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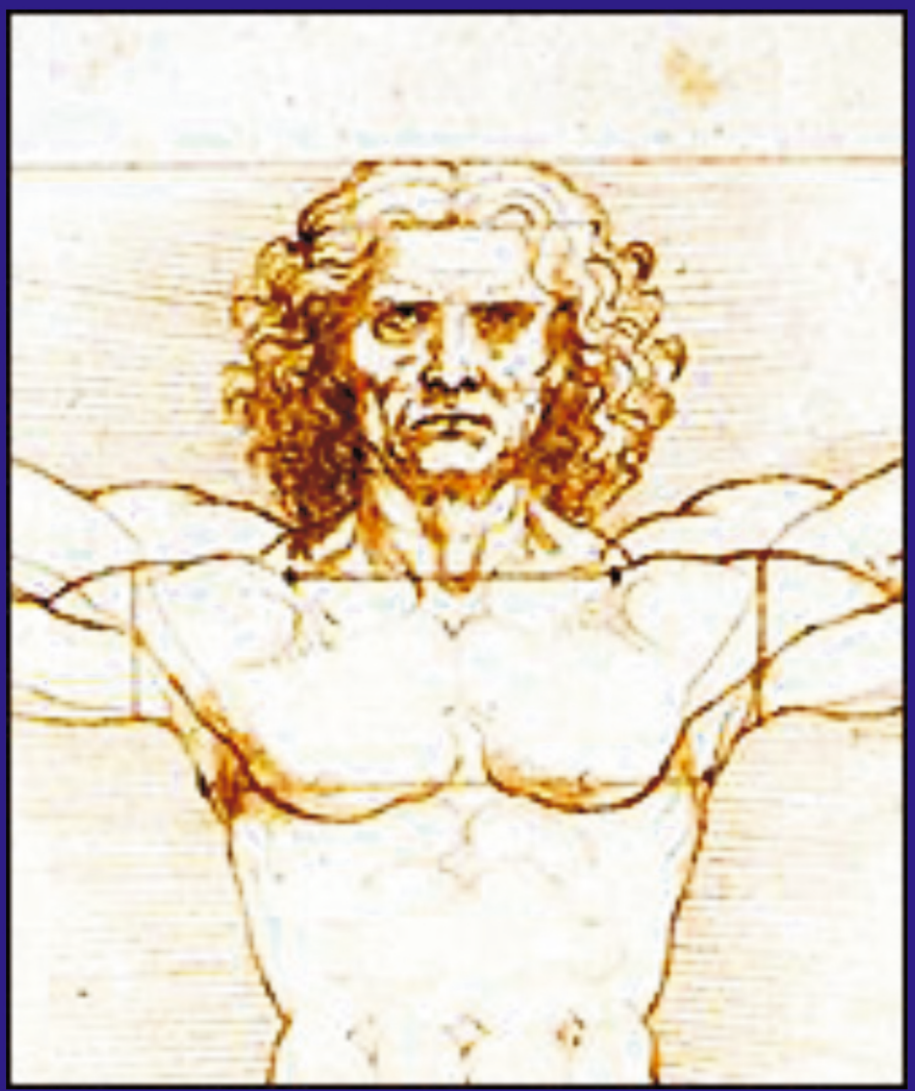

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Avdo Ćeranić

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Original article

THE IMPORTANCE OF DETERMINING THE UROMODULIN SERUM CONCENTRATION IN DIABETES MELLITUS TYPE 2 PATIENTS

Jordanova Elena,[1] Samardzic Vladimir,[2] Pekovic-Perunicic Gordana,[1] Tica-Jevtic Jelena,[2] Simic-Ogrizovic Sanja[3, 4]

[1] Department of Nephrology, Clinic for Internal Medicine, Clinical Hospital Center Zemun, Belgrade, Serbia
[2] Department of Endocrinology, Clinic for Internal Medicine, Clinical Hospital Center Zemun, Belgrade, Serbia
[3] Medigroup Hospital, New Belgrade, Belgrade, Serbia
[4] University of Banja Luka, School of Medicine, Banja Luka, Bosnia and Herzegovina

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Abstract: **Introduction:** In the kidney, cells in the thick ascending limb of the loop of the Henle synthesized uromodulin (UMOD). This study aims to present the evaluation of the uromodulin serum concentration in diabetes mellitus type 2 (T2DM) patients in the early detection of kidney damage.

Materials and methods: The study included 50 T2DM patients mean age of 60.75 ± 11.23 years estimated glomerular filtration rate (eGFR) 114.38 ± 22.12 ml/min and a control group of 20 healthy persons. We measured serum concentration of haemoglobin, urea, creatinine, uromodulin (ELISA method), and cystatin C (nephelometry). We determined formulas: Cockcroft-Gault# (combination Cockcroft- Gault for patients with BMI < 30 kg/m^2 and Cockcroft-Gault$_{LBW}$ for patients with BMI ≥ 30 kg/m2), CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration equation), and simple Cystatin C.

Results: T2DM patients had lower hemoglobin serum concentration as well as eGFR calculated by formulas: Cockcroft- Gault# and CKD-EPI. T2DM patients had significantly higher BMI and cystatin C compared to control group. T2DM patients had significantly lower serum uromodulin concentration (136.51 ± 84.34 vs 220.50 ± 92.39 ng/ml) than in controls. Significant positive correlation between uromodulin and Cockcroft- Gault# (r = 0.432, p = 0.000), CKD- EPI (r = 0.439; p = 0.000) formulas as well as simple cystatin C (r = 0.250, p = 0.02), but negative correlation with age (r = -0.476, p = 0.000), BMI (r = -0.313, p = 0.002) and cystatin C serum concentration (r = -0.293, p = 0.015) were found.

Conclusion: The role of serum uromodulin concentration is not still fortified. The results of this study showed that reduced uromodulin serum concentration indicated early kidney damage in T2DM patients.

Keywords: creatinine clearance, cystatin C, diabetes mellitus, eGFR, uromodulin.

INTRODUCTION

In the kidney, cells in the early distal tubule and the thick ascending limb (TAL) of the loop of the Henle synthesized uromodulin (UMOD). UMOD is an 80- 90 kDa molecule, also known as Tamm Horsfall protein (1). This protein is transported to the apical plasma membrane and then released into the tubular fluid (1, 2).

The role that UMOD has in the kidney remains unclear, although nephrologists have been researching this protein for the past 50 years. This proves the need for a better understanding of the role of this protein in health and disease states (3, 4). Although the physiological role of uromodulin is not clearly defined, there is growing interest in determining this glycoprotein in serum and urine of patients with acute and chronic renal failure as a marker of renal function (1, 3, 5).

In acute kidney injury (AKI), researchers showed a connection of UMOD to inflammation. A study by Säeman et al. (6) suggested a pro-inflammatory role of UMOD. Pfistershammer et al. (7) showed that scavenger receptors play a role in the anti-inflammatory effects of UMOD. El-Achkar and Wu (3) consider that during the AKI, on the basolateral side of the membrane, there is a change in the structure of uromodulin in the form of glycosylation and these changes determine whether the uromodulin will bind to one or another type of receptor, i.e. whether it will have a

pro-inflammatory or anti-inflammatory effect. However, these authors support the anti-inflammatory effect of uromodulin.

Associations between the estimated glomerular filtration rate (eGFR) and stage of chronic kidney disease (CKD) and single-nucleotide polymorphism (SNP) in the UMOD gene were significant (8, 9). The minor T allele of the SNP confirmed a 20 % reduction in risk for development of CKD that was shown in the Atherosclerosis Risk in Communities Study after 15 years of follow-up (10).

In the light of these findings and consequent potential diagnostic significance, this study aimed to evaluate the uromodulin serum concentration in patients with type 2 diabetes mellitus (T2DM) in the early detection of kidney damage.

MATERIALS AND METHODS

The study was approved by the institutional Ethical Committee and carried out following the principles of the Declaration of Helsinki. All patients comprehended in this study signed an informed consent form.

Patients

The cross-section study included 50 patients (18 males) with T2DM hospitalized in the Clinical Hospital Center Zemun, Clinic for Internal Medicine - Department of Nephrology. The controls were 20 healthy subjects. Participants were previously diagnosed with T2DM. The patients diagnosed with active neoplastic disease, autoimmune disease, the end stage of CKD, acute complications of T2DM, pregnancy, and acute urinary tract infection were excluded from the study. The duration of T2DM was 10.04 ± 5.77 years (range 5 - 30 years). The demographic characteristics of the patients and body mass index (BMI) were determined. Blood pleasure was measured in patients after 10 minutes of the rest period. Mean arterial pressure (MAP) was calculated according to the equation:

MAP = 1/3 (SBP- DBP) + DBP (11)

SBP - systolic blood pressure, DBP - diastolic blood pressure

Laboratory Methods

The serum concentration of hemoglobin (the hematological analyzer - the Beckman Coulter HMX), serum concentration of urea, and creatinine (the biochemical analyzer DXC- 800 Beckman Coulter) were measured. Jaffe method was used to measure the serum creatinine. Creatinine clearance was determined during 24-hour collection period from the measurement of creatinine concentration in urine and serum sample. Then creatinine clearance was calculated:

$$\text{eGFR (ml/min)} = \frac{\text{Creatinine urine x Days Urine Volumen}}{\text{Creatinine serum x t(1440 min = 24h)}} \quad (12)$$

The estimated glomerular filtration rate (eGFR) was determined according to the equations:

1. Cockcroft- Gault# - combination Cockcroft-Gault for patients with BMI < 30 kg/m^2 and modificated Cockcroft-Gault$_{LBW}$ for patients with BMI ≥ 30 kg/m^2 (13)

A. Cockcroft- Gault

eGFR = [((140–age) x body weight))/ (72xserum creatinine)] x 0.85 (correction factor for female) (13)

B. Cockcroft-Gault$_{LBW}$

eGFR= (140- age) x LBW / serum creatinine x correction factor

(correction factor for male =1.23; correction factor for female = 1.04)

LBW = 9720 x body weight/ 6680+ 216 x BMI for male

LBW= 9720 x body weight/ 8780+ 244 x BMI for female (14)

2. CKD - EPI (Chronic Kidney Disease Epidemiology Collaboration equation) (15)

eGFR = 141 x min(SCr/κ, 1)$^{\alpha}$ x max(SCr /κ, 1)$^{-1.209}$ x 0.993^{age} x 1.018 [female] x 1.159 [black]

Serum uromodulin was measured by ELISA method- test Euroimmune (Medizinische Labordiagnostica AG) (3). The cystatin C level was determined by immunonephelometric method commercially test N latex cystatin C using nephelometar BN II Sistems Assays (Siemens Healthcare). Simple cystatin C was calculated according to formula: 100/ serum cystatin C (16).

Statistical Analysis

The normal distribution of the variables was proved by the Kolmogorov-Smirnov test. The student's t-test and Pearson's $\chi 2$ test were used to analyze data. Relationships between variables were estimated using univariate and multivariate regression. Receiver operating curve (ROC) was used to detect the ideal values (cut-off points) in diagnostics i.e. separating T2DM patients from healthy subjects. SPSS software (version 10) was used to perform statistical analysis. The conventional p-value was used; all levels of significance were set as $p < 0.05$.

RESULTS

Table 1 presents the demographic and clinical parameters clinical in the two patient groups. T2DM

Table 1. *Demographic and clinical parameters in the two patient groups*

Variable X (SD)	T2DM[$]	Control group	Significance p
Age (years)	60.75 ± 11.23	30.80 ± 8.34	p < 0.01
Sex (m/f)	18/32	9/11	p > 0.05
BMI (kg/m^2)[&]	31.27 ± 5.59	24.44 ± 4.13	p < 0.01
MAP (mmHg)[*]	96.80 ± 10.93	95.33 ± 9.53	p > 0.05
Haemoglobin (g/l)	133.86 ± 13.08	146.45 ± 15.42	p < 0.01
Urea (mmol/l)	5.74 ± 2.24	4.52 ± 1.50	p < 0.05
Creatinine serum (μmol/ l)	71.60 ± 13.59	71.25 ± 13.89	p > 0.05
24 hour urine CrCl (ml/min) [†]	114.38 ± 22.12	112.48 ± 22.22	p > 0.05
Cockcroft-Gault# (ml/min)[‡]	81.05 ± 22.99	132.96 ± 39.59	p < 0.01
CKD-EPI (ml/min/1.73m^2) *§*	86.53 ± 14.96	108.60 ± 16.12	p < 0.01
Cystatin C (mg/l)	0.96 ± 0.22	0.78± 0.08	p < 0.01
Simple cystatin C (mg/l)	109.63 ± 20.47	128.71 ± 13.34	p < 0.01
Uromodulin (ng/ml)	136.51 ± 84.34	220.50 ± 92.39	p < 0.01

[$]T2DM - diabetes mellitus type 2; [&]BMI - body mass index; *MAP - Mean arterial pressure;[†]CrCl - creatinine clearance; [‡]Cockcroft - Gault#: Cockcroft-Gault for patients with BMI < 30 kg/ m^2 and modificated Cockcroft- Gault$_{LBW}$ for patients with BMI ≥ 30 kg/ m^2; *§ CKD-EPI* - Chronic Kidney Disease Epidemiology Collaboration equation

Table 2. *Univariate regression analysis with uromoduline as independed variable*

Parameter	Standardized Coefficients β (95% CI)	Significance p
Age	-0.440(-0.360--1.222)	0.000
Existence of T2DM[$]	0.413(40.107-131.85)	0.000
BMI[&]	-0.359(-9.320 - -2.115)	0.002
Cockcroft-Gault# [‡]	0.330(0.259-1.426)	0.005
Cystatin C	-0.031(-263.104--37.287)	0.01
Simple cystatin C	0.282(0.208-2.336)	0.02
CKD - EPI [§]	0.392(0.847 -3.068)	0.01

[$]T2DM - diabetes mellitus type 2; [&]BMI - body mass index; [‡]Cockcroft- Gault#: Cockcroft-Gault for patients with BMI < 30 kg/ m^2 and modificated Cockcroft- Gault$_{LBW}$ for patients with BMI ≥ 30 kg/ m^2; *§ CKD-EPI* - Chronic Kidney Disease Epidemiology Collaboration equation

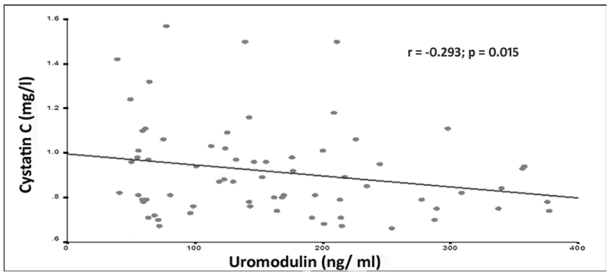

Figure 1. *Correlation between serum concentration uromodulin and Cystatin C*

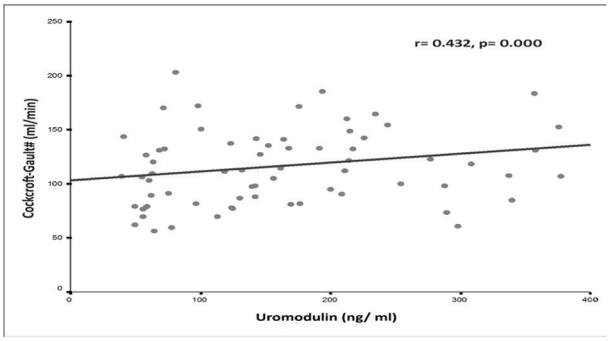

Figure 2. *Correlation between serum concentration uromodulin serum and eGFR calculated by formula Cockcroft-Gault#*

patients were significantly older (p < 0.01), had a significantly higher BMI (p < 0.01) and serum urea concentration (p < 0.05), but lower haemoglobin serum concentration (p < 0.01) compared to controls. There was not found significant difference in sex (p > 0.05), MAP (p > 0.05), serum creatinine concentration (p > 0.05) and 24 hour urine creatinine clearance (p > 0.05). T2DM patients had significantly lower eGFR calculated by formulas: Cockcroft- Gault# (p < 0.01) and

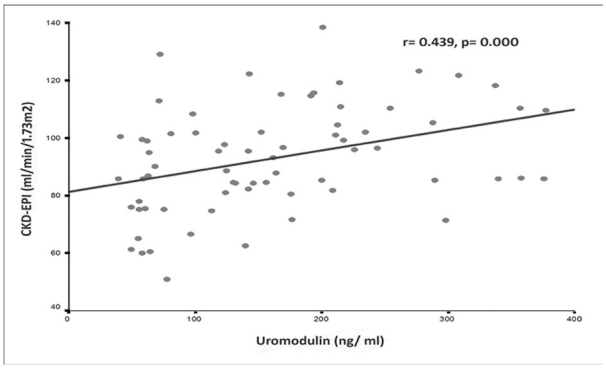

Figure 3. *Correlation between serum concentration uromodulin serum and eGFR calculated by formula CKD-EPI*

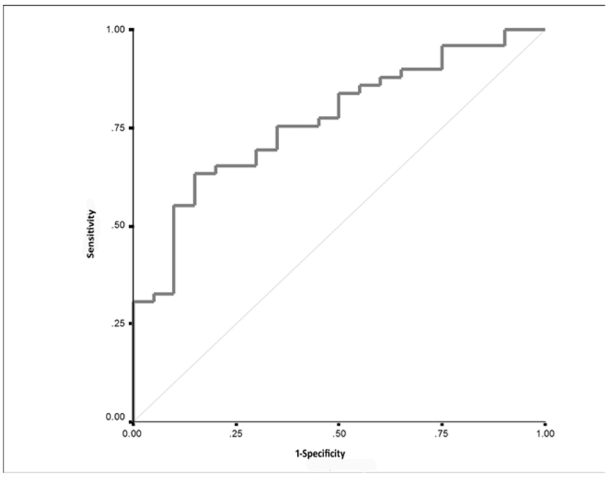

Figure 4. *ROC curve analysis of serum concentration uromodulin*

CKD- EPI ($p < 0.01$) as well as simple cystatin C formula ($p < 0.01$), but significantly higher the cystatin C serum concentration ($p < 0.01$). In addition, the uromodulin serum concentration was significantly lower in T2DM patients than in controls ($p < 0.01$) (Table 1).

Univariate analysis showed significant associations between uromodulin serum concentration and age ($p = 0.000$), existence of T2DM ($p= 0.000$), BMI ($p = 0.002$), cystatin C ($p = 0.01$), simple cystatin C ($p = 0.02$), eGFR calculated by formulas: Cockcroft-Gault# ($p = 0.005$) and CKD- EPI ($p = 0.01$) (Table 2). There were no associations between uromodulin and the duration of T2DM ($p > 0.05$). Multivariate analysis indicated that age is the most significant predictor of low uromodulin levels (β= -0.449, $p = 0.000$) and with each year of age lowers the uromodulin, when adjusted for the multivariate regression analysis of the existence of T2DM, age remains the most important predictor of low uromodulin.

Significant negative correlation between uromodulin and age ($r = -0.476$, $p = 0.000$), BMI ($r = -0.313$, $p = 0.002$) were found. Figure 1 shows significant negative correlation between uromodulin and cystatin C serum concentration ($r = -0.293$, $p = 0.015$). Significant positive correlation between uromodulin and eGFR calculated by formulas: Cockcroft Gault# ($r = 0.432$, $p = 0.000$) (Figure 2) and CKD- EPI ($r = 0.439$, $p= 0.000$) (Figure 3) as well as simple cystatin C ($r = 0.250$, $p = 0.02$) were found. Diagnostic accuracy (area under the ROC curve) was 0.767 (95% CI 0.652 - 0.883, $p < 0.01$). ROC showed that cut off point for serum uromodulin was 165 and this value provides sensitivity of 70% and specificity of 70% (Figure 4).

DISCUSSION

In the kidney, cells in the early distal convolute tubule and TAL of Henle´s loop produced UMOD. The daily secretion of UMOD in healthy persons is about 20 - 70 mg. On the surface of the TAL cells, there could be a gel structure formed by UMOD. Uromodulin is released by a specific unidentified protease from the luminal side of the membrane (3). Some studies demonstrated that there is also a basolateral secretion of uromodulin; this mechanism is not still clear enough. Bachmann et al. (17) showed, using immuno- electron microscopy of the animal model of kidney, that the ratio of apical to basolateral uromodulin is 2:1. A study by Jennings et al. (18) proved that 10% of UMOD secretion is basolateral.

The urinary uromodulin concentration is higher than serum uromodulin concentration. No circadian rhythm was found for the uromodulin serum concentrations (19). As uromodulin is produced by cells of the TAL of Henle, a lower serum concentration of UMOD may influence the function of these cells in CKD. In CKD, secretion of UMOD increases by functioning nephron. The increase in urinary excretion is connected with the increase in basolateral secretion and the increase of serum UMOD concentration in CKD. Lower eGFR and a higher tubular atrophy score are connected to lower serum UMOD concentration (20).

Our study aimed to evaluate the uromodulin serum concentration in T2DM patients. The mean uromodulin serum concentration was significantly lower in T2DM patients compared to controls. T2DM patients had the serum creatinine concentrations in the reference range, as well as 24 - hour urine creatinine clearance, and there was no difference compared to controls. However, T2DM patients were significantly elderly, had higher BMI and higher cystatin C serum concentration, significantly lower eGFR calculated by formulas: Cockcroft- Gault# and CKD-EPI. Although lower uromodulin serum concentration was in significant correlations with the duration of T2DM, higher BMI, eGFR calculated by those formulas, multivariate analysis indicated that age is the most significant pre-

dictor of low uromodulin levels. ROC showed that the cut-off point for serum uromodulin was 165, and this value provides the sensitivity of 70% and specificity of 70%.

To date, most studies have investigated the association of urinary uromodulin concentration with markers of kidney function and eGFR. Little is known about the significance of serum uromodulin concentration. Risch et al. (19), in the cohort study of 289 healthy participants (mean age 71 ± 7 years), investigated the uromodulin serum concentration. In this study, the association between uromodulin and age was significantly negative but between uromodulin and eGFR significantly positive which agrees with our findings. Age-related changes in renal structure and functions have been described, and they are not the only consequence of aging but also of hypertension, diabetes mellitus, and the frequency of glomerulosclerosis progressively increased to 30% after the eighth decade of life. Baltimore's longitudinal study (21) showed that after the third decade of life, eGFR decreased by 8 ml/ min per decade. Dawnay and Cattel's study (22) showed that anephric patients and some patients on hemodialysis had immeasurable concentrations of UMOD; serum concentration of UMOD decreased after unilateral nephrectomy. However, patients who had received transplants exhibited increased uromodulin serum concentrations (22). Our findings on the positive relationship between serum uromodulin and kidney function agree with those of Thornley et al. (20) and Dawney and Cattel (22) and contrast those to Prajczer et al. (23). Prajczer et al. (23) found an inverse relationship between serum uromodulin and eGFR.

Prajczer (23) studied patients with kidney biopsy-proven various glomerular diseases. In this glomerulonephritis, as inflammatory kidney diseases, basolateral secretion of uromodulin could be increased and furthermore could lead to higher serum concentrations despite a decrease in eGFR.

CONCLUSION

The results of the present study indicate that T2DM patients, after 5-30 years of follow-up with serum creatinine concentration and 24h urine creatinine clearance in the reference range, had significantly lower uromodulin serum concentration, lower eGFR calculated by formulas: Cockcroft-Gault# and CKD-EPI compared to controls. These results indicate that T2DM patients had impaired renal function initially, which was not detected only by determining serum creatinine and 24-hour urine creatinine clearance. The most significant predictor of low values of uromodulin, except the existence of T2DM, was age. Although the role of serum uromodulin concentration is not fortified yet, the results of this study show that reduced uromodulin serum concentration indicates early kidney damage in T2DM patients. So serum uromodulin could predict renal injury earlier when compared to conventional kidney function markers -serum creatinine and formulas: Cockcroft-Gault and CKD-EPI.

Abbreviations

AKI — acute kidney injury;
BMI — Body mass index;
CKD — chronic kidney disease;
CKD - EPI — Chronic Kidney Disease Epidemiology Collaboration equation;
CrCl — creatinine clearance;
DBP — diastolic blood pressure;
eGFR — estimated glomerular filtration rate;
MAP — mean arterial pressure;
ROC — receiver operating curve;
SBP — systolic blood pressure;
SNP — single-nucleotide polymorphism;
TAL — thick ascending limb;
T2DM — type 2 diabetes mellitus;
UMOD — Uromodulin

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Sažetak

ZNAČAJ ODREĐIVANJA KONCENTRACIJE UROMODULINA U SERUMU BOLESNIKA SA DIJABETES MELITUSOM TIP 2

Jordanova Elena,[1] Samardzic Vladimir,[2] Pekovic-Perunicic Gordana,[1]
Tica-Jevtic Jelena,[2] Simic-Ogrizovic Sanja[3, 4]

[1] Department of Nephrology, Clinic for Internal Medicine, Clinical Hospital Center Zemun, Belgrade, Serbia
[2] Department of Endocrinology, Clinic for Internal Medicine, Clinical Hospital Center Zemun, Belgrade, Serbia
[3] Medigroup Hospital, New Belgrade, Belgrade, Serbia
[4] University of Banja Luka, School of Medicine, Banja Luka, Bosnia and Herzegovina

Uvod. U bubregu, tubulske ćelije ushodnog kraka Henleove petlje sekretuju uromodulin (UMOD). Cilj ove studije je ispitati koncentraciju uromodulina u serumu pacijenata sa dijabetes melitusom tip 2 (T2DM) u ranom otkrivanju oštećenja bubrega.

Materijal i Metode. Studija je obuhvatila 50 T2DM pacijenata starosne dobi 60,75 ± 11,23 godina sa jačinom glomerulske filtracije (JGF)114,38 ± 22,12 ml/min i kontrolnu grupu 20 zdravih osoba. Merili smo serumsku koncentraciju hemoglobina, uree, kreatinina, uromodulina (ELISA metoda) i cistatina C (nefelometrija). Odredili smo formule: Cockcroft-Gault# (kombinacija Cockcroft-Gault za pacijente sa BMI < 30 kg/m^2 i Cockcroft-Gault$_{LBW}$ za pacijente sa BMI ≥ 30 kg/m^2), CKD-EPI (Chronic Kidney Disease Epidemiology Colaboration equation) i simple Cistatin C.

Rezultati. T2DM pacijenti su imali nižu koncentraciju hemoglobina u serumu kao i JGF određenu formulama: Cockcroft- Gault# i CKD-EPI. T2DM pacijenti su imali značajno viši BMI i cistatin C u poređenju sa kontrolnom grupom. T2DM pacijenti su imali značajno nižu serumsku koncentraciju uromodulina (136,51 ± 84,34 vs 220,50 ± 92,39 ng/ml) nego u kontrolnoj grupi. Pronađena je značajno pozitivna korelacija između uromodulina i formula: Cockcroft- Gault# (r = 0,432, p = 0,000) i CKD- EPI (r = 0,439; p = 0,000) kao i simple cistatina C (r = 0,250, p = 0,02), a negativna korelacija sa starošću (r = -0,476, p = 0,000), BMI (r = -0,313, p = 0,002) i serumskom koncentracijom cistatina C (r = -0,293, p = 0,015).

Zaključak. Uloga koncentracije uromodulina u serumu još nije utvrđena. Rezultati ove studije pokazuju da smanjena koncentracija u serumu ukazuje na rano oštećenje bubrega kod T2DM pacijenata.

Ključne reči: klirens kreatinina, cistatin C, dijabetes melitus, JGF, uromodulin.

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Correspondence to/Autor za korespondenciju
Elena Jordanova, MD, PhD
Department of Nephrology, Clinic for Internal Medicine,
Clinical Hospital Center Zemun
Vukova 9, 11080 Zemun, Belgrade, Serbia
Email: jordanova.elena@gmail.com
Phone: +381 11 3772 716

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Original article

THE EFFECT OF AGING ON THE DEMOGRAPHIC, INJURY AND HEALING PATTERNS OF BURN PATIENTS

Yigit Demir Yasemin,[1] Yigit Ebral[2]

[1] Gazi Yasargil Training and Research Hospital Department of General Surgery, Diyarbakır, Turkey
[2] Gazi Yasargil Training and Research Hospital Department of pediatrics, Diyarbakır, Turkey

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Abstract: **Introduction**: This study aims to investigate the effect of increasing age on the demographic, injury, and healing patterns of burn patients.

Material and Methods: Patients who were followed up for burns in the Diyarbakır Gazi Yaşargil Training and Research Hospital Burn Centre were examined.

Results: In this study, the data of the age groups of 1415 patients with burn injuries were examined. In all groups, the most frequent cause of burns was scalding. The right and left lower extremities were the areas most affected by burns in all age groups. When we examined the patients, 74.1% of them had 2nd-degree burns. After the age of 25, the rate of 3rd degree burns increased in parallel with age. The rate of patients with (+) wound culture results in all age groups was highest in the 1-month to 4-years-old groups and after 45 years of age. APACHE scores of our patients were significantly higher for patients especially for those over the age of 65. The rate increased in patients over 65 years of age.

Conclusion: We observed that the treatment of burns became more severe with increases in age, and mortality and morbidity rates increased.

Keywords: Burns, aging, morbidity, mortality.

INTRODUCTION

Burns are the fourth most common traumatic event globally after traffic accidents, falls, and violence between individuals; (1) burn injuries can lead to decreased quality of life, increased disability, and death.(2). According to the World Health Organization (WHO), more than 300 000 people die worldwide from burn injuries each year, with the highest number of deaths occurring in Southeast Asia and the Middle East (3).

Decreased immune response, serum albumin level, collagen production, pressure, tactile sensations, and tissue elasticity can negatively affect burn wound healing (4). Natural age progression significantly impairs wound healing, and increasing age makes burn patients more prone to infections and associated complications and worsens their clinical outcomes. Due to the physiology of aging, the dermis thickness of the skin decreases, which leads to a decrease in protection against microorganisms. Age is a crucial factor affecting the results of burns and post-burns (5).

This study aims to evaluate the patients treated in our burn center between 2016 and 2020 and to investigate the effect of increasing age on the demographic, injury, and healing patterns of burn patients.

MATERIAL AND METHODS

Between January 2016 and January 2020, patients who were followed up for burns in the Diyarbakır Gazi Yaşargil Training and Research Hospital Burn Centre, the only burn center in the southeastern Anatolia region of Turkey, were examined. This study was carried out in accordance with the principles of the 2008 Declaration of Helsinki. Medical records, causes of injury and related factors, pre-hospital and hospital treatment, demographic data (age, gender, location, application date, and discharge date), injury-related data (burn status, cause of burn injuries, total body surface area (TBSA) and degree of burn), major complications, and treatment outcomes (recovery, discontinuation, or death) were obtained from the hospital's electronic medical record system.

Statistical analysis

The data were collected and entered into Microsoft Excel 2007 (Microsoft Corp., Redmond, WA,

USA). An analysis of variance and Fisher's least significant difference post hoc test between different groups were performed using IBM SPSS Statistics. The mean ± standard deviation or median (interquartile range) was used to explain the distribution of the variables, and a Mann–Whitney *U* test was performed to compare two or more groups of categorical variables (age, gender, burn type, and outcome). A multivariate logistic regression analysis was used to screen for risk factors in burn patients, and a chi-squared test was used for pair and multiple group comparisons. The statistical significance was set as $p < 0$ .05.

RESULTS

During the study period, 1415 patients were admitted to the hospital due to burn injuries. Of them, 798 (56.4%) were male, and 617 (43.6%) were female; 705 (49.8%) patients were admitted from the emergency department and 710 (50.2%) patients from the outpatient clinic.

Patient ages were as follows: 10.7% of the patients were 1 month to 1 year old, 42.5% were 1 to 4 years old, 12.5% were 5 to 9 years old, 5.0% were 10 to14 years old, 8.9% were 14 to 24 years old, 7.7% were 25 to 34 years old, 4.8% were 35 to 44 years old age, 5.5% were 45 to 64 years old, and 2% of them were 65 and older.

More applicants were from rural areas than from urban areas in the 1-month to1-year-old, 25- to 34-year-old, and 35- to 44-year-old age groups. Of all the patients, 28.4% applied visited the hospital more than 1- day after the burn trauma occurred; the 1-month to 1-year-old and 65 and older age groups were the patient age groups with the highest late admission percentages (3.70% and 0.80%, respectively) (Figure 1). There was no statistically significant difference between age groups and late presentation (p: 0.764).

In all groups, the most frequent cause of burns was scalding. After 1 year of age, the frequency of scalding decreased as age increased. Flame burns showed a regular increase in parallel with an increase in age. Frostbite was seen in patients between the ages of 15 to 45 years old, while chemical burns increased after

Table 1. *The cause of burn injury by age group*

Age groups		Flame	Frosbite	Chemical	Scalding	Electrical	Hot object contact
1-11 months	In-group %	1.3%	0.0%	0.7%	89.3%	0.0%	7.9%
1-4 ages	In-group %	2.5%	0.0%	0.8%	89.9%	0.3%	6.5%
5 – 9 ages	In-group %	7.9%	0.0%	0.6%	79.1%	1.7%	10.8%
10 – 14 ages	In-group %	18.3%	0.0%	0.0%	67.6%	2.8%	5.1%
15 – 24 ages	In-group %	24.6%	2.4%	3.2%	50.9%	11.9%	5.4%
25 – 34 ages	In-group %	21.1%	0.9%	3.7%	53.2%	11.0%	5.4%
35-44 ages	In-group %	14.7%	1.5%	2.9%	58.8%	17.6%	2.9%
45-64 ages	In-group %	20.5%	0.0%	5.1%	55.1%	7.7%	5.1%
+65 ages	In-group %	24.2%	0.0%	3.0%	51.5%	3.0%	4.1%
Total		9.4%	0.4%	1.6%	76.2%	3.7%	7.2%

Table 2. *The most frequently injured body region in the burn trauma by age group*

Age groups		head neck	right upper extremity	left upper extremity	front of chest and abdomen	Chest posterior + back	perineum	right lower extremity	left lower extremity
1-11 months	% within age group	15.1%	30.3%	45.4%	23.7%	5.9%	2.6%	42.8%	42.1%
1-4 ages	% within age group	18.8%	30.8%	28.8%	30.1%	10.0%	5.2%	43.4%	42.1%
5-9 ages	% within age group	22.7%	19.3%	24.9%	28.4%	5.1%	7.9%	50.0%	41.8%
10-14 ages	% within age group	31.0%	31.0%	28.2%	32.4%	8.5%	9.9%	43.7%	43.7%
15-24 ages	% within age group	26.4%	36.5%	32.5%	28.8%	5.6%	8.8%	44.0%	42.4%
25-34 ages	% within age group	30.3%	45.9%	43.1%	24.8%	2.8%	3.7%	34.9%	25.7%
35-44 ages	% within age group	26.5%	57.4%	33.8%	27.9%	10.3%	1.5%	25.0%	32.4%
45-64 ages	% within age group	21.8%	32.1%	48.7%	20.5%	5.1%	0.0%	38.5%	38.5%
+65 ages	% within age group	12.1%	18.2%	27.3%	18.2%	9.1%	9.1%	51.5%	57.6%
total	% within age group	21.4%	32.0%	32.8%	27.9%	7.6%	5.3%	42.6%	40.6%

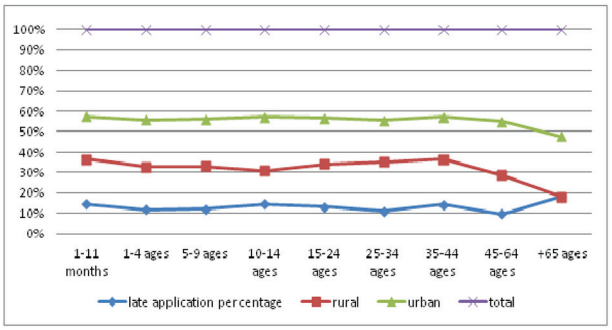


Figure 1. *Demographic distribution of patients by age groups*

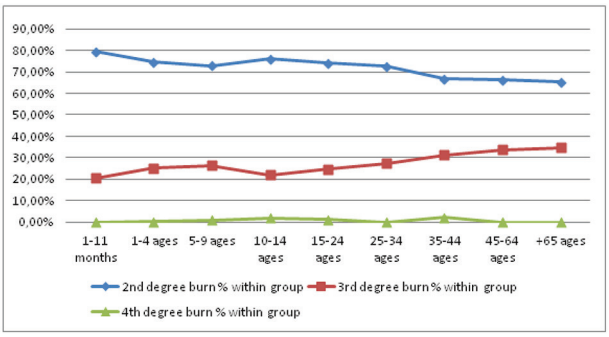
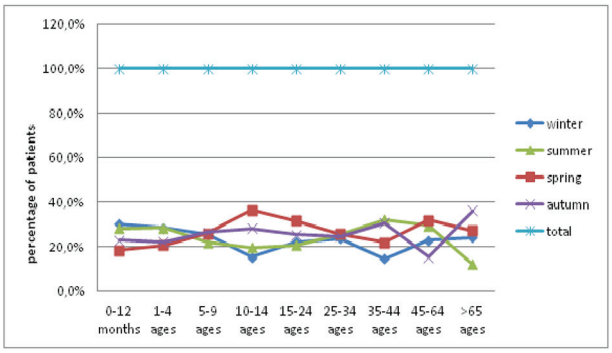


Figure 2. *Distribution of burn degrees by age groups*



Figiue 3. *Seasonal distribution of hospitalization*

the age of 15 and peaked between the ages of 45 to 65. Electrical burns were most common between the ages of 35-44. Hot object contact burns were most common in the 1-month to 1-year-old, 1- to 4-year-old, and 5- to 9-year-old age groups (Table 1).

A regular increase was observed in head and neck burns after one year of age that peaked between the ages of 25 to 34, after which it steadily decreased. However, it was not statistically significant (p: 0.12). The right and left lower extremities were the regions most affected by burns in all age groups, but this finding was not statistically significant (p: 0.24) (Table 2). Right upper extremity burns were mostly observed in the 25 to 44 age group, while left upper extremity burns were mostly observed between the ages of 45 to 64. Perineal burns were most common between the ages of 10-14 and 65 and older, but the results were not statistically significant (p: 0.45). The mean percentage of the TBSA was 9.23 ± 6.72 and peaked in the 35- to 44-year-old-age group (Table 3).

When we examined the patients, 74.1% of them had second-degree burns. There was no statistical difference between age groups and burn degrees (p: 0.10). After the age of 25, the rate of third-degree burns increased in parallel with age (Figure 2). Of the patients, 24.1% were hospitalized in winter, 24.1% in

Table 3. *Average percentage of burns by age groups*

Age groups	Average percentage of burns	STD Deviation
1-11 months	8.42	5.169
1-4 ages	9.52	6.658
5-9 ages	8.94	5.747
10-14 ages	9.41	7.543
15-24 ages	9.71	7.965
25-34 ages	8.41	6.419
35-44 ages	9.88	8.334
45-64 ages	9.67	8.046
+65 ages	7.24	5.568
Total	9.23	6.722

Table 4. *Percentage of distribution of wound culture results by age groups*

	1-11 months	1-4 ages	5-9 ages	10-14 ages	15-24 ages	25-34 ages	35-44 ages	45-64 ages	+65 ages
Staphylococcus culture (+) in its age group	14.5%	19.3%	13.56%	6.05%	17.4%	17.43%	13.2%	15.4%	21.2%
Streptococcus culture (+) in its age group	0.66%	0.67%	1.13%		1.58%	0.92%	1.47%		
Escherichia coli culture (+) in its age group	3.9%	3.17%	1.13%	1.40%			4.41%	2.56%	
Pseudomonas culture (+) in its age group	1.4%	2.0%	3.39%		3.96%	4.59%	2.94%	7.69%	3.03%
Culture (+) within its age group	24.3%	30.9%	22.0%	19.7%	29.4%	27.5%	26.5%	29.5%	31.3%

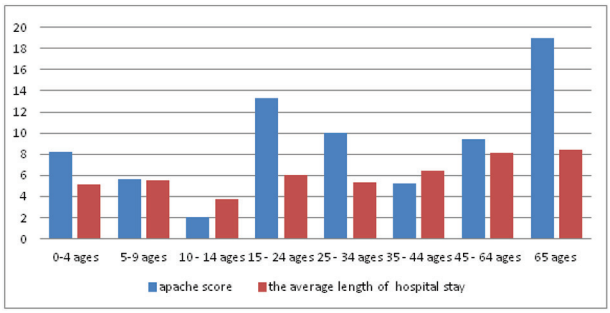


Figure 4. *Distribution of apache score and lenght of hospital stay according to age groups*

summer, 25.7% in spring, and 26.1% in autumn (Figure 3). There was no statistically significant difference between seasonal burns and age groups (p: 0.11).

The rate of patients with (+) wound culture results in all age groups was highest in the 1-month to 4-years-old groups and after 45 years of age. The most common bacteria were staphylococcus from gram (+), pseudomonas, and E. coli from gram (-). Staphylococcus, which was found to reproduce most in the 1-month to 4-years-old groups as a result of wound culture (+), decreased gradually after 5 years of age. It increased again at the age of 45 and above. The number of Pseudomonas culture (+) cultivars increased in parallel with increasing age (Table 4).

When we look at the Acute Physiology and Chronic Health Evaluation (APACHE) scores of our patients hospitalized in the intensive care unit, they were significantly higher for patients aged 15 to 25 and especially for those over the age of 65. The mean length of hospital stay increased systematically after 14 years of age, but it was not statistically significant (p: 0.33) (Figure 4). Our average length of stay is 5.5±5.19 days. Skin grafts were performed on 561 (39.64%) patients, and 854 (60.36%) patients were treated with silver nitrate dressings or nitrofurazone dressing after escharotomy.

A total of 22 (1.55%) of our patients died: 13 were under the age of 14, 6 were between the ages of 15 to 64, and 3 were 65 years or older.

DISCUSSION

The aging process occurs at the cellular and immunological levels, and we believe it to be a result of the accumulation of cellular damage over time (6). With increasing age, skin functions are affected by internal and external factors and deteriorate due to morphological and structural changes (7). Although wound healing does not deteriorate spontaneously with age, age-related changes are evident in all stages of wound repair (8). In patients 65 years and older, the interruption of any step in any wound healing phase has been reported to cause a 20 to 60% delay in healing (4). In our study, it was observed that the duration of patient hospitalizations increased consistently with increases in age since the healing of wounds was prolonged in individuals over the age of 44 years.

Most of the individuals living in the rural areas of the southeastern Anatolia region of Turkey live in low socioeconomic circumstances, similar to other rural families. In the spring and autumn seasons, one of their primary economic activities is producing dairy products. During the preparation process, milk is boiled in copper vessels and then allowed to cool to a sufficient degree to add a particular fermentation culture and is consequently stored in the optimum warm outdoor conditions for fermentation. Since it is produced in large containers, it creates a potentially dangerous situation for child burns during the production period. Children unintentionally bump into these copper pots and spill their contents on themselves or accidentally fall into them. Both cases cause scalding. Families with multiple children and environmental factors increase the risk of childhood injury (9). In our study, 53.2% of the patients with the most burn trauma were in the first four age groups, and their burn injuries predominately occurred in the spring and autumn seasons. The patients aged 65 years and older were mostly seen in the winter season. Burn trauma was most common in spring and autumn in all patients. Chien et al. (10) stated that the most common season of burns was spring, but Nilgün et al. (11) asserted that the most common season was summer.

The epidermis and dermis become thinner with age along with decreased sensation and sometimes decreased blood flow which makes the skin more susceptible to 3rd and 4th-degree burns, therefore increasing the need for surgery in burn patients (12). Consequently, our skin grafting rate increased in parallel with age, starting from the age of 25.

According to the studies of Ho and Rao et al., burns in all age groups most commonly affect the extremities, followed by the trunk, head, and neck (13, 14). Our study findings are consistent with their results.

Comorbid diseases that increase with age become more susceptible to infection due to aging and the weakening of immunity. Therefore, special care should be taken to prevent and treat infection in elderly burn patients (15, 16). In our study, higher wound culture (+) rates were found in the 1- to 5-year-olds and 65 and older age groups. We attributed this to the lack of development of the immune system in children and the suppression of the immune system in patients aged 65 and older.

In the literature, mortality rates among burn patients differ between studies but certainly increase with age (8). In our study, the mortality rate was 1.55% in all patients, while 9.09% in the 65 and older age group.

We attribute this to the increase of comorbid diseases with increasing age and the high APACHE scores in the intensive care unit.

CONCLUSION

Intrinsic factors that change with age affect the treatment of burns. In our study, we observed that the treatment of burns became more severe with increases in age, as a result of which the hospitalization period of the patient was prolonged and mortality and morbidity increased.

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Sažetak

UTICAJ STARENJA NA DEMOGRAFIJU, POVREDE I OBRASCE LEČENJA BOLESNIKA SA OPEKOTINAMA

Yigit Demir Yasemin,[1] Yigit Ebral[2]

[1] Gazi Yasargil Training and Research Hospital Department of General Surgery, Diyarbakır, Turkey
[2] Gazi Yasargil Training and Research Hospital Department of pediatrics, Diyarbakır, Turkey

Uvod: Cilj ove studije je da istraži uticaj godina na demografiju, povrede i obrasce lečenja pacijenata sa opekotinama.

Materijal i metode: Pacijenti koji su praćeni zbog opekotina u Centru za opekotine Diiarbakır Gazi Iasargil su pregledani.

Rezultati: U ovoj studiji ispitani su podaci starosnih grupa od 1415 pacijenata sa opekotinama. U svim grupama najčešći uzrok povreda bile su opekotine. Desni i levi donji ekstremiteti su bila područja koja su najviše zahvaćena opekotinama u svim starosnim grupama. Nakon što smo pregladali pacijente, ustanovili smo da 24.1% ima opekotine drugog stepena. Posle 25. godine, stopa opekotina 3. stepena se povećavala paralelno sa godinama.

Stopa pacijenata sa (+) rezultatima brisa rane u svim starosnim grupama bila je najveća u grupama od 1 meseca do 4 godine i nakon 45 godina.

APACHE rezultati naših pacijenata bili su značajno viši za pacijente, posebno za one starije od 65 godina. Stopa se povećala kod pacijenata starijih od 65 godina.

Zaključak: Primetili smo da je lečenje opekotina postalo teže sa porastom godina, uz porast stopa mortaliteta i morbiditeta.

Ključne reči: opekotine, starenje, morbiditet, mortalitet.

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Correspondence to/Autor za korespondenciju
Ebral Yiğit MD.
Address: Gazi Yasargil Training and Research Hospital Department of General Surgery, Diyarbakır, Turkey Turkey. Zipcode: 21090.
Phone: +90 5334889334
Fax:+90 4122580060
Email: ebralyigit@gmail.com
ORCID: 0000-0001-8766-0754

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Case report

OGILVIE SYNDROME FOLLOWING SPINAL SURGERY

Romulo Pedroza Pinheiro,[1] Nascimento Ribeiro Leonardo,[2]
Tavares Costa Rodrigo Herton,[2] Aparecido Defino Luiz Helton[2]

[1] Department of Orthopaedic and Anesthesiology and Doctoral Student,
Ribeirão Preto Medical School, University of São Paulo, Brazil
[2] Department of Orthopaedic and Anesthesiology, Ribeirão Preto Medical School,
University of São Paulo, Brazil

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Abstract: **Objective**: Ogilvie syndrome is a rare disease characterized by acute abdominal pain and distention in the absence of mechanical obstruction. It is a rare condition that usually affects hospitalized patients in association with severe illness or after surgery. A few cases have been reported after spinal surgery.

Material and Methods: Retrospective reports of Ogilvie syndrome in three patients that underwent spinal surgery (two posterior lumbar instrumented fusion and one anterior cervical fusion). Surgical treatment was required in two patients and conservative treatment in one out the three patients.

Results: Two patients had a complete recovery of symptoms and signs of the disease, and one died.

Conclusion: Ogilvie syndrome is rare, but it should be considered a differential diagnosis in patients who have undergone surgery and present with significant abdominal pain and distention.

Level of evidence II; Retrospective study.

Keywords: Ogilvie's syndrome, pseudo-obstruction, spinal fusion.

INTRODUCTION

Ogilvie syndrome is the eponym to describe a rare condition characterized by acute colonic dilation in the absence of mechanical obstruction colonic (1). Acute colonic pseudo-obstruction (ACPO) was first described by William Heneage Ogilvie in 1948 (2).

The incidence of ACPO is 100 cases per 10000 admissions (3, 4). ACPO has been described in hospitalized patients with severe illness, trauma, or after surgical procedures (cesarean, abdominal, pelvic ,urologic , thoracic, neurosurgical, coronary bypass, orthopaedic surgeries) (1, 2, 3, 5, 6). ACPO has also been described after some orthopedic procedures such as hip, knee, lumbar and cervical surgeries (8-12).

The clinical picture of Ogilvie syndrome includes abdominal distention and pain (80%), nausea with or without vomiting (60%) (1). Bowel sounds are preserved in almost 90% of patients associated with the tympanic abdomen (13). Abdomen radiographs and CT show varying degrees of bowel distention without mechanical obstruction (14). Colonic ischaemia or perforation can occur in 15% of the patients and is associated with 40% mortality. Early diagnosis and adequate treatment have a crucial role in the prognosis of ACPO (3, 15, 16).

ACPO is an unusual complication following spinal procedures, and it was the motivation to report the occurrence of ACPO during our practice. The goal of the study is to retrospectively report the occurrence, treatment, and results of Ogilvie's syndrome in patients that underwent spinal surgery to highlight the clinical features of ACPO so that it can be considered in the possible postoperative complications of spinal surgery.

MATERIAL AND METHODS

The study was approved by the local IRB and it is a retrospective report of Ogilvie syndrome in patients that underwent spinal surgery. Three patients presented Ogilvie syndrome after posterior spinal fusion (2 patients) and anterior cervical fusion (1 patient). Two patients were female, and the age of patients ranged from 41 to 83 years (61.33 ± 29). The detailed clinical picture and procedures are described:

Patient No 1: An 83-year-old female with degenerative scoliosis and lumbar stenosis underwent posterior standalone deformity correction, lumbar

decompression, and T10-L5 fixation with a pedicle screw-based system. The surgery was uneventful without complications. On the second postoperative day, the patient had increased abdominal distension, abdominal pain, nausea, and vomiting. At the time, abdominal plain radiography showed a dilated cecum and colon (Figure 1). After general surgery consultation, a nasogastric tube was placed as well as medical management, replacement of electrolytes and fluid. On the sixth postoperative day, the patient experienced increased abdominal distension, and neostigmine administration was planned after transfer to the intensive care unit as a result of monitoring requirements, oxygen support, and orotracheal intubation. CT showed dilated bowel of ascending colon without evidence of perforation with suffering from the colon mucosa was observed. (Figure 2). At this time, a decompressive colonoscopy was performed due to abdominal distention. The clinical picture presented partial recovery. The patient died on the 20th postoperative day after worsening of the clinical and respiratory function.

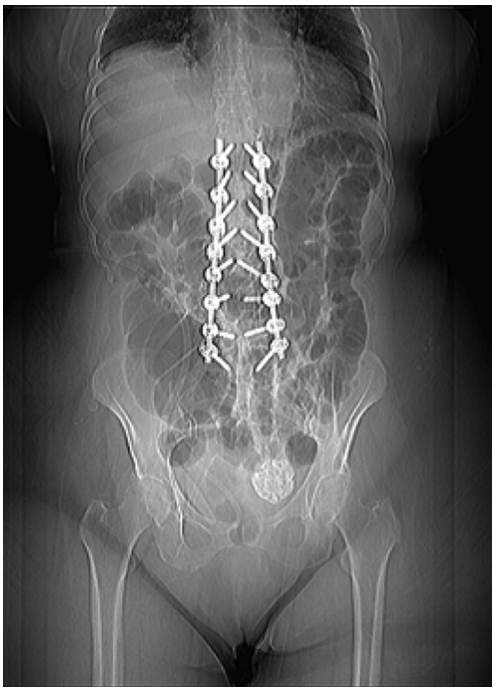

Figure 1. *Postoperative radiograph (2nd day) showing dilatation of cecum*

Patient No 2: A 60-year-old female with degenerative lumbar stenosis underwent posterior lumbar decompression and L1-S1 fixation with a pedicle screw-based system. The surgery was uneventful without complications. On the third postoperative day, the patient presented abdominal pain and distention. Abdominal plain radiography and CT showed dilated bowel without evidence of perforation (Figure 3). On the fourth postoperative day, the patient presented worsening of clinical picture associated with nausea, vomiting, and increased abdominal distension. Exploratory laparotomy was performed associated with right hemicolectomy, the burial of the distal transverse, and terminal ileostomy. It was necessary to introduce parenteral nutrition, and the patient presented a good outcome without recurrence of symptoms.

Patient No 3: A 41-year-male presented a traumatic bilateral facet dislocation of C5-C6 after diving into shallow water. The neurological status was classified as Frankel A. Anterior C5-C6 fixation was performed after open discectomy and reduction. The surgery was uneventful without complications. On the

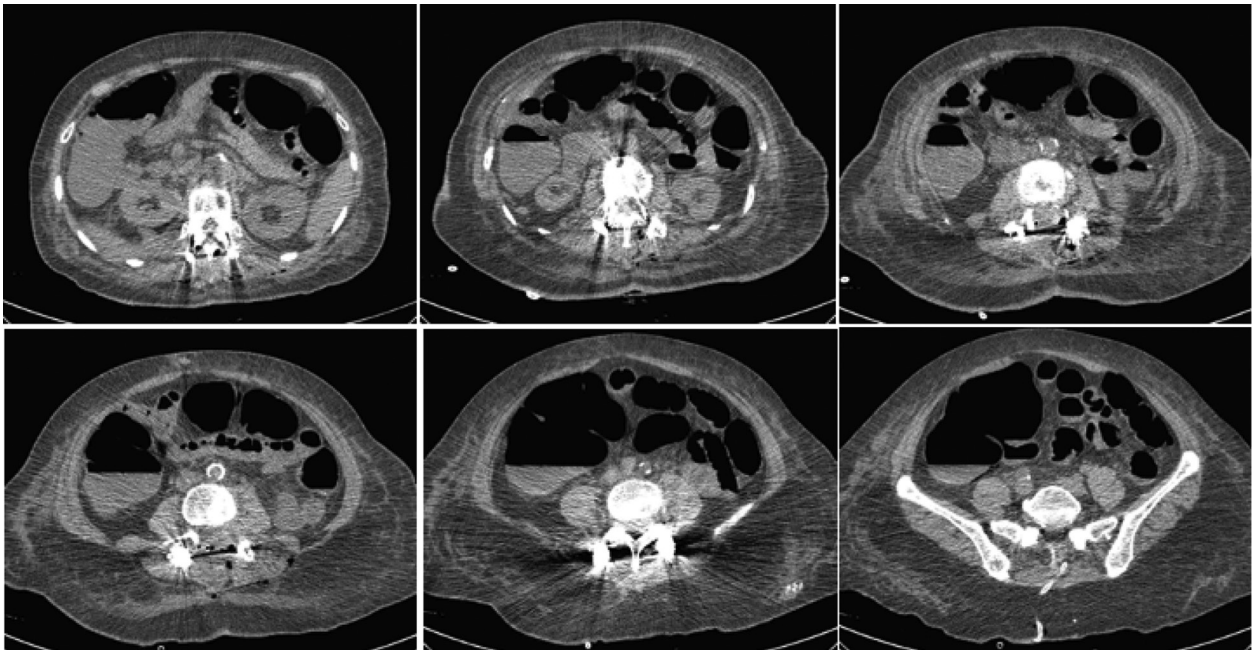

Figure 2. *Postoperative CT showing dilated bowel of ascending colon without evidence of perforation*

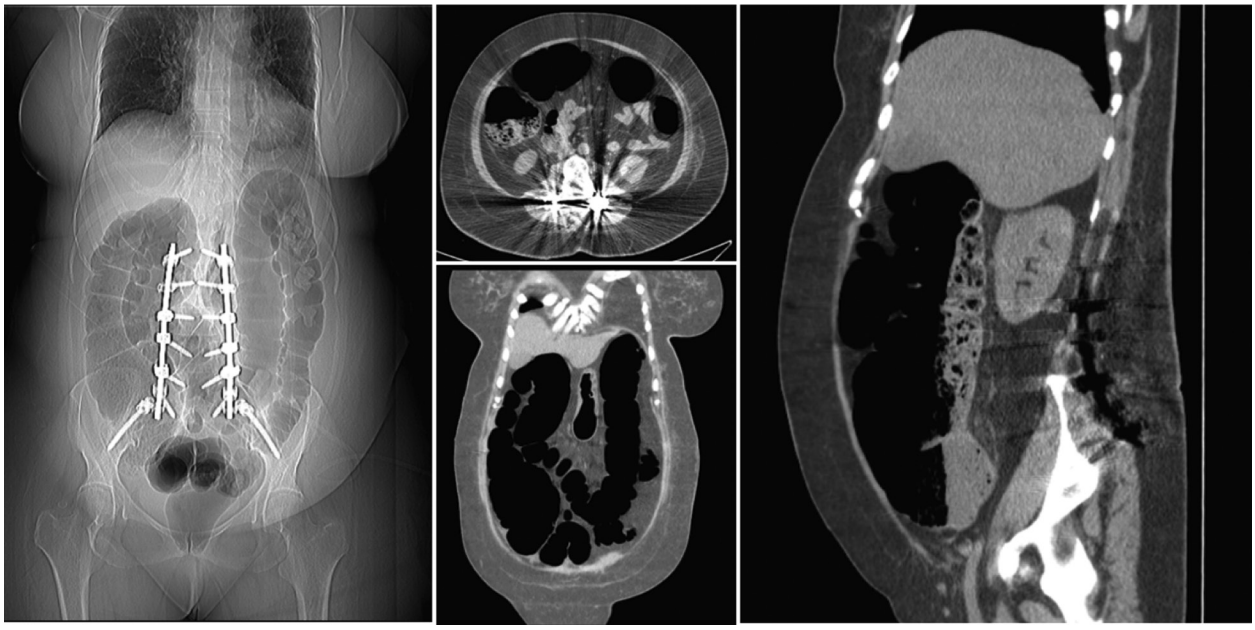

Figure 3. *Plain radiography and CT showing dilated bowel without evidence of perforation*

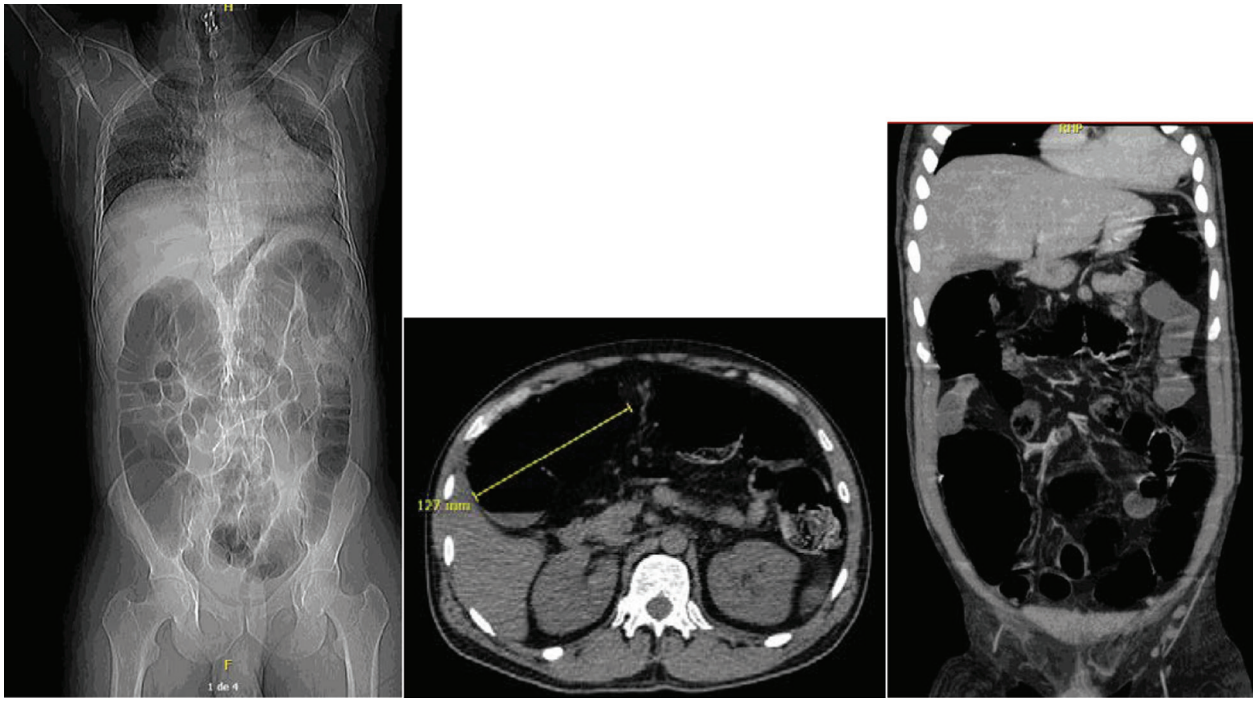

Figure 4. *Plain radiography and CT showing dilated bowel without evidence of perforation*

second postoperative day, the patient presented with diffuse abdominal pain, vomiting, and watery diarrhea. The abdominal plain radiography showed a dilated cecum and colon of 12 cm, and CT showed dilated bowel without evidence of perforation (Figure 4). The Ogilvie syndrome was treated conservatively. The patient was kept nil per orally (NPO) with serial measurement of abdominal girth and serum electrolytes monitoring. A nasogastric tube was being inserted, and aggressive fluid and electrolyte resuscitation was initiated. Appropriate antibiotics were started infection is suspected. The abdominal distention and symptoms improved in 5 days.

RESULTS

One out of the three patients with Ogilvie syndrome died after clinical and respiratory complications besides the surgical treatment. Two patients had a complete recovery of the symptoms and signs of Ogilvie syndrome. One after surgical treatment and the other after conservative treatment. These two patients did

not have any significant abdominal problems during the 2-year follow-up period.

DISCUSSION

The occurrence of Ogilvie syndrome in three patients within the scope of our practice shows that despite being rare, it should be included in the spectrum of postoperative complications of spinal surgery. Abdominal distention and pain are presented in 80% of the patients accompanied by nausea with or without vomiting in 60% of the patients. Ninety percent of the patients present tympanic abdomen and preserved bowels sounds (1).

So far, its pathology remains poorly understood. A multifactorial etiology is supported by the abundance of identified risk factors that lead to common or similar effects on the colon (1). An impairment of the autonomous system is observed with an imbalance between sympathetic and parasympathetic, an atonic distal colon, and a functional proximal obstruction (17).

The diagnosis of Ogilvie syndrome is mainly based on clinical symptoms and signs. Differential diagnosis should be considered in postoperative patients with abdominal pain and distention, although various intestinal diseases have to be ruled out before (18). It has been observed in patients with predisposed medical and surgical conditions. However, our three patients had no medical comorbidities. The use of medication such as opioids, calcium channel blockers, and anticholinergics can predispose to this syndrome (18). ACPO is more frequent in males (1,5:1) (20), although two out of the three patients were female.

The average age of presentation is approximately 60 years, and surgical patients are most likely to be diagnosed on postoperative days 3 to 5, as we have observed in our patients (21).

The clinical picture of our patients characterized by unexplained abdominal pain and distention, nausea with or without vomiting, and plain abdominal radiographs or CT showing varying degrees of colonic dilation is the typical presentation of the disease. Abdominal distention and pain are observed in 80% of patients, and nausea with or without vomiting in 60%. Diagnosis of ACPO is one of exclusion, and more common causes of functional or mechanical bowel dilation must be investigated (2, 3, 22). In the presence of bowel ischemia, peritonitis, or perforation, ACPO is considered complicated, and it is directly related to the duration of the illness and increased cecal diameter (23).

The primary treatment is based on supportive care with close observation. Nasal gastric tube placement aids bowel decompression and nothing by month. Medication that impacts colonic mobility, such as opiates and anticholinergics, should be discontinued, and early pharmacological therapy has been encouraged. Neostigmine (short-acting anticholinesterase) has been recommended as a drug of choice. Invasive procedures and surgery are indicated for patients with severe disease (ischemia or perforation) or refractory to conservative treatment. The management of ACPO should be multi-professional, and the primary goal of the treatment is urgent bowel decompression (19).

The reported success rate of conservative treatment is 96%, and early diagnosis and conservative treatment reduce the risk of surgical intervention (20, 21). However, we have not observed this picture in our patients. Besides the early diagnosis and conservative treatment according to the protocols (22), two patients underwent surgical intervention, and one of them died beside the surgical intervention. The general expected mortality of Ogilvie syndrome is 15% in uncomplicated patients and 30-40% in complicated ones. Cecal diameter and duration of illness are associated with the development of complications (21).

ACPO has been observed in 1-2% of spinal or othopaedic procedures. In the field of spinal surgery, Ogilvie syndrome was reported after posterior fixation for thoracolumbar fractures, lumbar disc, cervical discectomy, lumbar decompression for stenosis, correction of spinal deformity, and lumbar surgery (8, 9, 18, 23, 24, 25).

The general expected mortality of Ogilvie syndrome is 15% in uncomplicated patients and 30-40% in complicated ones. Cecal diameter and duration of illness are associated with the development of complications (21). Although rare, this syndrome should be included in the differential diagnosis of postoperative abdominal pain and distention.

CONCLUSION

Although Ogilvie syndrome is a rare disease, it should be suspected in patients that presented unexplained abdominal pain and distention in the postoperative period. Early diagnosis and conservative treatment can prevent bowel ischemia that leads to morbidity and mortality.

Acknowledgment

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Sažetak

OGILVIJEV SINDROM NAKON OPERACIJE KIČMENOG STUBA

Romulo Pedroza Pinheiro,[1] Nascimento Ribeiro Leonardo,[2]
Tavares Costa Rodrigo Herton,[2] Aparecido Defino Luiz Helton[2]

[1] Department of Orthopaedic and Anesthesiology and Doctoral Student,
Ribeirão Preto Medical School, University of São Paulo, Brazil
[2] Department of Orthopaedic and Anesthesiology,
Ribeirão Preto Medical School, University of São Paulo, Brazil

Cilj: Ogilvijev sindrom je retka bolest koju karakteriše akutni bol u stomaku i distenzija u odsustvu mehaničke opstrukcije. To je redak sindrom koji obično pogađa hospitalizovane pacijente zajedno sa teškom bolešću ili posle operacije. Nekoliko slučajeva je prijavljeno nakon operacije kičme.

Metode: Retrospektivni izveštaji Ogilvijevog sindroma kod tri pacijenta koji su podvrgnuti operaciji kičme (dve zadnje lumbalne instrumentalne fuzije i jedna prednja cervikalna fuzija). Hirurško lečenje je bilo potrebno kod dva pacijenta, a konzervativno lečenje kod jednog od tri pacijenta.

Rezultati: Dva pacijenta su imala potpuni oporavak simptoma i znakova bolesti, a jedan je preminuo.

Zaključak: Ogilvijev sindrom je redak, ali ga treba uzeti u obzir u okviru diferencijalne dijagnoze kod pacijenata koji su bili podvrgnuti hirurškoj intervenciji, a imaju izražen abdominalni bol i distenziju.

Nivo dokaza II; Retrospektivna studija.

Ključne reči: Ogilvijev sindrom, pseudo-opstrukcija, spinalna fuzija.

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Correspondence to/Autor za korespondenciju
Romulo Pedroza Pinheiro
Department of Orthopaedic and Anesthesiology and Doctoral Student,
Ribeirão Preto Medical School, University of São Paulo, Brazil
Av. Bandeirantes 3900, Monte Alegre, 14049900, Ribeirão Preto, SP-Brazil
Phones: (16) 3602-2513, (85) 99610-3964
E-mail: romulopinheiro@usp

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Review article

JOD-BASEDOW PHENOMENON: PHENOMENAL THYROTOXICOSIS?

Ozturk Tuncer,[1] Sengul Demet,[2] Sengul Ilker[1, 3]

[1] Department of General Surgery, Giresun University Faculty of Medicine, Giresun, Turkey
[2] Department of Pathology, Giresun University Faculty of Medicine, Giresun, Turkey
[3] Division of Endocrine Surgery, Giresun University Faculty of Medicine, Giresun, Turkey

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Abstract: *A Deucalione* iodine is an essential mineral vital for the optimal function of the thyroid gland in human beings. Apart from being found in a variety of foods, it is a component of various medications, amiodarone and expectorants, iodine-based swabs used for skin cleaning before interventional and surgical procedures, and iodinated contrast media in medical settings. Jod-Basedow Phenomenon, also known as Jod-Basedow Syndrome or iodine-induced thyrotoxicosis, is a rare cause of thyrotoxicosis that characteristically refers to a paradoxical phenomenon in which large loads of exogenous iodine can cause hyperthyroidism. This phenomenon is mainly seen in populations already at risk for thyroid diseases, such as autoimmune thyroid diseases, prior thyroid surgical history, latent Graves' disease, and prior non-toxic diffuse or nodular goiter formation, or those with underlying kidney disease, such as chronic kidney disease and end-stage renal disorders, which can impact iodine excretion. Typically, it is recognized in those with the administration of a large iodine load, dietary supplement, iodinated contrast media used in conjunction with computed tomography scans, angiography, and various other imaging studies, iodinated antiseptic solutions and oral supplements, or a medication, mainly amiodarone, class III antiarrhythmic drug used in the treatment of recurrent severe ventricular arrhythmias, paroxysmal atrial tachycardia, atrial fibrillation and maintenance of sinus rhythm after cardioversion of atrial fibrillation. Prophylactic medical management of the phenomenon may include antithyroid drugs, methimazole, or perchlorate, to be considered for patients at risk for developing iodine-induced thyrotoxicosis that is scheduled for imaging modalities by using iodinated contrast media. Moreover, the preliminary management modality comprises cessation of iodine administration, avoiding further exposure, administration of beta-adrenergic antagonists, thionamides, corticosteroids, and rarely lithium. Prognosis is usually favorable, although a small percentage of cases could suffer permanent sequelae from iodine-induced thyrotoxicosis. Nevertheless, complications are remarkable including thyroid storm, permanent hyperthyroidism, atrial fibrillation, and fetal hypothyroidism with goiter development, in terms of ordering iodinated contrast media in pregnants. Jod-Basedow Phenomenon should not be overlooked and should be managed by an interprofessional healthcare team serving and officiating not only to treat it but also to concern themselves, actively in the relevant prophylaxis.

Key words: Jod-Basedow Phenomenon, Jod-Basedow Syndrome, Iodine-induced thyroidoxicosis, Thyrotoxicosis, Thyroid gland, Thyroidology, Iodine, Graves' Disease, Goiter, Pathology, Endocrine Surgery.

INTRODUCTION

The Jod-Basedow Phenomenon comes from "Jod", meaning iodine in German, and the German scientist Karl Adolph von Basedow (1799-1854). Jod-Basedow Syndrome has diverged from Basedow's disease, occasionally used as a synonym for Graves' disease. Jod-Basedow effect, the so-called Jod-Basedow Syndrome, and Jod-Basedow Phenomenon is a kind of thyrotoxicosis following administration of iodine or iodide through a dietary supplement, iodinated contrast medical imaging, or a medication, mainly amiodarone. Iodine, a member of group 17 in the periodic table, is the fourth halogen, below fluorine, chlorine, and bromine. Iodine is the heaviest stable member of its group and has an electron configuration of [Kr]4d105s25p5 with the seven electrons in the fifth and outermost shell as its valence electrons and atomic weight 126,90447 u. Iodine is crucial for the regular functioning of the most important endocrine gland, the thyroid. The human body would not carry on to syn-

thesize the vital hormones for maintaining metabolic homeostasis of homo sapiens: the thyroid hormones, T3 and T4. On the other side, excess iodide, such as iodinated contrast media (ICM) administration, may impact the normal functioning thyroid gland (1, 2).

JOD-BASEDOW PHENOMENON

Iodine Sources

Iodine can be obtained by consuming foods that contain it. Dietary iodine is absorbed from the stomach and duodenum at the rate of > 90% as iodide and is rapidly distributed in the extracellular fluid. It is also transported to the papillon-shaped gland by sodium/iodide symporter (NIS) with a considerable gradient of 25-50 times of plasma content. Iodide leaves this pool by being transported to the thyroid and excreted in the urine. The minimum recommended daily intake of iodine is 150 µg for non-pregnant adults, 220-250 µg for pregnant women, 290 µg for lactating, and 90-120 µg for children (2, 3).

Etiology

Jod-Basedow Phenomenon scarcely arises in the absence of an underlying thyroid gland disease, such as autoimmune thyroid diseases, iodine-induced thyroiditis, previous thyroid surgical procedures, latent Graves' disease, and nontoxic diffuse or nodular goiter, or underlying kidney disease, such as chronic kidney disease and end-stage renal disorders, which can impact iodine excretion, all which are considered as its predisposing factors. Patients at risk are elderly and those from low iodine intake topographic areas. In addition, chronic and end-stage renal diseases are also known as the risk factors for the phenomenon as iodine is excreted through the kidneys. It is also worth noting that Jod-Basedow Phenomenon is interrelated with ICM. Moreover, other exogenous sources such as oral supplements and iodinated antiseptic solutions may also lead to iodine-induced thyrotoxicosis. Furthermore, amiodarone-induced thyrotoxicosis (AIT), which is classified as type I, AIT 1; which may develop in the presence of latent autoimmune hyperthyroid status (routinely requires treatment with thionamides) and type II, AIT 2; which develops in a normal thyroid status resulting from destructive thyroiditis (requires steroids), is accepted as a separate entity and its underlying mechanism may be different from the other counterparts (2, 4).

Epidemiology

Jod-Basedow Phenomenon has been revealed as a rare situation with just a small collection of reports determining its features as if it has been under-reported. Physicians may consider that diagnostic contingency with increased awareness in terms of this entity (1, 2, 3).

Pathophysiology

Jod-Basedow Syndrome, iodine-induced thyrotoxicosis, typically occurs in a case with an endemic goiter due to iodine deficiency who has later been relocated to an iodine-abundant topographic area. Risky individuals for the Jod-Basedow effect include the ones with Graves' disease, toxic multinodular goiter, and thyroid adenoma while taking iodine due to the thyroid gland then not responding to negative feedback from increased thyroid hormones. Hyperthyroidism frequently emerges within 2 to 12 weeks following iodine administration which may involve diet, administration of ICM for medical imaging, or an antiarrhythmic drug, so-called amiodarone. Intercalary, excess iodide load may impact this crucial endocrine gland functioning. In this case, a transient attenuation in thyroid hormone production is the expected initial response. This phenomenon, the Wolff-Chaikoff effect, is predicted as an output of a temporary downregulation of the sodium iodide transporter in the thyroid. Most cases can provide a euthyroid state in their organism within 24 to 48 hours, whereas some exhibit the opposite response for the mentioned condition. By escaping the physiologic negative feedback mechanism of the Wolff-Chaikoff effect they evolve the hyperthyroid status instead of a transitory hypothyroid hormonal state. Last but not least, the mentioned pathologic response to the exogenously administered iodine charge is described as the Jod-Basedow Phenomenon which is thought to emerge from an output of impaired autoregulation (1, 2, 5, 6). The key factor protecting organisms against wide variations in dietary iodine intake is described as autoregulation by thyroid follicular cells. Sudden exposure to excess serum iodide inhibits iodide organification, thereby reducing hormone biosynthesis, and this phenomenon is called the Wolff-Chaikoff effect (2, 5, 6). However, iodide overload, iodide organization, and thyroid hormone biosynthesis continue normally two to four weeks after ongoing exposure (7). Experimental studies have propounded and suggested that this escape from the Wolff-Chaikoff effect is due to the attenuation of iodide uptake, thus getting back of the intrathyroidal iodide pool to its normal available value even if serum concentrations of iodide remain high (8-10). The mechanism of this escape is unknown but may be related, in part, to a decrease in iodide uptake caused by a downregulation in NIS activity for the thyroid. This phenomenal thyrotoxicosis appears to result from loss

of the normal adaptation of the gland to iodide overcharge (11 ,12).

Iodine-effects on thyroid hormone secretion

The pharmacological doses of iodine attenuate thyroglobulin proteolysis by reducing thyroid hormone secretion by using its most rapid effects. A transient augmentation in serum concentrations of thyroid-stimulating hormone (TSH) occurs through a mild decrease in serum T4 and T3 hormones (13-15). Serum TSH augmentation may not be present in the presence of increased iodine intake in the elderly (16). The effects of iodine charge in cases with abnormal thyroids are different from those in normal individuals. It depends on the underlying disease process, e.g. iodine administration may lead to thyrotoxicosis in cases with nodular goiter involving autonomously functioning parenchyma or with endemic goiter. A high incidence, 10-20%, of thyrotoxicosis is revealed in people with nodular goiter living in iodine-deficient areas while a lower prevalence of hyperthyroidism, 1-20%, has been expressed after the iodine introduction (17, 18). Autonomous areas within the gland may lead to hyperthyroidism, *exempli gratia*, increasing iodine supply, producing thyroid hormones in autonomous areas independently of normal regulatory mechanisms: Jod-Basedow Phenomenon (19). Jod-Basedow Syndrome may scarcely appear in cases without underlying a thyroid disease such as iodine-induced thyroiditis (20).

Diagnosis

Diagnosis of Jod-Basedow Phenomenon may be achieved concerning nodular diseases on physical examination, particularly in cases with iodine exposure like coronary angiography and imaging contrast media and clinical manifestations of thyrotoxicosis, such as tachycardia, tremor, heat intolerance, restlessness, diarrhea, and insomnia. Besides this phenomenon, severe cases may lead to thyroid storm, characteristically exhibiting a constellation of symptoms including tachycardia, diarrhea, fever, altered levels of consciousness, even development of atrial fibrillation in rare cases. Diagnosis should be confirmed by the hormonal status of the thyroid gland. Jod-Basedow Syndrome characteristically initiates weeks or even months after an initial iodine administration (21, 22).

Evaluation of underlying thyroid disease

Even though the phenomenon most frequently occurs in patients with underlying thyroid disease, other causes of thyrotoxicosis should be considered, as it may not be associated with iodine exposure. Besides the physical examination, multinodular gland suggestive of thyroid autonomy, diffuse goiter suggestive of Graves' disease, ophthalmopathy, dermatopathy, the biochemical, thyroid-stimulating immunoglobulin (TSI) level, and radiologic imaging, radioactive iodine uptake, thyroid nodularity in sonography, and vascularity in doppler ultrasound, tests may be beneficial for the diagnostic purposes even in the differential diagnosis (2).

Prognosis

As a result of prolonged iodine deficiency, thyrocyte proliferation and mutation rates increase leading to multifocal autonomous growth. Thyrocytes that change in this way form cell clones in the thyroid parenchyma which results in mutations in TSH receptors. This fine nodular pattern exhibits autonomy within the gland following iodine intake and rapidly synthesizes thyroid hormones inducing a hyperthyroid hormonal status in human beings. *In fine*, it is obvious to expect possessing hyperthyroidism through administration of iodine in already autonomous glands in individuals with long-term iodine deficiency (23-25).

The prognosis for the Jod-Basedow Phenomenon is usually affirmative. Iodine-induced thyrotoxicosis is ordinarily self-limited with a time interval of 1-18 months subject to the condition, cessation of iodine repletion, while delay in recovery may exist in amiodarone-induced thyrotoxicosis. Though a small percentage of cases may have difficulty in a persistent sequela, most patients return to their baseline hormonal status of the thyroid (2, 3, 26, 27).

Management

Prophylactic medical management may involve antithyroid drugs, methimazole, or perchlorate, to be considered for cases at risk for developing iodine-induced thyrotoxicosis that is scheduled for imaging modalities by using ICM. The preliminary management modality for patients with Jod-Basedow Phenomenon includes discontinuation of iodine administration, avoiding further exposure, and administration of a beta-adrenergic antagonist, like atenolol 25-50 mg/day, as an initial dose, to alleviate the symptoms of thyrotoxicosis (27). The thyroid hormonal status should be followed up considering its baseline levels, individually. Beta-blockers can be reduced and discontinued after thyroid tests return to normal. Thionamide administration may accelerate the recovery (20). Methimazole with a starting dose once daily 10 to 20 mg, due to long duration of action, faster efficacy, and lower incidence of side effects, can be used in case of severe or prolonged, > 1 month, symptoms of hyperthyroid-

ism or elderly with underlying cardiovascular disease. *Inter alia*, corticosteroid therapy is recommended to expedite the return of the gland hormones to their normal ranges. Corticosteroids were asserted as might delay or circumvent surgical management thus refraining from its possible complications. Providers may regard to prescribe lithium by virtue of inhibitory impacts on the thyroid gland under the circumstances of the antithyroid drugs failing to reduce thyroid hormone production (2, 26, 28-36).

CONCLUSION

Iodine is an essential mineral vital for the optimal function of the thyroid gland in human beings. Apart from being found in a variety of foods, it is a component of various medications, amiodarone and expectorants, iodine-based swabs used for skin cleaning prior to interventional and surgical procedures, and iodinated contrast media, in medical settings. *A Deucalione*, this delicate and crucial endocrine gland, remains its great emphasis on a human being. However, the debate is still ongoing, particularly, in remarkable controversial issues in Thyroidology, to date.

Jod-Basedow Phenomenon, so-called Jod-Basedow Syndrome or iodine-induced thyrotoxicosis, is a seldom cause of thyrotoxicosis of a paradoxical phenomenon in which large loads of exogenous iodine can be a causative agent. Prior settlement in an iodine-deficient area, possessing an underlying thyroid or kidney disease with the administration of a large iodine load are the prominent features. The phenomenon is ordinarily self-limited though a small percentage of cases may have difficulty in a persistent sequela. Nevertheless, complications of the Jod-Basedow Phenomenon are remarkable. As well as prophylactic medical management, the preliminary management modality with cessation of the causative agent, avoiding further exposure, administration of beta-adrenergic antagonists, thionamides, corticosteroids, and even rarely lithium is referred to. Jod-Basedow Phenomenon should not be overlooked or be managed by an interprofessional healthcare team serving and officiating not only to treat it, but also regarding relevant prophylaxis. *Bene diagnoscitur, bene curatur*.

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Sažetak

JOD-BASEDOW FENOMEN: FENOMENALNA TIROTOKSIKOZA?

Ozturk Tuncer,[1] Sengul Demet,[2] Sengul Ilker[1, 3]

[1] Department of General Surgery, Giresun University Faculty of Medicine, Giresun, Turkey
[2] Department of Pathology, Giresun University Faculty of Medicine, Giresun, Turkey
[3] Division of Endocrine Surgery, Giresun University Faculty of Medicine, Giresun, Turkey

Deukalion jod je esencijalni mineral od vitalnog značaja za optimalno funkcionisanje štitne žlezde kod ljudi. Osim što se nalazi u raznim namirnicama, sastavni je deo raznih lekova, amiodarona i ekspektoransa, sredstava na bazi joda koji se koriste za čišćenje kože pre intervencijskih i hirurških zahvata, i jodiranih kontrastnih sredstava u medicinskim ustanovama. Jod-Basedov fenomen, takođe poznat kao Jod-Basedov sindrom ili tireotoksikoza izazvana jodom, je redak uzrok tireotoksikoze koji se karakteristično odnosi na paradoksalan fenomen u kojem velika opterećenja egzogenog joda mogu izazvati hipertireozu. Ovaj fenomen se uglavnom primećuje kod populacije koja je već izložena riziku od oboljenja štitne žlezde, kao što su autoimune bolesti štitne žlezde, prethodna istorija hirurške intervencije na štitnoj žlezdi, latentna Grejvsova bolest i prethodno formiranje netoksične difuzne ili nodularne strume, ili kod onih sa osnovnom bolešću bubrega, kao npr. hronična bolest bubrega i bubrežni poremećaji u završnoj fazi, koji mogu uticati na izlučivanje joda. Obično se prepoznaje kod onih sa velikim opterećenjem jodom, dijetetskim suplementima, jodnim kontrastnim sredstvima koji se koriste kod kompjuterizovane tomografije, angiografije i u raznim drugim imidžing studijama, jodiranim antiseptičkim rastvorima i oralnim suplementima ili lekovima, uglavnom amiodaron, antiaritmik koji se koristi u lečenju ponavljajućih teških ventrikularnih aritmija, paroksizmalne atrijalne tahikardije, atrijalne fibrilacije i održavanja sinusnog ritma nakon kardioverzije atrijalne fibrilacije. Profilaktički medicinski tretman ovog fenomena može uključivati lekove protiv štitne žlezde, metimazol ili perhlorat, koji se razmatraju za pacijente sa rizikom od razvoja tireotoksikoze izazvane jodom, koja je predviđena za modalitete radio-snimanja

korišćenjem jodiranih kontrastnih sredstava. Štaviše, preliminarni modalitet lečenja uključuje prestanak primene joda, izbegavanje daljeg izlaganja, primenu beta-adrenergičkih antagonista, tionamida, kortikosteroida i retko litijuma. Prognoza je obično povoljna, iako bi mali procenat slučajeva mogao imati trajne posledice od tireotoksikoze izazvane jodom. Ipak, komplikacije su velike, uključujući štitnu žlezdu, trajnu hipertireozu, atrijalnu fibrilaciju i fetalnu hipotireozu sa razvojem strume, u smislu korišćenja jodiranih kontrastnih sredstava kod trudnica. Jod-Basedov fenomen ne treba zanemariti i njime treba upravljati interprofesionalni zdravstveni tim koji služi ne samo da ga leči već i da se brine aktivno u relevantnoj profilaksi.

Ključne reči: Jod-Basedov fenomen, Jod-Basedov sindrom, tireotoksikoza izazvana jodom, tireotoksikoza, štitna žlezda, tiroidologija, jod, Grejvsova bolest, struma, patologija, endokrina hirurgija.

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Correspondence to/Autor za korespondenciju
Prof (Assoc) Demet Sengul, M.D.
Founder Chair, Department of Pathology
Founder Chair, Scientific and Research Laboratories
Giresun University Faculty of Medicine
Gazipasa Compound, Gazi Avenue, Giresun, Turkey
E-mail: demet.sengul.52@gmail.com

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Review article

HIGH FLOW NASAL OXYGEN THERAPY (HFNO) IN OPPOSITION TO NON-INVASIVE MECHANICAL VENTILATION (NIV): ADVANTAGES, DISADVANTAGES AND THEIR USE IN COVID-19 INFECTION: BRIEF REVIEW

Dmitrovic Radmila, Lazovic Biljana, Simonovic Isidora

Department of pulmonology, University Clinical Center "Zemun", Belgrade, Serbia

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Abstract: In the last few decades, different devices for oxygen application have become available, such as low flow systems, high flow systems (HFNO), and non-invasive ventilation (NIV). They are widely applicable and have many advantages as well as disadvantages. HFNO modalities decrease dead space, improve alveolar ventilation, and apply oxygen up to 60 l/min, delivering it humidified and heated opposite NIV, which increases anatomical dead space, maintains adequate minute ventilation, and is used in more conditions than HFNO, etc.

In our research, we included 12 articles. The study was conducted using literature published up from 2013 to July 2020. In our research we used following keywords: 'non-invasive ventilation', 'high-flow nasal oxygen', 'advantages', 'disadvantages', 'COVID-19'.

The HFNO system appears to be more successful than standard oxygen treatment and non-inferior to NIV. It is simple, easy to apply but still insufficiently researched. More research is needed in the future on the benefits and disadvantages of the HFNO system.

Keywords*:* HFNO, NIV, COVID-19, advantages, disadvantages.

INTRODUCTION

Various oxygen application devices, such as low flow systems (basic facemask, nasal cannula, non-rebreathing reservoir mask) and high flow systems (high-pressure oxygen and air sources, and air-oxygen blender, or a high-flow "Venturi" mask), have been available in recent decades. Alternatives to traditional oxygen therapy include high-flow nasal oxygen therapy (HFNO). HFNO is more sophisticated than the Venturi mask, which operates on the Bernoulli principle and offers a flow of 30-50 l/min of oxygen and air, with an inspiratory oxygen fraction (FiO_2) ranging from 24 to 60%. HFNO can supply up to 60 l/min of heated and completely humidified gas with a FiO_2 range from 21% to 100% (1). The main indications for HFNO are de novo hypoxemic acute respiratory failure (ARF), in the periods before intubation, prevention of post-extubation ARF, and in immunocompromised patients (2). HFNO has several physiological benefits, including reduced exertion of breathing, the formation of various levels of positive airway pressure (PEEP), the release of a steady FiO_2, enhanced mucociliary clearance, patient comfort, and the washout of pharyngeal dead space (1). It is crucial to notice that measuring the basic parameters of the respiratory system is extremely important for assessing its functionality and capacity during a greater or lesser load (3). On the other side, non-invasive mechanical ventilation (NIV) represents ventilatory support with positive airway pressure, where the endotracheal tube, laryngeal mask, or endotracheal cannula are not used to secure the airway. The use of an oronasal mask for NIV is a common practice in both clinical and homecare mechanical ventilation. The system can be used to treat a variety of conditions, including ARF and chronic respiratory failure (CRF) caused by exacerbation of chronic obstructive pulmonary disease (COPD), neuromuscular illnesses, heart failure, immunocompromised individuals, high-risk surgical operations, and respiratory insufficiency following elective extubation (4, 5). We will discuss the advantages and disadvantages of HFNO and NIV and examine their imperfections and their use in COVID-19 infection.

MATERIAL AND METHODS

We selected substantial studies from databases of PubMed, Embase, and Cochrane library. The following keywords were used: 'non-invasive ventilation', 'high-flow nasal oxygen', 'advantages', 'disadvantages', 'COVID-19 infection'. Headlines, abstracts, and full-text articles of possibly useful studies were independently checked by two researchers. We analyzed papers published in English and Serbian language. The study was conducted using literature published up from 2013 to July 2020. In our research, we included 12 articles.

Comparison and advantages of HFNO and NIV

HFNO has shown many advantages over conventional devices with low oxygen flow. Devices with low oxygen flow can deliver up to 15 l/min of oxygen without the ability to heat and humidify it. The HFNO system can apply oxygen up to 60 l/min, delivering it humidified and heated. The ability of the system to humidify and heat the delivered gas has been shown to have a significant physiological effect, especially in critically ill patients. As we mentioned in the introduction, FiO_2 in HFNO is between 21%-100%, while in low oxygen systems, FiO_2 is inconstant and generally lower than expected. In addition to the physiological advantages, HFNO also has an advantage in how oxygen is delivered. Compared to a basic facemask or nasal cannula, an air/oxygen blender, active heated humidifier, single heated circuit, and high-flow nasal cannula (HFNC) give greater respiratory support, notably the HFNC, which produces medicinal gases at a higher flow and with more predictable FiO_2 than other devices in this group. According to some writers, while this open circuit cannot provide high-end expiratory pressure, it does produce PEEP and may raise end-expiratory lung volume (EELV). Many differences can be seen when comparing NIV with HFNO. According to the general literature data, NIV has more indications for usage than HFNO, however, the primary difference between these two modalities is in the interface. HFNC interfaces reduce anatomical dead space, whereas NIV interfaces increase it. When the circuit is open, however, HFNC cannot actively increase tidal volume since there is no effective inspiratory push or expiratory pull (VT). HFNC not only reduces anatomical dead space but also enhances alveolar ventilation. Because of these advantages, which compensate for some of the shortcomings of traditional oxygen delivery systems, and the apparent physiological benefits, the use of HFNC for critically sick people has been steadily rising. On the other hand, to guarantee proper minute ventilation, minute volume was "manipulated" during invasive (MV) or non-invasive (NIV) ventilatory support, particularly for patients with COPD exacerbation, where NIV has been the recommended primary modality for breathing support since it enhances inspiratory VT and maintains optimal alveolar ventilation, but in certain patients, NIV is inapplicable due to inadequate tolerating masks. According to data from various studies, one of the crucial advantages is that HFNO is simple and easy to use and can reduce the use of mechanical ventilation (6). Some authors compared the effects of HFNO versus NIV, emphasizing the primary goal. In one study involving 310 medical intensive care units (ICU), the primary endpoint was intubation, and results showed lower rates in the subgroup of patients with a PaO_2/FiO_2 200 mmHg (7), while in another involving 49 medical ICU, NIV+HFNO showed higher values of SpO_2 during intubation in comparison to the primary endpoint- lowest SpO_2 during intubation (8). In one randomized controlled trial (RCT) where the primary goal was to calculate intubation rate, data showed a lower intubation rate with HFNO than with NIV and standard oxygen therapy (9).

Disadvantages

According to research data, HFNO should be avoided in those patients where NIV is also contraindicated. The crucial point to remember when utilizing an HFNC is that recourse to more invasive care may be delayed, which may be harmful in patients with respiratory instability, therefore in ARF, extended efforts with HFNC may postpone intubation with negative effects (10). Instead, following NIV, its advantages and disadvantages are more researched and better known to the professional public. Leakage is a well-known disadvantage of NIV. Although bridge fans have NIV modes with customized alarm settings, it is unclear how much ventilation is supplied to patients. The measurement of end-tidal carbon dioxide is untrustworthy, and changes to the fan setting may enhance and decrease ventilation by increasing the amount of leakage. What further exacerbates the leakage is the insertion of a nasogastric tube in patients on NIV to reduce gastric pressure and the possibility of aspiration of the contents. The burden for the nurse is also a pivotal disadvantage of NIV in ICU. Patients on NIV require continual attention and particular care, which is not a problem as long as the attending nurse has prior expertise and is solely assigned to NIV patients. A lack of care may increase the risk of deterioration of the patient's condition (11), while other authors also described drying cornea, conjunctivitis, aerophagia, and skin lesions (5).

The use in COVID-19 infection

According to Northern Devon Healthcare (NHS), the use of HFNO in suspected or proven COVID-19 infection is not recommended since it is a high-risk aerosol-generating therapy that is also hazardous to the staff (12). Although there are clear contraindications for its use, many researchers have tried HFNO to treat this pandemic. They discovered that HFNO provides a high concentration of oxygen, can reduce the need for intubation in COVID-19 patients, can reduce the length of intensive care unit stay and complications associated with mechanical ventilation, and can achieve apneic oxygenation in patients during airway management. Because HFNC can create aerosols, the treatment should be performed in a negative pressure room, and where this is not practicable devices should be housed in a single room (13). The role of NIV is well-known in treating COVID-19 patients, and its benefit is reflected in the reduced risk to healthcare professionals by eliminating the need for intubation, a potentially highly contagious procedure (14).

CONCLUSION

According to published statistics, the HFNO system appears to be more successful than traditional oxygen treatment and non-inferior to NIV. It is simple to implement, yet it has received limited investigation. Although its use in COVID-19 infection is prohibited by the NHS, many researchers have dared to apply it by describing the positive effects of its use. However, all of this is still an under-explored field that poses a challenge for future research.

Abbreviations

ARF — acute respiratory failure
COPD — chronic obstructive pulmonary disease
CRF — chronic respiratory failure
EELV — end-expiratory lung volume
FiO_2 — inspiratory oxygen fraction
HFNC — high flow nasal cannula
HFNO — high flow nasal oxygen
ICU — intensive care unit
MV — invasive mechanical ventilation
NIV — non-invasive ventilation
NHS — Northern Devon Healthcare
PEEP — positive airway pressure
RCT — randomized controlled trial
VT — tidal volume

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VISOKO PROTOČNA KISEONIČKA TERAPIJA U POREĐENJU SA NEINVAZIVNOM VENTILACIJOM: PREDNOSTI, NEDOSTACI I NJIHOVA PRIMENA KOD COVID-19 INFEKCIJE: KRATAK PREGLED LITERATURE

Dmitrovic Radmila, Lazovic Biljana, Simonovic Isidora

Department of pulmonology, University Clinical Center "Zemun", Belgrade, Serbia

U poslednjih nekoliko decenija različiti uređaji za primenu kiseonika su dostupni, kao što su nisko protočni, visoko protočni system (HFNO) i neinvazivna ventilacija (NIV). Rasprostranjeni su širom sveta i imaju mnogo prednosti, ali i svojih mana. Neke od koristi visoko protočnih sistema su: smanjivanje anatomski „mrtvog" prostora, poboljšanje alveolarne ventilacije i sposobnost primene protoka kiseonika od 60 l/min, isporučujući ga vlažnog i zagrejanog, za razliku od modaliteta neinvazivne ventilacije (NIV) koja ima širu primenu u odnosu na visoko protočne uređaje, dovodi do porasta anatomski „mrtvog" prostora, održava adekvatnu minutnu ventilaciju itd. U naše istraživanje smo uvrstili podatke iz 12 članaka. Koristili smo literaturu publikovanu u periodu od 2013. do jula meseca 2020. godine. Za pretraživanje literature koristili smo sledeće ključne reči: 'neinvazivna ventilacija', 'visoko protočna kiseonična terapija', 'prednosti', 'mane', 'COVID-19'. Visoko protočni kiseonik je superiorniji u odnosu na nisko protočni, ali i dalje inferioran u odnosu na neinvazivnu ventilaciju. Jednostavan, lak za primenu, ali i dalje nedovoljno istražen. Neophodno je u budućnosti više istraživanja o primeni visoko protočne kiseonične terapije, njenih prednosti i mana.

***Ključne reči**:* visoko protočni, neinvazivna ventilacija, COVID-19, prednosti, mane.

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Correspondence to/Autor za korespondenciju
Radmila Dmitrovic
University Clinical Center "Zemun"
Belgrade, Serbia
Vukova 9, Zemun, 11080 Belgrade
Self-phone: +381601322400
e-mail: radadmitrovic94@gmail.com

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Letter to the editor

LEVERAGING THE SYNERGY BETWEEN ANTIMICROBIAL STEWARDSHIP AND INFECTION PREVENTION AND CONTROL IN FIGHTING ANTIMICROBIAL RESISTANCE

Massimo Sartelli[1, 2]

[1] Department of Surgery, Macerata Hospital, Macerata, Italy
[2] Global Alliance for Infections in Surgery

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Abstract: The COVID-19 pandemic had a great impact on the understanding of both antimicrobial stewardship (AS) and infection prevention and control (IPC).

During the COVID-19 pandemic, the collaboration between AS and IPC has mitigated the shortcomings experienced by health systems around the world, enhancing the performance of both, reinforcing the synergy between them, and increasing their preparedness in fighting antimicrobial resistance.

In planning the post-pandemic era, health systems worldwide should invest in reinforcing the synergy between AS and IPC highlighted during the pandemic.

Letter to the editor

The COVID-19 pandemic had a great impact on the understanding of both antimicrobial stewardship (AS) and infection prevention and control (IPC).

While AS focuses on optimizing antimicrobial use to improve the patients' outcomes and decrease the emergence of antimicrobial resistance (AMR), IPC focuses on reducing healthcare-associated infections (HAIs). The intersection between AS and IPC stands in preventing HAIs caused by multidrug-resistant organisms (MDROs) and Clostridioides difficille infections (1).

During the COVID-19 pandemic, the collaboration between IPC and AS has mitigated the shortcomings experienced by health systems worldwide, enhancing the performance of both, reinforcing the synergy between them, and increasing their preparedness in fighting other pandemics, including a more "silent" one such as AMR. In planning the post-pandemic era, health systems worldwide should invest in reinforcing the strict synergy between AS and IP highlighted during the pandemic (2).

AMR is emerging as one of the biggest public health problems of the 21st century threatening the effective treatment of some infections caused by bacteria, parasites, viruses, and fungi that are becoming resistant to the most common antimicrobials used to treat them. AMR is a complex phenomenon developing across animal, human, and environmental habitats. Among these habitats, there is a well-known interconnected sharing of pathogens. AMR does not show any signs of decline, even if it may shift the direction.

A report published in 2014 by Lord Jim O'Neill and his team estimates an increase in deaths caused by AMR, from the current toll of 700,000 to 10 million every year by 2050 (3). This scenario will not occur if all together respond adequately to this "silent" pandemic.

The World Health Organization is on the front line against AMR and voted for a global action plan to tackle AMR at the 68th World Health Assembly in May 2015 (4).

Despite the complexity of the problem, healthcare professionals can play a significant role in combating AMR.

The burden of AMR is especially urgent for antibiotic resistance in bacteria. Antibiotic resistance is a natural phenomenon. However, it is accelerated by both the misuse and overuse of antibiotics in healthcare, as well as by poor IPC. Early antibiotic therapy to treat infections reduces morbidity and saves lives, like in cases of sepsis. However, a significant number of antibiotics prescribed in acute care facilities worldwide are either unnecessary or suboptimal concerning the choice, dose, and duration.

Moreover, patients receiving medical care can get serious HAIs. Many HAIs are caused by MDROs such as methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), extended-spectrum-producing Enterobacteriaceae (ESBL), carbapenem-resistant Enterobacteriaceae (CRE). MDROs can spread inside and between healthcare facilities when patients are transferred from one facility to another without respecting the IPC appropriate measures. IPC initiatives work to limit the spread of MDROs in health care facilities. Effective IPC measures can reduce the need for antibiotics, prevent the spread of infections caused by MDROs and help combat the emergence of AMR. This was highlighted in the Global Action Plan on Antimicrobial Resistance (4), where one of the five strategic objectives concerns the reduction of the incidence of infections through effective IPC measures.

AS programs aim to help clinicians improve patients' outcomes by optimizing antibiotics prescribing. AS programs can increase infection cure rates and reduce:

- Treatment failures;
- C. difficile infections;
- Adverse effects;
- Antibiotic resistance;
- Hospital costs and lengths of stay.

A key strategy of AS promotes the message that antibiotics should not be prescribed for viral infections. COVID-19 is a viral respiratory tract infection and is, in most cases, self-limiting.

Bacterial secondary infections in patients with COVID-19 were not common, according to the published epidemiologic data. However, in the early stages of the pandemic, using antibiotics for the empiric treatment of secondary infections in hospitalized patients with COVID-19 was very common (5, 6). A meta-analysis found that 71.9% of patients hospitalized with COVID-19 before mid-April 2020 received antibiotics, although only 6.9% of these admissions were also associated with bacterial infections (6).

These results have highlighted the need for adequate use of antibiotics in managing COVID-19 and implementing AS programs around the world.

IPC has been repeatedly proved to be effective at containing the incidence of HAIs. It has been estimated that a great number of HAIs could be prevented if the evidence-based recommendations for IPC are appropriately followed in clinical practice.

The COVID-19 pandemic had an immense impact on the understanding of IPC. Around the world, people and healthcare workers implemented hand-washing techniques and social distancing, and other measures to prevent infections. In those healthcare settings that required frequent and close contact between healthcare workers and COVID-19 patients, IPC measures such as the use of personal protective equipment (PPE), hand hygiene, and cleaning and sanitization were essential to mitigate the spread of Sars-Cov-2.

However, it should be noted that the stringency of IPC measures was not possible in all settings. In those acute care facilities reaching inpatient capacity, isolation of all patients with signs of COVID-19 disease into specialized wards was not possible, and compliance with IPC measures was a real challenge (7).

IPC plays a pivotal role in containing AMR by assisting with prompt detection of MDROs and promoting compliance with standard and transmission-based precautions.

IPC should be seen as complementary to the AS initiatives as they have a shared objective and are synergistic. Where there is no transmission of infection, there is no need for antibiotic treatment, thus reducing the development of AMR.

The COVID-19 pandemic has not only created new activities for AS and IPC, but it has also created new opportunities for a bidirectional synergy. It has created new needs and increased concerns about rising rates of AMR and HAIs, both of which overlap significantly and are key focus areas for both AS and IPC. These issues have highlighted the need for new team models in which both AS and IPC are interconnected.

Healthcare system leaders should prioritize IPC and AS, as part of a vaster patient safety strategy, creating an infrastructure that can promote and disseminate the patient safety culture and best practice across the continuum of patient care. Both AS and IPC should seize all the opportunities to benefit from the expertise of each other.

The pandemic has created new opportunities for collaboration in communication and infrastructure enhancement. The infrastructure created for data access, reporting, and collaboration, even if born out of necessity, can be used in the post-pandemic era and serve as a powerful catalyst for a future synergy between IPC and AS infighting AMR.

There are numerous opportunities for IPC programs and AS programs to collaborate in sharing resources and personnel. Data review, monitoring, reporting, as well as interventions such as audit and feedback and healthcare worker education, are critical processes to both AS and IPC. Especially in resource-poor settings, integrating these activities can reduce redundant work and make for a more efficient and comprehensive workflow for both programs (2). IPC and AS programs should work together to line their programs, promote collaboration, and reduce redundant initiatives.

AS and IPC have similarities in terms of goals, strategies, infrastructure, and metrics. The potential for collaboration has long been recognized yet underutilized. Especially in resource-poor settings, the opportunities for synergy between AS and IPC should be explored and reinforced to fight the "silent" AMR pandemic.

Abbreviations

AS — antimicrobial stewardship
IPC — infection prevention and control
AMR — antimicrobial resistance
HAIs — healthcare-associated infections
MDROs — multidrug-resistant organisms

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UPOTREBA SINERGIJE IZMEĐU ANTIMIKROBNOG UPRAVLJANJA I PREVENCIJE I KONTROLE INFEKCIJA U BORBI PROTIV OTPORNOSTI NA ANTIMIKROBNE LEKOVE

Massimo Sartelli[1, 2]

[1] Department of Surgery, Macerata Hospital, Macerata, Italy
[2] Global Alliance for Infections in Surgery

Pandemija KOVID-19 imala je veliki uticaj na razumevanje antimikrobnog rukovođenja (AS), kao i na prevenciju i kontrolu infekcija (IPC).

Tokom pandemije KOVID-19, saradnja između AS-a i IPC-a ublažila je nedostatke sa kojima se suočavaju zdravstveni sistemi širom sveta, poboljšavajući njihova dostignuća, jačajući sinergiju među njima i povećavajući njihovu spremnost u borbi protiv rezistencije na antimikrobne supstance.

U planiranju postpandemijske ere, zdravstveni sistemi širom sveta treba da ulažu u jačanje sinergije između AS i IPC naglašene tokom pandemije.

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Correspondence to/Autor za korespondenciju
Massimo Sartelli
Department of Surgery, Macerata Hospital, Macerata, Italy
Global Alliance for Infections in Surgery
email: massimosartelli@gmail.com

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Letter to the editor

PUBLIC HEALTH SIGNIFICANCE OF UNFULFILLED HEALTH NEEDS OF THE POPULATION OF SERBIA

Khoitar Samir,[1] Simic Svetlana,[2] Jevtovic Obradovic Ivana,[2] Janicijevic Katarina[3]

[1] Health Center Nova Varos, Serbia
[2] Health Center Cacak, Serbia
[3] University of Kragujevac, Faculty of Medical Sciences, Department of Social Medicine, Kragujevac, Serbia

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To the Editor,

Health care is a comprehensive and organized activity of society in preserving and improving the health of citizens and families. It represents society's response to unplanned and unpredictable events that endanger the health and ensure levels of health and the causes of illness. The availability of public health is determined by various factors that relate to both the patient and the health system. Health insurance coverage, coverage in staff, space, equipment and financial resources, scheduling and referral systems, quality of services provided, and continuity of health care are factors of the health system that can affect the availability of health care. However, factors such as age, socioeconomic status, previous experiences with health services, perceptions of the quality of public health, and health literacy constitute the characteristics of the individual, which may also influence their decisions to provide health care (1). One of the socio-economic aspects of health is unequal aging health care (2). A key indicator for monitoring a degree of inequality in health care, and through the approach, use, and realization of health care, is the satisfaction or dissatisfaction of clients (3). Unmet needs represent diversity in the provision of health services: needs that are considered necessary and essential for the care of specific health issues (4). Unmet public health needs affect people's health and quality of life. They can also directly alter mortality risks and/or be indirectly linked to the statuses of several psychosomatic and psychiatric illnesses today (5, 6). Numerous factors related to real unmet health needs are reflected in gender, age, lack of insurance, education, unemployment, low wages, and more. All of the above points to unequal access to health care from a socio-economic point of view. The characteristics of the health care system, such as the number of doctors or dentists, the method of payment of primary health care doctors, and the amount of money for out-of-pocket services, also have a severe impact on unmet health care needs. The results of many studies show that the frequency of unmet medical or dental needs varies significantly from country to country, which can be partly explained by differences in health care financing (6). Since inequalities in access and usage of health services are some of the determinants of health (socioeconomic, etc), public policymakers must identify these determinants to understand the specific barriers that health care users are faced with, in terms of physical, geographical, cultural, and financial accessibility of the health care (7).

Identifying such barriers is a crucial indicator for measuring health inequalities at both local and national levels (8).

The results of research conducted in neighboring countries show that: reasons for non-fulfillment of health achievements are lack of necessary financial resources, the inadequate expectation of a scheduled medical examination, a greater distance of residence from health care providers with a frequency of (about) 13% in Montenegro, 108% in Macedonia, 8% in Croatia, and 0.5% in Slovenia (9). In many EU countries, unmet health care needs have nearly doubled from 5.26% to 9.99%, while in other there has been a significant increase of 15% (10). There has also been a growth expressed as a percentage of people reporting unmet health needs in the United States and Canada. Rates of unmet public health needs in the United States are higher (5-20%) compared to the same in Canada (4-12%), (11). In New Zealand, 16.5% of respondents in primary public health missed a visit to a general practitioner due to costs, while 9.3% reported unmet

health needs in secondary healthcare (12). Research related to the prevalence of unmet health needs in a survey of (around) 13760 citizens of Serbia, conducted by the Ministry of Health of the Republic of Serbia in 2013, showed that the biggest obstacles to meeting the needs of health care in this population group are due to financial reasons (20%), long wait for an appointment with a doctor (8%), and problems with transportation to a remote place where health care is provided (5%). The biggest obstacles in achieving health care relate to dental (13.5%), general health care (13%), prescribing necessary medications (11%), and care for patients with altered and impaired mental health (2.5%) (13). The estimated number of people with unmet health needs in our country indicates that significant changes in health policy are necessary. The fact is that various barriers prevent people from accessing existing health services. In Serbia and the other countries in transition, demographic and socioeconomic inequalities in health care have not been realistically and sufficiently studied. Public health policies do not receive the necessary and sufficient social attention. Reducing disparities in health and health care is a crucial precondition for the future evolution of health systems and their institutions (13).

The health needs of the entire population, which are unmet in the health system, represent a significant challenge for any health system. Therefore, more detailed analyzes in the future and revealing the factors that are related to them are important for creating health policies that would contribute to reducing inequalities in access, use, and realization of health care needs.

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Correspondence to/Autor za korespondenciju
Katarina M. Janicijevic
University of Kragujevac, Serbia, Faculty of Medical Sciences, Department of Social Medicine
Svetozara Markovica 69, 34000 Kragujevac
e-mail: kaja.andreja@yahoo.com

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UPUTSTVO AUTORIMA

SANAMED je medicinski časopis osnovan 2006. godine. Časopis objavljuje: originalne naučne i stručne članke, prikaze bolesnika, revijske radove, pisma uredniku, članke iz istorije medicine, prikaz objavljenih knjiga i druge medicinske informacije.

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Prim. dr Avdo Ćeranić,
(za Sanamed)
Ul. Palih boraca 52, 36300 Novi Pazar
Email: sanamednp2006ªgmail.com
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Časopis se štampa na engleskom jeziku, sa kratkim sadržajem prevedenim na srpski jezik.

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Tekst rada kucati u programu za obradu teksta *Word*, latinicom, sa dvostrukim proredom, isključivo fontom *Times New Roman* i veličinom slova 12 tačaka (12 pt). Sve margine podesiti na 25 mm, a tekst kucati sa levim poravnanjem i uvlačenjem svakog pasusa za 10 mm, bez deljenja reči (hifenacije).

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Svaki deo rukopisa (naslovna strana, itd.) mora početi na posebnoj strani. Sve strane moraju biti numerisane po redosledu, počev od naslovne strane. Podaci o korišćenoj literaturi u tekstu označavaju se arapskim brojevima u zagradama, i to onim redosledom kojim se pojavljuju u tekstu.

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Naslovna strana. Naslovna strana sadrži naslov rada, kratak naslov rada (do 50 slovnih mesta), puna prezimena i imena svih autora, naziv i mesto institucije u kojoj je rad izvršen, zahvalnost za pomoć u izvršenju rada (ako je ima), objašnjenje skraćenica koje su korišćene u tekstu (ako ih je bilo) i u donjem desnom uglu ime i adresu autora sa kojim će se obavljati korespondencija.

Naslov rada treba da bude sažet, ali informativan.

Ako je potrebno, može se dodati i podnaslov.

Kratak naslov treba da sadrži najbitnije informacije iz punog naslova rada, ali ne sme biti duži od 50 slovnih mesta.

Ako je bilo materijalne ili neke druge pomoći u izradi rada, onda se može sažeto izreći zahvalnost osobama ili institucijama koje su tu pomoć pružile.

Treba otkucati listu svih skraćenica upotrebljenih u tekstu. Lista mora biti uređena po abecednom redu pri čemu svaku skraćenicu sledi objašnjenje. Uopšte, skraćenice treba izbegavati, ako nisu neophodne.

U donjem desnom uglu naslovne strane treba otkucati ime i prezime, telefonski broj, broj faksa i tačnu adresu autora sa kojim ce se obavljati korespodencija.

Stranica sa sažetkom. Sažetak mora imati do 350 reči. Treba koncizno da iskaže cilj, rezultate i zaključak rada koji je opisan u rukopisu. Sažetak ne može sadržati skraćenice, fusnote i reference.

Ključne reči. Ispod sažetka treba navesti 3 do 8 ključnih reči koje su potrebne za indeksiranje rada.

U izboru ključnih reči koristiti Medical Subject Headings — MeSH.

Stranica sa sažetkom na engleskom jeziku. Treba da sadrži pun naslov rada na engleskom jeziku, kratak naslov rada na engleskom jeziku, naziv institucije gde je rad urađen na engleskom jeziku, tekst sažetka na engleskom jeziku i ključne reči na engleskom jeziku.

Struktura rada. Svi podnaslovi se pišu velikim slovima i boldovano.

Originalni rad treba da ima sledeće podnaslove: uvod, cilj rada, metod rada, rezultati, diskusija, zaključak, literatura.

Prikaz bolesnika čine: uvod, prikaz bolesnika, diskusija, literatura.

Pregled iz literature čine: uvod, odgovarajući podnaslovi, zaključak, literatura.

Bolesnici i metode/materijal i metode. Treba opisati izbor bolesnika ili eksperimentalnih životinja, uključujući kontrolu. Imena bolesnika i brojeve istorija ne treba koristiti.

Metode rada treba opisati sa dovoljno detalja kako bi drugi istraživači mogli proceniti i ponoviti rad.

Kada se piše o eksperimentima na ljudima, treba priložiti pismenu izjavu u kojoj se tvrdi da su eksperimenti obavljeni u skladu sa moralnim standardima Komiteta za eksperimente na ljudima institucije u kojoj su autori radili, kao i prema uslovima Helsinške deklaracije. Rizične procedure ili hemikalije koje su upotrebljene se moraju opisati do detalja, uključujući sve mere predostrožnosti. Takođe, ako je rađeno na životinjama, treba priložiti izjavu da se sa njima postupalo u skladu sa prihvaćenim standardima.

Treba navesti statističke metode koje su korišćene u obradi rezultata.

Rezultati. Rezultati treba da budu jasni i sažeti, sa minimalnim brojem tabela i slika neophodnih za dobru prezentaciju.

Diskusija. Ne treba činiti obiman pregled literature. Treba diskutovati glavne rezultate u vezi sa rezultatima objavljenim u drugim radovima. Pokušati da se objasne razlike između dobijenih rezultata i rezultata drugih autora. Hipoteze i spekulativne zaključke treba jasno izdvojiti. Diskusija ne treba da bude ponovo iznošenje zaključaka.

Literatura. Reference numerisati rednim arapskim brojevima prema redosledu navođenja u tekstu. Broj referenci ne bi trebalo da bude veći od 30, osim u pregledu literature, u kojem je dozvoljeno da ih bude do 50.

Izbegavati korišćenje apstrakta kao reference, a apstrakte starije od dve godine ne citirati.

Reference se citiraju prema tzv. Vankuverskim pravilima, koja su zasnovana na formatima koja koriste *National Library of Medicine* i *Index Medicus*.

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1. **Članak:** (svi autori se navode ako ih je šest i manje, ako ih je više navode se samo prvih šest i dodaje se *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

2. **Knjiga:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Poglavlje ili članak u knjizi:**

Latković Z. Tumori očnih kapaka. U: Litričin O i sar. Tumori oka. 1. izd. Beograd: Zavod za udžbenike i nastavna sredstva, 1998: 18–23.

Tabele. Tabele se označavaju arapskim brojevima po redosledu navođenja u tekstu, sa nazivom tabele iznad.

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Prim. dr Avdo Ćeranić,
(for Sanamed)
Ul. Palih boraca 52, 36300 Novi Pazar
Email sanamednp2006[a]gmail.com
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The manuscript should be arranged as following: title page, abstract, key words, introduction, patients and methods/material and methods, results, discussion, conclusion, references, tables, figure legends and figures.

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Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

2. **Book:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Chapter or article in a book:**

Trier JJ. Celiac sprue. In: Sleisenger MH, Fordtran J5, eds. Gastro-intestinal disease. 4 th ed. Philadelphia: WB Saunders Co, 1989: 1134–52.

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