10). The absence of lactobacilli (11) is a characteristic of AV and in this study lactobacilli haven't been found in the examinees with AV. Donders also, in several of his studies, records abnormal status of lactobacilli, that is, their absence, which is a negative factor and enables development of infection, especially in pregnancy (11, 12, 13, 14, 15). Enhanced number of leukocytes has been found in 100% (N-51) of the examinees. The other studies also confirm abnormal vaginal flora in women with the risk for preterm labor and presence of E.coli with or without signs of inflammation and increased number of leukocytes in secretion (16, 17, 18). AV is frequent infection of lower genital system and it doesn't differentiate from other vaginal infections by its clinical characteristics. In high percentage it is as-

sociated with other infections. It is very important to pay attention to presence of AV as mixed infection or special entity when diagnosing vaginitis, especially in pregnancy. Therapeutic treatment of AV differentiates from other types of vaginitis and wrong diagnose can lead to wrong treatment and complications.

CONFLICT OF INTEREST: NONE DECLARED

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## ORIGINAL PAPER

# Air Pollution in Pristina, Influence on Cardiovascular Hospital Morbidity

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**Introduction:** Numerous studies have been observed health effects of particulate air pollution. Ambient air quality is particularly bad in Pristina. The principal sources of contaminants are sulfur dioxide (SO<sub>2</sub>), nitrogen oxides NO and NO<sub>2</sub> (NO<sub>x</sub>), ozone (O<sub>3</sub>), lead (Pb), carbon dioxide (CO<sub>2</sub>), particulate matter (PM or dust). **Objective:** to investigate effects of concentrations of pollutants in ambient air on hospital admissions for cardiovascular disease in UCCK- Pristina. **Methods:** Retrospective ecological study. During the three year analytical research predict the potential benefit of decreasing for concentration of PM<sub>2.5</sub>, PM<sub>10</sub> were measured in two station in Pristina. The study population consisted of all hospitalization patient in intern clinic for 2010, 2011 and 2012 year. Air pollution measurements will be used by KHMI data for the year of 2010, 2011 and 2012 for the municipality of Pristina in the measurements point in: KHMI-MESP which is equipped with automatic analyzer- Air Compact Monitoring System (Version 2.2) recordum MESSTECHNIK GmbH. Statistical data processing will be done with SPSS 17.0 statistical package. **Results:** Based on the results obtained during the study period concentrated PM are higher level than standards value. The results showed that the number of hospital admissions for cardiovascular disease are positively correlated with concentration pollutants. Results show clear seasonal variation in the effects of PM on hospital admissions in Kosovo. The study period was short but the mean daily admissions for cardiovascular illnesses were quite large. **Conclusion:** The main source for these air pollutant was coal-burned power plant and traffic (old vehicles) in Kosovo. **Key word;** hospital admissions, cardiovascular disease, air pollution, airborne particle

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## 1. INTRODUCTION

Kosovo is a mountains farm region which at past was in the process of industrialization, because of its reach coal and mineral resource.<sup>1</sup>

Pristina is located at the geographical coordinates 42° 40' 0" North and 21° 10' 0" East and covers 572 square kilometers. The population of Pristina: 550,000 people.<sup>2</sup>

The major contributors to air pollution in Pristina are:

- The largest air polluting source is the coal-burned power plant in Obiliq 5 km near Pristina.
- Air pollution such as CO<sub>2</sub>, SO<sub>2</sub>, NO<sub>2</sub>, O<sub>3</sub>, Pb, dust, smoke, dioxin and

particulate matter are emitted from the plant and contribute significantly to the bad air in Pristina and surroundings.

- Road transport is another major source of air pollution.
- About 80-85% of all heating in Kosovo come from firewood.
- Dust in the cities from increased traffic and old vehicles are other more recent concern.
- Many people in Kosovo are expose to health risks resulting from environmental pollution.<sup>3</sup>
- Kosovo have Law on air protection from pollution, Nr.03/L-160.<sup>4</sup>

Clean air is considered to be a basic requirement of human health and well being.<sup>5</sup>

In 2004, the American Heart Association (AHA) publish its first scientific statement regarding air pollution and cardiovascular disease (CVD). The rationale was to provide researchers, healthcare providers, and regulatory agencies with a comprehensive review of the evidence linking air pollution and exposure with cardiovascular morbidity and mortality.<sup>6,7,8</sup>

There is growing epidemiological evidence on adverse effects of particulate air pollution on cardiovascular health. These effects include increased hospital admissions and mortality (Schwartz, 1999; Samet et al., 2000; Brunekreef and Holgate, 2002)

Air pollution from PM<sub>2.5</sub> has also been associated with increased incidence morbidity and mortality from coronary disease, stroke, heart failure;<sup>9, 10, 11, 12</sup>.

Alternatively, it has been hypothesized that an increase in air pollution levels could modify autonomic nervous control of the heart in subjects with existing cardiovascular disease and thus lead to increased morbidity and mortality (Watkinson et al., 1998; Stone and Godleski, 1999; Godleski et al., 2000). In addition, it has been shown that inhaled ultrafine particles diffuse rapidly into the systemic circulation, and this process could account for extra pulmonary effects of air pollution (Nemmar et al., 2002).

Positive associations between individual air pollutants and mortality or morbidity have been found in many American and European studies 13,14,15.

PM is a widespread air pollutant present wherever people live. The health effects of PM<sub>10</sub> and PM<sub>2.5</sub> are well documented. Most, but not all, epidemiological studies corroborate the evaluated risk for cardiovascular events associated with exposure to fine PM<sub><2.5</sub> in aerodynamic diameter (PM<sub>2.5</sub>) which has been associated with increased risks of myocardial infarction (MI), stroke, arrhythmia and heart failure exacerbation within hours to days of exposure in susceptible individuals.16,17.

In this context, the assess the lag structure between air pollution exposure and elderly cardiovascular hospital admission shown in many study 18,19,20.

## 2. GOAL

Aim of the current study was to investigate the relationship between hospital admission and cardiovascular disease in Pristina and exposure to ambient PM for the period 2010-2012. The reduction of the annual PM<sub>10</sub> air pollution level will lead to significant reduction of mortality rates in Pristina population.

## 3. MATERIAL AND METHODS

The research material is presented as eco-media data (the ambient air: air pollution data for PM<sub>2.5</sub>, PM<sub>10</sub> and O<sub>3</sub>) as well as mortality and morbidity data for Pristina as urban area.

The analytical research has predicted the potential benefit of decreasing of daily PM<sub>2.5</sub> and PM<sub>10</sub> and O<sub>3</sub> for long time period in order to carry out the epidemiological description and analyze of main characteristics in the period 2010-2012 and forecasting the future trend as benefit for the Republic Of Kosovo.

UCCK is the only referral tertiary care center in Kosovo with 2344 beds and approximately 60.000 admissions per year. It is the main research institution in the field of clinical research.

Hospital admissions for cardiovascular disease in UCCK for 2010-2012 were collected.

Patient data captured age, year of admission and diagnosis on discharge from the ten revision of the International classification of diseases (ICD-10). As well as all hospital admissions, those specific disease for the circulatory system (I 00-I 99).

Air quality data for the study period were obtained from the KHMI which manages two stations for the municipality of Pristina in the measurements point in: KHMI-MESP which is equipped with automatic analyzer sulfur dioxide (SO<sub>2</sub>), nitrogen oxides (NO<sub>x</sub>) carbon monoxide (CO), suspended particle analyzer PM<sub>10</sub> / PM<sub>2.5</sub> with air pointer Automatic Air Compact Monitoring System (Version 2.2) recordum MESSTECHNIK GmbH.

Pristina Rilindja- Second station MESP/IHMK. This station is equipped with optical analyzer three channels (Makeup Model 180) which is configured to measure fractions (particle matter) PM<sub>10</sub>, PM<sub>2.5</sub> and meteorological parameters, wind direction, wind speed, air temperature humidity relative air, atmospheric pressure.

Distance from the source of gases contaminates 1 km as the crow flies, sampling height of 2.3 and 4 m from ground level.

Sampling procedure and semi automatic, automatic aspiration through the air samples. Preparation of samples and their analysis based on standard methods of operation according to Directive 2008/50/EC, for each parameter.

### 3.1. Statistics

Data management was performed with SPSS 17.0. Effects estimates and 95 % confidence interval (CI) were calculated per 10 Mg/m<sup>3</sup> increase in PM.

Of statistical parameters to calculate the average Arithmetic, SEM (standard error of the sample), IC (confidence interval) with 95% reliability, minimum and maximum concentration of pollutant and Geometric mean and standard deviation (SD).

Data testing would be done with appropriate statistical tests like t-test and analysis of Varians for parametric data, whereas for non-parametric data Kruskal-Wallis test would be used to compare differences in concentration of air pollutants in different months. The difference would be significant if P < 0.05 and P < 0.01.

## 4. RESULT

This is the first study to investigate the effects of ambient air pollution on population health in Republic of Kosovo. Using health outcomes, air quality, visibility and meteorological data, the association of particulate air pollution with cardiovascular morbidity was investigated using multivariable pollutant models in a case-cross-over analysis.

Results show clear seasonal variation in the effects of PM on hospital admissions in Kosovo. The study period was short but the mean daily admissions for cardiovascular illnesses were quite large. From all number of hospitalization 1789, biggest number of hos-

Age group	Gender				Total	
	F		M		N	%
	N	%	N	%		
100-102	1	0.1	-	-	1	0.1
105-109	4	0.5	6	0.6	10	0.6
110-115	55	7.0	64	6.4	119	6.7
120-125	428	54.5	607	60.5	1035	57.9
126-128	2	0.3	2	0.2	4	0.2
130-152	292	37.2	317	31.6	609	34.0
160-169	3	0.4	6	0.6	9	0.5
180-189	1	0.1	-	-	1	0.1
195-199	-	-	1	0.1	1	0.1
<b>Total</b>	<b>786</b>	<b>100.0</b>	<b>1003</b>	<b>100.0</b>	<b>1789</b>	<b>100.0</b>

Table 1. Hospital admission about gender and diagnosis

Age group	Gender				Total	
	F		M		N	%
	N	%	N	%		
20-29	9	1.1	13	1.3	22	1.2
30-39	14	1.8	36	3.6	50	2.8
40-49	60	7.6	95	9.5	155	8.7
50-59	150	19.1	195	19.4	345	19.3
60-69	246	31.3	336	33.5	582	32.5
70+	307	39.1	328	32.7	635	35.5
<b>Total</b>	<b>786</b>	<b>100.0</b>	<b>1003</b>	<b>100.0</b>	<b>1789</b>	<b>100.0</b>
Mean ± SD	65.4 ± 12.3		63.0 ± 12.3		64.1 ± 12.4	
Rank	20 - 108		20 - 99		20 - 108	
Unpaired T-test	T=4.1, P<0.0001					

Table 2. Number of hospital admission about gender and age group

pitalization was in 2010 with 634 (35.4%), from which 1003 (56.1%) male and 786 (43.9%) female.

Positive association between male and female had found in study Antonela Zarobeti et al.

Based on diagnosis when looking across all seasons I 20-I25 had the highest number hospital admissions and diagnosis I30-I52 in both gender. Ischemic heart disease and cerebrovascular diseases were not significantly associated with any of pollutants.

This findings is in accordance with the results from 1996-1997 in Helsinki, Erfurt and Alkmaar (Ruuskanen et al,2001).

Relative risk among those ages > 69 years were higher than in other age groups for all pollutants except PM 10. Number of hospital admission was for women between 20 year and 108 year old, and men from 20 to 99 year old. Based on this we can say that men in Kosovo has biggest possible to be attack from myocardial infarct than women. (Tab.2)

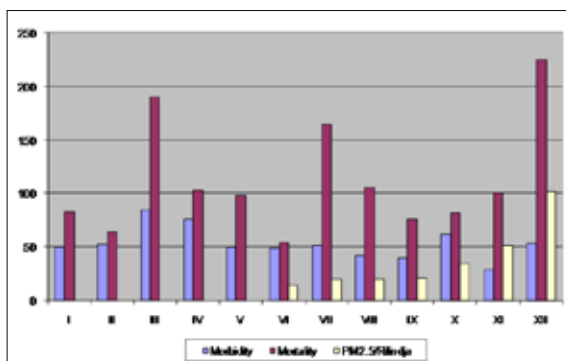
Positive associations were seen in each age group expect those ages 69 years and over. Elevated concentrations of fine particles PM 2.5were associated with a transient risk of acute miocardi.16,17

High levels of dust (particles) in urban air and smoke caused the average value of PM 2.5 in Pristina Rilindja measuring point was 49.7 (SD ± 31.0). The lowest value was in 2010 with average 43.0 (SD ± 32.0) and the highest average in 2011 to 57.3 (SD ± 36.2), which corresponds to the number of patients per year.Yaer level PM10=83.1(SD ± (33.8) /Rilindja, 2012 and 74.3(SD ±50.4) /KHMI

The trend of the ratio, percentage between the two fractions in the sampling points that measures the urban / traffic pollution, reflects to be comparable between the three years for the months with available measurements, with a quite stable trend, with no major changes from year to year. In the

Year hospitalization	PM 2.5/Rilindja	PM 10/Rilindja	PM 10/HMK
	Mean ± SD	Mean ± SD	Mean ± SD
2010	43.0 ± 32.0	80.2 ± 30.2	50.4 ± 15.1
2011	57.3 ± 36.2	84.5 ± 35.3	49.1 ± 12.5
2012	44.6 ± 20.6	-	116.1 ± 61.4
Total	49.7 ± 31.0	83.1 ± 33.8	74.3 ± 50.4

Table 3. Measurements point and value for PM 2.5 and PM 10 in Pristina



Graph 1. Number of hospital admission, number mortality and PM concentration

Month	Year hospitalization								
	2010			2011			2012		
	Morbidity	Mortality	PM 10/HMK	Morbidity	Mortality	PM 10/HMK	Morbidity	Mortality	PM 10/HMK
I	49	82	72.3	43	107	-	48	127	-
II	52	63	-	42	129	-	53	119	-
III	84	189	44.5	43	166	56	81	127	-
IV	76	102	37.2	39	99	45.2	57	138	91.5
V	49	98	36.2	46	132	37.2	48	118	79.1
VI	48	54	43.3	48	153	38.9	48	130	56.3
VII	51	164	47.1	32	99	78.6	36	113	86.0
VIII	42	105	44.9	45	64	41.7	48	94	104.0
IX	40	76	40.5	49	60	52.3	40	117	74.4
X	62	81	42.7	44	193	-	49	121	71.2
XI	28	100	78.8	46	222	-	44	121	-
XII	53	224	-	61	148	-	65	148	213.6
Total	634	1338	50.4	538	1572	49.1	617	1473	116.1

Table 4. Number of hospital admission, mortality about particulate matter PM 10

study of air pollution, measurement of fractions smaller than PM2.5, in the content of PM10 particles is of considerable importance, due to the impact on health. The pollutant concentration for particles PM 2.5 and hospital admissions during the study period was higher. The mean numbers of admissions were slightly higher in month with the cold weather.

The correlation between different measures of particulate air pollution were also clearly higher in Pristina, than in suburban area, suggesting a difference in the air pollution mixture or meteorological conditions. Based on year hospitalization about month we found highest number in 2010, mortality on year 2011. PM10 concentration was in 2012, 116.1 highest and lower in 2011 with 49.1.

The air-quality data from KHMI show that PM, notably, exceeds the EC limit value of an average annual concentration of 40 micrograms per cubic meter ( $\mu\text{g}/\text{m}^3$ ) for  $\text{PM}_{10}$ , both in the city center and in the suburban area and often exceeds the one-day limit value (not to be exceeded more than 35 times a year) of  $50 \mu\text{g}/\text{m}^3$ . Similar study was founding De Hartog et al,2005.

## 5. DISCUSSION

Air pollution and effect on human health is clearly evident on Pristina city. Association with mean monthly hospital admissions for cardiovascular disease were highest on month during the cool season and days with dust.

Our findings were broadly consistent with those in European and American country. 23,24,25,26,27,28,29,30,31.

Hospital admissions by gender in UCKK on Intern hospital in Pristina for

the years 2010-2012 were hospitalized patients total 1789, of whom 786 women (43.97%) and 1003 men (56.1%).

Those ages > 69 years were at higher risk.

Elevated concentrations of fine particles PM 2.5 were associated with a transient risk of acute myocardial infarction.

High levels of dust (particles) in urban air and smoke caused the average value of PM 2.5 in Pristina Rilindja measuring point was 49.7 (SD ± 31.0). The lowest value was in 2010 with average 43.0 (SD ± 32.0) and the highest average in 2011 to 57.3 (SD ± 36.2), which corresponds to the number of patients per year. Year level PM10=83.1(SD ± (33.8) /Rilindja, 2012 and 74.3(SD ±50.4) /KHMI.

Mean monthly hospital admissions for cardiovascular disease were high-



est on month during the cool season and days with dust. The present study is the largest study conducted until today on the effects of particulate air pollution and CVD. In many study we found a significant associations between PM 2.5, PM 10 and Cardiovascular hospital admissions. In Pristina Ischemic heart disease is the first most common cause of cardiovascular disease, and second most common cause of all hospital admissions was I 30-I 52.

## 6. CONCLUSION

Adoption and complete transposition of legislation on air, in accordance with European Union legislation, the World Health Organization and other international organizations; Implement the strategy and action plan on air protection from pollution and other national programs and projects for improving the air quality; Reduction number old car on traffic; Adding green surface in urban areas. Using renewable energy. cycling and increased community by public transport.

**CONFLICT OF INTEREST: NONE DECLARED**

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## PROFESSIONAL PAPER

# Pneumonia as the Most Common Lower Respiratory Tract Infection

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**Introduction:** Pneumonia is the most serious inflammatory disease of the respiratory system and also the most common infectious disease. Even now, in the 21<sup>st</sup> century, pneumonia occupies a prominent place in clinical medicine and public health. We are confronted daily with the increased number of patients, as well as the constant increase in annual mortality due to this infectious disease. **Goal:** The goal was to investigate the prevalence and pneumonia characteristics as the most serious lower respiratory tract infection, the incidence of typical and atypical pneumonia, hospitalization duration of the patients at the Clinic of Infectious Diseases, Clinical Center of Sarajevo University CCUS. **Patients and Methods:** From January 2011 until December 2012 the study involved 100 hospitalized patients with infections of the lower respiratory tract at the Clinic of Infectious Diseases CCUS. **Results:** Among the most common infections the pneumonia is highly represented. Lung X-Ray in two planes, by all protocols, demonstrated with the auscultatory finding the highest value in the diagnosis of clinical pneumoniae. A statistically significant difference among our hospitalized patients, compared to typical and atypical pneumonia, is in favor of the first—typical bacterial pneumonia. Hospitalization duration ranges between 7-14 days. **Conclusion:** We believe that the introduction of the pneumococcal vaccine (PCV) should reduce the number of pneumonia caused by this bacterium. Recommendations for its use also come from the WHO. Until December 2012, WHO added 86 states in the PCV immunization as a part of their national immunization programs. Pneumococcal conjugate vaccine (PCV) is safe and effective for the reduction in number of patients suffering from pneumonia caused by *St. pneumoniae*. In particular, the vaccine is a significant protection to children which because of their age and severity of the disease must remain under medical supervision. However, in elderly vaccine is important and useful preventive measure, because of their biological characteristics and life circumstances marks this group as vulnerable population, like the youngest, and can be fatal for them. **Key words:** pneumonia, increased mortality, vaccine.

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## 1. INTRODUCTION

Pneumonia is an acute, potentially severe disease with the rapid development of a number of symptoms and complications so it represents an important cause of morbidity and mortality, especially in older people with chronic diseases (1,2). Pneumonia is now classified into three groups according to the location and cause of the occurrence into:

- Community-acquired pneumonia;
- Hospital acquired (nosocomial) pneumonia;
- Pneumonia in patients with impaired immunity.
- Epidemiologic causes

The most important bacterial cause of community-acquired pneumonia is *Streptococcus pneumoniae*, which is responsible for 80% of cases and is rep-

resented in all age groups (5,6,7). Out of 82 *Streptococcus pneumoniae* serotypes the disease is caused by nine (1, 3, 4, 5, 7, 8, 9, 10 and 12), while the most severe clinical presentation causes serotype 3 (2).

By frequency it is followed by *Haemophilus influenzae*, which is the second most important bacterial pathogen in the incidence of pneumonia and other gram-negative bacteria, *Staphylococcus aureus* and anaerobic bacteria. Gram-negative bacteria, like *H. influenzae*, *Moraxella catarrhalis* and *Klebsiella pneumoniae* cause pneumonia in people with weakened resistance, in newborns, infants and the elderly who are chronically ill. The hospital treatment of pneumonia is almost obligatory for bacterial origin (*St. aureus*, followed by *Legionella* and anaerobic bacteria and rarely pneumococcus).

The most important cause of atypical pneumonia is *Mycoplasma pneumoniae*, besides which we are facing other two *Chlamydia psittaci*, the causative agent of psittacosis and *Coxiella burnetii*, the cause of Q fever. The microorganisms that cause pneumonia enters the lung in 4 ways: by inhalation of infected aerosols, nasopharyngeal aspiration from the oral cavity, hematogenous spreading of inflammatory foci, and direct expansion from the adjacent organs. The causes of atypical pneumonia, but also the bacteria enter the lungs by inhalation of infected aerosols, while other three modes are reserved for spread of bacteria (5, 6).

### 1.1. Clinical presentation

The main clinical symptoms of pneumonia are fever and cough, with or without sputum, accompanying by stabbing pain in the chest and shortness of breath. However these two parameters are not always present. Bacterial pneumonia, especially caused by pneumococcus, has sudden onset of symptoms. The body temperature is moderately high or very high, accompanied with chills. Fever is accompanied with tachycardia and increase in respiratory frequency. In case of the classical bacterial pneumonia also occurs productive cough. Sputum is purulent and may contain blood. Relatively often chest pain, pleural effusion and dyspnea are present. Stabbing chest pain symptoms are very important for the diagnosis of pneumonia. Characteristic physical examination finding: examination reveals flushed face, dry skin with pronounced turgid. Tachycardia and cyanosis may be present as a result of hypoxia but also the cardiovascular failure. Auscultation of the lungs is not safe diagnostic parameter and should be confirmed with the X-ray. In the developed bacterial pneumonia auscultation finding have signs of bronchial breathing and appearance of crepitations, also sometimes can be heard pleural friction. However, at the early stage of the disease only vesicular breathing is found. Many crepitation sounds and moist rales which indicate exudation in the alveoli.

Atypical pneumonia have less boisterous clinical image, because the clinical symptoms develop gradually. The body temperature rises up to high values, but it is rarely accompanied with chills. A common finding is also bradycardia. Clinical picture besides fever prevails general symptoms (headache, muscle aches, fatigue, malaise, loss of appetite). Cough is usually observed after 3-6 days and it is dry with irritation. Specific is the discrepancy between normal or small auscultation findings and X-ray clearly expressed pneumotic infiltrates (1,2).

### 1.2. Diagnosis

Diagnosis and treatment of pneumonia is still a big problem in everyday medical practice, which affects the clinician in the hospitals, and even

more the general practitioners in case of outpatient diagnosis and treatment of pneumonia. There are many difficulties and shortcomings in reaching the final etiological diagnosis and the proper procedure. Results of bacteriological evaluation of various samples are known only after few days. That is why today, and will continue in the future, most pneumonia are treated without determined causative agent. Diagnostic sequence for pneumonia includes the following: clinical assessment (history, clinical status, particularly physical findings on the lungs), x-ray, laboratory and microbiological diagnostics (2,5,7,8).

### 1.3. Treatment

Penicillin has until recently been the main antibiotic in treatment of primary bacterial community-acquired pneumonia, but due to the high resistance on penicillin in the treatment of pneumonia today are mostly used oral cephalosporins and macrolides in the treatment of minor or moderate form of primary pneumonia, especially in outpatient settings. In case of hospitalized patients is administered penicillin G or more usually cephalosporins from 2<sup>nd</sup> or 3<sup>rd</sup> generation. It is important to emphasize that azithromycin in comparison to erythromycin has better effect against *Haemophilus influenzae*. It is a unique antibiotic by shortness of application. The causes of atypical pneumonia are located intracellularly, so they are not affected by beta-lactam antibiotics and aminoglycosides. Against them are effective antibiotics from tetracycline and macrolides group (2,10,13).

## 2. GOAL

To investigate the incidence and characteristics of pneumonia as the most serious lower respiratory tract infection, the incidence of typical and atypical pneumonia and hospitalization duration of patients at the Clinic of Infectious Diseases CCUS.

## 3. MATERIAL AND METHODS

This retrospective-prospective study included 100 patients with lower respiratory tract infections hospitalized at in Clinic of Infectious Disease, Clinical Center of Sarajevo University. The study was conducted in the period from

January 2011 until December 2012. It included patients suffering from infection of the lower respiratory system at all ages. As data source are used medical records of hospitalized patients with lower respiratory tract infections, which are treated in the Clinic of Infectious Diseases. Criteria for inclusion in this study were physical findings and clinical symptoms in favor of infection and X-ray finding with lung infiltration, increased parameters of laboratory parameters suggestive of infection of the lower respiratory tract, while the criteria for exclusion from the study were patients with PA X-ray of the lungs with infiltrations that by differential diagnosis does not correspond to infections of the lower respiratory tract.

## 4. METHODS

The diagnosis is based on: clinical evaluation (medical history, clinical status, particularly physical findings of the lungs), X-ray of the lungs, laboratory and microbiological diagnostics. From history data analysis included leading clinical symptoms due to which the patient was admitted at the Clinic of Infectious Diseases CCUS (fever, cough, sputum, shortness of breath, shivering, fatigue). From clinical findings we analyzed age, gender and local auscultatory findings which was different in case of infections in the lower respiratory tract. In case of developed bacterial pneumonia auscultatory finding is characterized by bronchial breathing and appearance of crepitation, while occasionally can also be heard pleural friction. However, at the beginning of the disease only weakened vesicular breathing can be heard. In case of atypical pneumonia findings in the lungs at the beginning of the disease was generally normal, while later can be noticed crepitation and high frequency noise at the end of inhalation. From laboratory parameters were analyzed following biochemical parameters: erythrocyte sedimentation rate, blood count and hematocrit, differential blood count (mostly focused on neutrophils), C-reactive protein, X-ray findings (the majority of patients with infections of the lower respiratory tract had a standard PA and left lateral chest X-ray on which can be seen various pulmonary infiltra-

tions and the remaining patients had normal X-ray of lungs) and microbiological analysis (analysis of the nose and throat swabs, sputum smear). All the above tests were performed at the Clinic of Infectious Diseases, Clinic of Radiology, Institute of Microbiology and the Department of Pulmonary Diseases CCUS.

## 5. RESULTS

Between January 2011 and December 2012 analysis involved 100 hospitalized patients with infections of the lower respiratory tract from the Clinic of Infectious Diseases CCUS. In relation to the total number of patients pneumonia was present in 79 (79%) cases, more among men 62.025% than among women 37.97%. The most common age group in our study was over 65 years of age, and the pneumonia occurred the least among patients at age from 25-44 years.

FEATURES	N	%
FEVER	68	86
CHILLS	4	5
COUGH	46	58.1
ERYTHROCYTE SEDI-MENTATION RATE	56	70
CRP	66	83.5
BLOOD LEUKOCYTES	35	44.3
NEUTROPHILS	4	5
AUSCULTATION FIND-ING	61	77
LUNG X-RAY	74	93.6

Table 1. Characteristics of the pneumonia

Figure 1 shows the incidence of infections of the lower respiratory tract, of which the largest number represented pneumonia with 79%. Next by the frequency is acute bronchitis with 10%, chronic obstructive pulmonary disease (COPD) with 7%, while chronic bronchitis was present in only 4%.

In patients with pneumonia are the most common is characteristic X-ray of the lung represented in 93.6% and auscultatory pathological findings of the lungs in 77%. From clinical symptoms follows fever with 86%, cough 58.1% and shivering with 5%. Among laboratory parameters dominated the pathological CRP (C-reactive protein) 83.5%, erythrocyte sedimentation rate (SE) 70%, leukocytes count 44.3% and 5% neutrophils (Table 1).

DISEASE	LUNG X-RAY	AUSCULTATION FINDING
PNEUMONIA	74 (90.2)	61
ACUTE BRONCHITIS	3 (3.66)	8
CHRONIC BRONCHITIS	3	4
COPD	2	1
TOTAL	82	74

Table 2. Analysis of the auscultation findings and X-ray of the lungs in case of the lower respiratory tract infections

The normal sound	13
Weakened respiratory sound right	14
Weakened respiratory sound left	8
Weakened respiratory sound bilaterally	11
The intensified pulmonary sound	10
Not audible breathing	2
Vesicular breathing	2
Accompanying pathological phenomena:	
Inspiratory crackles	32
Expiratory crackles	2
Crepitation	4

Table 3. Analysis of the auscultation findings of the lungs

X-ray of the lungs in two planes in all the protocols has a key value for clinical diagnosis of the pneumonia. It gives a decisive answer to the question "which part of the respiratory system is affected by inflammation?" In our research, we found that X-ray of the lung was the most common pathological characteristic among the patients.

During the analysis of the lung X-ray was observed that in the group of patients with infections of the lower respiratory tract most common disease is the pneumonia with 74%, followed by acute and chronic bronchitis with 3% and 2% with COPD. Similar data were obtained during auscultatory examination, where pneumonia was the most common with 61%, followed by acute bronchitis.

When analyzing the relationship of auscultation findings and x-ray of the lungs, in all lower respiratory tract infections, was used "t" test (Student) for significance of the difference,

which amounted to 0.93 for paired samples (Table 2).

The incidence of bacterial (typical) and atypical pneumonia was significantly higher in favor of typical with 97.47% (77 patients), whereas atypical were represented only 2.53% (2 cases) as shown in Figure 2. In support of bacterial pneumonias speaks also the parameters of inflammation (erythrocyte sedimentation rate) and CRP (C-reactive protein), which have been elevated. Mean CRP was 107.19 mg/dl and ranged from 6 to 335.3 mg/dl. While sedimentation rate ranged between 11mm/hour and 125 mm/hour with the mean value of 55.05 mm/hour (Figure 3).

In the study group of patients was evaluated auscultatory findings in the lungs. Weaker breathing on the right side was present in majority of patients 17.72% with concomitant pathological inspiratory crackles 40.50% (Table 3).

In case of patients with pneumonia hospitalization duration in our analysis was most often from 7-14 days and the smallest number of the patients stayed at the clinic up to 6 days (Figure 4).

## 6. DISCUSSION

Donowitz and Mandell in their study conducted in the UK showed that pneumonia is responsible for 10 times

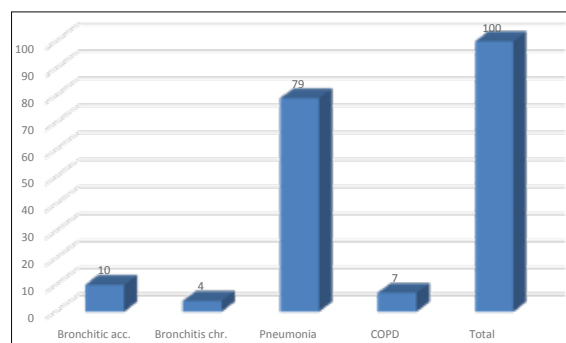


Figure 1. The incidence of infections of the lower respiratory tract

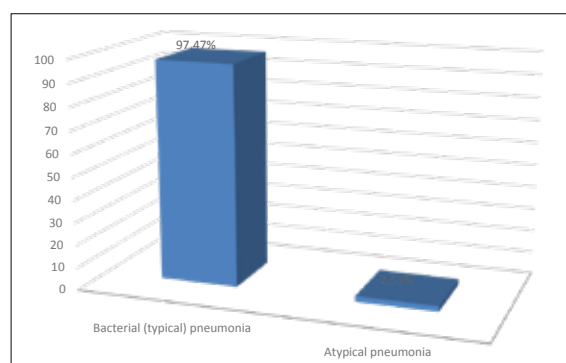


Figure 2. The ratio of typical and atypical pneumonia



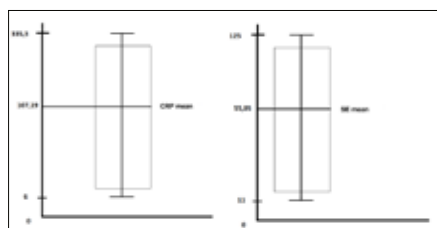


Figure 3. Analysis of inflammation parameters in pneumonia: a) erythrocyte sedimentation rate (SE) and b) C-reactive protein (CRP)

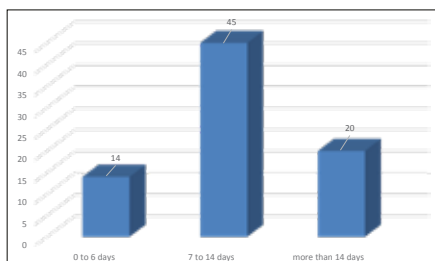


Figure 4. Duration of the hospitalization

more deaths than any other infectious disease. While in the U.S. the pneumonia is among the leading causes of death (6,7). In developing countries, infections of the lower respiratory tract are the most common cause of death, especially when it comes to pneumonia as determined by the WHO (World Health Organization). In our research, we reached the similar results that the most common infectious disease of the lower airways is pneumonia. Our study showed a predominance of male patients suffering from pneumonia with 62.025% as also noticed by other authors. Kuzman in his study found that there were more men than women and the ratio is higher in favor of men 1.5:1 (2). Also, all causes of pneumonia are more common in men than in women. One of the several studies conducted by Champam and his associates suggest that adults over 65 get sick more than 915,000 times each year in the USA. They claim that the age is one of the important factors for the development of pneumonia (7). Certainly these data coincide with our research. Bern-tsson et al. simultaneously examined the ratio of typical and atypical pneumonia in their studies and came to the fact that bacterial pneumonia are more common in hospitalized patients than atypical because such patients are hospitalized because of severe symptoms and complications. It is evident that our results coincide with the results of authors dealing with the same topic. A statistically significant differ-

ence is found among our hospitalized patients between typical and atypical pneumonia in favor of the first—typical bacterial pneumonia. In our study, the mean value of C-reactive protein (CRP) in patients with pneumonia who had elevated levels amounted to 107.19 mg/dL. Lehtomäki and associates in their research found the average value of CRP that was 149 mg/dL, with 90% of bacterial pneumonia, which is similar to results of our research (15) Kuzman et al. found high mean value of 232.1 mg/dL in bacterial and 132.6 in case of atypical pneumonia (1). Kerttula et al. in their study of pneumonia in hospitalized patients found the mean value of C-reactive protein, which amounted to 164 mg/dL in bacterial and 51 mg/dL in atypical (14). Like our results, Holmberg and colleagues found that in bacterial pneumonias the mean value of the sedimentation was 57 mm/hour (13). Unlike Harambasic and collaborators who conducted two large studies and shown that pneumonia is more often present in lower than in the upper parts and that there are no major differences in the involvement of the left and right lung (16). Research by Fill and Mandell showed that pneumonia without complications and without major associated chronic diseases should be treated for 7-10 days, with a tendency of shortening of this period (6,11).

## 7. CONCLUSIONS

Among infections of the lower respiratory tract at the Clinic of Infectious Disease CCUS most often is present pneumonia. This information should be taken seriously, whereby we must seriously reflect on the WHO report and the fact that in some countries, pneumonia is responsible for 10 times more deaths than any other infectious disease. Infections of the lower respiratory tract are more present in male population. A statistically significant difference in our hospitalized patients sample was found in comparison of typical and atypical pneumonia, in favor of the first-typical bacterial pneumonia. Hospitalization duration ranged between 7-14 days.

We believe that the introduction of the pneumococcal vaccine (PCV) will reduce the number of pneumonias

caused by this bacterium. Recommendations for their use are also set by the WHO. By December 2012, 86 WHO member states has added the PCV in the immunization protocol in their national immunization programs. Pneumococcal conjugate vaccine (PCV) is safe and effective in the reduction of number of suffering from pneumonia caused by *St. pneumoniae*. In particular, the vaccine is a significant protection to children, who regarding their age and severity of the disease must remain under medical supervision. Also, in elderly vaccine is important and useful preventive measure, because of their biological characteristics and life circumstances put this group in vulnerable population like the youngest, and can be fatal for them.

CONFLICT OF INTEREST: NONE DECLARED

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## ORIGINAL PAPER

# Endoprosthesis and Obesity

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**Introduction** Obesity represents a significant risk factor in the pathophysiology of degenerative changes in coxarthrosis. **Objective** The study is aimed at establishing, in the examined sample comprising 136 patients, how great a risk factor obesity is when implanting a hip endoprosthesis. **Material and methods** The series comprised 136 patients with a hip endoprosthesis implanted and the patients' BMI, amount of blood used, duration of surgery, number of assistants, and type of anaesthesia were observed. Wounds and late post-operative complications, infections, haemorrhage, vein thrombosis, endoprosthesis dislocations, length of inpatient stay, start of physical therapy and full weight-bearing were also observed. The observation period lasted six months on average. **Discussion** In simple terms, the three greatest factors when implanting a hip endoprosthesis are as follows: properties of the endoprosthesis, the orthopaedic surgeon's skill and experience, and individual characteristics of the patient, i.e. age, sex, health condition, body weight, BMI, adequate physical therapy. **Conclusion** We believe that the implantation of a hip endoprosthesis should be postponed for patients with a BMI exceeding 29.99. Such patients should receive endocrine treatment, they should undergo a weight loss programme in order to reduce their body weight and in order to reduce their BMI to under 29.99. **Key words:** obesity, endoprosthesis

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## 1. INTRODUCTION

Obesity means over accumulation of fat in the body (1) and it is connected with arterial hypertension, diabetes mellitus type 2, cardiovascular diseases, carcinomas (endometrial, renal, colon, prostate, vesica phela, mammary, ...) (2) and development of arthritis of the hip, knee .. (2).

There are a number of formulae based on which „ideal“ body weight is determined. Nowadays, the most commonly used is the so-called body mass index (BMI) (1). In order to define obesity (with different body heights) the BMI that is taken into account is the one calculated by dividing a person's weight by the square of their body height (although there is a margin of error of ap-

proximately 4% when calculating BMI). Example: a patient who weighs 100 kilograms and stands 2 metres tall has a BMI of 25, i.e. ( $BMI = 100/2^2 = 25$ ) (1).

If a patient's BMI is less than 18.5, we say that the patient is thin/underweight (1). A patient with a BMI between 18.5 and 24.99 has normal weight. Patients with a BMI between 25.00 and 29.99 are called overweight. They have increased comorbidity rates (1). Patients with a BMI between 30.00 and 34.99 have obesity Class I and a medium risk of comorbidities is characteristic of it. Patients with a BMI between 35.00 and 39.99 have obesity Class II which carries a serious risk of comorbidities. Patients with a BMI over 40 have obesity Class III and they are very prone to co-

morbities(1). In everyday clinical practice we come across both android and ginoid obesity (1). Android obesity (apple-shaped body) is characterised by the storage of fat in the abdominal area, upper chest region, nape of the neck, ... People suffering from this type of obesity are prone to heart diseases, metabolic syndrome, gout, hypertension, .. (3). Gynoid obesity is characterised by the presence of fat on the hips, thighs and buttocks. These people have pear-shaped bodies and are less prone to heart diseases. Technically, it is more difficult to implant an endoprosthesis in such patients(3).

In their study, Oliveira *et. al* maintain that obesity causes degenerative changes of the hip 25% more often in fat people and the risk is five times greater in women who have had their BMI greater than 30 since they were 18 (4). In the obese, coxarthrosis is more connected with clinical symptoms than with X-ray finding (4,5).

In their study, Bergschmidt and Chee state that the risk factors for development of coxarthrosis are as follows: age, BMI and physical activity (5,6). Possible complications that may occur when implanting an endoprosthesis in obese people are pre-operative: wounds do not heal easily, infections, thrombophlebitis, dislocations, and frequently manifested post-operative complications are dislocations and prosthesis instability (6). As for fat people, deep vein thrombosis and pulmonary embolism are 50% more common

Body mass index	Secondary illness												Total	
	Renal failure		Diabetes mellitus		Chronic cardiomyopathy		High blood pressure		Rheumatoid arthritis		No secondary illness			
	f	%	f	%	f	%	f	%	f	%	f	%	f	%
25–29.99	2	40.00	12	27.27	2	11.76	19	33.33	0	0.00	11	22.00	46	26.59
> 29.99	3	60.00	32	72.73	15	88.24	38	66.67	0	0.00	39	78.00	127	73.41
Total	5	100.00	44	100.00	17	100.00	57	100.00	0	0.00	50	100.00	173	100.00

Table 1. Distribution of patients by body mass index in relation to secondary illness

in patients whose BMI is over 40 (7). In their study, Kessler S. *et. al* also state that the risk of knee arthritis is three-four times greater in people with a BMI greater than 30(8).

Obese people comprise up to 30% of population in developed countries. There are over one billion obese people in the world, and over 300 million suffer from severe obesity (4).

## 2. OBJECTIVE

The study is aimed at establishing, in the examined sample comprising 136 patients, how great a risk factor obesity is when implanting a hip endoprosthesis.

## 3. MATERIAL AND METHODS

136 patients were treated for hip fractures and coxarthrosis by implantation of total hip endoprosthesis at the Orthopaedics and Traumatology Clinics in Banja Luka and Nis in the period between 1 September 2010 and 31 December 2011. All patients were treated identically, and the research results were recorded in a questionnaire containing the following data: first and family name, sex, age, secondary illnesses, BMI, amount of blood used, duration of surgery, number of assistants, type of anaesthesia. Both early and late post-operative complications, such as infections, haemorrhage, vein thrombosis, endoprosthesis dislocations, length of inpatient stay, start of physical therapy and full weight-bearing, were observed. The observation period lasted six months on average.

## 4. RESULTS

The research was conducted on 136 patients treated for hip fractures and coxarthrosis at the Orthopaedics and Traumatology Clinics in Banja Luka and Nis between 1 September 2010 and 31 December 2011.

There were no patients in the examined sample with a BMI under 25, i.e. there were no underweight patients. Out of the 136 patients, 35 (25.74%) (13 men and 22 women) had a BMI between 25 and 29.99, and they belonged to the overweight group. The obese group with a BMI over 30 (I<sup>o</sup>, II<sup>o</sup>, III<sup>o</sup>) was made up of 101 patients (74.26%); 37 men and 64 women.

As far as age is concerned, we had 35 patients (25.74%) with a BMI between 25 and 29.99: 10 of them were aged between 40 and 50, 13 between 51 and 60, 9 between 61 and 70, and 3 were aged between 81 and 90. 101 patients (74.26%) with a BMI over 30 were aged as follows: 25 were aged between 40 and 50, 38 between 51 and 60, 30 between 61 and 70, 2 between 71 and 80, and 6 were aged between 81 and 90.

A hip endoprosthesis for fracture was performed on 52 (38.2%) out of the 136 patients, while the indication in 84 patients (61.8%) was coxarthrosis. 4 patients whose BMI was between 25 and 29.9 had Garden Type III fractures, while 9 had Garden Type IV. 12

patients whose BMI was over 30 had Garden Type III fractures, while 27 had Garden Type IV. Out of the 84 patients (100%) who had an endoprosthesis implanted for coxarthrosis 22 (26.19%) had a BMI between 25 and 29.9, and 62 (73.81%) had a BMI over 30.

The distribution of patients by their BMI in relation to secondary illnesses is shown in **Table 1**. Patients suffered from chronic illnesses for which they had already been treated. Table 1 shows that the results of the t-test according to which, with a 5% risk, an alternative hypothesis is accepted whereby there is a significant statistical difference between chronic illnesses of patients with a BMI between 25 and 29.99 and those with a BMI over 29.99, and it amounts to  $p = 0.000521$ .

The Austin-Moore surgical access was used on all patients. The surgical access in patients with a BMI between 25 and 29.9 was 15cm long, while it amounted to 24cm in patients with a BMI over 30. The lead surgeon always had three assistants, irrespective of the patient's BMI. The duration of sur-

Body mass index	Amount of blood used (ml)										Total	
	0		320		640		960		1280			
	f	%	f	%	f	%	F	%	f	%	f	%
25-29.9	5	55.56	13	30.95	11	26.83	6	16.67	0	0.00	35	25.74
> 29.9	4	44.44	29	69.05	30	73.17	30	83.33	8	100.00	101	74.26
Total	9	100.00	42	100.00	41	100.00	36	100.00	8	100.00	136	100.00

Table 2. Distribution of patients by body mass index in relation to amount of blood used (ml)

Body mass index	Post-operative complications										Total	
	Infection		Haemorrhage		Vein thrombosis		Dislocation		No post-operative complications			
	f	%	f	%	f	%	f	%	F	%	f	%
25-29.99	1	12.50	1	33.33	4	30.77	2	33.33	27	25.47	35	25.74
> 29.9	7	87.50	2	66.67	9	69.23	4	66.67	79	74.53	101	74.26
Total	8	100.00	3	100.00	13	100.00	6	100.00	106	100.00	136	100.00

Table 3. Distribution of patients by body mass index in relation to post-operative complications

Body mass index	Quality score with weight coefficients of variables										Total	
	Inpatient length of stay (days)		Amount of blood used (ml)		Incision area size (cm)		Number of assistants		Duration of surgery (min)			
	f	%	f	%	f	%	f	%	f	%	f	%
25-29.9	5.7	28.79	17.4	29.59	10.1	34.36	10.7	35.68	21	28.57	65	30.68
> 29.9	14.1	71.21	41.4	70.41	19.2	65.64	19.2	64.32	53	71.43	146	69.32
Total	19.8	100.00	58.8	100.00	29.3	100.00	29.9	100.00	74	100.00	211	100.00

Table 4. Distribution of patients by body mass index in relation to quality (with different weight coefficients for variables)

gery in patients whose BMI ranged between 25 and 29.9 was 90 minutes, and in those whose BMI was over 30 the surgery took 120 minutes on average. BMI did not affect the waiting time for surgeries. BMI had a significant effect on the use of blood when implanting endoprostheses. (Table 2)

BMI had a significant effect on the selection of anaesthesia for surgery. Thus, general anaesthesia was used for 24 patients with a BMI between 25.00 and 29.99 and spinal anaesthesia for 11. In order to implant an endoprosthesis in patients with a BMI over 30, general anaesthesia was used on 44, and spinal on 57 patients.

We had 23 patients with a BMI between 25 and 29.9 whose physical therapy started the first day, for 8 patients it started on the second day, and for 4 on the third. As for patients with a BMI over 30, 35 of them started their physical therapy on the first day, 35 on the second, 27 on the third and 4 on the twelfth. With 10 patients whose BMI was between 25 and 29.9 we achieved full-weight bearing on their operated leg on the first day, with 14 it was on the second, with 6 on the third, with 2 on the fourth, and with 3 patients it was on the fifth day. With 5 patients whose BMI was over 30 we achieved full-weight bearing on their operated leg on the first day, with 15 it was on the second, with 23 on the third, with 20 on the fourth, and with 9 patients it was on the fifth day.

4 patients with a BMI between 25 and 29.9 spent up to 6 days in hospital, 14 spent 10 days, 16 up to 15 days and 1 patient spent over 15 days in hospital. 3 patients with a BMI over 30 spent up to 6 days in hospital, 35 spent up to 10 days in hospital, 56 up to 15 days and 7 patients spent over 15 days in hospital.

Early post-operative complications were as follows: infection, haem-

orrhage (post-operative haematoma), vein thrombosis, dislocations (Table 3). We obtained the Chi-square test value (54.84) > (5.99) ( $p < 0.05$ ) according to which, with a 5% risk, a hypothesis is accepted whereby there is a significant statistical difference between patients with a BMI of up to 29.9 and those with a BMI over 30 (Table 3).

There is a significant statistical difference between patients with a BMI of up to 29.99 and those with a BMI over 30.00. Distribution of patients by body mass index in relation to the quality score with weight coefficients of the variables is best shown in Table 4. It is obvious from Table 4 that the results of the t-test according to which, with a 5% risk, an alternative hypothesis is accepted whereby there is a significant statistical difference between the quality score with weight coefficients of the variables of patients with a BMI between 25 and 29.99 and those whose BMI was higher than 29.99, and it amounts to  $p = 0.000521$ .

## 5. DISCUSSION

A suitable hip joint endoprosthesis is the greatest modern achievement in orthopaedics(5,8,9). A number of factors influence a more long-term proper functioning of an endoprosthesis and better movement of persons with an artificial joint. In simple terms, we talk about three most important factors: properties of the endoprosthesis, the orthopaedic surgeon's skill and experience, and individual characteristics of the patient, i.e. age, sex, health condition, body weight or BMI, and physical activity(8,9). The effect that body weight has on the musculoskeletal system and damages that occur are well known, and we have been telling patients for a long time about the value of controlling and reducing their body weight, which is very important in endoprosthetics(9).

Due to the build and biomechanical relationships, the body weight at one stage of movement eccentrically loads the weight-bearing hip joint, and a muscle force that is approximately three times greater than the weight is required for balancing the pelvis, which results in the load-bearing force being three-four times greater than the weight(9). A weight gain of only 1kg results in a load increase of approximately four times in the hip with an endoprosthesis(9).

While monitoring long-term function of endoprostheses, Cooper and the group of authors do not indicate any significant statistical differences in the number of complications between normal weight and obese patients (10). They infrequently implant endoprostheses in obese persons(10), which would definitely be recommendable here too.

In a prospective clinical trial, Slavica Jandric *et. al.*, using a randomised method on 394 patients diagnosed with coxarthrosis, concluded that the average BMI value was 30.61 kg/m<sup>2</sup>. In men, the average BMI value was at the overweight level (28.66 kg/ m<sup>2</sup>), and in women it was at the obesity level (31.49 kg/ m<sup>2</sup>) (11). The statistical difference between the BMI for women and the BMI for men was significant ( $p = 0.016802$ ,  $p < 0.05$ ). BMI was at the obesity level in 27 or 60% of patients with coxarthrosis, at the overweight level in 11 or 24.4% of patients, and only 15.5% of patients had normal weight. 91.11% or 41 patients with symptomatic coxarthrosis were aged over 50. The statistical correlation between BMI and age was not significant in the total sample of patients suffering from coxarthrosis ( $r = -0.32799$ ). The correlation between ages was significant ( $r = -0.34745$ ,  $p > 0.05$ ) (11). The results showed that there was a difference in the connection between age and BMI in patients with symptomatic coxarthrosis in relation to sex. The younger the men suffering from coxarthrosis were, the higher their BMI was (11).

Carrying a few extra kilograms may pose a health risk, while morbid obesity may cause serious health problems. The studies conducted by Natvig (12) have shown that patients with a BMI over 30.00 suffer 3.3 times more often from infections as a complication following



endoprosthesis implantation, have a loosened endoprosthesis 1.5 times more often and experience thromboembolic complications 0.7 times more often (12). A number of orthopaedic surgeons suggest implanting a hip endoprosthesis in patients suffering from obesity with a BMI over 35.00 (13). In the USA, the increase in obesity has triggered the need for many more endoprostheses and thus increased the risk of lifelong complications (12,13). One group of authors, in extreme cases when endoprosthesis implantation is the only solution, are adamant that the patient should be requested to lose weight (minimum to obesity Class I) before the endoprosthesis can be implanted, in order to reduce the risk of complications(14).

Andrew *et. al* (15) conducted a prospective study on 1421 patients who had an endoprosthesis implanted for coxarthrosis in the period between January 1999 and 2007 (15). They examined whether and to what extent obesity had an effect on the clinical outcome(15). The patients were classified into three groups: non-obese patients with a BMI less than 30 kg/m<sup>2</sup>, obese patients with a BMI between 30 and 40 kg/m<sup>2</sup>, and morbidly obese patients with a BMI over 40 kg/m<sup>2</sup> (15). The study showed a significant statistical difference in increased haemorrhage, infections, deep vein thromboses and pulmonary embolism, and duration of hospital treatment between morbidly obese and non-obese patients (15). Radiological analyses of heterotopic ossification of the femur were statistically significantly increased in the morbidly obese (15). The morbidly obese group was considerably younger and they required a longer surgical work(15).

Obesity has reached epidemic proportions in the USA, and it is expected that the rest of the developed world will follow in their wake. As obesity is a well documented risk factor for developing osteoarthritis(16), what can be expected is the increased need for joint arthroplasty in obese people(16,17). Surgeries alone take longer time on obese patients (17), the rates are higher and complications during hospital stay last longer, and some authors have even suggested refusing to implant endoprostheses in obese patients(17).

Todkar *et. al* (18) established that having a higher BMI is related to less physical activity, which in turn resulted in less wear and tear of the endoprosthesis(18). On the other hand, there was a greater force affecting the prosthesis of obese patients and led to early loosening of the prosthesis(18).

Walter *et. al* (19) in their study state that patients with a BMI over 25.00 had early complications such as infection, post-operative haematoma, deep vein thrombosis and pulmonary embolism, and endoprosthesis dislocation 3, 4, 2 and 0.5 times more often(19).

Most authors in their work mention the BMI cut-off point(4,9,12,19,20) on which they base their consensus BMI for implanting a hip endoprosthesis. They believe that a BMI of up to 30 is the cut-off point between obesity and non-obesity(20) and patients with their BMI over 30 do not need endoprosthesis implantation until they have reached a BMI of up to 30 [20]. Another group of authors do not recommend endoprosthesis implantation when the BMI is over 35(21).

## 6. CONCLUSION

Obesity is a factor in developing coxarthrosis early, especially in women. A decrease in the number of people who are overweight would certainly result in fewer joint damages and endoprosthetic indication. Surgical implantation of endoprostheses in obese persons is technically more difficult and it is related to more complications than in case of normal weight patients. Both objective and subjective results in obese patients are less successful.

The examined sample has therefore led us to believe that the implantation of a hip endoprosthesis should be postponed for patients with a BMI exceeding 29.99. Such patients should receive endocrine treatment, they should undergo a weight loss programme in order to reduce their body weight and in order to reduce their BMI to under 29.99.

**CONFLICT OF INTEREST: NONE DECLARED**

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## ORIGINAL PAPER

# Single Stage Turn in Perforator Infraorbital Artery Island Flap for Nasal Ala Reconstruction

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**B**ackground: The reconstruction of full-thickness nasal ala defects is challenging procedure. Use of local flaps is acceptable approach. Flap based on infraorbital artery could be used for primary reconstruction of nasal ala defects. Methods: The prospective study include consecutive series of 15 patients with advanced skin carcinoma of the nasal ala and medial cheek staged T4 by TNM, in whom the turn in infraorbital flap was used. The patient characteristics, type of carcinoma and complications were analyzed. Results: The turn in infraorbital flap was used mostly in male patients (80%), mean age 64 years. The basal cell skin carcinoma was found in 60%. Skin layer was skin grafted. All flaps survived, but in one case a partial wound dehiscence. In one partial skin graft loss was found, and in two patients partial nasal obstruction occurred. These three complications were solved as secondary procedures under local anesthesia. Conclusion: Full-thickness defect of the nasal ala can be properly reconstructed using flap based on infraorbital artery providing exceptional esthetic and functional results, as single stage procedure. **Key words:** nasal reconstruction, infraorbital artery, infraorbital flap, perforator flap, nasal ala

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## 1. INTRODUCTION

Skin carcinomas in facial region frequently appear in the nasal ala where advanced disease and recurrent tumors could infiltrate alar cartilage (staged as T4 by TNM system for non-melanoma skin carcinoma). In those patients radical surgery with excision of full-thickness nasal ala is obligatory as curative procedure. If skin carcinoma spreads from the nasal ala to the medial cheek region or in the upper lip, the tumor excision is more challenging. In some cases, the carcinoma spreads into the subcutaneous tissue and the excision of the adjacent tissue in the cheek region is necessary, frequently reaching the bones of piriform aperture.

The reconstruction of full-thickness nasal ala defects is still demanding

problem. The aim of the reconstruction is to meet esthetic and functional goals. [1] The nose cheek groove must be reconstructed, enabling the nose breathing. [2] One of frequently used flaps for this reconstruction is the nasolabial flap supplied by facial and angular artery. [3,4] That flap can not be used in cases where: the tumor infiltration is deep and facial- angular arterial arcade is interrupted during surgery, or when this flap has been used in previous surgery. The use of perforator infraorbital island flap based on infraorbital artery is described as insular flap for reconstruction of nasal dorsum and side walls. [5]

Regional anatomy important for study: The infraorbital artery continue maxillary artery. It emerges on the face through the infraorbital foramen.

Facial branches enter the face deep to the infraorbital head of the quadratus labii superioris muscle, where they provide labial, nasal and palpebral branches to serve the lacrimal sac, nose and upper lip. The various branches anastomose with angular branch of the facial artery; others run toward the nose, anastomosing with the dorsal nasal branch of the ophthalmic; and others descend between the quadratus labii superioris and the caninus muscle and anastomose with the facial, transverse facial, and buccinator arteries. The skin territory of the perforator infraorbital flap based on infraorbital artery takes approximately 8 cm<sup>2</sup>, and it is in high 2 cm below the orbital rim and in wide 4 cm lateral from the alar cartilage. [6] The infraorbital island perforator flap can be used for the reconstruction of the whole nasal ala.

**Flap design:** The flap elevation begins with incision of the skin and subcutaneous tissue through the tailored margins according the defect size. During the preparation through subcutaneous layer, the medial margin of zygomaticus major muscle must be identified. Blunt dissection is performed and the flap raised from levator anguli oris and quadratus labii superioris muscle. The vascular pedicle consisting infraorbital artery and vein has to be preserved and flap raised and mobilized from lateral to medial. The perforator infraorbital flap is used as turn in flap

placed in defect of nasal ala, and re-sorbable sutures are used for flap positioning. The wound is closed in layers (flap skin and mucosa, and other layer is the flap subcutaneous tissue and surrounding subcutaneous tissue in defect edge). The reconstruction of external skin layer is performed using a partial thickness skin graft. The donor region is primary closed.

The simultaneous use of perforator island infraorbital flap and nasolabial flap on facial artery is advised for defects in the nasal ala and upper lip including the anterior part of the floor of the nose. Anterior nasal tamponade is used after surgery for three days.

## 2. MATERIAL AND METHODS

The prospective study (2000-2010) includes consecutive series of patients operated in an Univesity Clinical Centre for skin carcinoma in the nasal alla infiltrating the cartilage and staged as T4 according to the TNM classification for non-melanoma skin carcinoma. In all patients fullthickness nasal alla defect is combined with a defect of medial cheek region or upper lip including anterior part of the nasal floor. In all cases, the turn in infraorbital island perforator flap was used for full-thickness nasal ala reconstruction. We analyzed the patient characteristics (age, sex), tumor histology, size of skin flap, early and late complications and duration of hospital stay. The study was approved by the Ethical Committee of the Faculty of Medicine University of Nis, and the written consent from all patients.

## 3. RESULTS

The perforator island infraorbital flap was used in 15 patients for the full-thickness nasal ala reconstruction. In 12 patients, a part of the medial cheek was removed, but in three patients the tumor was infiltrated into the nasal ala and a part of the upper lip and nasal floor. Most patients were males. The mean age of the patients was 64 years (58 to 77)(Table 1). The primary carcinoma were found in five patients, and in 10 the recidivant disease. In nine patients the histology revealed the basal cell carcinoma (BCC), while other forms of non-melanoma skin carcinoma (squamous cell carcinoma (SCC)

Characteristic		No
Sex	Male	12
	Female	3
Age (years)	<60	3
	61-70	10
	71 +	2
Histological Type	BCC	9
	SCC	4
	Mixed BCC/SCC	2
Total		15

Table 1: Patient characteristics and histological type

Complication	No
Skin graft loss	1
Wound dehiscence	1
Delayed nasal obstruction	2
Total complication	4
Uneventful course	11
Total	15

Table 2: Postoperative course

or mixed type (SCC/BSS)) were less frequent (Table 1). All patients were operated with 5 -8 mm clinically clear margins, and the clearance of excision margins was proved histologically in all patients. All surgeries were performed under general anesthesia.

All flaps had isosceles triangle shape with its base medially. The size of the skin island was from 1.8x3.4 cm<sup>2</sup> to 2.2x 3.6 cm<sup>2</sup>. The counted surface of the skin island was on average 3.75 cm<sup>2</sup>. In all patients, the perforator island infraorbital flap was well vascularised and we did not register total flap loss (Figure 1,2). The partial loss of the skin graft was found in one case, but the defect healed by secondary intention during 14 days. In one case, a partial wound dehiscence was found near the nasal septum (the most distal part of the flap) and managed with secondary procedure under local anesthesia. The donor area healed without complications in all patients. In two patients during the follow-up we found the nasal breathing problems and partial nasal obstruction. The delayed trimming of flap was performed under local anesthesia in those

patients. The overall complications are presented in Table 2. All patients scars were inconspicuous. The hospital stay was 3 to 8 days (5 days on average).

## 4. DISCUSSION

The nose is the most prominent esthetic structure in the facial region, and the reconstruction is demanding. The nasal reconstructions were described in bibliographic data from the XVth century.[7] The description of nasal reconstruction with arm flap was described in the first textbook for plastic surgery “De curtorum chirurgia per insitio-nem” in 1597 by Gaspare Tagliagozzi. [8] The reconstruction of the nasal skin defects could be performed by different procedures. The most simple one is the reconstruction with full- thickness skin graft; the next one is the use of local and regional flaps.[9] A well-known and mostly used skin flap from the nasolabial region is supplied by the facial, angular and infraorbital artery. [7] For the reconstruction of skin de-



Figure 1: A- Preoperative view of skin carcinoma on nasal ala. B- defect, C- Flap raised, scissors point at flap pedicle, D- Early postoperative result, E and F postoperative view after 3 years.

fects in the lateral nasal wall there are different advanced, rotation or transposition flaps on infraorbital artery. [10-12] For the reconstruction of the defect on the nasal ala base, a jigsaw puzzle flap can be used.[13] For the lateral side of the nose and nasal cheek groove, a shark island pedicle flap from nasolabial fold can be used.[14] The defect on the nasal tip can be solved by a myocutaneous flap m.orbicularis oculi based on angular and infraorbital arteries.[15] In the available literature the use of glabellar, forehead flap, cheek advancement flap, temporo-



Figure 2: A- Preoperative view of skin carcinoma on nasal ala. B- Early postoperative result, C and D postoperative view after 6 years.

mastoid flap and microvascular flaps (forearm flap) have been described.[16] All flaps have been described with all their advantages and disadvantages, and in some of them the need for secondary reconstruction has been referred.[15] The infraorbital artery is a permanent anatomic structure with rich anastomotic network, including the facial artery and transversal facial artery. Skin flap based on infraorbital artery has been described in the last years for the reconstruction of paranasal region after burn injury or for the saddle nose deformity after surgery for Wegener's granuloma.[17,18] Some authors have used this flap in oncologic surgery for facial and nasal reconstruction.[19] Another authors have described the flap for nasal reconstruction based on transversal facial artery or as a flap on cutaneous zygomatic branch (from facial artery).[18,20,21] Gardeto et al. defined the flap for nasal reconstruction as a flap on infraorbital artery with strong anastomosis with transverse facial artery (branch of facial artery).[20] Some authors have defined the flap in nasolabial fold as reverse vascularized flap on angular artery but additionally supplied by infraorbital artery.[22] In recent reports the infraorbital flap is described for reconstruction of penetrated nasal defects as a single procedure. [5]

The reconstruction of full-thickness of the nasal ala must be analyzed as esthetic and functional problem. The re-

constructed ala has to be concave in shape. Lining of the ala has to be stable, and the flap from the nasal septum, skin graft or turn in the skin flap can be used. Sometimes, the reconstructed ala is too bulky causing airway problems. For the defects larger than 1.5 cm in diameter, the nasolabial flap is preferred, and the donor area is closed primary. [23] We did not use the cartilage support but in only 2 cases had moderate airway obstruction and performed correction under local anesthesia. Some authors have described the vascular supply of nasolabial flap with angular artery and lateral nasal artery.[24] The investigation of Rochrich et al. described the vascularization of the nasolabial flap as a random pattern on narrow subdermal plexus, and they favor neither angular nor flacial artery with its perforating branches through the muscle.[25] The insular flap based on infraorbital artery can be used in size 4 x 3 cm.[17] We found that smaller flap is sufficient for nasal ala. The infraorbital artery and its anastomosis with angular artery participate in vascularization of frontal region, additionally supplying the glabellar flap.[26] The esthetic requirement in the nasal reconstruction is aimed to form the nasal cheek groove. This can be obtained using pedicle flaps from nasolabial fold.[2] The biggest problem in the reconstruction of the nasal ala is obtaining the vestibular lining.[27] The disadvantage of the skin grafting as lining of the vestibule

is a potential graft loss and prolonged use of splint.[21] We used the turn in flap and skin graft for reconstruction. In our study, we found that the turn in flap achieved proper lining, but only in two cases we found partial airway obstruction. The use of turn in flap is previously referred for nasolabial flap. [28,29] As the flap is well-vascularized, while we did not find any partial or total flap loss. The infraorbital artery is sufficient vascular supply for the perforator infraorbital flap, and its vascular supply does not depend on the facial artery.

## 5. CONCLUSION

Turn in the infraorbital island perforator flap has well-defined pedicle, and can be used for reconstruction of full-thickness nasal ala defects. The flap can be safely used in cases where the nasolabial flap based on facial artery has been used for previous surgery, or in cases where the facial-angular artery arcade had been cut during the previous tumor removal or injury. The flap can be used without cartilage support and the obstruction is rare. The technique for flap harvesting is quite versatile and we can suggest its use for nasal reconstruction.

CONFLICT OF INTEREST: NONE DECLARED

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## ORIGINAL PAPER

# Are We on the Path to Solve the Enigma of Resistant Hypertension: Renal Sympathetic Denervation

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**R**enal sympathetic denervation (RSD) opens new perspectives and possibilities not only in the treatment of resistant hypertension but also of other cardiometabolic diseases. In patients with hypertension, it has been demonstrated that activity of the sympathetic nervous system correlates with grade of hypertension. Decreasing sympathetic activity using RSD significantly reduces blood pressure in resistant hypertension. It is too early to say a definite opinion about appropriateness of this method in the treatment of resistant hypertension, because there are not great studies with huge number of the patients. After we get and evaluate these results through a longer span of time, only then we shall know what is the role of RSD in the treatment of resistant hypertension and other cardiometabolic conditions related to increased function of the sympathetic nervous system, such as heart failure, diabetes mellitus, obstructive sleep apnea, renal disease with microalbuminuria and macroalbuminuria. **Key words:** resistant hypertension, sympathetic denervation.

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## 1. INTRODUCTION

Unlike the other risk factors of cardiovascular diseases, arterial hypertension has got a special position. Today it's known that arterial hypertension is one of the most important health problems, maybe the most important one which implicates early disease, disability and mortality in adult population. According to its characteristics, essential hypertension has assumed the features of the biggest non infectious epidemic of the 21st century. According to great *Global Burden of Disease Study* in 2010, 9.4 million of people in the world died because of hypertension (1).

Hypertension treatment was effective during a few last decades thanks to very impressive palette of antihypertensive medicaments. However, although when a few drugs are administered, the target values of blood pressure are not reached in some patients. In these

cases we talk about resistant hypertension. In the latest guidelines for the management of hypertension issued by the European Society of Hypertension (ESH) and European Society of Cardiology (ESC), resistant hypertension is defined as failure to achieve a blood pressure (BP) goal of <140/90 mm Hg, despite treatment with  $\geq 3$  different antihypertensive medication classes at a maximally tolerated dose and, including a diuretic (2). Nowadays it is considered that prevalence of resistant hypertension is 5 to 30% (3, 4, 5, 6). Resistant hypertension is associated with an increased risk of cardiovascular events, including myocardial infarction, stroke, congestive heart failure, and chronic kidney disease (7, 8, 9). Besides, there is often decreased stress tolerance in the patients with resistance hypertension, and at the same time they suffer from anxiety and depression. Qual-

ity of life of those patients is decreased significantly as well as their quality of sleep. Also, with the time, cognitive dysfunctions develop. Resistant hypertension has a substantial impact on many areas of everyday life, including attitudes, functional abilities, and interpersonal relationships (10). In these patients, one should consider new therapeutic options, because their arterial blood pressure can't be normalized by already used drugs.

## 2. CENTRAL ROLE OF THE SYMPATHETIC NERVOUS SYSTEM IN THE PATHOPHYSIOLOGY OF RESISTANT HYPERTENSION

Man is exposed to a fast way of living and, at the same time, to the chronic hyperactivity of the sympathetic nervous system with more or less stress, which results in serious consequences. Sympathetic overactivity is during long period associated with arterial hypertension, reduced renal function, left ventricular hypertrophy, heart insufficiency, arrhythmia, obstructive sleep apnea syndrome (OSA), insulin resistance and diabetes mellitus. Relationship between increased activity of the sympathetic nervous system and arterial hypertension is of a particular importance (11). Activity of the sympathetic nervous system in patients with hypertension is proved to correlates with the degree of hypertension. The

sympathetic nervous system overactivity involves the kidney and increases progressively and parallel with hypertension severity stages (12).

In other words, the higher value of arterial hypertension is measured, the more activity of the sympathetic nervous system is found. The kidneys have a very important role in long term regulation of blood pressure. The kidney is an organ where efferent sympathetic impulses are active, but the activity of the sympathetic nervous system is also mediated by the afferent nervous fibers.

Efferent impulses of sympathetic nervous system make a greater resistance in kidneys, reducing of blood flow in kidneys, increasing of reabsorption of sodium and water, and at the same time they stimulate production of renin.

It leads to increasing of blood pressure and creates a vicious circle: development of renal ischemia activates renin-angiotensin system (RAS) and, through the oxidative stress, it activates the afferent sympathetic renal fibers which go from kidneys to central nervous system, and continue to activate sympathetic nervous system (13, 14).

Pathophysiological concept that high blood pressure can be lowered if overactivity of the sympathetic nervous system is reduced is not recent information. In the first half of the 20th century when there were no antihypertensive drugs available, surgical sympathectomy was used as a last resort. But this procedure was not used in everyday practice because of high peri- and postoperative mortality, as well as because of other adverse events such as postural hypotension, functional disorder of the bladder and intestines, anhidrosis, perioperative death, stroke, myocardial infarction, paraplegia and spinal cord injury.

At the same time, the intervention was unpleasant for patient and the success of the intervention could not be estimate. In the 50s of the past century, the interest for this procedure declined when reserpine was discovered. The discovery of diuretic chlorothiazide in 1957 and its use in the therapy of hypertension caused the surgical sympathectomy to become definitely obsolete.

### 3. RENAL SYMPATHETIC DENERVATION

Nowadays there is an alternative access to drug treatment in resolving of resistant hypertension using new access and method. Percutaneous transluminal radiofrequency sympathetic denervation (RSD) of the renal artery for resistant hypertension aims to disrupt neurogenic reflexes involved in blood pressure control. Intervention is performed under local anesthesia. The patient will receive an adequate premedication in term of analgesics (e.g. morphine 5-10 mg), as well as sedation (e.g. midazolam 1-3mg). Unfractionated heparin is given intravenously at a dose aimed at reaching an activated clotting time (ACT) of > 250 seconds. Besides, dosed 100 µg nitroglycerine must be introduced through the guiding catheter before the procedure to avoid vasospasm (15). Device consists of a catheter with tip connected to the radiofrequency generator (50 Hz, 5–8 W). Catheter-based renal denervation is a minimally-invasive procedure in which doctors use a catheter, inserted through the femoral artery in the groin, to send radio waves that burn away nerve tissue around the kidney arteries. The catheter is connected to a generator which delivers low-power radiofrequency energy in 2-minute applications to each renal artery at 4–6 points along its length, in a spiral pattern. The catheter tip requires multiple rotations and application of further radiofrequency energy in a spiral pattern to ensure all nerves are evenly exposed. Continuous temperature monitoring assures that the power unit detects any overheating of the arterial wall and the application of energy interrupted immediately. Then it should be repeated on the contralateral kidney. The intervention lasts about 45 min. Next day, the patient will be discharged. In Symplicity HTN-1 as well as in Symplicity HTN- 2 studies, Medtronic Symplicity catheter system is used. Currently, more than 50 companies are developing renal denervation systems. Techniques beyond radiofrequency include: ultrasound, “external ultrasound”, direct drug delivery/pharmacological injection system, microwave. Single electrode based system is now considered “first generation”. Use

of multielectrode devices appear to improve outcomes and increased safety.

### 4. INDICATIONS AND CONTRAINDICATIONS FOR RENAL SYMPATHETIC DENERVATION

In the meantime, International Society of Hypertension and European Society of Cardiology have published guidelines for patient selection and also the intervention itself (16, 17). Indications for renal denervation in patients with resistant hypertension are: a) on at least 3-4 antihypertensive drugs; and b) blood pressure under treatment >140/90 mmHg. Anatomically favorable factors are following: one renal artery supplying each kidney length of main renal artery >20 mm and renal artery diameter more than 4 mm (15).

Contraindications for renal sympathetic denervation are the following: previous renal artery intervention (balloon angioplasty or stenting), evidence of renal artery atherosclerosis (defined as a renal artery stenosis >50%), presence of multiple main renal arteries in either kidneys or main renal arteries of less than 4 mm in diameter or less than 20 mm in length and estimated glomerular filtration rate <45 ml/min per 1.73m (16).

### 5. CLINICAL STUDIES

Clinical studies of this therapeutic option, show that systolic pressure decreases significantly and in average by 25 to 30 mmHg and diastolic by 10 to 15 mmHg and that antihypertensive effect is lasting at least for two years. Symplicity HTN-1 was the first great study where the procedure of renal sympathetic denervation was used (18). In this study 153 patients (mean age 58+<sub>9</sub> years) with severe resistant hypertension (office systolic blood pressure  $\geq$ 160mmHg with at least three or more antihypertensive medications, including a diuretic) were included. Baseline office systolic blood pressure/diastolic blood pressure values were 177/101 mmHg with 5.1 antihypertensive drugs on average. RSD was achieved using a radiofrequency ablation catheter inserted through the femoral artery. After RSD was performed and controls

were made after 1, 3, 6, 9, 12, 18 and 24 months, blood pressure values were lower by 20/10, 24/11, 25/11, 23/11, 26/14 and 32/14 respectively. Renal noradrenaline spillover was found to be reduced by 47% thereby demonstrating the effectiveness of sympathetic renal fibers ablation. Noradrenaline spillover is a marker of sympathetic overactivity. Measurements of noradrenaline spillover may help with estimating the activity of the efferent renal sympathetic nerve (19, 20, 21). Besides, it's important that the effects of denervation persist at least until 24 months. The intervention was free of complications in 97% of patients (149 of 153). Neither reported adverse effects associated with hemodynamics, electrolytic abnormalities, or reducing of the renal function. Together with the decreasing of blood pressure, improvement in health-related quality of life was observed (22).

The Symplicity HTN-2 trial is an international, multi-center, prospective, randomized, controlled study of the safety and effectiveness of renal denervation in patients with treatment-resistant hypertension. Patients with baseline systolic blood pressure of 160 mmHg or more were randomly assigned to renal denervation with previous treatment or to maintaining previous treatment alone (control group). A group of 106 patients were randomized to renal denervation (52) or control (54) groups. Office based blood pressure measurement in the renal denervation group decreased by 32/12 mmHg, whereas they did not differ from baseline in the control group. Between group differences in blood pressure at 6 months were 33/11 mmHg. At 6 months, 41 (84%) of 49 patients who underwent renal denervation had a reduction in systolic blood pressure of 10 mmHg or more, compared with 18(35%) of 51 controls (23).

## 6. "NON DIPPING" AND "REVERSE DIPPING"

It's important to emphasize that in context of Symplicity HTN-1, Symplicity HTN-2 trial and RSD, activity of the sympathetic nervous system is significantly decreased in both non dipping and reverse dipping patients. Today it is known that, during the night, blood

pressure doesn't decrease in patients so called *non dippers*, and the risk of cardiovascular death increases by 2,5 in relation to *dippers*, what is demonstrated with help of ambulatory blood pressure measurement (ABPM). The risk is still higher *in reverse dippers*, in patients who suffer from increasing of blood pressure during the night. In these patients risk of lethal cardiovascular event is four times higher in relation to *dippers* (24). RSD decreases activity of the sympathetic nervous system, as mentioned above. Because of that it's expected that renal denervation will be effective *in non dippers*.

Consequently, RSD is safe and effective in reducing office blood pressure, home blood pressure, and 24 h blood pressure in patients with drug resistant hypertension. The positive effect persisted during the period of 36 months. However, blood pressure did not decrease immediately after the RSD. That means that RSD changes neurohumoral control of excretion of water and salt and blood pressure, accordingly. RSD did not cause any damage of the vessel wall. No serious adverse events related to the procedure were reported either in Symplicity HTN-1 or in Symplicity HTN-2 trial.

## 7. SYMPPLICITY HTN-3 TRIAL

Symplicity HTN-1 and HTN-2 have shown sustained blood pressure reduction at 24 months. It is not a long period when considered essential hypertension to be a chronic disease with permanent medical treatment. And after all, the crucial question whether that effect of decreasing blood pressure will continue and how long. Maybe Symplicity HTN-3 trial will solve the dilemmas. This trial is a multicentre, prospective, single-blind, randomized, and controlled study. In this study, 530 patients aged 18 to 80, with average systolic blood pressure  $>160$  mmHg will participate. The patients will be on stable medication regimen of full tolerated doses of  $> 3$  antihypertensive medications, with one being a diuretic (25).

## 8. ROLE OF THE SYMPATHETIC NERVOUS SYSTEM IN RENAL DENERVATION IN CONGESTIVE HEART FAILURE

Today it is well known that disturbed neurohumoral system has a key role in the process of chronic heart failure. In patients with heart failure several neurohumoral systems are activated, especially the sympathetic nervous system and renin-angiotensin system (RAS). The mentioned systems contribute to deterioration of heart failure. The long-term activation of neurohormonal systems has a toxic effect upon heart failure. Catecholamines and angiotensin II have negative effect upon heart failure. Activation of RAS can produce peripheral edemas and increased retention of sodium and water. At the same time, the activation of RAS contributes to hemodynamic abnormalities, leading to constriction of peripheral arteries and veins. The longer the period of heart failure, the higher is the level of noradrenalin. The patients with the highest values of noradrenalin have the worst perspective (26). Noradrenalin can cause dysfunction and death of cardiac myocytes. Increasing of cyclic AMP, noradrenalin can rise concentration of intracellular calcium which, if prolonged, causes the state of calcium overload and cell necrosis (27). Following prolonged activation of the sympathetic nervous system, the cellular pathways that respond to and mediate the effects of catecholamines are altered in heart failure. Activation of the sympathetic nervous system increases heart rate, which negatively influences upon further development of chronic heart failure. Further effects of the intensified secretion of angiotensin and aldosterone together with simultaneous increasing of already mentioned heart rate, have negative effects on the heart. The increased renal afferent sympathetic activity contributes, on its part, to worsening of the pathophysiology mechanism, so making RSD to be one of therapeutic options in management of heart failure. A study which enrolled patients with resistant hypertension who were treated using RSD recorded not only significant decreasing of sys-

tolic and diastolic blood pressure, but also significant regression of the left ventricular hypertrophy (28). Results of this study have very important prognostic implications in high risk patients with resistant hypertension. In another study involving patients with resistant hypertension, RSD led to significant decrease of systolic and diastolic blood pressure. At the same time, the number of premature ventricular contractions was significantly decreased. The total number of premature supraventricular contractions was also significantly decreased after RSD (29). Symplicity HF Study (Renal Denervation in Patients With Chronic Heart Failure) will answer the question how effective RSD is in patients with heart failure. The study will enroll approximately 40 adult subjects with chronic heart failure (NYHA II-III) and renal impairment and ejection fraction less than 40% with optimal medical therapy.

## 9. INFLUENCE OF RENAL DENERVATION OF THE SYMPATHETIC NERVOUS SYSTEM ON REGULATION OF GLUCOSE AND DIABETES

It's not rare that hypertension is associated with damaged glucose tolerance, type 2 diabetes, obesity or increased values of cholesterol. In patients with both hypertension and type 2 diabetes increased activity of the sympathetic nervous system is observed (30). Studies show that people with sympathetic reactivity are inclined to develop insulin resistance with increased glucose values (31). Just because of that, resistant hypertension is discovered in great number of patients with diabetes (32). Obesity, hypertension and insulin resistance have common pathophysiology mechanism. Insulin resistance is found in both thin and fat people suffering from hypertension which means that insulin resistance is related to the basic determinants of blood pressure. Consequently, adrenergic nervous system plays a crucial role in glucose and insulin metabolism regulation, and insulin resistance may represent an important determinant of the adrenergic activation detectable in cardiometabolic disease (33). As mentioned above,

obviously decreasing of sympathetic activity with RSD can improve insulin sensitiveness and glucose metabolism. Two studies have observed changes in insulin resistance following renal denervation for the treatment of resistant hypertension (34, 35). Another meta-analysis shows that ablation of efferent and afferent sympathetic renal nerves improves glucose metabolism, reducing the incidence of glucose intolerance, fasting hyperglycemia and diabetic state in resistant hypertensive patients (33).

The effect of RSD was assessed in a sub-study of the Symplicity HTN-2 trial in 37 patients and 13 controls. Three months after the procedure, the authors observed a significant decrease in fasting glucose, insulin, and C-peptide levels. Oral glucose tolerance and the sensitivity to insulin measured by the HOMA-IR (homeostasis model assessment-insulin resistance) were both significantly improved compared to the control group where no significant changes were observed (36). Also, it was demonstrated that the level of glycosylated hemoglobin (HbA1c) decreased after RSD was performed.

In another sub-study of the Symplicity HTN-2 trial, where ten patients with resistant hypertension, obstructive sleep apnea, and metabolic syndrome were included, evident significant decreasing of the office blood pressure by 34/13 mmHg, together with improvement of the glucose homeostasis, as well as reduction in severity of the obstructive sleep apnea were demonstrated after 6 months (37). Useful effects of RSD effects upon metabolic syndrome can be explained in the following way: inhibition of central sympathetic tonus, reduced noradrenalin release, better perfusion of skeletal muscles, which is achieved reducing alpha adrenergic tonus that gives rise to enlarged glucose uptake. Other mechanisms such as inhibitor effect on renin-angiotensin system, reduced glucogenesis and reduced secretion of glucagon are included.

The role of renal denervation in improving of insulin resistance will be topic of DREAMS (Denervation of the Renal Artery in Metabolic Syndrome) study. This study is an observational study, with the aim to investigate the

effect of renal denervation on changes in insulin resistance and blood pressure in patients with obesity related hypertension.

## 10. EFFECT OF RENAL DENERVATION UPON OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea, often considered a cause of resistance in patients with essential hypertension, may also be a consequence of increased central sympathetic tone (38, 39). Obstructive sleep apnea syndrome is associated to increasing incidence of sudden cardiac death, heart failure and ischemic heart disease (40, 41). In these patients with dream disturbance, during the night, very strong activity of the sympathetic nervous system is present, which could be a cause of arterial hypertension. Because of that, influence of renal denervation on development and clinical features of obstructive sleep apnea syndrome has been studied. Witkowski studies series of patients with sleep apnea and pre and post renal denervation for resistant hypertension suggesting that denervation and/or blood pressure reduction alone reduces the frequency of apneic-hypopneic episodes. Apnea/hypopnea index was reduced from an average of 16.9 to 4.5 episodes per hour, with a concomitant decrease in oxygen desaturation index (37).

## 11. CONCLUSION

RSD is a new method in treatment of resistant hypertension. This procedure opens new perspectives and possibilities in management of resistant hypertension. Perhaps one day it will be used for treatment of grade 1 and grade 2 hypertension, which would be important not only from medical aspect, but from economical one, also. However, it is too early to define final attitude towards appropriateness of this method in treatment of resistant hypertension, because we still do not have results of huge studies with great number of patients. After we get and evaluate these results through a longer span of time, only than we shall know what is the role of RSD in the treatment of resistant hypertension and other cardiometabolic conditions related to increased func-



tion of the sympathetic nervous system, such as heart failure, renal disease with microalbuminuria and macroalbuminuria, diabetes mellitus, obstructive sleep apnea or intolerance to drugs. Current studies should answer a few questions, such as what are long-term consequences upon kidney function after RSD, and others. Also, evaluation of eGFR (glomerular filtration rate) should be done in significantly greater number of patients than before. We should get the answer concerning effect of RDS on cardiovascular morbidity and mortality through longer period. Another important question is whether re-innervation develops, in other words, whether regeneration of afferent and efferent fibers arise. The problem why 23% of patients did not respond to RSD treatment expects the answer. Finally, there is an important question if RSD can be repeated in the patients with whom we did not succeed on the first time to burn the afferent and efferent fibers. Resistant hypertension is still actual and complicated problem, despite of great number of antihypertensive drugs which block the sympathetic nervous or renin-angiotensin system on a few levels, but without significant effects. However, it must be emphasized that the studies with RSD involving relatively small number of patients and sometimes without a control group, speak in favor that renal denervation, may solve the problem of resistant hypertension.

**CONFLICT OF INTEREST: NONE DECLARED**

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## REVIEW

# New Views On Cesarean Section, Its Possible Complications And Long-Term Consequences For Children's Health

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**H**istorical developments and advancements in cesarean section techniques and logistics have reduced the maternal and neonatal risks associated with the procedure, while increasing the number of operatively completed pregnancies for medically unjustifiable reasons. The uncritical attitude towards cesarean section and the fast emergence of 'modern' diseases such as obesity at a young age, asthma, type 1 diabetes mellitus and various forms of dermatitis have stimulated researches associating cesarean section with these diseases. Intestinal flora of the children born by cesarean section contains less bifidobacteria, i.e. their intestinal flora is similar to the intestinal flora in diabetic individuals. In children born by cesarean section, the 'good' maternal bacterial that are normally found in the maternal birth canal and rectum are lacking, while the 'bad' bacteria that may endanger the child's immune system are frequently present. In children born by vaginal delivery, the 'good' maternal bacteria stimulate the newborn's white blood cells and other components of the immune system, which has been taken as a basis for the hypotheses explaining the evident association of the above morbidities and delivery by cesarean section. **Key words:** cesarean section, complications, obesity, asthma, dermatitis, type 1 diabetes mellitus

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Cesarean section is the most common major obstetric surgery and the oldest operation in the field of abdominal surgery, used for delivering the newborn and the placenta through the abdominal wall incision (laparotomy) and uterus incision (hysterectomy), followed by suture of the uterus and abdominal wall layers. Until the 17<sup>th</sup> century, cesarean section was exclusively lethal operation for the mother, performed to save the newborn's life from dead or dying mother. Although the term 'cesarean' was long believed to derive from the Roman emperor Gaius Julius Caesar (100-44 B.C.), according to legend born by cesarean section, it is

now considered quite unlikely because his mother was found to have lived for years after the delivery. In the first half of the 19<sup>th</sup> century, maternal mortality after cesarean section was 60%-100%; at the beginning of the 20<sup>th</sup> century, cesarean section was associated with 25% maternal mortality and 24% neonatal mortality, mostly due to sepsis or exsanguination. The operating technique has gone through a millennial evolution, having developed according to professional achievements of the time and depending on improvements in aseptis, abdominal surgery, anesthesia, and transfusion medicine. There have been a number of laparotomy modifications

(e.g., lower medial laparotomy, Pfannenstiel, Pandolf, Maylard, pararectal Kullisen, Joel-Cohen laparotomy), extraperitoneal and transperitoneal access to gravid uterus, various types of hysterotomy (classic longitudinal Sännger corporeal, longitudinal Selheim isthmic, cross Kerr isthmic incision), various techniques of uterus suture (hysterotomy non-suture, multi-row, double-row and single-row suture), suturing materials (wire, catgut, silk, synthetic absorbable materials, etc.), and suture of laparotomy layers. Dörffler made a breakthrough in the then operating techniques in 1929, when he published a description of the cesarean section technique, which has been used down to the present in some hospitals. Dörffler unified Pfannenstiel laparotomy and Kerr hysterotomy, and inaugurated a new technique, *sectio caesarea transperitonealis isthmica in situ sec. Dörffler*, which then considerably reduced the overall maternal mortality while enabling future deliveries after cesarean section either by repeat cesarean section or by vaginal delivery (1,2).

Improvements in the obstetric surgical techniques based on modern, scientifically evidenced concepts were made in the last decades of the 20<sup>th</sup> century, having led to a simpler and less traumatizing approach to cesarean section with better postoperative recovery and outcome. Starck has rationalized

all the new approaches and introduced a new technique of cesarean section, Misgav Ladach cesarean section, named after the hospital in Jerusalem where the method had been developed from 1983 and published in 1994, since when it has been accepted all over the world (3,4). This new method of cesarean section is based on Joel-Cohen laparotomy from the 1970s, originally intended for abdominal hysterectomy respecting structural anatomy and following the principles of surgical minimalism (5). Misgav Ladach cesarean section is the result of critical assessment of each surgical step, with the aim to cause minimal tissue damage, eliminate unnecessary and some harmful steps, and improve the procedure safety, simplicity and efficiency. Blunt abdominal entry is preferred, which is achieved mostly by tissue stretching by fingers and minimal use of sharp surgical instruments, while suturing of the abdominal wall layers is reduced to only three layers (uterus, muscular fascia and skin). In this way, the likelihood of postoperative adhesions within the abdominal cavity is reduced because the amount of surgical stitches that induce foreign body reaction in spite of all advancements is by far lower. In addition, the length of operation, and thus of anesthesia, as well as the loss of blood and the need of antibiotics, analgesics and antipyretics are reduced, along with earlier patient mobilization, faster recovery and earlier discharge from the hospital. Cesarean section performed by the Misgav Ladach method is closer to the natural, vaginal delivery. Misgav Ladach cesarean section can also be called a minimally invasive cesarean section, and currently it is the cesarean section method of choice. Its value has been demonstrated by numerous evidence based medicine reports and its utilization in daily practice all over the world for more than 15 years now (1,6-8).

The rate of cesarean section has been on a continuous increase for justifiable as well as unjustifiable medical and non-medical reasons, and this trend should preferably be discontinued. The recommended rate of cesarean sections is around 15% in the largest and best-equipped obstetric tertiary centers with a high concentration

of gestational and obstetric pathology, whereas in smaller maternity units it should be even lower (1). Although the operative technique and logistics have considerably improved, thus reducing the morbidity and mortality associated with cesarean section, it should still be borne in mind that cesarean section remains a serious operation burdened with certain risks and complications, as well as with long-term consequences for both the mother and the child. The incidence of intraoperative complications is estimated to 12%-15%; complications are less common during elective cesarean section (2.6%-6.8%) versus emergency cesarean section (5.2%-14.8%) (9). The possible intraoperative complications include fetal head impaction in the pelvis (head extraction impossible), uterocervical lacerations with hemorrhage, damage to the peritoneal vasculature on the inferior uterine segment incision, bleeding from the placental bed, invasive malplacenta, uterine atony, lesions of the urinary bladder, ureter and intestine, neonatal lesions, and complications associated with anesthesia (1). The most common early postoperative complications are wound infection (in 3%-15% of patients), seroma, wound dehiscence, anterior abdominal wall hematoma, endometritis (13%), very rarely necrotizing fasciitis, which is associated with a high maternal mortality, and pelvic vein thrombophlebitis. The incidence of septic thrombophlebitis is 1 per 9000 deliveries in vaginal delivery and 1 per 800 deliveries in cesarean section (10). The incidence of deep vein thrombosis is 1 per 1000 deliveries; in cesarean section, it is 20-fold that recorded in vaginal delivery. Pulmonary embolism occurs in 1% of cases with deep vein thrombosis. The incidence of postpartum urinary infection and hemorrhage is 2%-4% and 5%-8%, respectively (10). Scar rupture during subsequent pregnancy or delivery should be taken in consideration as a possible late postoperative complication. The incidence of scar rupture varies according to the type of cesarean section scar, as follows: classic incision 4%-9%; T-incision 4%-9%; low vertical incision 1%-7%; and low transverse incision 0.2%-1.5% (11). In subsequent pregnancies, *placenta previa*, *placenta*

*accreta*, *placenta increta* and *placenta percreta* are more commonly found after previous cesarean section. The women with a history of cesarean section are at a 2- to 5-fold greater risk of *placenta previa*, with the risk increasing with the number of previous cesarean sections (12). Endometriosis in the cesarean section scar is found in 0.03%-0.4% of cases (13), while the incidence of ectopic pregnancy within the previous cesarean section scar is estimated to 1 per 2000 pregnancies (14). The incidence of postoperative complications is 35.7%, with minor complications accounting for 23.7% in elective cesarean section and for 34% in emergency cesarean section. In case of massive postpartum hemorrhage threatening the mother's life, laparotomy and hysterectomy are indicated, the latter being 13 times more frequently performed in deliveries completed by cesarean section as compared with vaginal deliveries (1). In cesarean section, neonatal lesions occur in 1.1% of cases, most frequently superficial incisional wounds of the leading part inflicted by the scalpel (0.7%), cephalhematoma (0.2%), fractures of the skull and other bones with peripheral nerve lesions (0.02%), lesions of the brachial plexus (0.02%), and facial nerve palsy (0.03%) (15). The children born by cesarean section may have a lower Apgar score, mostly due to anesthesia. They may also suffer breathing difficulties, which may occur in the first few hours of the procedure. Cesarean section as an unnatural type of delivery definitely implies neonatal stress and shock because the neonate does not pass through the birth canal; that is why in the past, these newborns used to be called 'cut out' (*caesones*) or 'unborn' (*nonatus*). In case of erroneous gestational age assessment, immature children are being born by cesarean section (1). The risk for the neonate is only reduced but not eliminated by cesarean section, while maternal morbidity and mortality are increased 3 to 8 times relative to spontaneous delivery (8). In addition to the potential maternal and neonatal intraoperative and early postoperative complications of cesarean section listed above, the issue of long-term consequences for the child born by cesarean section has been increasingly



tackled in recent years. As cesarean section for unjustified reasons still shows a rising tendency in many countries (e.g., in China and Brazil, where it is related to the socioeconomic status), a number of studies investigating the long-term consequences in children born by cesarean section have been launched (16). Some large studies found correlation of the type of delivery completion and numerous today's morbidities such as obesity, asthma, various forms of dermatitis, type 1 diabetes mellitus, etc. (15,17-20). As reported by Ziegler *et al.*, based on the results obtained in their BABYDIAB study, the children born by cesarean section have a twofold risk of developing type 1 diabetes mellitus recorded in children born by vaginal delivery (incidence 4.8% vs. 2.2%). The mechanism by which a delivery by cesarean section increases the risk of developing type 1 diabetes mellitus remains obscure. It has been postulated that the intestinal flora of these children contains a lower number of bifidobacteria, i.e. that their intestinal flora is similar to that of diabetic individuals. Bifidobacteria belong to the most important group of efficient intestinal bacteria (21). Studies conducted in Brazil and Norway demonstrated the association between the type of delivery and development of obesity, asthma and various forms of dermatitis in children born by cesarean section. Results of the Brazilian studies indicate the prevalence of obesity in children born by cesarean section to be higher by 33% and in those aged 19 years by even 50% in comparison with children born by vaginal delivery, while Norwegian studies suggest the prevalence of asthma to be significantly higher in the first 36 months of life in children born by cesarean section (17-19).

There are two hypotheses on the possible causation and association of the mode of delivery and the mentioned diseases. According to one hypothesis, during delivery, the children born by vaginal delivery come in contact with the maternal 'good' bacteria, which are normally found in the maternal birth canal and rectum. When these bacteria are transferred to the newborn, they pass along the newborn's gastrointestinal system and settle in the small and

large intestine. In children born by vaginal delivery, the maternal 'good' bacteria stimulate neonatal white blood cells and other components of the immune system (production of type 1 and type 2 T-helper cytokines in particular) for body's defense (19,22). On the other hand, the children born by cesarean section are deprived of coming in contact with the bacteria mostly found in the maternal birth canal and rectum. In case of elective cesarean section, there is no contact of the newborn with maternal bacteria, whereas in emergency cesarean section such a contact may still occur. In these children, their gastrointestinal system is colonized by cutaneous and nosocomial bacteria (19). They lack the 'good' maternal bacteria, while 'bad' bacteria that may aggravate the neonatal immune system are frequently present. According to some studies, these children have a higher incidence of neonatal respiratory infections, which are associated with the development of asthma, obesity, type 1 diabetes mellitus, various forms of dermatitis, etc., later in life (17,18,20,22).

While the historical development of the cesarean section techniques and logistics has reduced the rate of maternal and neonatal complications associated with the procedure, it has also entailed an uncritical increase in the rate of operative pregnancy completion irrespective of indications. This uncritical attitude towards cesarean section, along with the fast emergence of the 'modern' diseases such as young age obesity, asthma, type 1 diabetes mellitus and various forms of dermatitis, have suggested the possible association between the mode of delivery and these morbidities. The studies cited above have hypothesized and pointed to this association. In many countries, a variety of the potential short- and long-term complications associated with cesarean section described over time did not result in critical reduction of the procedure; however, the long-term unfavorable consequences observed in children born by cesarean section should urge us to turn to a clearer and more rational reasoning. Results of the mentioned studies on the potential long-term consequences in children born by cesarean section should be re-evaluated and ad-

ditionally corroborated in future studies. The newer, simple and sparing Misgav Ladach method of cesarean section is closer to the natural, vaginal delivery and currently is the method of choice, its value being demonstrated by many evidence based medicine studies, as well as by its utilization in daily routine all over the world for more than fifteen years now.

**CONFLICT OF INTEREST: NONE DECLARED**

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