Acta Medica Croatica

Vol. 75 2021.
Broj 1
Zagreb

UDC 61 • AMCREF 75 (1)
1-108 (2021)
ISSN 1330-0164

ACTA MEDICA CROATICA

GLASILO AKADEMIJE MEDICINSKIH ZNANOSTI HRVATSKE

Journal of the Academy of Medical Sciences of Croatia

Adresa Uredništva – Address of the Editorial Board
ACTA MEDICA CROATICA
Akademija medicinskih znanosti Hrvatske
Praška 2/III, 10000 Zagreb, Hrvatska
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The Journal is published four times a year. Conveniently may be publish supplements.
Naručuje se neposredno od Uredništva. Godišnja pretplata u zemlji iznosi za ustanove 350 kn, za pojedince 150 kn, a uplaćuje se na račun IBAN: HR5423600001101481831 pri Zagrebačkoj banci.

Orders can be placed directly to our Editorial Office. The annual subscription outside Croatia is US $150 to be paid to our bank account Akademija medicinskih znanosti Hrvatske, Privredna banka Zagreb d.d., Radnicka cesta 50, 10000 Zagreb, Croatia, SWIFT PBZGHR2X IBAN: HR6323400091110089793 (for Acta Medica Croatica).

Tisak – Print:
Gradska tiskara Osijek d.d., 31000 Osijek, Croatia
Tiska se u 500 primjeraka - Printed in 500 copies

Tiskanje časopisa potpomognuto je financijskim sredstvima Ministarstva znanosti i tehnologije RH.
The printing of the Journal is subsidized by the Ministry of Science and Technology of the Republic of Croatia

acta medica croatica

Časopis Akademije medicinskih znanosti Hrvatske
Acta Med Croatica • Vol. 75 Br. 1 • Str. 1-108 • Zagreb, travanj 2021.
The Journal of the Academy of Medical Sciences of Croatia

Indexed/abstracted in:
SCOPUS
Biosis Previews
Cancerlit
Embase/Excerpta Medica
Health Planning and Administration
Toxline
EBSCO

ACUTE KIDNEY INJURY IN PATIENTS WITH COVID-19: A CHALLENGE FOR NEPHROLOGISTS

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Acute kidney injury (AKI) is a common finding in patients with coronavirus disease 2019 (COVID-CoV-19), and it is associated with long-term hospital treatment, more frequent admission to intensive care units (ICUs), and higher mortality compared with COVID-CoV-19 patients without kidney disease. Moreover, mortality rate is directly proportional to the severity of AKI. The pathophysiology of COVID-19 associated AKI could be related to specific and unspecific mechanisms. COVID-19 - specific mechanisms are direct cellular injury resulting from viral entry through the ACE-2 receptor, which is highly expressed in the kidney, an imbalanced renin-angiotensin-aldosterone system (RAAS), severe respiratory failure, proinflammatory cytokines elicited by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, coagulopathy, microangiopathy, and collapsing glomerulopathy. Nonspecific mechanisms include hemodynamic alterations, high levels of positive end-expiratory pressure in patients requiring mechanical ventilation, sepsis, hypovolemia, rhabdomyolysis, and administration of nephrotoxic drugs. Today, we do not know enough about the prevention and management of COVID-19. Treatment of AKI includes general management, pharmacological management of COVID-19, hemodynamic and volume optimization, renal replacement therapy, and other extracorporeal organ support. As of now, long-term prognosis is unknown. However, it may be safe to speculate that prognosis will be associated to the etiology of AKI. Patients with thromboembolic complications and collapsing glomerulopathy may develop a more severe degree of chronic kidney disease compared to those with other types of renal injury (e.g., acute tubule-interstitial nephritis). Early studies suggest that about one-third of patients who survived AKI caused by COVID-19 will remain dialysis-dependent.

Key words: acute respiratory distress syndrome, acute kidney injury, angiotensin-converting enzyme 2 receptor, COVID-19, cytokine release syndrome, extracorporeal organ support, renal replacement therapy, SARS-CoV-2

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On April 9, 2021, 133,552,774 confirmed cases of coronavirus disease 2019 (COVID-19) including 2,894,295 confirmed deaths were reported by the World Health Organization (WHO) (1). Since the onset of the new severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) outbreak, a lot of research has been focused on pulmonary complications, namely, acute respiratory distress syndrome (ARDS), which is the leading condition in intensive care unit (ICU) admission and associated with a high mortality rate (2-5). Initially, little attention was paid to kidney abnormalities, primarily acute kidney injury (AKI) (7). However, today, it is evident that AKI is prevalent in patients with COVID-19 and that SARS-CoV-2 specifically invades the kidneys. Moreover, a recently published study that utilized autopsy specimens from patients who died from COVID-19 demonstrated evidence for the SARS-CoV-2 invasion of the kidney tissue, along with significant tubular epithelial and peritubular capillary endothelial injury, as well as glomerular changes (8, 9).

EPIDEMIOLOGY

Acute kidney injury is strongly associated with increased mortality and morbidity, and is a complication that can occur during progression of COVID-19 in patients suffering from chronic kidney disease (CKD), as well as in those who are not sick (10). According to the analysis of several studies, the incidence of AKI varies from 0.5% to 23%, with higher rates reported in countries outside China (11). The pooled incidence of COVID-19-associated AKI in different regions of China from 26 peer-reviewed studies was 6.5%, with a much higher rate in patients admitted to ICU (32.5%) than in patients treated at non-intensive departments (5.1%) (12). Studies from Wuhan showed a higher AKI incidence (9.7%) (6) than studies from other provinces in China (2.8%) (12), which may be explained by difference in disease severity.

Recently published studies on COVID-19 worldwide report AKI rates in hospitalized patients of 17.9%-

72.7% in Italy, 9.2%-18.3% in Korea, 19.7%-69.2% in Spain, 5.8%-56.9% in the USA, 52.2%-74.6% in Germany, and 4.7%-64.1% in France and Belgium, which are much higher than the rates in China (12-17). The difference may be explained by the fact that only very sick COVID-19 patients were admitted to hospitals in those countries compared to the admission of less sick patients in China. Health care systems and policies for hospitalization and assigning levels of care are widely different across the world, as well as demographic characteristics, risk factors, morbidities, definition of AKI, and admission rate of COVID-19 patients (Table 1).

Patients who developed AKI had a more critical prognosis in terms of mortality rate compared with those that had only chronic illness as comorbidity (e.g., diabetes mellitus, arterial hypertension, cardiovascular diseases, chronic respiratory diseases and neoplasms). AKI increased the risk of death 5.3 times in these patients (18). In patients with COVID-19, mortality rates increase with age, as well as with the number of chronic pre-existing diseases (especially CKD) (19). All these observations suggest that mortality rate from AKI may be 13 times higher, and that either the presence of CKD at hospital admission or development of AKI during the COVID-19 infection have been both recognized as two independent risk factors for mortality (19, 20).

Table 1.
Potential risk factors for COVID-19 acute kidney injury (AKI)

Demographic risk factors	Risk factors for AKI at admission	Risk factors for AKI during hospitalization
Older age	Severity of COVID-19	Nephrotoxins (e.g., drugs, contrast exposure)
Hypertension	Degree of viremia	Vasopressors
Diabetes mellitus	Respiratory status	Fluid dynamics (fluid overload/hypovolemia)
Cardiovascular diseases	Non-respiratory organ involvement	Ventilation, high positive end-expiratory pressure
Chronic kidney disease	Leukocytosis	
High body mass index	Lymphopenia	
Immunosuppressed state	Hypovolemia/ dehydration	
Genetic risk factors (e.g., APOL1 genotype, ACE-2 polymorphisms)	Elevated markers of inflammation (e.g., CRP, D-dimers, ferritin)	
Smoking history	Rhabdomyolysis	
	Medication exposure (e.g., ACEi, ARB, statin, NSAID)	

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; COVID-19, coronavirus disease 2019; NSAID, nonsteroidal anti-inflammatory drug

ETIOLOGY

Coronaviruses are a group of single-stranded RNA viruses with positive polarity, belonging to the Coronavirus family. Until 2019, six coronavirus strains, which were able to infect humans, were known. Four strains usually circulate in the human population causing mild respiratory infections. In 2003 and 2012, the first two zoonotic strains of coronaviruses capable of infecting humans through an animal were identified. These caused severe lung syndromes in recent times, i.e. the severe acute respiratory syndrome (SARS) in 2003 and Middle East respiratory syndrome (MERS) viruses in 2012 (21). In December 2019, unusual cases of pneumonia were reported in the city of Wuhan, located in the Hubei Province in central China. On January 12, 2020, the WHO stated that the disease was caused by a novel coronavirus named SARS-CoV-2. The resulting SARS-CoV-2 related disease was defined as a novel COVID-19 that rapidly spread throughout China, followed by an increasing number of cases in all continents, resulting in a global pandemic (19).

It has been documented that SARS-CoV-2 is a chimeric virus resulting from pre-existing viruses, namely, a bat coronavirus and a coronavirus of unknown origin. Its genomic sequence corresponds to the bat coronavirus with 88% identity and the pangolin coronavirus with 99% identity (22, 23). The genetic analysis performed on the pangolin coronavirus involved only a specific site known as the receptor-binding domain (24). However, it emerged that SARS-CoV-2 and the pangolin coronavirus did not share the same structural characteristics. Therefore, pangolin was identified as the intermediate species of transition from bat to humans rather than being directly responsible for the SARS-CoV-2 pandemic (23, 25). Common routes of transmission of this highly contagious virus are as follows: 1) close contact (the most usual way of infection); 2) transmission *via* aerosols; 3) it has been identified in tears and conjunctival secretions of COVID-19 patients; and 4) SARS-CoV-2 has been found in gastrointestinal tissue of COVID-19 patients (26).

PATHOPHYSIOLOGY

The genomic sequence of SARS-CoV-2 was compared with SARS-CoV and MERS-CoV, and it was found that SARS-CoV-2 has a sequence identity of 79% with SARS-CoV and 50% with MERS-CoV. Upon analysis of certain proteins (coronavirus main proteinase, papain-like protease and RNA-dependent RNA polymerase), it was observed that the sequence identity value between SARS-CoV and SARS-CoV-2 is 96%, on the basis of which it was concluded that there is a similarity in the pathophysiological effects of these two coronaviruses (27).

The SARS-CoV-2 infection represents a major challenge to our homeostatic response. The renin-angiotensin-aldosterone system (RAAS) is a key homeostatic system within our bodies that involves the lung, kidneys, brain, liver and other organs, to regulate fluid volume, blood pressure and electrolyte balance. The first step in COVID-19 pathogenesis is viral invasion *via* its target host cell receptors. SARS-CoV-2 is mostly transmissible through large respiratory droplets, directly infecting cells of the upper and lower respiratory tract, especially nasal ciliated and alveolar epithelial cells. In addition to the lungs, angiotensin-converting enzyme 2 (ACE-2) receptors are also expressed in various other human tissues such as the kidneys, small intestine, heart, thyroid, testis, and adipose tissue, indicating that the virus may directly infect cells of other organ systems when viremia is present. ACE-2 is a carboxypeptidase expressed on the cell surface that cleaves angiotensin I (Ang I) into angiotensin 1-9 and angiotensin II (Ang II) into angiotensin 1-7, counteracting the vasoconstrictor, proliferative and fibrotic effects of angiotensin II generated by angiotensin converting enzyme (ACE). It now appears that the ACE-2 receptor, which is ubiquitous throughout our bodies, facilitates entry of SARS-CoV-2 into host cells and disrupts the normal homeostatic response.

However, for many coronaviruses, including SARS-CoV-2, host cell binding alone is insufficient to facilitate viral and cell membrane fuse, requiring S-protein priming or cleavage by host cell proteases or transmembrane serine proteases. Recently, it was demonstrated that S-protein priming by transmembrane serine protease 2 (TMPRSS2) is required to facilitate SARS-CoV-2 entry into host cells (28).

After entering the cell and becoming activated, SARS-CoV-2 uses the endogenous transcription mechanism of the cells to replicate and spread. Cells infected by SARS-CoV-2 can recruit and modulate immune cells through secretion of chemokines or cytokines. The interaction between macrophages and cells expressing ACE-2 suggest a primary role of macrophages as a sentinel during viral infection. A recent study, however, has shown a downregulation of mitochondrial proteins that interact with SARS-CoV-2. This mechanism could be interpreted as a process through which the virus prevents apoptosis induced by mitochondria (29, 30).

Finally, targeting of ACE-2 by SARS-CoV-2 results in angiotensin dysregulation, innate and adaptive immune pathway activation, hyper-coagulation, and consequent multiple organ damage (Figure 1).

Epithelial cells of the lungs and gut are prime target of SARS-CoV-2 infection and COVID-19 symptoms. The expression of ACE-2 has been shown also in the kidney, heart, liver, esophagus, stomach, ileum, colon, and epithelial cells in the nose and mouth (31, 32). These data associated with the evidence that reduction of taste and/or smell, myocardial dysfunction with acute cardiovascular events, gastrointestinal disorders and AKI are among the most frequent clinical manifestations of COVID-19, suggest that SARS-CoV-2 can infect these organs causing functional damage.

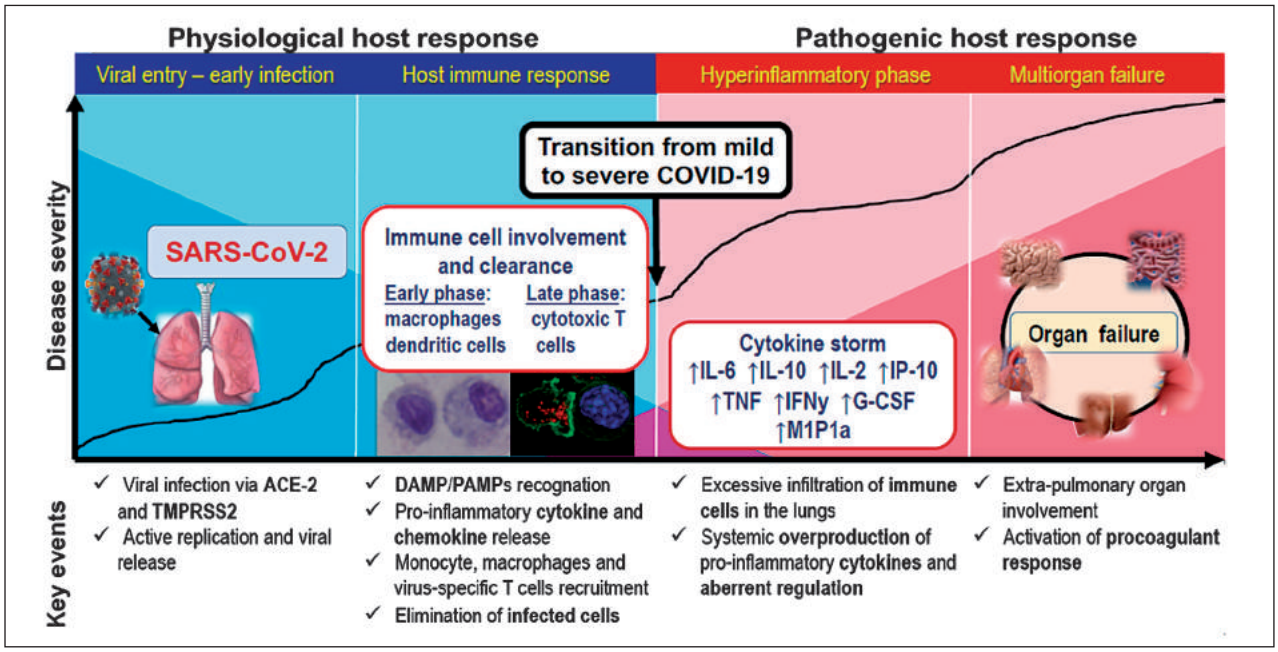

Fig. 1. *Key developments during COVID-19 infection.*
Dark blue shading indicates physiologic viral host response over time; dark red shading indicates pathogenic hyper-inflammatory host response over time.

PATHOPHYSIOLOGY OF ACUTE KIDNEY INJURY CAUSED BY SARS-COV-2

Recent studies with SARS-CoV-2 infected patients have reported that human kidney is a specific target for COVID-19 infection (33, 34). The presence of viral particles in the renal tubular epithelium, which were morphologically identical to SARS-CoV-2, and with viral arrays and other features of virus assembly, provide evidence for a productive direct infection of the kidney by SARS-CoV-2. This finding offers confirmatory evidence that direct renal infection occurs in the setting of AKI in COVID-19 (35). Further, Diao *et al.* (36) examined viral nucleocapsid protein in the kidney of postmortem patients and found that SARS-CoV-2 antigens accumulated in renal epithelial tubules, suggesting that SARS-CoV-2 infects the human kidney directly, which leads to kidney dysfunction and contributes to viral spreading in the body.An additional study of 26 autopsies found virus particles characteristic of SARS-CoV-2 in the proximal tubular epithelium and podocytes by electronic microscopy. This finding was associated with foot process effacement and occasional vacuolation and detachment of podocytes from the glomerular basement membrane (9).

However, several articles disputed whether the particles identified were virus in origin and suggested that multivesicular bodies or clathrin-coated vesicles had an identical appearance (37). Although direct viral infection of the kidney is possible, it is certainly not a common or even widespread finding reported.

The results of these, but also numerous other researches, along with the consensual physiological role of ACE-2 in the kidneys, raise the possibility of a complex multifactorial pathophysiology explaining kidney abnormalities in COVID-19, involving a direct cytopathic effect of the virus, local disruption in RAAS homeostasis, and a systemic inflammatory response to infection (Figure 2).

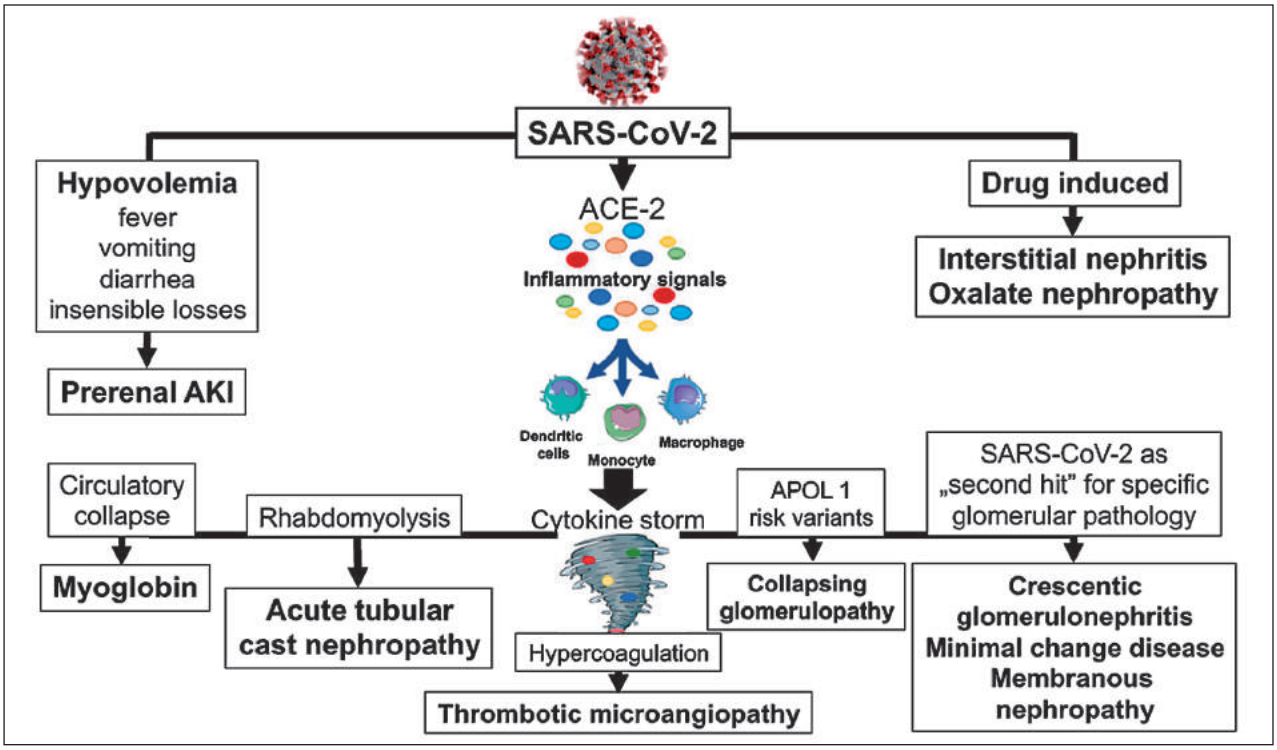

Fig. 2. *Pathophysiology of acute kidney injury caused by SARS-CoV-2.*

Aberrant immune host response together with cytokine storm and lymphocytopenia, followed by ARDS, are relevant problems that influence the severity of COVID-19, and modulation of the immune response and inflammation may thus be considered crucial (37).

ARDS, acute respiratory distress syndrome

Angiotensin II pathway activation

Interaction between SARS-CoV-2 and angiotensin II receptors has been proposed as a potential mechanism contributing to the virus infectivity. The main binding site for SARS-CoV-2 is the ACE-2 protein, which is expressed by the kidney much more than the lungs (37, 38). ACE-2 is expressed on the brush border apical membrane of the proximal tubule, where it colocalizes with ACE. It is also present at lower levels in podocytes. The virus could enter the kidney by invading podocytes first. Injured podocytes often are shed in

urine and podocytes harboring viral particles if shed in urine may contribute to the disease transmission in the proximal tubules (Figure 3). Coronavirus entry into the host target cells also requires fusion of the viral envelope with cellular membranes. Fusion-activated SARS-CoV-2 peptides are created by specific proteolytic cleavage of the S proteins, in a step called 'priming'. As a consequence, cell infectivity not only depends on ACE-2 expression, but is also governed by the types of proteases found in a given cell type. In the kidney, TMPRSS2, which primes the SARS-CoV-2 S protein, is robustly expressed in the distal nephron rather than the proximal tubule. It remains to be determined if other TMPRSS such as TMPRSS 4, 5, or 9in the proximal tubule can mediate the priming step. Therefore, the coexpression of ACE-2 and TMPRSS2 is a determining factor for the entry of SARS-CoV-2 into the host cells (19).

After entering the cell and becoming activated, SARS-CoV-2 uses the endogenous transcription mechanism of the cells to replicate and spread (19). Cells infected by SARS-CoV-2 can recruit and modulate immune cells through the secretion of chemokines or other cytokines. The role of macrophages remains to be defined. In fact, the interaction between macrophages and cells expressing ACE-2 is known, suggesting a primary role of macrophages as a sentinel during viral infection. A recent study has shown downregulation of mitochondrial proteins that interact with SARS-CoV-2. By that mechanism, the virus prevents apoptosis induced by mitochondria (30).

Viral replication in podocytes and the consequent podocyte injury during COVID-19 infection is a great challenge for the patients to deal with and to the nephrologists to strategize treatment options.

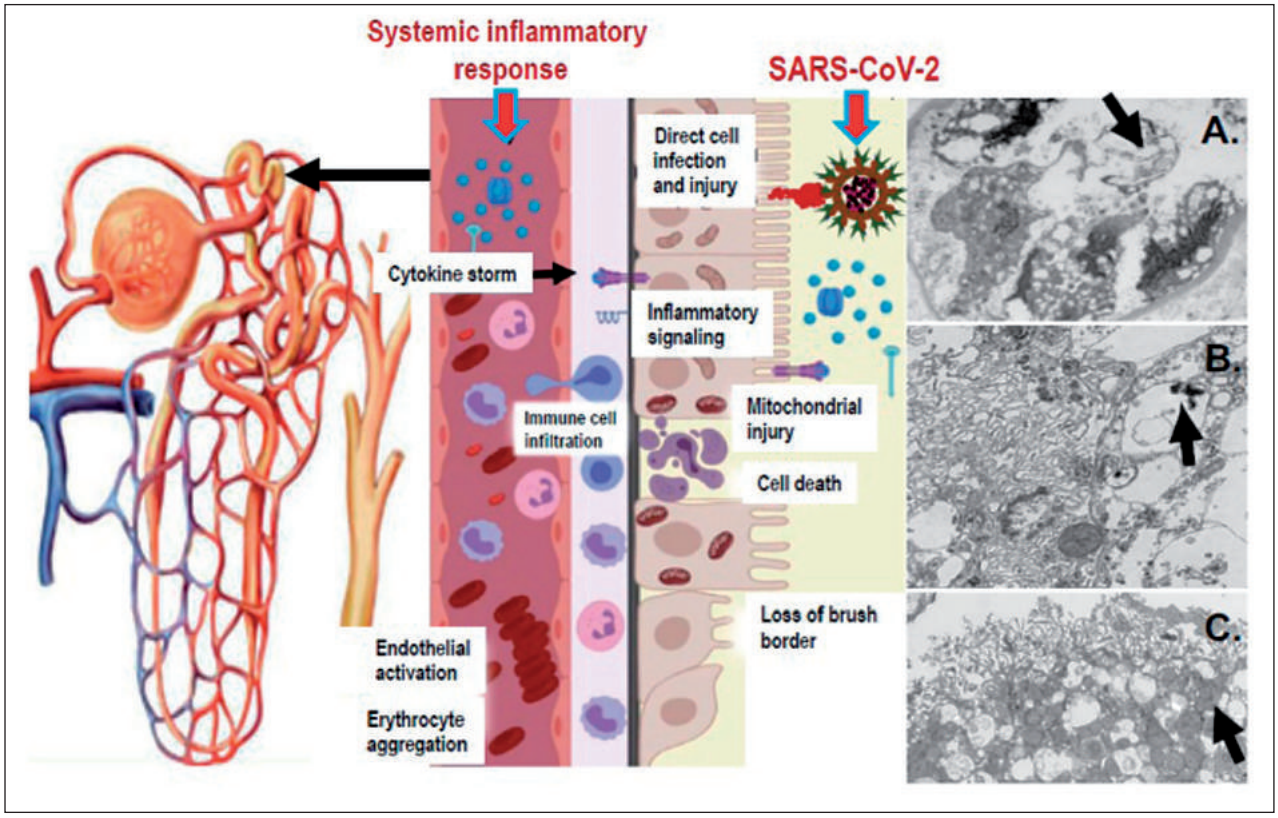

Fig. 3. *Possible mechanisms of kidney damage by severe SARS-CoV-2 infection.*

Angiotensin-converting enzyme 2 expression in proximal epithelial cells makes them a direct target of SARS-CoV-2 infection and virus-related injury. This process could be aggravated first by local inflammation,and after that uncontrolled systemic inflammatory response involving a cytokine storm.

A. Electron micrograph of proximal tubule with severe epithelial cell injury with cell sloughing and denudation of the basement membrane (fragments of membranes appear in the lumen – arrow). The nuclei appear pyknotic and the cytoplasm severely vacuolated.
B. Cytoplasmic dissolution and widespread densities consistent with damaged phospholipids suggestive of oxidative membrane injury (arrow).
C. Disintegration of the brush border and extensive cytoplasmic vesiculation. The mitochondria appear markedly swollen. The clusters of small mitochondria are kept in places (arrow).

Customized according to: Papadimitriou JC et al. Kidney Int Rep. (2020) doi: https://doi.org/10.1016/j.ekir.2020.10.029(8); Martinez-Rojas MA et al. Am J Physiol Renal Physiol. 2020; 318: F1454-62 (33).

Even more, regardless of direct viral infection of the kidney, ACE-2 is increased in the context of acute lung injury and there is evidence that it is downregulated in AKI. This may lead to type 1 angiotensin receptor activation, as well as decreased angiotensin (1-7) formation and subsequent worsening of AKI (Figure 4), which has special significance in the subpopulation of patients with diabetes mellitus (DM), cardiovascular disease (CVD), and CKD (Table 1).Thus, patients with CKD, especially those with diabetic kidney disease (DKD), who develop COVID-19 may be at a higher risk of AKI because of baseline upregulation of the ACE and downregulation of ACE-2, a combination that primes a proinflammatory (including complement activation) and profibrotic state in the kidneys of those with DKD. Pre-existent CKD could worsen the expected outcomes of patients with COVID-19 and may involve many pathophysiological mechanism is dependent on comorbidities (39).

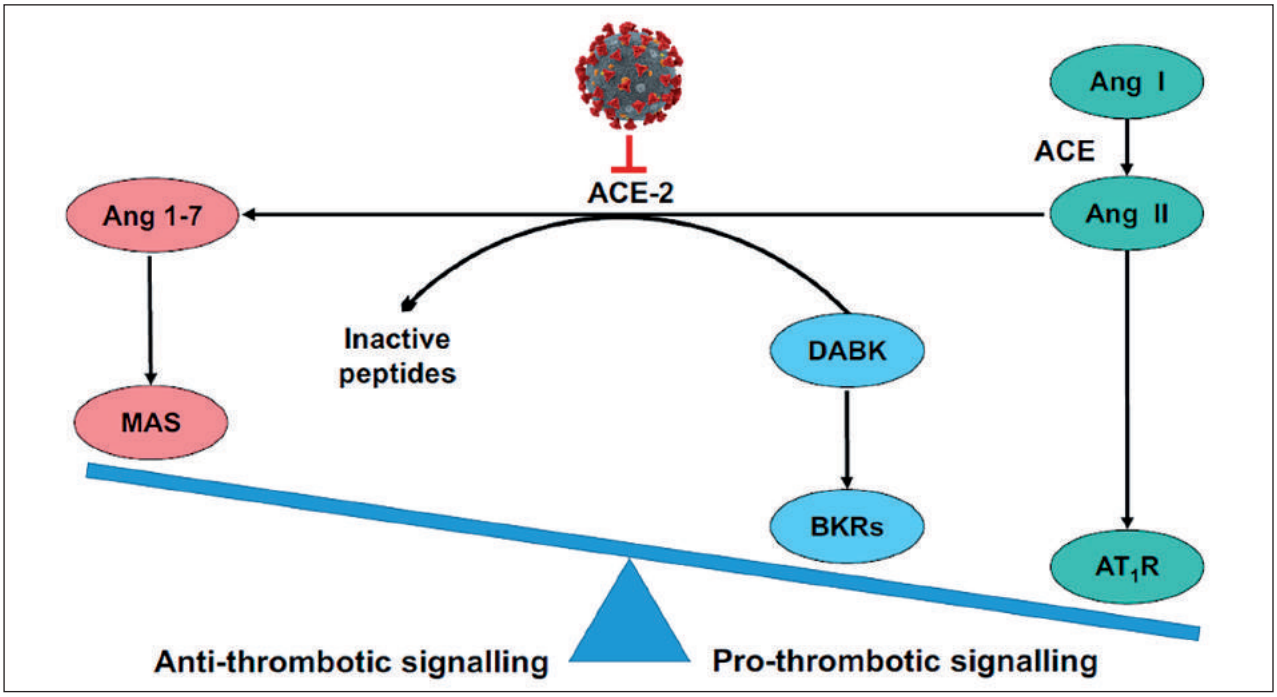

Fig. 4. *Effect of SARS-CoV-2 infection on endothelial cell function.*

SARS-CoV-2 directly infects endothelial cells owing to their high expression levels of ACE-2 and TMPRSS2. After binding by SARS-CoV-2, ACE-2 is internalized, and downregulated on endothelial cells, which favor progression of inflammatory and pro-fibrotic processes in the lung,kidney, heart and some other organs, triggered by Ang II hyperactivity. Inhibition of ACE-2 by binding of SARS-CoV-2 reduces the ACE-2 mediated conversion of Ang II to Ang 1-7, which act on the MAS receptor. The reduction of MAS receptor activation induces a pro-inflammatory phenotype through increased activation of AT1Rs. Furthermore, reduced expression of ACE-2 might in turn indirectly activate the KKS, which ultimately leads to increased vascular permeability (60). Additionally, reduction in the levels of ACE-2 limits degradation of DABK into inactive peptides, ultimately leading to increased pro-thrombotic signaling via the activation of BKRs.

ACE-2, angiotensin-converting enzyme 2; Ang 1-7, angiotensin 1-7; Ang II, angiotensin II; AT1R, type 1 angiotensin receptor; BKR, bradykinin receptors; DABK, des-Arg9 bradykinin; KKS, kallikrein-kinin system; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, transmembrane protease serine 2

Dysregulation of immune response and cytokine storm

Renal impairment in patients with COVID-19 is partly due to acute tubular necrosis (ATN) resulting from the direct influence of SARS-CoV-2, but also indirectly through the complex immune mechanisms triggered by cellular damage. Histopathologic examination performed on kidney specimens obtained from autopsy of COVID-19 patients with AKI showed viral antigens in the cytoplasm of tubular cells, C5b-9 depositions on the apical brush border of tubular epithelial cells, and presence of CD68+ macrophages in the tubul-interstitium (19). Recent research has revealed that patients infected by SARS-CoV-2 showed lymphopenia, mainly related to the significant reduction in absolute T cell counts, particularly cytotoxic T lymphocytes (CD8+), increased neutrophil counts, and elevated levels of proinflammatory interleukins (IL-2, IL-6, IL-10) and interferon-γ (IFN-γ). It is known that T cells are important for dampening overactive innate immune responses, and that a loss of T cells during viral infection may result in enhanced inflammatory responses. Moreover, it has been observed that when

the T cell count drops serum levels of IL-2, IL-4, IL-10, INF, and tumor necrosis factor-α (TNF-α) (40). Due to the decrease in CD4+, CD8+ and NK lymphocytes, COVID-19 patients with more severe clinical manifestations have higher serum concentrations of IL-6 and lower IFN-γ than those with mild forms of the disease.

Normally, the IFN-receptor binding induces a cascade of signals with activation of the genes coding for proteins with antiviral, anti-proliferative or immunomodulatory properties (41), but in patients infected by SARS-CoV-2, a higher IL-6/IFN-γ ratio can be related to an enhanced cytokine storm (42). These observations suggest that in patients with COVID-19, AKI may have an inflammatory etiology mediated by a cytokine storm, an inflammatory process that originates at a local site and spreads *via* systemic circulation (41, 42).

In the lung-kidney crosstalk, a close bidirectional relationship between alveolar and tubular damage because of toxic overproduction including cytokines and growth factors, as well as the release of damage-associated molecular patterns (DAMPs) from injured tissue in COVID-19 patients has been reported. When a cytokine storm occurs, the immune system may not be able to kill SARS-CoV-2, while it may kill large numbers of normal cells, damage tissues, organs, and finally become the cause of multiple organ failure (MOF). Cytokine storm can lead to severe ARDS. This type of inflammatory response may also harm the kidney. Many studies have emphasized the potential involvement of IFN pathways and viral trigger in podocyte and consequently glomerular injury. Podocyte dysregulation might be due to an infection-driven inflammatory response that releases cytokines or DAMPs. In turn, this product circulates and interacts with receptors on podocytes, which can be one of the important factors in the development of collapsing glomerulopathy (focal segmental glomerulosclerosis, FSGS) (43). In some settings, collapsing FSGS is closely related to the genetic expression of APOL1 G1 and/or G2 risk variants (which are observed in people of African American origin). SARS-CoV-2 infection may unmask APOL1-conferred genetic susceptibility to podocyte injury and development of collapsing FSGS (43).

In addition to being frequently associated with the cytokine storm, severe lung infections and/or ARDS often require prolonged mechanical ventilation. COVID-19-associated ARDS is often treated by increasing positive end-expiratory pressure (PEEP). During PEEP, there is an increase in intrathoracic pressure, which can lead to increased intrathoracic pressure, as well as increased renal venous pressure and reduced glomerular filtration rate (GFR). In addition, PEEP can also increase sympathetic tone (leading to secondary activation of RAAS), which also contributes to the development of AKI (11).

Moreover, patients who develop secondary infections (bacterial, fungal or viral) are at a higher risk of secondary sepsis-associated AKI. Sepsis is classically defined by marked hypotension that requires treatment with inotropic drugs. Therefore, in patients with sepsis, it is plausible that persistent hypotension and vasoconstriction induced by inotropics can participate in the development of renal medullary hypoxia, which is an additional insult to tubular cells and consequent ATN (44).

Rhabdomyolysis in the setting of COVID-19 can be a consequence of direct cytotoxic effect of SARS-CoV-2 on muscles, drug-induced or tissue hypoxia due to hypoxemia. Myoglobin demonstrates its toxicity by direct damage to renal tubular cells, renal vasoconstriction related to the hyperactivation of RAAS by hypoperfusion and intratubular cast formation, leading to ATN (45).

It is also important to note that a handful of studies have described COVID-19 patients presenting with primary cardiac symptoms referred to cardio-renal syndrome type 1 (46). Patients usually had myocarditis and stress-related cardiomyopathy due to respiratory failure and hypoxemia, but in some patients, concomitant heart and kidney failure may occur during sepsis (47). There is insufficient evidence to support direct viral infection of cardiomyocytes, but it should be remembered that maladaptive cytokine release directly affects cardiomyocytes and leads to endothelial cell dysfunction (48).

It is clear that the inflammatory process might contribute to the pathogenesis of COVID-19-associated MOF through the infiltration of infected tissue by host immune cells in order to contain viral replication. However, hyperactivation of these immune cells may lead to fibrosis, epithelial cell apoptosis and microvasculature damage participating in the pathogenesis of CKD.

Lymphopenia

The expression of ACE-2 in lymphocytes turns them into potential targets of SARS-CoV-2, which consequently results in cell death of both $CD4^+$ and $CD8^+$ T cells leading to an imbalance in both innate and acquired immune responses, neutrophils, macrophage hyperactivation, and delayed clearance of viruses (9, 11, 19). The consequent lymphopenia is most likely the result of a combined action of the inflammatory response (which leads to lymphocyte apoptosis), direct role of virus in lymphocyte death, or/and de-

struction of lymphatic organs by virus.The effects of SARS-CoV-2 on lymphocytic apoptosis, as well as on CD169⁺ macrophages present in lymph nodes and spleen, was proven at autopsy of patients who died from COVID-19 (33).

Dysregulation of complement system

The complement system, a significant component of native immunity, is critical to rapid response to infections. Its dysfunction leads to acute lung injury following a highly severe SARS-CoV-2 infection. COVID-19 activates the complement system *via* lectin and alternative pathways. The complement system produces anaphylatoxins (e.g., C3a and C5a), which bind to their specific receptors and stimulate the leukotrienes, histamine, and prostaglandins, which are responsible for the main symptoms of hypersensitivity (vasodilation, flushing, hypoxia, and hypotension). Assembly of complement C5b-9 through the alternative pathway in tubular apical brush border consequent to their accumulation in tubular lumen leads to tubulo-interstitial damage (36) (Figure 5). The complement activation and pro-coagulation pathways can stimulate one another.

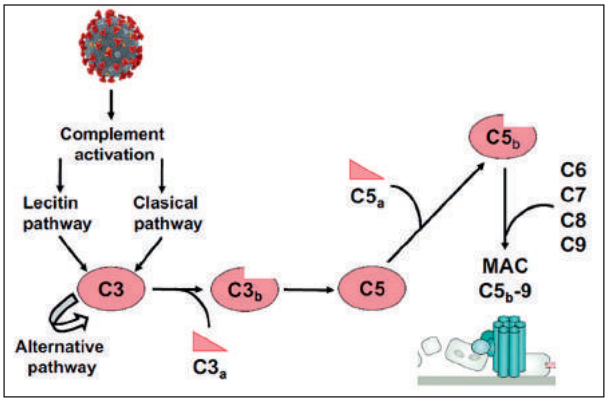

Fig. 5. *Effect of SARS-CoV-2 infection on the complement system.*

Complement cascade can be activated by three different pathways, the classic, lectin and alternative pathways. All three participate in creating the formation of C3 convertases that cleave C3, generating the pro-inflammatory peptide C3a and a large amount of C3b that opsonizes pathogens. The latter also forms the C5 convertase, which leads to release of the potent anaphylatoxin C5a, as well as the fragment C5b responsible for the formation of MAC C5b-9 on target cells, which is considered to be the terminal event of complement activation. Furthermore, complexes of SARS-CoV-2-specific antibodies and viral antigens might induce endothelial cell injury through activation of the C1 complex of the classic pathway and induction of ADC (60). Clinical insights into complement activation following SARS-CoV-2 infection are limited; there are indications that the downstream terminal phases of the complement cascade may contribute to endothelial cell injury, intravascular coagulation and thrombosis, leading to MOF in COVID-19 patients (49, 51, 60).

ADC, antibody-dependent cytotoxicity; MAC, membrane attack complex

Coagulopathy and microangiopathy

According to the latest data, the incidence of thrombotic complications in critically ill patients with COVID-19 is up to 49%, and it is accompanied by a significant mortality rate (>70%) (49). Critically ill patients are generally predisposed to thromboembolism, mainly due to a combination of favorable factors such as systemic inflammation, endothelial dysfunction, platelet activation, immobility, and stasis of blood flow. COVID-19-associated thrombotic complications seem to resemble systemic coagulopathies such as disseminated intravascular coagulation (DIC) or sepsis-induced coagulopathy (SIC). However, analysis of hematologic findings in COVID-19 patients indicates higher plasma levels of fibrinogen and D-dimers, as well as significantly elevated C-reactive protein(CRP) and ferritin values, associated with thrombocytopenia and relatively modest changes in prothrombin time (PT) and activated partial thromboplastin time (APTT) (19, 50, 51). Patients with COVID-19 have a specific procoagulant profile that manifests by a significant increase in D-dimer and fibrinogen levels, which significantly correlate with elevated IL-6 levels (52) and have good specificity and sensitivity in predicting the potential worse outcomes (53).

The rapid worsening of respiratory symptoms is accompanied by extremely marked and uncontrolled increase in pro-inflammatory cytokines (IL-2, IL-6, IL-7, IL-10, TNF-α, MCP-1, MIP-1A and IP-10), commonly referred to as the cytokine storm. Playing a critical role in acute inflammation, pro-inflammatory cytokines (especially IL-6) induce a wide spectrum of proteins including fibrinogen and thrombopoietin (54), activating complement pathway on endothelial cell membranes, mediating vascular endothelial growth factor (VEGF), signaling and promoting destabilization of vascular endothelial-cadherin resulting in increased vascular permeability (54, 55). Moreover, IL-6 can increase the level of tissue factor allowing the conversion of prothrombin to thrombin, and then permits fibrin clot formation. On the other hand, thrombin is able to induce IL-6 expression forming a reciprocal feedback. Therefore, in COVID-19 patients, acute uncontrolled inflammation and elevated IL-6 can affect coagulation and fibrinolysis in several ways and amplify hypercoagulability.

Otherwise, infection with SARS-CoV-2 directly or indirectly induces vascular endothelial dysfunction and thus increases the possibility of thrombosis. Due to COVID-CoV-2 infection mediated by ACE-2 and TMPRSS2, co-presence of the two proteins may underpin the tropism of virus attack. ACE-2 and TMPRSS2 are co-expressed in cells of the lung, heart, kidney, smooth muscle and neurons, but also in vas-

cular endothelium (50, 55, 56). Normally, in endothelial cells of the kidney, only ACE is expressed without detectable ACE-2 (57). However, ACE-2 expression can be changed in pathologic states or by some drugs (9), which may allow SARS-CoV-2 to infect directly renal endothelium (58). Recruitment of immune cells, either by direct viral infection of the vascular endothelium or immune-mediated, can result in widespread endothelial dysfunction associated with apoptosis. Endothelial dysfunction is a principal determinant of microvascular dysfunction by shifting the vascular equilibrium towards more vasoconstriction with subsequent inflammation associated with tissue edema, organ ischemia, and a procoagulant state (59). SARS-CoV-2 infection facilitates the induction of endothelitis, apoptosis and pyroptosis in several organs as a direct consequence of viral involvement and of the host inflammatory response. COVID-19-endothelitis could explain the impaired systemic microcirculatory function in different vascular beds and their clinical sequels in patients with COVID-19 (19, 49-52, 59, 60) (Figure 6).

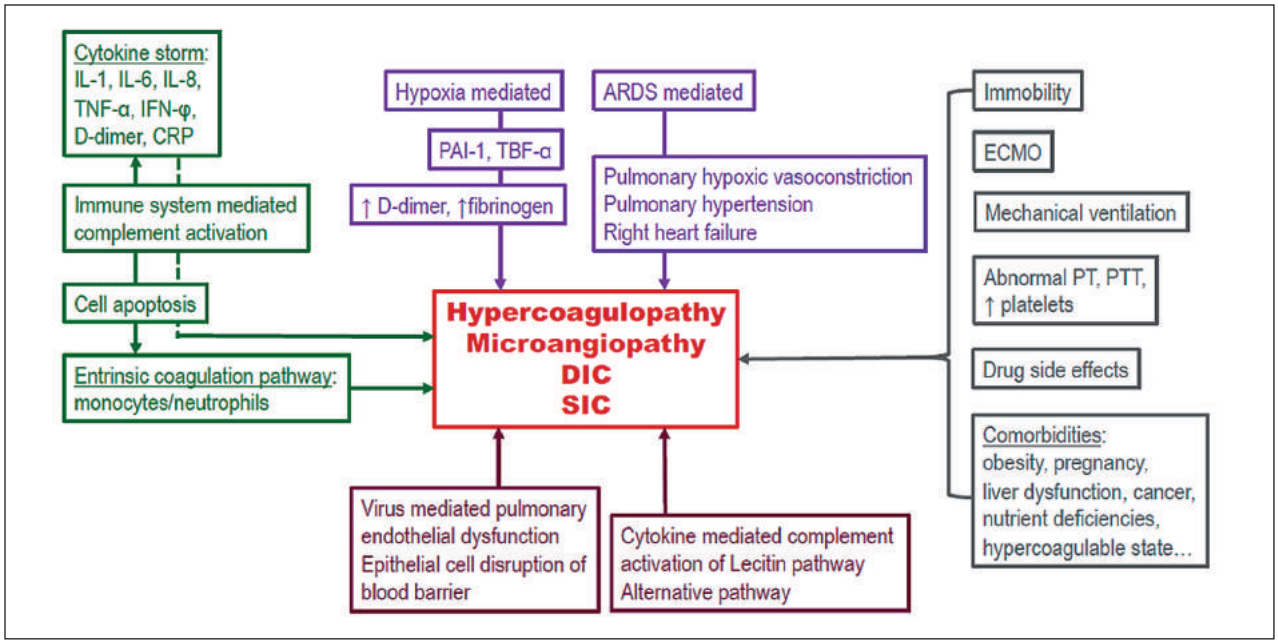

Fig. 6. *Multifactorial pathogenesis of coagulopathy in COVID-19.*

Hypoxia

Up to 35% of hospitalized patients with COVID-19 are treated in ICU, most commonly due to hypoxemic respiratory failure, with 29% to 91% of them requiring invasive mechanical ventilation (61). In addition to respiratory failure, hospitalized patients may develop AKI, mainly induced by ARDS (attributed to an infection driven inflammatory response that releases cytokines and viral products that can interact with podocytes and tubular cells and damage them) (62). The coexistence of hypoxia could further enhance the process and move the inflammatory response towards maladaptation. The involvement of the hypoxia-inducible factor (HIF) system, critical for inflammation and control of immune cell metabolism and function, is very likely. Hypoxia and inflammation are unequivocally linked, since hypoxia causes inflammation in exposed tissues and inflammation induces severe hypoxic response. The involvement of the HIF pathway during AKI effects a span from an increase of oxygen supply and adaptation to limited oxygen demand to a decrease in oxidative stress and regulation of inflammatory processes, stimulation of erythropoietin synthesis, improvement of mitochondrial metabolism, and reduced apoptosis (63).

Non-specific mechanisms

Non-specific mechanisms include older age, pre-existing comorbidities, hemodynamic alterations, hypovolemia, nosocomial sepsis, nephrotoxic drugs, angiographic contrast media, and high levels of PEEP in patients requiring mechanical ventilation.

As previously mentioned, mortality rates increase with age categories (e.g., mortality rate of 1.3% in the 50-59 age group, 3.6% in the 60-69 age group, 8% in the 70-79 age group, and 14.8% in the ≥80 age group), presence of CVD (10.5%), diabetes mellitus (7.3%), chronic pulmonary disease (6.3%), arterial hypertension (6%), neoplasms (5.6%) (4), and somewhat less frequently in the immune compromised status, smoking and obesity (64). According to data from the Italian Health Institute, the most common chronic diseases in patients who died from COVID-19 were arterial hypertension

(70%), diabetes mellitus (31.7%), CKD (23.1%), atrial fibrillation (22.5%), chronic obstructive pulmonary disease (COPD) (18.1%), active neoplasm (16.8%), ischemic heart disease (16%), and obesity (10%). Approximately 47% of the patients who died suffered from 3 or more chronic diseases, 26% had 2 diseases, 26% had only one disease, and 1% did not suffer from any other disease (19). Patients with increased baseline serum creatinine (sCr) levels were more likely to develop AKI (11.9%) than patients with normal baseline values (4.0%). This means that, while renal complications are more likely in patients with pre-existing chronic renal failure, moderate-to-severe AKI can also be found in patients with normal sCr levels and these may represent a higher-risk subset of patients with ARDS (19). On hospital admission, a significant percentage of CKD patientspresented proteinuria and micro-hematuria (37). A higher incidence of proteinuria and micro-hematuria has been reported in patients with severe or critically ill COVID-19 pneumonia.

Due to these pre-existing comorbidities, patients are frequently treated with drugs that interfere with renal blood flowregulation, such as diuretics, ACE inhibitors, and other antihypertensive drugs. This could be of importance because many patients experienced prolonged fever, tachypnea and gastrointestinal symptoms (nausea, vomiting and diarrhea), which could lead to hypovolemia and subsequent pre-renal AKI. Cardiomyopathy and acute viral myocarditis can both contribute to renal venous congestion, hypotension, and renal hypo-perfusion, leading to reduction of GFR (34).

Similarly, critically ill patients might be exposed to nephrotoxic or/and hepatotoxic drugs as part of their clinical care, including antibiotics, lopinavir/ritonavir, remdesivir, tenofovir, nucleoside analogs, hydroxychloroquine sulfate and chloroquine phosphate (46, 65). Moreover, administration of angiographic contrast media also potentiates the risk of tubular toxicity (66).

Patients who develop secondary infections (regardless of whether they are viral, bacterial or fungal) are at a higher risk of secondary sepsis-associated AKI (11, 67).

Patients with severe COVID-19-associated ARDS and/or pneumonia are also at a high risk of AKI as a complication of mechanical ventilation. Specifically, COVID-19-associated ARDS is often treated by increasing PEEP, which leads to increased intra-thoracic pressure and can ultimately result in increased renal venous pressure and reduced GFR and urine output, which may be further amplified if intra-abdominal pressure is elevated (e.g., with fluid overload). In addition, all forms of positive pressure ventilation can increase sympathetic tone, leading to secondary activation of the RAAS. Recently, it has been found that, in the early phase of COVID19 pneumonia, pulmonary mechanics may be different from traditional ARDS, characterized by normal compliance, low lung recruit ability, and without the need for very high PEEP or even deleterious effects of the latter (68). In other words, high and kidney-unfriendly levels of PEEP may not be required in the early phase of COVID-19 ARDS. Finally, inflammatory effects of invasive mechanical ventilation *per se*, especially when a non-protective strategy is applied, could also contribute to AKI (44, 46).

PATHOLOGY

In one of the first rapid autopsy series (postmortem interval was ≤6 h) performed on patients with COVID-19, all cases showed mild to severe AKI characterized by the loss of proximal tubular brush borders, vacuolar degeneration, pigmented casts in tubular lumens, pigmented granules within tubular cytoplasm, and frank epithelial cell necrosis (9) (Figure 7). In seven cases, there was evidence for glomerular ischemia, and fibrin thrombi within the glomerular capillary loops were found in three of them. In another retrospective study of 81 patients, 41 (50.6%) patients experienced AKI, and autopsy findings were consistent with acute tubular injury (ATI) (69). More recently, several kidney autopsy series from the USA and United Kingdom showed a high incidence of AKI with varying degrees of severity. The authors also report platelet-rich fibrin microthrombi in scattered peritubular capillaries and venules in most cases (36, 70-73).

No significant glomerular disease has been described in patients with COVID-19, with the exception of collapsing focal segmental glomerulosclerosis, which has been reported in approximately 40 patients (either alone or in combination with other pathologic findings in the kidneys) (37, 60), and seems to be associated with the presence of genetic risk variants of APOL1 G1 (74) (Figure 7). This pattern of injury is most strongly associated with viral infection and may increase the risk of interfe ron mediated podocyte injury due to COVID-19. Homozygosity for high-risk APOL1 allele is present in 14% of African Americans who collectively represent 12.9% of the USA population but account for an estimated 25.1% of USA COVID-19 deaths (75).

Microscopic changes associated with comorbid conditions such as hypertension and diabetes showed characteristic findings in glomeruli, which included nodular mesangial expansion and hyalinosis of arterioles (associated with diabetic nephropathy) and arteriosclerosis

of medium-sized arteries with ischemic glomeruli (9, 73). Finally, in addition to the possible contributors of kidney dysfunction during active COVID-19, preexistent CKD is a known independent risk factor to develop AKI. This could worsen the expected outcomes of these patients and may involve many pathophysiologic mechanisms dependent on comorbidities (33, 34).

In support of the hypothesis that SARS-CoV-2 exerts tropism in the kidney electron microscopy (EM) examination of autopsy samples from 26 patients who had died with COVID-19 demonstrated clusters of viral particles in the podocytes and tubular epithelium (9). Another study that involved microdissection of the tissue obtained on autopsy demonstrated detectable SARS-CoV-2 viral load in three of six deceased patients. In all positive samples, virus was detected in all kidney compartments examined, mostly targeting glomerular cells (76). In line with this finding, active viral replication in different tissues, including kidney tissue, was found in a subset of patients with COVID-19 (72), although it is still not clear whether this renal active replication contributes to viral burden in the body.

However, most analyses of kidney tissue used light microscopy, immunohistochemistry and/or EM, which cannot conclusively ascertain whether the identified particles are actually SARS-CoV-2 or merely viral-like structures. The identification of viral particles in kidney tissue by EM has been questioned given the resemblance of these particles to other cellular structures (e.g.,clathrin-coated vesicles) (77). The fact is that several studies were unable to confirm the presence of virus in the kidney, and that studies of SARS-CoV-2 in biologic fluids rarely showed viral shedding in the urine (78).

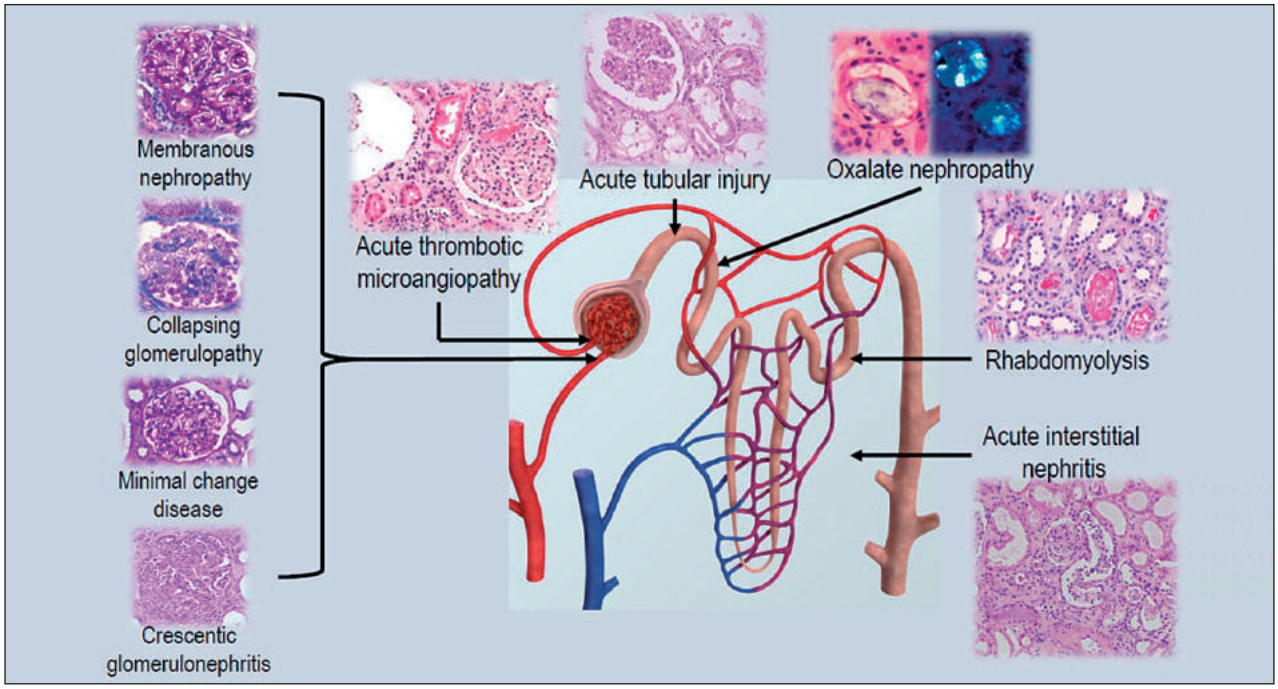

Fig. 7. *Histopathologic changes of the kidney that may be seen in COVID-19 patients with AKI.*

Evidence to date shows that the vast majority of AKI cases in patients with COVID-19 were related to ATI. This form of AKI has components of ischemia-reperfusion injury, direct inflammatory injury, coagulation and endothelial cell dysfunction, and apoptosis (34, 49, 53, 63). Tubular injury from rhabdomyolysis and severe hyperinflammation should be considered in the differential diagnosis of AKI in patients with COVID-19. The kidney autopsy samples from patients with COVID-19 showed prominent tubular injury, including the initial part of the proximal tubule, with loss of brush borders, epithelial cell necrosis, and collections of intraluminal debris. Interstitial disease was not as common as tubular injury (37). TMA has been described in patients with COVID-19, with the kidney biopsy showing diffuse cortical necrosis and widespread glomerular microthrombi. Collapsing glomerulopathy is the most common form of glomerular disease in association with COVID-19. The pathogenesis of COVID-19-associated collapsing glomerulopathy is unclear, but it has emerged as a distinct pathology associated with SARS-CoV-2 infection, which seems to specifically affect individuals of African ancestry who have high-risk APOL1 genotypes (G1/G1, G1/G2, or G2/G2) (37). Other glomerular diseases such as ANCA-associated vasculitis, anti-GBM disease, IgA vasculitis without nephropathy, membranous nephropathy and minimal change disease have been reported in patients with COVID-19. There are two possible explanations for the variety of glomerular diseases seen in patients with COVID-19: predilection for a specific glomerular pathology in these patients (SARS-CoV-2 acting as a 'second hit'); and these processes may be unrelated to SARS-CoV-2 (representing incidental findings).

AKI, acute kidney injury; ANCA, antineutrophil cytoplasmic antibody; ATI, acute tubular injury; GBM, glomerular basement membrane; IgA, immunoglobulin A; TMA, thrombotic microangiopathy

DIAGNOSIS

The diagnosis of COVID-19 itself is based on the history of contact, clinical and laboratory evidence with hemogram, biochemical parameters, chest imaging with computerized tomography (CT), and virologic examination.

The clinical spectrum of SARS-COV-2 infection ranges from asymptomatic infection to critical and fatal illness. The proportion of infections that are asymptomatic is about 40%. According to the European Centre for Disease Prevention and Control, evidence from analyses of cases showed that up to 80% of patients with COVID-19 had mild disease, without pneumonia or with mild pneumonia, most of whom recovered spontaneously (79). Severe disease (e.g., with pneumonia and hypoxia) has been reported in 15% to 20% of symptomatic infections, and 6% become critically ill (79). It can occur in otherwise healthy individuals of any age, but predominantly occurs in adults with advanced age or certain underlying medical comorbidities (Table 1). Males, compared with females, have a disproportionately higher death rate (80).

The most frequent serious clinical manifestation of infection is pneumonia, which can be complicated with ARDS even in patients with initially mild symptoms. The range of associated symptoms was illustrated in a report of over 370,000 confirmed COVID-19 patients with known symptom status reported to the CDC in the USA, as follows: dry cough (50%), fever (43%), myalgia (36%), headache (34%), dyspnea (29%), sore throat (20%), diarrhea (19%), nausea/vomiting (12%), and loss of smell or taste, rhinorrhea and abdominal pain in fewer than 10% each (81). Other reported complications are thromboembolic events, including pulmonary or coronary embolism and stroke, encephalitis and encephalopathy, Guillain-Barre and Miller-Fischer syndrome, olfactory and taste dysfunction, conjunctivitis, cardiac injury, arrhythmias, liver and pancreas injury, intestinal inflammation, thyroid gland dysfunction, acute adrenal insufficiency, diffuse myalgia and rhabdomyolysis, lymphopenia, neutrophilia, DIC,testis dysfunction and spermatogonia, and cutaneous adverse events (82).

The rates of reported AKI vary considerably among studies (0.5% to 46%). Reports from the EU and USA describe a great burden of comorbid disease in association with higher rates of AKI (74). One possible explanation of the high prevalence of kidney involvement at hospital admission is that some of COVID-19 patients may have already had a history of CKD. Such patients tend to have a pro-inflammatory state with functional defects in their immune system, and are at a higher risk of upper respiratory tract infection, pneumonia and ARDS. In ARDS, the severity of illness, patient age and presence of diabetes and/or hypertension are all risk factors for acute-on-chronic kidney injury. Interestingly, a recent prospective study including 701 patients with moderate or severe COVID-19 showed that 43.9% exhibited proteinuria and 26.7% hematuria at hospital admission, while 13% presented elevated levels of sCr, blood urea nitrogen (BUN) or both (20). During hospitalization, AKI occurred in 5.1% of COVID-19 patients. Patients with different degrees of proteinuria and hematuria had a significantly higher risk of in-hospital death after adjusting for age, gender, comorbidity, disease severity and leukocyte count (20, 33).

Polymerase chain reaction and serology

Reverse transcription polymerase chain reaction (PCR) based SARS-CoV-2 RNA detection from respiratory samples (e.g., nasopharynx) is the standard for diagnosis. The sensitivity of testing varies with the timing of testing relative to exposure. One modeling study estimated sensitivity at 33% four days after exposure, 62% on the day of symptom onset, and 80% three days after symptom onset (83). Factors contributing to false-negative test results include the inadequacy of the specimen collection technique, time from exposure, and specimen source. Lower respiratory samples such as broncho-alveolar lavage fluid are more sensitive than upper respiratory samples (84).

Wang *et al*. examined the credibility of PCR among 1070 specimens collected from 205 patients with COVID-19 and found that broncho-alveolar lavage fluid specimens had the highest positive rates of SARS-CoV-2 PCR test results (93%), followed by sputum (72%), nasal swabs (63%), and pharyngeal swabs (32%) (83). SARS-CoV-2 can also be detected in feces, while the finding in the urine is still questionable.Saliva may be an alternative specimen source, but requires further validation.

Several serologic tests can also aid in the diagnosis and measurement of responses to novel vaccines. However, the presence of antibodies may not confer immunity because not all antibodies produced in response to infection are neutralizing. IgM antibodies are detectable within 5 days of infection, with higher IgM levels during weeks 2 to 3 of illness, while an IgG response may be seen approximately 14 days after symptom onset (84, 85). Higher antibody titers occur with more severe disease. Available serologic assays include point-of-care assays and high throughput enzyme immunoassays (85).

Laboratory features

Based on the analysis of 19 studies involving 2874 patients with SARS-CoV-2 infection, of whom 88% were hospitalized, a typical profile of laboratory abnormalities seen in COVID-19 was made. Serum CRP, lactate dehydrogenase (LDH), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were elevated inapproximately 60%, 50%, 25% and 33% of patients, respectively (86). Approximately 75% of patients had low serum albumin, and the most common hematologic abnormality was lymphopenia, which was present in up to 83% of hospitalized patients with COVID-19 (4). In conjunction with coagulopathy, modest prolongation of prothrombin times, mild thrombocytopenia and elevated D-dimer values have been reported (49). More severe laboratory abnormalities have been associated with more severe infection. However, most of these laboratory characteristics are nonspecific and common in pneumonia. Patients with COVID-19 AKI have also been reported to have higher levels of systemic markers of inflammation, particularly CRP, ferritin, pro-calcitonin and LDH than patients with COVID-19 and normal kidney function (11).

The standard assessment and staging of AKI is still based on sCr levels and hourly urine output (Kidney Disease Improving Global Outcomes /KDIGO/AKI guideline) (87). The lack of sCr measurements prior to hospital admission often impedes the ability to identify underlying CKD and creates challengers for the reliable detection and staging of AKI, emphasizing the need to define baseline sCr clearly. To improve understanding of the temporal nature of COVID-19 AKI, physicians must correlate the timing of AKI with COVID-19 symptom onset confirmation of SARS-CoV-2 infection, hospitalization, disease severity, and level of care when reporting AKI rates (11).

Although urine volume is reported infrequently, 70% of patients have low urinary sodium concentrations at the time of AKI, and the majority are anuric at renal replacement therapy (RRT) initiation (3, 11). Urine analysis is frequently abnormal in patients with COVID-19 and could be used to characterize AKI in these patients. Hirsch *et al*. report that among 32% of hospitalized COVID-19 patients in whom urine analysis was available, 42.1% had significant proteinuria, with hematuria and leukocyturia in 40.9% and 36.5%, respectively (88). Examination of urine sediment can be an effective tool in clinical practice in which more than one possible cause of AKI may exist that could affect medical management (e.g., to distinguish pre-renal AKI from ATN).

Viral factors

Patients with severe disease have also been reported to have higher viral RNA levels in respiratory specimens than those with milder disease, although some studies found no association between respiratory viral RNA levels and disease severity. Detection of viral RNA in the blood has been associated with severe disease, including organ damage (e.g., lung, heart, and kidney), coagulopathy, and mortality (58).

Imaging

The characteristic chest CT imaging abnormalities in COVID-19 are diffuse, peripheral ground-glass opacities with ill-defined margins, air bronchograms, smooth or irregular interlobular or septal thickening, and thickening of the adjacent pleura (85). Some patients admitted to the hospital with PCR-confirmed SARS-CoV-2 infection have normal CT imaging findings, whereas in other patients, abnormal chest CT imaging findings compatible with COVID-19 occur days before detection of SARS-CoV-2 RNA. Rapid evolution of abnormalities can occur in the first two weeks of symptom onset, after which they subside gradually.Chest CT scan remains the most sensitive imaging modality in initial diagnosis and management of suspected and confirmed patients with COVID-19 (89). Other diagnostic imaging modalities (e.g., lung ultrasound, chest x-ray, or positron emission topography/computed tomography (PET/CT) scan) could add value in evaluating disease progression and monitoring critically ill patients with COVID-19 (90).

The diagnostic criteria and AKI staging is not different from AKI in other situations (91-95).

MANAGEMENT OF ACUTE KIDNEY INJURY

Given the high incidence of kidney involvement in SARS-CoV-2 infection and the lack of specific treatment options, the care strategy for patients with COVID-19 in the ICU remains largely supportive.

In current circumstances, it is essential to reinforce the need for close collaboration between intensivists and nephrologists. The nephrologist should be contacted even in the case of a patient with relatively small renal impairment, since its involvement in ICU is not limited to AKI. Kidney involvement in COVID-19 patients may precede, be concomitant, or follow other organ system failure. This situation can require fully competent and trained personnel to implement all therapeutic options for critically ill patients. Therefore, intensivists and nephrologists should discuss all diagnostic and therapeutic possibilities in individual pa-

tients, taking into account hemodynamic parameters, volume status, electrolyte and acid-base disturbances, degree of kidney injury, comorbid conditions, and adjustment of drug doses. This is especially true for patients with COVID-19 who, according to the KDIGO classification of AKI, meet the criteria for stage 2 renal impairment. Patients classified as stage 3 have a high probability of requiring RRT, which requires an urgent call to the nephrologist team.

Non-dialytic management

All patients with AKI need careful assessment of hemodynamic and volume status using vital signs and physical examination. Critically ill patients may benefit from more invasive hemodynamic monitoring (arterial line, central venous pressure, or cardiac output monitoring). Measurement of fractional excretion of sodium and urea in urine may be helpful in diagnosing decreased kidney perfusion in oligo-anuric patients. However, the utility of these diagnostic methods tends to be more limited in critically ill adults, likely as a result of coexisting pre- and intra-renal disease. Urinary microscopy for renal tubular epithelial cells and granular casts may be helpful to make the concomitant diagnosis of ATN, which is the most common cause of AKI occurring in the hospital.

Measures to prevent AKI include optimization of volume status and avoidance of nephrotoxic medications. Volume depletion at admission might be common in patients with COVID-19, as they typically present with fever and pre-hospital fluid resuscitation is rarely performed. Crystalloids are preferred over colloids for most patients, and hydroxyethyl starches should be avoided. Patients with reduced renal blood flow who can augment their cardiac output by expansion of their intravascular volume would benefit from fluid resuscitation (96). Balanced crystalloids should be considered in patients with hypotension, severe systemic inflammatory response, and elevated sCr on presentation. After significant volume resuscitation, even if patients remain volume responsive, vasopressor support should be considered to avoid markedly positive fluid balance (97). Escalating dosages of intravenous loop diuretics in patients with volume overload, intravenous sodium bicarbonate solution in patients with severe metabolic acidosis, and use of rapid acting potassium binders (e.g., sodium zirconium cyclosilicate) for hyperkalemia can potentially delay RRT. The potential renal benefit in glucose control was demonstrated, but it is certainly necessary to avoid hypo- and hyperglycemia (both are associated with increased morbidity and mortality in a variety of clinical scenarios) (98) (Figure 8).

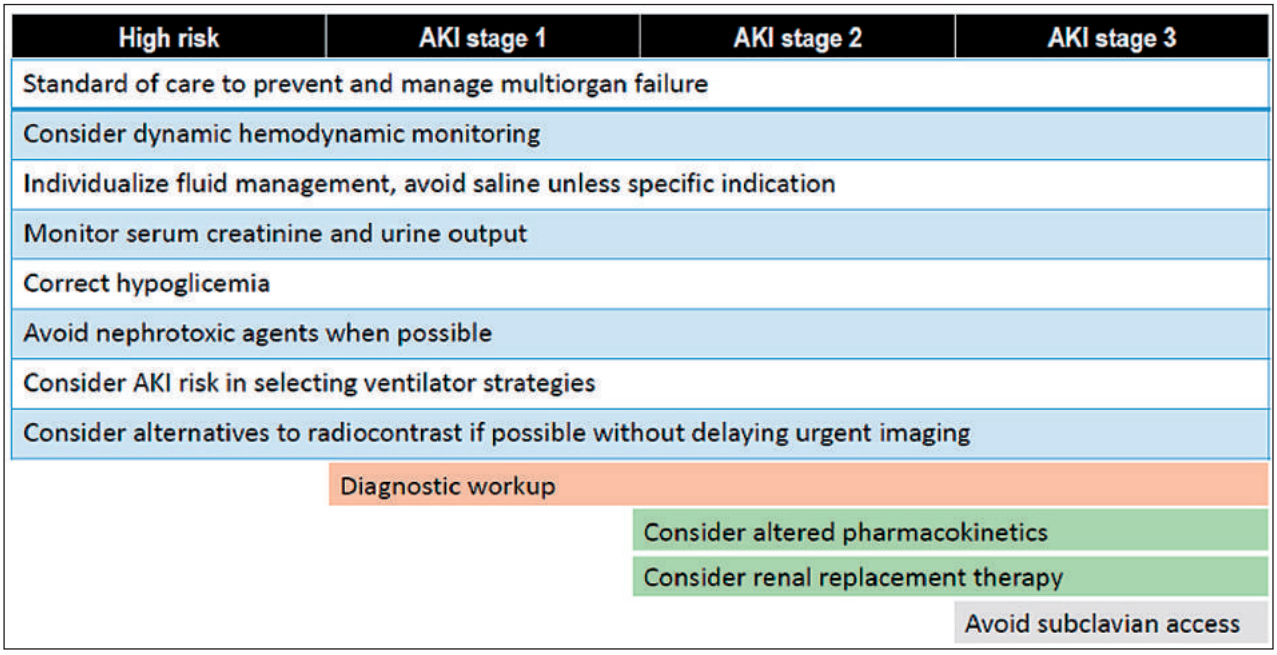

Fig. 8. *Stage-based management of COVID-19 acute kidney injury (AKI).*
The pathogenesis of AKI in patients with COVID-19 involves direct viral effects, indirect effects and sequels of disease management. There is no specific evidence to suggest that COVID-19 AKI should be managed differently from other causes of AKI in critically ill patients. However, all features of the underlying disease, as well as associated chronic diseases should be considered during the treatment of patients with COVID-19 AKI.

Renal replacement therapy

Timing of RRT initiation in AKI is still controversial because multicenter studies in patients with sepsis and other causes did not clearly demonstrate benefit with early initiation of dialysis (99). Currently, there are no data to support early initiation of RRT in patients with COVID-19-associated AKI. Initiation of RRT should not be based on the stage of AKI, but should be considered when life-threatening complications of AKI (e.g., volume overload, acute pulmonary edema, severe metabolic acidosis /pH <7.1/, severe hyperkaliemia /K >6.5 mmol/L/) cannot be treated with conservative measures.

Furthermore, it is considered in patients with severe COVID-19 who developed AKI of KDIGO standard grade ≥2, particularly with sepsis, as well as in patients with severe systemic inflammatory response when the serum inflammatory mediator levels reach more than 5 times the upper limit of normal or increase more than one time within 24 hours (100).

The basic principles of RRT for patients with severe COVID-19 include the following: 1) removal of metabolic products, various inflammatory mediators and balancing of the immune homeostasis; 2) correction of electrolyte and acid-base balance disorders to maintain internal environment stability; 3) regulation of volume and correction of fluid overload to help maintain hemodynamic stability in critically ill patients; 4) control of high fever; and 5) combined RRT treatment with extracorporeal organ support (ECOS).

Prescribing blood purification treatment for patients with severe COVID-19 must be goal-oriented. The specific contents include the choice of blood purification treatment mode, vascular access, selection of blood purification filters, selection of anticoagulant, treatment dose, and initial parameter settings (Figure 9). In the face of shortage of RRT machines and medical staff capable to provide therapy, institutions had to adjust standard treatment practice. Higher dialysate flow rates were used in continuous renal replacement therapy (CRRT) modalities when treatment time was decreased. In order to place hemodialysis (HD), CRRTor HT machines outside patient rooms and minimize exposure to SARS-CoV-2 for physicians and nurses, an additional extension tubing was used. However, extension tubing increases circuit length and thus carries a risk of blood loss, hypothermia, and thrombosis. Therefore, appropriate warming systems should be implemented. Video monitors can help nurses supervise dialysis process without entering patient room. Isolated slow continuous ultrafiltration (SCUF) sessions were implemented in-between treatments for volume management. IHD treatment time and frequency were decreased if metabolic derangements and volume status would permit.

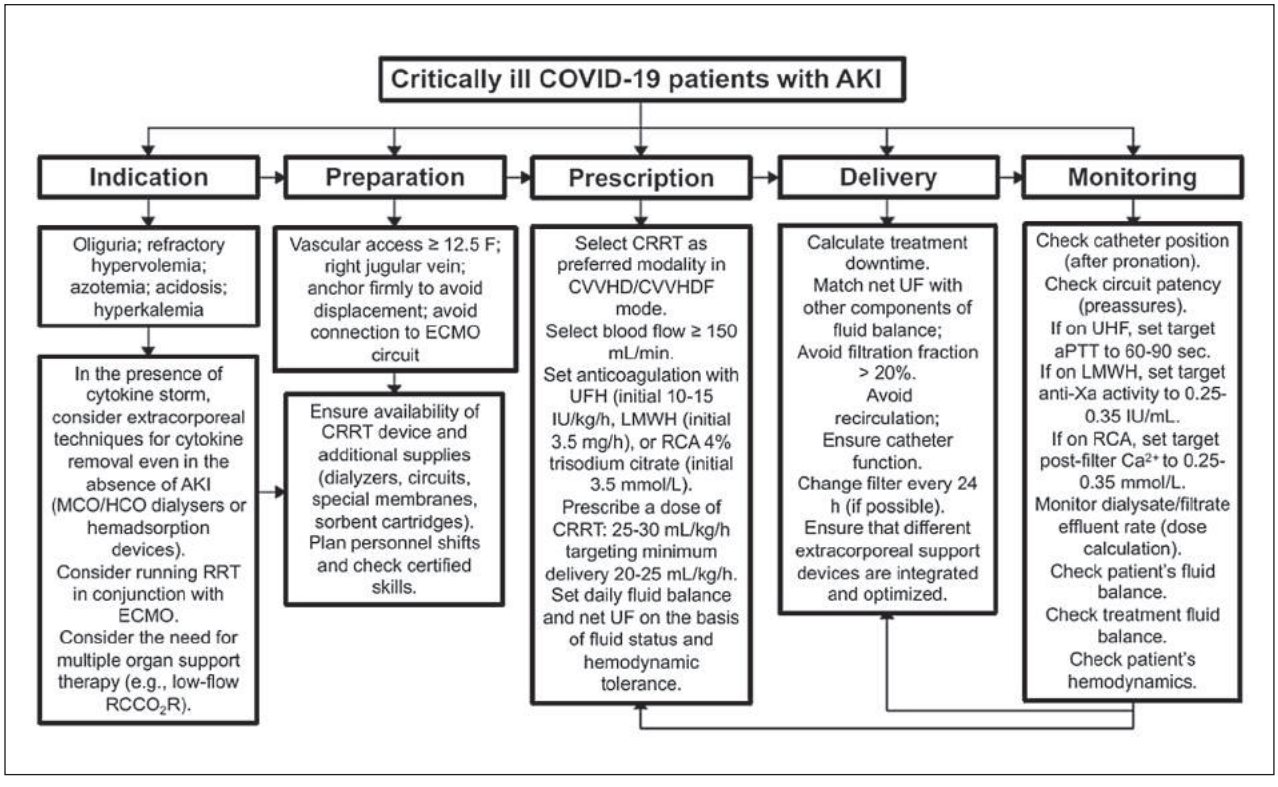

Fig. 9. *Prescribing blood purification treatment for critically ill COVID-19 patients with acute kidney injury.*

Continuous renal replacement therapy

In COVID-19 patients with refractory fluid overload and/or marked hemodynamic instability, there is a strong physiologic rationale for initial support with CRRT to offer greater hemodynamic tolerance, consistency in ultrafiltration (UF), and less osmotic and metabolic fluctuations (87, 99). Depending on the mechanism of clearance, CRRT can be delivered as continuous veno-venous hemodialysis (CVVHD), continuous veno-venous hemofiltration (CVVH), and continuous veno-venous hemo-diafiltration (CVVHDF). CVVHDF (convective clearance) is not superior to CVVHD (diffusive clearance). In fact, CVVHDF may be associated with higher rates of filter clotting due to higher filtration fraction.

When the main purpose is to remove inflammatory mediators in patients with severe COVID-19 and cytokine storm, it may be recommended to use high volume hemofiltration (HVHF), high cutoff molecular weight hemofiltration, or continuous plasma filtration absorption (CPFA) (100, 101). In patients with severe SARS-CoV-2 infection combined with simple volume overload and acute pulmonary edema, slow continuous ultrafiltration (SCUF) is recommended (99). When severe COVID-19 coexists with ARDS, CRRT with extracorporeal membrane oxygenation (ECMO), or extracorporeal CO_2 removal (ECC_2R) can be recommended.

Prolonged intermittent hemodialysis (hybrid therapy)
Alternatively, forms of prolonged (hybrid therapy, HT) and conventional intermittent RRT have an important complementary role in the support of critically ill patients with COVID-19 infection. These patients may frequently require mobilization and pronation to improve pulmonary gas exchange. In these circumstances, treatments of 8 to 12 hours may represent a good compromise between CRRT and intermittent hemodialysis (IHD) (102).

Hybrid dialysis modality is increasingly used in critically ill patients since it allows to maintain acceptable hemodynamic stability and to overcome the increased clotting risk of the extracorporeal circuit, especially when regional citrate anticoagulation (RCA) protocols are applied. HT can be performed either with CRRT, IHD or hybrid therapy device (GENIUS®, Fresenius Medical Care, Bad Homburg, Germany), providing adequate daily treatment dose in less time compared with CRRT, thus optimizing the often limited available resources in the overcrowded clinical context of SARS-CoV-2 in the ICUs. Notably, given the mainly diffusive mechanism of solute transport, HT is associated with lower stress on both hemofilter and blood cells as compared to convective RRT modalities. Finally, RCA, as compared with heparin-based protocols, does not further increase the already high hemorrhagic risk of patients with AKI. Based on these premises, Di Mario *et al*. performed a pilot study on the clinical management of critically ill patients with COVID-19 associated AKI who underwent HT with a simplified RCA protocol. Low circuit clotting rates were observed and adequate RRT duration was achieved in most cases, without any relevant metabolic complication or worsening of hemodynamic status (103).

Intermittent hemodialysis

Intermittent hemodialysis is a traditional modality for providing RRT in hemodynamically stable patients. It may be employed as a second-line option for COVID-19 patients with AKI. In patients with ARDS who require prone positioning, IHD needs a coordinated protocol to provide adequate ventilator support in the prone position and HD therapy in the supine position. A synchronized team approach should be implemented to coordinate and maintain the safety of vascular access during prone positioning (104).

Potential practice change in a setting of COVID-19 AKI surge is to decrease treatment time and frequency (e.g., two times *per* week) to optimize medical supplies and decrease medical staff exposure to SARS-CoV-2 infection (105). Consideration for patient safety should be paramount when implementing any resource conservation and exposure reduction measures. Patients should be carefully monitored for manifestations of inadequate dialysis.

Providing IHD to a patient with COVID-19 may require one-on-one dialysis nursing support, whether in the ICU or on the general hospital floor. Strategies proposed to conserve human and material resources, and decreased exposure includes decreasing duration of treatments, decreasing frequency of IHD to twice a week, and tele-monitoring (e.g., use of monitors or tablets to visualize patients from outside the room).

Peritoneal dialysis

Experiences from resource-limited countries have shown adequate metabolic and fluid control with acute peritoneal dialysis (PD) in AKI. Under usual circumstances, acute PD is used in adult patients with AKI because regulation of UF and metabolic control is superior with CRRT in patients who are hemodynamically unstable. However, owing to acute surge during the pandemic, acute PD and continuous automated peritoneal dialysis (CAPD) have been implemented in hospitals because of shortage in extracorporeal RRT consumables, fluids, and nursing. Bedside catheter placement of a cuffed PD catheter is preferred for critically ill patients.

In the COVID-19 crisis, CAPD would be a preferred modality because it minimizes the number of connections and disconnections. Automated cycler use and extension tubing to keep device outside the patient room may limit exposure of healthcare staff. An average-sized adult can usually tolerate 2-L exchanges, but reduced volume should be considered for the initial few exchanges to decrease the risk of peri-catheter leaks. To maximize efficiency of acute PD, an exchange time of 1-2 hours should be used. Assuming a 2-L exchange volume with 60-minute exchange time, UF of about 1.2-3.6 L/day can be achieved with 1.5%, 2.4-7.2 L/day with 2.5%, and 7.2-9.6 L/day with 4.25%. As such, for patients with severe pulmonary edema, initial rapid in-out exchanges using 4.25% can be considered (105). The recommendation of weekly Kt/V urea is 3.5 (which provides results comparable to those of daily HD). This dose may not be necessary for all patients, and a lower goal of weekly Kt/V about 2.1 may be acceptable (106, 107).

Peritoneal dialysis can increase intra-abdominal pressure, interfere with respiratory mechanics, and may theoretically worsen respiratory failure, particularly in mechanically ventilated patients. Therefore, expert recommendations mention that PD can be started early, before patients develop ARDS. However, when ARDS occurs, PD should not be used as the first option for RRT (except when other options such as IHD, HT and CRRT are not available) (106). In patients requiring prone positioning, PD may not be feasible.

Vascular access

Appropriate central venous access is imperative to provide sufficient blood flows during RRT. Hemodialysis catheter length for adults according to the vein puncture site (15-18 cm for right internal jugular, 18-20 cm for left internal jugular, 24-28 cm for femoral, 15-18 cm for right subclavian, 20-24 cm for left subclavian) and location must be carefully selected, as inappropriate catheter length can lead to inadequate blood flow that leads to increased filter clotting. The right internal jugular vein is the preferred access for RRT as it offers a direct path for the catheter tip to be placed at the junction of the superior vena cava and right atrium. There is some controversy whether the second choice should be the left internal jugular or the femoral vein. The femoral vein site may be associated with a higher risk of infections and blood flow may be affected in patients who need to be in the prone position for ventilation. The left internal jugular vein can provide inadequate blood flow (especially when shorter catheters are inadvertently placed) (108). Vascular access *via* the subclavian vein is not recommended. If possible, ultrasound guidance should be used when placing the central venous catheters.

Blood purification filters

The choice of filter depends on the method of blood purification. Filters with synthetic biocompatible membrane and a high ultrafiltration coefficient are generally used to perform CRRT. Filters with absorption properties (e.g., oXiris membrane, AN69ST) or hemofilters with super high-flux (SHF) or high cut-off (HCO) membranes should be selected to remove inflammatory mediators. The SHF/HCO membranes also restore immune cell function, attenuate hemodynamic instability, decrease plasma IL-6 levels, and eliminate larger late-phase inflammatory mediators with acceptable albumin losses (109).

When performing plasma replacement and blood/plasma absorption, the corresponding plasma filter, blood perfusion device, or absorber can be selected depending on the procedure to be applied.

Anticoagulation

There is growing evidence for endothelial activation causing a hypercoagulable state, leading to a higher incidence of thrombotic complications in patients with COVID-19 (49-52). In addition to deep vein thrombosis, pulmonary embolism and ischemic stroke, clotting of extracorporeal circuits is a major concern, as it decreases dialysis filter and extracorporeal circuit lifespan. Despite disparities in outcome among individual anticoagulation strategies, it is an undisputed fact that circuits without anticoagulation tend to perform poorly in COVID-19 patients with AKI, when compared to anticoagulated systems. The bleeding risk of each individual patient needs to be considered prior and during the implementation of any anticoagulation options summarized in Table 2, given that anticoagulation (especially when systemic) may increase the propensity for bleeding (105, 110).

Table 2.
Anticoagulation strategies for kidney replacement therapy in COVID-19 patients with acute kidney injury

Anticoagulant	Dose	Remarks
Pre-filter unfractionated heparin	Loading dose: 2.000-5.000 units Maintenance: 10-15 units/kg/h Check PTT: 2-4 h after initiation Target: 5-s increase	Anticoagulation is intended for the circuit, not for the patient Higher risk of circuit clotting in high-risk patients
Systemic unfractionated heparin	Loading dose: 50-80 units/kg Maintenance: continuous drip at 18-20 units/kg/h Target PTT: 80-100	Protocols may vary. Higher risk of bleeding when comparted to pre-filter heparin Increased risk of HIT and heparin resistance Short half-life
Systemic low-molecular-weight heparin	Dose may be variable, and single pre-dialysis dose may be sufficient	Risk of accumulation in kidney failure Monitoring requires anti-Factor Xa Reduced risk of HIT
Regional citrate anticoagulation	No universal protocol	Requires institutional commitment Better safety profile than heparin Risk of overdose, metabolic acidosis, and hypocalcemia Increased monitoring of iCa and titration of CaCl
Argatroban	0.5 mcg/kg/min if normal liver function 0.2-0.25 mcg/kg/min in patients with liver dysfunction Target PTT: two times the normal value and titrate based on institutional protocol	Variable institutional protocols Dose different for those with and without liver dysfunction Use if HIT

PTT, partial thromboplastin time; HIT, heparin induced thrombocytopenia; iCa, ionized calcium; CaCl, calcium chloride

Renal replacement therapy dose

The dose of RRT should be based on KDIGO recommendations and adjusted in response to changes in clinical, physiologic and/or metabolic status (87). The standard recommended dose for CRRT is delivered effluent flow rate of 20-25 mL/kg/h (prescribed dose of 25-30 mL/kg/h). The minimum weekly dose of IHD and HT is three times *per* week (alternative days). Interruption of prolonged RRT modality (CRRT, IHD or HT) sessions due to circuit clotting can have a substantial impact on the actual delivered dose and the dose may therefore need to be adjusted to account for this disruption. Acute PD might also be an effective option for patients who are unable to receive anticoagulants. The recommendation of weekly Kt/V urea is 3.5, but a lower goal of weekly Kt/V about 2.1 may be acceptable (11).

In case of the increased need for RRT or shortages of CRRT, IHD or HT devices, as well as shortages of consumable medical materials, it is possible to reduce the dose of dialysis. In that case, it is necessary to make appropriate adjustments in fluid removal targets and RRT dose to achieve appropriate fluid balance targets and metabolic control (e.g., increase ineffluent dose).

Extracorporeal organ support

The majority of patients with COVID-19 admitted to the ICU have bilateral pneumonia with single-organ failure and consequent refractory hypoxemia. Other patients with SARS-CoV-2 infection suffer from significant derangement of the immune system, producing multisystem inflammatory syndrome, ARDS, sepsis, condition similar to DIC, rhabdomyolysis and damage to or failure of various organ systems. Severe AKI occurs mostly in the context of MOF. In such circumstances, RRT alone is usually not enough, but the function of several organs needs to be replaced at the same time. Extracorporeal organ support encompasses all forms of organ support by an extracorporeal circuit (e.g., RRT, ECMO, ECC_2R, hemoperfusion, high-volume HVHF, CPFA, therapeutic plasma exchange /TPE/, various blood purification devices, ventricular assist devices and extracorporeal liver support system) (99-101). In COVID-19 patients, recent platforms allow circuit adjustment to perform different ECOS techniques besides RRT.

Lung-protective ventilation and ECOS are the current standard of care for COVID-19 patients with ARDS. This approach can limit ventilation-induced lung injury, but it may be associated with respiratory acidosis and insufficient correction of hypercapnia (44).The technique of $ECCO_2R$ has been introduced for hypercapnic respiratory failure not requiring significant oxygen support. The effective amount of extracorporeal CO_2 removal from patients depends on blood flow. Studies have shown progressive CO_2 removal until blood flow of 800-1,000 mL/min where the ceiling is reached. Low blood flow $ECCO_2R$ devices (<0.5 L/min) achieve partial CO_2 removal (111).To date, several $ECCO_2R$ devices are available that can be used in conjunction with RRT hardware using variable blood flows. This may be particularly appealing in patients with ARDS and concomitant AKI, where compensatory renal mechanisms are less effective in regulating acid-base homeostasis during hypercapnic acidosis (111).

Lung and cardiac injury with COVID-19 can lead to hypoxia and decreased kidney perfusion, which in turn can lead to kidney medullary hypoxia and cardio-renal syndrome. Therefore, treatment of MOF in critically ill patients with COVID-19 may necessitate ECOS, including RRT, ECMO, and a left ventricular assist device (LVAD). Supporting the heart and lung in these conditions using LVAD and ECMO can potentially help with kidney perfusion (104). Direct hemoperfusion using a macro-porous sorbent has been suggested as a treatment to adsorb and remove circulating cytokines and prevent cytokine release syndrome (CRS)-induced end-organ damage (112). All these modalities can be used in conjunction with CRRT to help manage the MOF commonly seen in critically ill patients with COVID-19 (Table 3, Figure 10).

Table 3.
Pathophysiology of AKI and treatment strategies in COVID-19

Etiology	Pathophysiology	Treatment strategy
Systemic effects		
Positive fluid balance	Renal compartment syndrome	Diuretics, SCUF
Endothelial damage, third-space fluid loss, hypotension	Renal hypoperfusion	Fluid expansion, vasopressors
Rhabdomyolysis	Tubular toxicity	CRRT using MCO or HCO membrane
Endotoxins	Septic AKI	Endotoxin removal using polystyrene fibers functionalized with polymyxin-B
Cytokine overproduction		
Cytokine release syndrome	Direct cytokine injury	Cytokine removal using various approaches: high dose CRRT with MCO and HCO membranes; CRRT with hollow fiber filters with adsorptive properties; direct hemoperfusion using a neutro-microporous sorbent; plasma adsorptiom on resin after separation from whole blood
Increased cytokine generation owing to ECMO, invasive mechanical ventilation and/or CRRT		
Hemophagotic syndrome		
Organ crosstalk		
Viral myocarditis and/or cardiomyopathy	Cardiorenal syndrome type 1	LVAD, arteriovenous ECMO
Alveolar damage	Renal medullary hypoxia	
Rhabdomyolysis	Tubular toxicity	CRRT using MCO or HCO membrane
High peak airway pressure and intra-abdominal hypertension	Renal compartment syndrome	Venovenous ECMO, extracorporeal CO^2 removal, CRRT

AKI, acute kidney injury; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; HCO, high cut-off; LVAD, left ventricular assist device; MCO, medium cut-off

Although bacterial sepsis is not a common feature in COVID-19 patients, the immune response to SARS-CoV-2 may lead in some patients to severe CRS with consequent organ dysfunction or even MOF. Thus, life-threatening organ dysfunction caused by a dysregulated host response to infection depends not only on systemic inflammation due to innate immunity but also on the possible severe immunosuppression due to adaptive immunity (111). In case of COVID-19 infection and CRS, with superimposed gram-negative bacterial infections, hemoperfusion with polymyxin-B (PMX-HP, Toraymyxin, Japan) should be used for two consecutive days, followed by the methods of cytokine adsorption (CytoSorb, Cytosorbents, USA or oXiris, Baxter, USA), and if organ support is required, CRRT should be implemented in conjunction or afterwards (105, 111-113).

Cascade hemofiltration, HVHF, TPE, hemoperfusion, CPFA, high-adsorption hemofiltration, as well as HCO or medium cut-off (MCO) membranes have been proposed based on the pathophysiologic rationale of cytokine and chemical mediator removal and/or modulation of the inflammatory response to sepsis. This removal may result in a decrease of the peaks of cytokine concentrations and/or modification of the cytokine/chemokine ratio from the tissues to the blood, positively affecting the leukocyte trafficking. However, it should be taken into account that patients are not homogeneous in terms of their inflammatory phenotype and have widely varying levels of cytokines in their blood. Therefore, these procedures may not help all patients. Unfortunately, specific criteria have not yet been defined.

It has been suggested that the use of ECOS (e.g., invasive mechanical ventilation and ECMO) may further stimulate inflammatory response involved in the lung-kidney and heart-kidney interaction. Consequently, more than 70% of patients receiving ECMO develop AKI, and the majority are treated with RRT (114). There are multiple reasons for AKI in patients who need ECMO; the exact contribution from ECMO support *per se* is unknown. The potential contributing factors may be inflammatory reactions in response to contact with artificial membrane, hemolysis and iatrogenic plaque rupture during arterial cannulation, and cannula malposition leading to kidney congestion (111). Therefore, the interaction between different types of ECOS support needs to be considered.

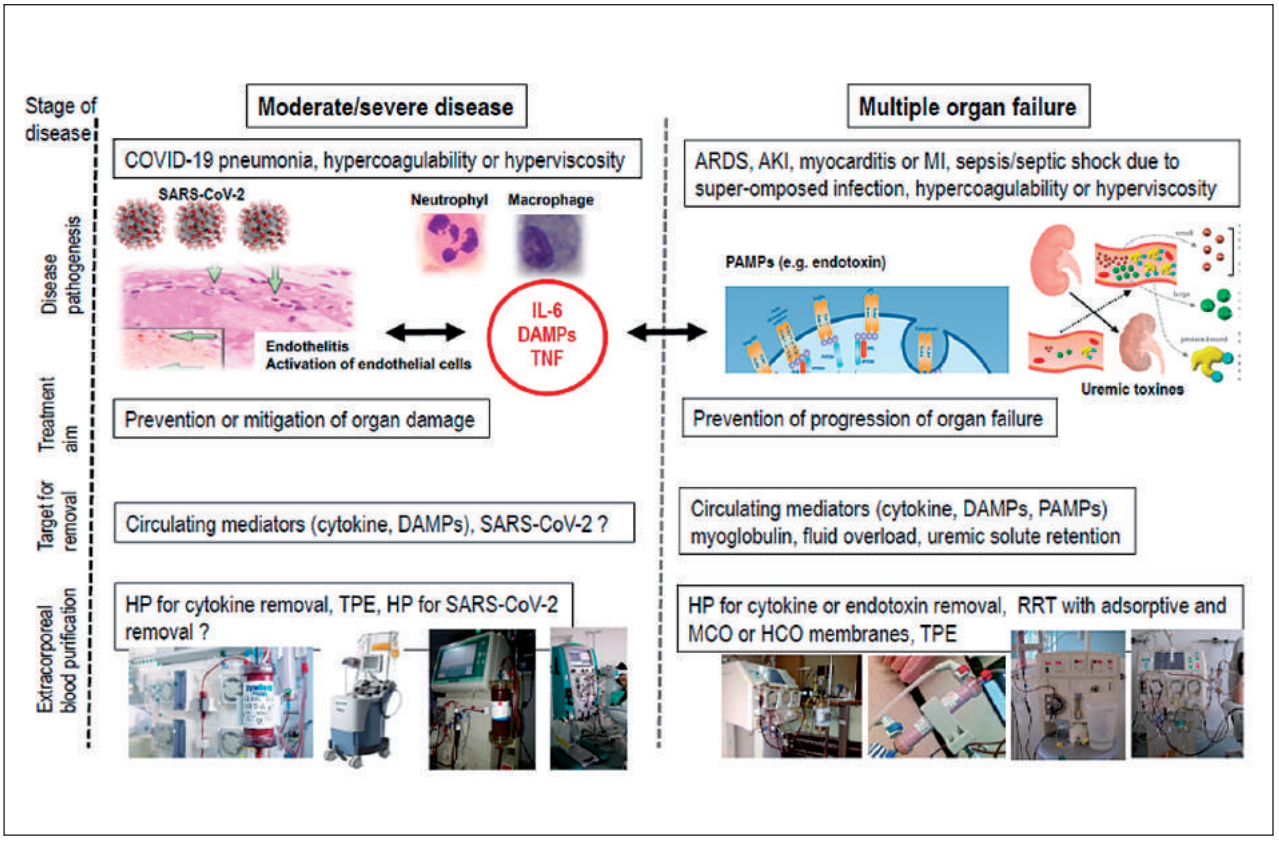

Fig. 10. *Potential extracorporeal blood purification treatment optionsbased on underlying COVID-19 pathophysiology.*

Extracorporeal blood purification (EBP) has been proposed as a possible adjuvant therapy for critically ill patients with COVID-19, considering that removal of circulating immunomodulatory factors that might contribute to disease processes and/or development of MOF, might improve outcomes. MOF in COVID-19 might result from propagation of an uncontrolled host immune response involving the release of various immune mediators such as cytokines, DAMPs and PAMPs, endothelial dysfunction, and hypercoagulability (11). The benefits and adverse effects of EBP in patients with COVID-19 have not been formally studied. Therefore, patients in whom EBP is being considered need to be selected carefully. If used, EBP therapies should be selected on the basis of the pathophysiology they are designed to target. Numerous clinical criteria (body temperature, hemodynamic status, need for vasopressor support, respiratory status and oxygenation, multiorgan failure score, cardiac and kidney function), as well as laboratory parameters (lymphocyte count, concentration of cytokines, ferritin, LDH, D-dimers, monocytic expression of HLA, myoglobin, troponin, CRP, endotoxin activity, procalcitonin and culture results) may be useful in evaluating the suitability of a patient for initiation of EBP (11, 13, 15). The precise indication for EBP in patients with COVID-19 remains to be determined. There are limited data regarding the timing of initiation or duration of using EBP, and further researches are needed.

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; DAMPs, damage-associated molecular patterns; EBP, extracorporeal blood purification; HCO, high cut-off; HP, hemoperfusion; LDH, lactate dehydrogenase; MCO, medium cut-off; MOF, multiorgan failure; PAMPs, pathogen-associated molecular patterns; RRT, renal replacement therapy; TPE, therapeutic plasma exchange.

OUTCOME

Although the reported incidence of AKI among hospitalized patients with COVID-19 varies widely, recent studies from the EU and USA have suggested an incidence of up to 40% (78, 88, 115). Evaluation and treatment of AKI in COVID-19 patients are similar to AKI in non-COVID-19 patients, with supportive measures being the cornerstone of management.AKI among hospitalized patients is associated with poor prognosis, increased length of stay, and increased health care costs. Patients who survive AKI appear to be at an increased risk of death and incident CKD or even end-stage renal disease (ESRD) (116, 117) (Figure 11).

Regardless of the need for dialysis or recovery of kidney function at discharge, hospitalized patients with COVID-19 who experience any form of AKI should probably be followed up closely after discharge to assess the ongoing kidney function.

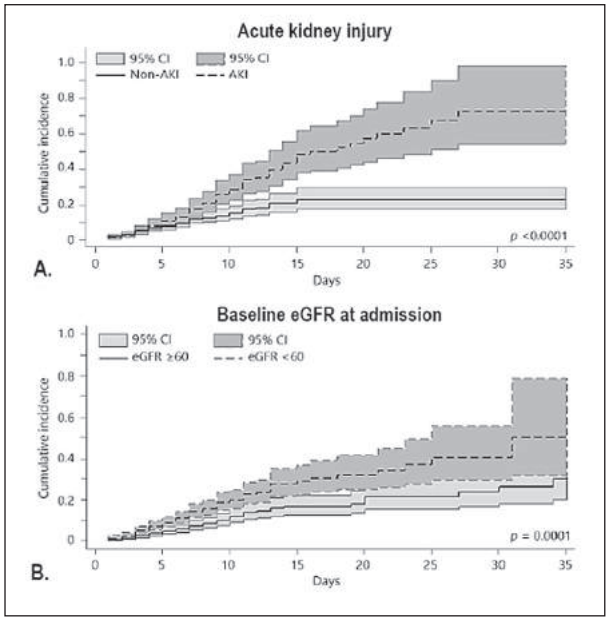

Fig. 11. *PAKI and in-hospital mortality*

Cumulative incidence of in-hospital mortality in COVID-19 patients by AKI:

A. Admitting estimated glomerular filtration rate (eGFR);
B. Shadows show the 95% confidence interval (117).

Zahid et al. investigated in-hospital mortality associated with AKI in COVID-19 patients (117). Overall, the in-hospital mortality was 40.1% in COVID-19 patients. A significantly higher in-hospital mortality was observed in patients with an eGFR <60 mL/min/1.73 m2 and elevated BUN at presentation. Furthermore, patients aged ≥75, those with preexisting comorbidities (diabetes mellitus, stroke and malignancy), arterial oxygen partial pressure/fractional inspired oxygen ratio <200 mm Hg, initial systolic blood pressure <100 mm Hg, elevated presenting BUN, eGFR <60 mL/min/1.73 m2 at presentation, and in-hospital AKI stage 2 and stage 3 were all associated with a higher in-hospital mortality. RRT did not improve survival (117)

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SAŽETAK

AKUTNO OŠTEĆENJE BUBREGA U BOLESNIKA S COVID-19: IZAZOV ZA NEFROLOGE

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Akutno oštećenje bubrega (AOB) čest je nalaz u bolesnika s korona-virusnom bolešću 2019 (COVID-CoV-19), a povezano je s dugotrajnim bolničkim liječenjem, češćim prijmom bolesnika na odjel intenzivne skrbi i većom smrtnosti u usporedbi s bolesnicima s COVID-19 bez bolesti bubrega. Štoviše, stopa smrtnosti je izravno proporcionalna težini AOB-a. Patofiziologija AOB-a u bolesnika s COVID-19 posljedica je različitih specifičnih i nespecifičnih uzročnika. Mehanizmi specifični za COVID-19 su izravna stanična ozljeda zbog ulaska virusa u stanice putem ACE-2 receptora (koji su jako izraženi u bubrezima), neuravnoteženosti sustava renin-angiotenzin-aldosteron, teškim oštećenjem dišnog sustava i otpuštanja proupalnih citokina izazvanog teškom akutnom infekcijom koronavirusom 2 (SARS-CoV-2), koagulopatijom, mikroangiopatijom i kolapsnom glomerulopatijom. Nespecifični mehanizmi uključuju hemodinamske poremećaje, visoku razinu pozitivnog tlaka na kraju izdisaja u bolesnika kojima je potrebna mehanička ventilacija, sepsu, hipovolemiju, rabdomiolizu i primjenu nefrotoksičnih lijekova. Danas još ne znamo dovoljno o prevenciji i liječenju COVID-19. Terapijske mjere AOB-a u bolesnika s COVID-19 uključuju opće postupke i farmakološku terapiju COVID-19 s ciljem da se poprave poremećaji u hemodinamici i volumenu tjelesnih tekućina, nadomještanje bubrežne funkcije i uporabu uređaja za potporu drugim organskim sustavima. Dugoročna prognoza je zasad nepoznata. Međutim, može se s velikom vjerojatnosti pretpostaviti da će prognoza biti povezana s etiologijom AOB-a. Bolesnici s tromboembolijskim komplikacijama i kolapsnom glomerulopatijom mogu razviti teži stadij kronične bolesti bubrega u usporedbi s onima koji imaju drugu vrstu oštećenja bubrega (npr. akutni tubulointersticijski nefritis). Rezultati ranih istraživanja upućuju na to da će oko trećine bolesnika koji prežive AOB uzrokovan bolešću COVID-19 ostati ovisni o dijalizi.

Ključne riječi: **sindrom akutnog respiratornog distresa, akutno oštećenje bubrega, receptor enzima konvertaze angiotenzina 2, COVID-19, sindrom otpuštanja citokina, izvantjelesna potpora organima, nadomještanje bubrežne funkcije, SARS-CoV-2**

POVEZANOST RATNIH ZBIVANJA SA STRUKTUROM MORBIDITETA I KOMORBIDITETA VETERANA DOMOVINSKOG RATA NA PODRUČJU VUKOVARA

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Cilj: **Cilj istraživanja je ispitati utjecaj ratnih zbivanja na strukturu morbiditeta i komorbiditeta kod veterana Domovinskog rata.** ***Ispitanici i metode:*** **Istraživanje je provedeno pomoću anketnog upitnika koji se sastojao od 20 pitanja. Ispitano je 60 branitelja i 51 osoba, jednake dobne i spolne strukture, koji nisu aktivno sudjelovali u borbenim aktivnostima, svi sa područja Vukovara.** ***Rezultati:*** **Utvrđena je statistički značajna razlika, prvenstveno u učestalosti psihičkih poremećaja, a zatim i bolesti srca. Branitelji češće obolijevaju od PTSP-a (χ2=52,486; p=0,000), depresije (χ2=7,150; p=0,007), anksioznog poremećaja (χ2=6,678; p=0,010), poremećaja spavanja (χ2=6,678; p=0,010) te bolesti srca (χ2=5,409; p=0,020). Istovremeno je prisutan veći broj psihičkih tegoba kod branitelja u odnosu na kontrolnu skupinu.** ***Zaključak:*** **Velik udio branitelja boluje od PTSP-a uz koji se nerijetko u komorbiditetu javljaju depresija, anksiozni poremećaj te poremećaji spavanja. Uz to, među braniteljima su češće prisutne bolesti srca.**

Ključne riječi: **ratni veterani, morbiditet, komorbiditet**

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UVOD

Hrvatski domovinski rat obuhvaća razdoblje rata u Republici Hrvatskoj od 1991. do 1995. godine (1). Gotovo 50 % kopnene površine Hrvatske bilo je obuhvaćeno ratom, dok je 11 % populacije Hrvatske krajem 1991. godine živjelo u djelomično ili potpuno okupiranim naseljima. Još i danas je teško procijeniti točan broj žrtava. U saborskom izvješću 2016. ravnatelj Hrvatskoga memorijalno-dokumentacijskog centra Domovinskog rata navodi kako Centar raspolaže imenima 14.912 smrtno stradalih osoba za vrijeme Domovinskoga rata od čega je 8.262 branitelja, a 5.650 civila. Više od pola milijuna ljudi za vrijeme rata bilo je prognano i izbjeglo (2).

Rat sa sobom donosi prisilno iseljavanje iz vlastitog doma ili njegovo razaranje, gubitak voljenih osoba, bolesti, ranjavanja i mnoge druge strahote što neizbježno dovodi do raznih socijalnih i zdravstvenih posljedica. Utjecaj ratnih događaja na psihosomatski status pojedinca ne smije se podcjenjivati zbog mogućih kasnih posljedica, premda samo jedno za život opasno iskustvo može dovesti do posljedica. U slučaju rata stresno stanje traje duže te dovodi do ozbiljnih posljedica, što nerijetko završava nastankom posttraumatskog stresnog poremećaja (PTSP) (2,3).

Nije upitno da su ratni stresori utjecali na cijelo hrvatsko društvo, međutim nikako se ne može govoriti o ravnomjernoj eksponiranosti svih građana Republike Hrvatske. Osobama na prvoj crti bojišnice bili su ugroženi temelji socijalne i fizičke egzistencije što može dovesti do ozbiljnih posljedica. Dodatni stresor je činjenica da se često ne radi samo o pojedincu već je nekoliko članova ili su čak svi članovi izloženi višestrukim prolongiranim stresnim utjecajima (smrt, ranjavanje, zatočeništvo, progonstvo) (4). Ovo može dovesti do učestalije pojave posttraumatskog stresnog poremećaja, te pojave više bolesti, odnosno komorbiditeta istovremeno (5).

Pojava komorbiditeta među braniteljima može se smatrati pravilom a ne iznimkom te je teško naći ratnog veterana koji nema barem dvije bolesti, bilo tjelesne ili duševne. Naime, dosadašnja istraživanja pokazuju da je kronični PTSP kod ratnih veterana gotovo uvijek praćen višestrukim psihijatrijskim i često somatskim komorbiditetom (6). U 80 % bolesnika s PTSP-om može se pronaći najmanje još jedan psihijatrijski poremećaj kao što su depresija, drugi anksiozni poremećaj, ovisnosti, poremećaj ličnosti, disocijativni poremećaj, somatski poremećaji itd. (7).

Simptomi PTSP-a javljaju se najčešće šest mjeseci nakon izlaganja traumi, a mogu se očitovati i do 30 godina nakon traume. Karakterizirani su ponovnim doživljavanjem traumatskog događaja te su ta sjećanja praćena i mučnom emocionalnom reakcijom. Javljaju se u obliku mučnih snova, iluzija, halucinacija i disocijativnih – „*flashback*" epizoda. Također, javljaju se psihogene amnezije, odnosno osobe se ne sjećaju nekih aspekata traume. Nadalje, javljaju se prekomjerna napetost, preosjetljivost, smetnje koncentracije, pretjerani strah. Bolesnik pokušava izbjegavati misli, osjećaje, određene aktivnosti i bilo kakve poticaje vezane uz traumu. Prisutni su i simptomi pojačane pobuđenosti zbog izloženosti poticajnim događajima kao i agresivne reakcije različitog intenziteta. Često se javljaju osjećaji krivnje i stida, anksioznosti, depresije. Pogoršanje depresivnih osjećaja može dovesti do suicidalnosti, a anksioznost može biti temelj za ovisnost o alkoholu ili drogama. Somatske tegobe kao što su glavobolja, bol u prsima i impotencija često prate PTSP (8).

PTSP se ubraja u veliku skupinu anksioznih poremećaja, zajedno s paničnim poremećajem, agorafobijom, specifičnim i socijalnim fobijama, opsesivno-kompulzivnim poremećajem i općim anksioznim poremećajem. Dosta je zahtjevno i teško postaviti ispravnu dijagnozu posttraumatskog stresnog poremećaja u kliničkom radu. PTPS se može dijagnosticirati prema dviju vrsta dijagnostičkih kriterija: Međunarodna klasifikacija bolesti (MKB-10) i Dijagnostički i statistički priručnik Američkog udruženja psihijatara (DSM-5) (9). Iako se u mnogočemu ove dvije vrste kriterija podudaraju postoje i razlike. Razlikuju se akutni PTSP kod kojega simptomi traju kraće od tri mjeseca, odnosno kronični kada traju duže od navedenog razdoblja, te odgođeni PTSP kad simptomi počinju šest mjeseci nakon traume (8).

Branitelji čine socijalno iznimno osjetljivu skupinu što zahtijeva posebnu skrb. Narušeni obiteljski odnosi, visok stupanj siromaštva te sklonost nizu bolesti samo su neke od tegoba s kojima se susreću branitelji nakon završetka rata (10).

Cilj istraživanja je ispitati utjecaj ratnih zbivanja na strukturu morbiditeta i komorbiditeta veterana Domovinskog rata na području Vukovara usporedbom branitelja i onih koji to nisu.

ISPITANICI I METODE

Istraživanje je provedeno pomoću nevalidiranog anketnog upitnika koji se sastojao od 20 pitanja, a koji je konstruiran prigodno za ovo istraživanje. Prvih pet pitanja odnosilo se na sociodemografska obilježja ispitanika (spol, dob, obrazovanje, radni status, bračni status). Idućih šest pitanja odnosila su se na uključenost osobe u ratna zbivanja (izloženost za vrijeme rata, boravak u zarobljeništvu, žrtva mučenja ili ranjavanja, dijagnosticiran PTSP, gubitak doma ili bliske osobe povezan s ratnim zbivanjima). Ostalih devet pitanja bila su vezana uz sadašnje zdravstveno stanje i neke navike ispitanika (broj posjeta liječniku, bolesti od kojih boluje, uzimanje lijekova, bavljenje fizičkom aktivnosti, odnosi u obitelji, konzumiranje alkohola, opijata i cigareta).

Anketiranje je bilo anonimno a ispitanici su u bilo kojem trenutku mogli odustati od ispunjavanja ankete. Anketu su ispunjavali branitelji članovi braniteljskih udruga iz Domovinskog rata na području Vukovara, dok su kontrolnu skupinu činili ispitanici s istog područja izabrani slučajnim odabirom pod uvjetom da su istog spola i dobi kao i branitelji te da nisu aktivno sudjelovali u ratu. Kriterij uključivanja u skupinu branitelja bio je aktivno sudjelovanje u obrani, dok je to kod kontrolne skupine bilo posve obrnuto. S obzirom da su osobe iz kontrolne skupine, kao i branitelji, s područja Vukovara koji je pretrpio najveća razaranja za vrijeme Domovinskog rata, teško je bilo naći ispitanike koji ni na koji način nisu bili uključeni u rat te je stoga veliki broj ispitanih osjetio izravno ratna stradavanja kao što su gubitak doma ili smrt bliske osobe, premda nisu aktivno sudjelovali u obrani. Svi ispitanici su potpisali informirani pristanak na istraživanje. Sudjelovanje ispitanika bilo je dobrovoljno i anonimno.

Pri obradi podataka korištene su metode deskriptivne statistike. Za kategoričke varijable korišten je χ^2 test za utvrđivanje razlike među skupinama pri čemu je određena razina značajnosti $p < 0,05$. Prikupljeni podatci su obrađeni pomoću kvantitativne analize u programu za statističku obradu podataka IBM SPSS *(Statistical Package for the Social Sciences) Statistics (IBM, Armonk, New York*).

REZULTATI

U istraživanju je sudjelovalo 111 ispitanika, od čega je 60 branitelja (54,1 %) te 51 ispitanik iz kontrolne skupine (45,9 %). Muškog spola je njih 95 (85,6 %), a ženskog 16 (14,4 %). Prosječna dob ispitanika uključenih u istraživanje iznosi 56 godina i 8 mjeseci. Najmlađi ispitanik ima 44, a najstariji 74 godine.

Većina ispitanika (73 %) ima završenu srednju školu, dok je 8,1 % ispitanika završilo samo osnovnu školu. Preddiplomski studij završilo je 11,7 %, diplomski studij 6,3 % ispitanika, a samo jedan ispitanik (0,9 %) ima završen doktorat.

Usporedbom radnog statusa ispitanika u vrijeme anketiranja utvrđena je statistički značajna razlika (χ^2 = 51,015; p = 0,0001)između branitelja i kontrolne skupine. Najveća razlika je u zaposlenosti i starosnoj mirovini (znatno niža kod branitelja - 18,3 % i 13,3 %), te u udjelu onih koji su u braniteljskoj mirovini (znatno viša među braniteljima - 66,7 %).

U odnosu na bračni status nije utvrđena statistički značajna razlika između ispitivanih skupina (χ^2 = 2,959; p = 0,398). U braku je 91,7% branitelja u odnosu na 84,3 % nebranitelja, dok ih je razvedeno svega 5 % u odnosu na 5,9 %.

Razlika između ispitanika s obzirom na izloženost ratnim zbivanjima statistički je značajna (χ^2 = 140,64;p < 0,0001) i očekivana, jer je to bio jedan od kriterija odabira ispitanika. Većina branitelja (95 %) navodi da su za vrijeme rata boravili na prvoj borbenoj liniji, dok je 13,7 % nebranitelja boravilo u pozadini, bez aktivnog sudjelovanja u obrani.

Prosječno vrijeme koje su branitelji proveli na prvoj borbenoj liniji iznosi 3 godine i 4 mjeseca, a kretalo se u rasponu od tri do 70 mjeseci.

U zarobljeništvu je bilo čak 41,7 % anketiranih branitelja. Razlika između skupina je očekivano statistički značajna (χ^2 = 24,23; p < 0,0001). Prosječnadužina boravka u zarobljeništvu iznosi šest mjeseci. Najkraće vrijeme provedeno u zarobljeništvu je tri dana, a najduže devet mjeseci.

Od 60 branitelja 27 ih navodi kako su bili žrtve ranjavanja ili fizičkog mučenja. Većina (26) ih je bila istovremeno žrtva i fizičkog i psihičkog mučenja, dok je u kontrolnoj skupini pet osoba bilo žrtva psihičkog mučenja. Razlika između skupina statistički je značajna u pogledu fizičkog (χ^2 =30,327; p <0,001) i psihičkog mučenja (χ^2 =22,046; p <0,001).

Među braniteljima je 80 % onih koji su izgubili dom prilikom ratnih aktivnosti, dok je taj postotak u kontrolnoj skupini nešto manji (64,7 %), a razlika nije statistički značajna (χ^2 = 3,269; p >0,05).

Gubitak člana obitelji ili bliske osobe povezan s ratnim zbivanjima može biti snažan stresogeni faktor. Većina branitelja (76,7 %) doživjela je takvu traumu, dok je u kontrolnoj skupini podjednak udio onih koji su to doživjeli (49,0 %) i onih koji to nisu (51,0 %) doživjeli. Razlika je statistički značajna na štetu branitelja (χ^2 = 24,23; p <0,001).

Među braniteljima je 80 % onih koji redovito posjećuju liječnike zbog zdravstvenih tegoba, dok je u kontrolnoj skupini taj postotak nešto manji i iznosi 66,7 %, a razlika nije statistički značajna (χ^2 = 2,539; p >0,05).U skupini branitelja prevladavaju oni koji liječnika posjećuju dva puta godišnje (56,2 %,), dok je u kontrolnoj skupini većina ispitanika navela da liječnika posjećuje jedanput godišnje (52,9%). U obje skupine gotovo je jednak udio (15 %) onih koji svaki mjesec posjećuju liječnika. Razlika u pogledu odlazaka na liječničke preglede statistički je značajna (χ^2 = 8,325; p<0,05). Bolesti i tegobe od kojih pate ispitanici prikazane su u tablici 1.

Tablica 1.
Bolesti i tegobe ispitanika

Bolest/tegoba		Branitelji (%)	Nebranitelji (%)	χ^2	p
Kronična bol	Da Ne	10 (16,7) 50 (83,3)	3 (5,9) 48 (94,1)	3,101	0,079
Hipertenzija	Da Ne	16 (26,7) 44 (73,3)	11 (21,6) 40 (78,4)	0,389	0,533
Respiratorna bolest	Da Ne	7 (11,7) 53 (88,3)	5 (9,8) 46 (90,2)	0,099	0,753
Karcinom	Da Ne	1 (1,7) 59 (98,3)	2 (3,9) 49 (96,1)	0,533	0,465
Dijabetes	Da Ne	13 (21,7) 47 (78,3)	7 (13,7) 44 (86,3)	1,177	0,278
Astma	Da Ne	1 (1,7) 59 (98,3)	2 (3,9) 49 (96,1)	0,533	0,465
Bolesti srca	Da Ne	18 (30) 42 (70)	6 (11,8) 45 (88,2)	**5,409**	**0,020**
Digestivni problemi	Da Ne	14 (23,3) 46 (76,7)	16 (31,4) 35 (68,6)	0,903	0,342
Moždani udar	Da Ne	0 (-) 60 (100)	0 (-) 51 (100)	-	-
Neurološke bolesti	Da Ne	8 (13,3) 52 (86,7)	2 (3,9) 49 (96,1)	2,979	0,084
Artritis	Da Ne	3 (5) 57 (95)	2 (3,9) 49 (96,1)	0,075	0,785
Bol	Da Ne	5 (8,3) 55 (91,7)	2 (3,9) 49 (96,1)	0,908	0,341
Depresija	Da Ne	20 (33,3) 40 (66,7)	6 (11,8) 45 (88,2)	**7,150**	**0,007**
PTSP	Da Ne	43 (71,7) 17 (28,3)	2 (3,9) 49 (96,1)	**52,486**	**0,000**
Anksiozni poremećaj	Da Ne	10 (16,7) 50 (83,3)	1 (2) 50 (98)	**6,678**	**0,010**
Ovisnost o alkoholu, drogama ili lijekovima	Da Ne	4 (6,7) 58 (93,3)	0 (-) 51 (100)	3,527	0,060
Poremećaji spavanja	Da Ne	24 (40) 36 (60)	7 (13,7) 44 (86,3)	**9,455**	**0,002**
Druge psihijatrijske bolesti	Da Ne	15 (25) 45 (75)	0 (-) 51 (100)	**14,742**	**0,000**
Bolesti mišića i kostiju	Da Ne	15 (25) 45 (75)	7 (13,7) 44 (86,3)	2,205	0,138
Ostalo	Da	5 (8,3)	6 (11,8)	0,364	0,547

Među braniteljima znatno je veći broj oboljelih od bolesti srca (χ^2=5,409; p <0,02), depresije (χ^2=7,150; p <0,001), PTSP-a (χ^2=52,486; p <0,01), anksioznog poremećaja (χ^2=6,678; p <0,01), poremećaja spavanja (χ^2=9,455; p <0,01) i drugih psihijatrijskih bolesti (χ^2=14,742; p <0,001). Ne postoji značajna razlika u pobolu od ostalih bolesti. Ni jedan ispitanik nije doživio moždani udar.

Što se tiče redovitosti uzimanja lijekova među braniteljima je veći udio onih koji to čine redovno (80 % : 51 %). Razlika je značajna (χ^2 = 10,447; p <0,001).

Među braniteljima je veći udio onih koji se redovno bave fizičkom aktivnošću (70 %), a razlika je značajna (χ^2 = 5,072; p <0,05). Razlika nije utvrđena u varijabli koja pokazuje odnose u obitelji (χ^2 = 2,447; p >0,05), premda je udio dobrih odnosa kod branitelja nešto niži u odnosu na nebranitelje 44 % : 57 %, dok povremene svađe navodi 54 % : 43 %.

Što se tiče konzumiranja alkohola svakodnevno to čini tek 3 % branitelja, dok 67 % to čini ponekad. U kontrolnoj skupini udio povremenih konzumenata je nešto niži (59 %), a razlika nije značajna (χ^2 = 2,949; p >0,05). Većina branitelja (95 %) i ispitanika iz kontrolne skupine (96 %) nikada ne konzumira opijate te među njima ne postoji razlika ni u ovoj varijabli (χ^2=0,075; p >0,05). Podatci o pušenju cigareta pokazuju kako je među braniteljima nešto veći udio onih koji puše svaki dan (37 % : 25 %), dok je u obje skupine podjednaki udio onih koji nikada ne puše 63 % : 69 %, a razlike nisu statistički značajne (χ^2=4,739; p >0,05). Broj popušenih cigareta/dan značajno je veći među braniteljima (χ^2 = 2,137; p <0,05). Oni u prosjeku popuše 21 cigaretu/dan, dok ispitanici u kontrolnoj skupini popuše u prosjeku 11 cigareta/dan. U tablici 2 prikazana je razlika u broju psihičkih poremećaja.

Tablica 2.
Udruženi psihički poremećaji ispitanika

Broj psihičkih poremećaja	Branitelji (%)	Nebranitelji (%)
0	15 (25,0)	42 (82,0)
1	17 (28,0)	9 (18,0)
2	17 (28,0)	0 (-)
3	7 (12,0)	0 (-)
4	4 (7,0)	0 (-)

χ^2 = 42,803; p < 0,0001

Branitelji i ispitanici iz kontrolne skupine statistički se značajno razlikuju prema broju psihičkih poremećaja od kojih boluju (χ^2=42,803; p <0,0001). Većina ispitanika iz kontrolne skupine (82 %) ne boluje ni od jednog psihičkog poremećaja, dok je među braniteljima takvih znatno manje (25 %). Čak 7 % branitelja boluje od sva četiri istraživana psihička poremećaja (PTSP, depresija, anksiozni poremećaj, poremećaji spavanja).

RASPRAVA

Raspodjela ispitanika s obzirom na aktualni radni status pokazala je statistički značajnu razliku. Branitelji bilježe manju zaposlenost u odnosu na kontrolnu skupinu što je i očekivano uzevši u obzir da je većina njih u braniteljskoj mirovini. Izloženost ratnim zbivanjima očekivano pokazuje statistički značajnu razliku između dviju skupina. Među braniteljima je više onih koji su izgubili dom zbog ratnih zbivanja, u čemu nema značajne razlike. Posljedica je to velikih ratnih razaranja na čitavom području grada pri čemu su jednako stradali domovi i branitelja i onih koji to nisu. Međutim, više branitelja je znatno češće doživjelo smrt bliske osobe. Razumljiva je i značajna razlika u boravku na prvoj crti bojišnice, jer je to bio jedan od kriterija odabira ispitanika. Prosječno vrijeme boravka branitelja na prvoj liniji iznosi tri godine i četiri mjeseca, a kretalo se u rasponu od tri mjeseca do pet godina i 10 mjeseci. Istraživanja pokazuju da je dužina boravka u neposrednoj borbenoj životnoj opasnosti značajna za nastanak PTSP-a (11).

Boravak u zarobljeništvu sigurno je značajan stresogeni faktor. U zarobljeništvu su boravila 25 branitelja. Prosječno je trajalo šest mjeseci, u rasponu od tri dana do devet mjeseci. Čak ih je 22 oboljelo od PTSP-a. Jedina osoba iz kontrolne skupine koja je boravila u zarobljeništvu, također ima dijagnosticiran PTSP. Tijekom zarobljeništva bili su žrtve psihičkog i fizičkog mučenja ili ranjavanja. Nitko iz kontrolne skupine nije bio žrtva ranjavanja, dok ih je petoro navelo psihičko zlostavljanje.

O strahotama koje su se događale za vrijeme zarobljeništva najbolje pokazuje istraživanje provedeno na 47 ratnih zarobljenika koji su 14. kolovoza 1992. razmijenjeni. U zarobljeništvu su boravili šest do devet mjeseci. Ovdje se radi o osobama u aktivnoj službi u policiji ili vojsci što zbog prethodne zdravstvene selekcije isključuje mogućnost postojanja mentalnih poremećaja prije zarobljavanja. Prema intervjuu PTSP, 16 testiranih zarobljenika (34 %) je ispunilo kriterije za trenutni PTSP, dok je psihijatrijska pomoć odmah preporučena svima (12).

Većina branitelja u ovom istraživanju boluje od PTSP-a. U kontrolnoj skupini, jedina osoba koja je bila u zarobljeništvu ima također dijagnozu PTSP-a, a značajna razlika između skupina ispitanika je razumljiva. Ovaj rezultat se podudara s podatcima o učestalosti psihičkih poremećaja među veteranima Zaljevskog rata (13).

Kada se radi o zdravstvenom stanju i navikama ispitanika, rezultati pokazuju da većina ispitanika iz obih skupina redovito posjećuje liječnika. Razlika nije statistički značajna. Značajna razlika je u učestalosti odlaska liječniku. Većina branitelja liječniku odlazi dva puta godišnje, dok ispitanici iz kontrolne skupine to čine jedanput. To se može pripisati većem broju bolesti među braniteljima, osobito većem udjelu psihičkih poremećaja. Pitanje u anketnom upitniku sastojalo se od nabrojanih bolesti i tegoba koje su ispitanici trebali označiti ako među njima prepoznaju svoje probleme. Značajna razlika među ispitivanim skupinama očitovala se u učestalosti depresije, PTSP-a, anksioznog poremećaja, poremećajima spavanja, drugih psihijatrijskih bolesti te bolesti srca.

Dosadašnja istraživanja pokazuju povezanost između bolesti srca i psihijatrijskih poremećaja (14-17). Najčešći psihički poremećaji koji se pojavljuju kod srčanih bolesnika su depresivni i anksiozni poremećaj te povratni depresivni poremećaj, distimija, panični poremećaj, agorafobija, socijalna fobija, generalizirani anksiozni poremećaj, specifične fobije i PTSP. Depresija i anksioznost bitno utječu na oporavak i prognozu srčanih bolesti, te se pojavljuju kao komorbiditetna stanja u srčanih bolesnika (18). Slični rezultati dobiveni su i u ovom istraživanju u kojem je gotovo trećina branitelja navela kako boluju od neke bolesti srca. Gotovo 90 % navodi udruženi psihički poremećaj uz bolest srca (PTSP, anksioznost, depresija, poremećaj spavanja ili druge psihijatrijske bolesti).

Očekivano, najveće razlike između dviju ispitivanih skupina bilježe se na području psihičkih poremećaja. Branitelji značajno češće obolijevaju od depresije, PTSP-a, anksioznog poremećaja te poremećaja spavanja uz česte komorbiditete navedenih bolesti. Posebno se to odnosi na osobe oboljele od PTSP-a uz koji se, prema jednom istraživanju, u 80 % slučajeva očekuje barem još jedan psihički poremećaj (6), što potvrđuju rezultati i ovog istraživanja. PTSP je najčešće povezan s depresivnim poremećajem, anksioznim poremećajem, paničnim poremećajem, alkoholizmom, ovisnostima o psihoaktivnim tvarima i poremećajem ličnosti (19,20). Istraživanja potvrđuju da 15 % veterana, uz utvrđeni PTSP, kao komorbiditet ima depresiju (21).

Polovica branitelja koji boluju od PTSP-a razvila je depresiju. To je nešto veći postotak u odnosu na ranije istraživanje na 200 bolesnika s dijagnozom PTSP-a gdje se depresija javila kod 39 % bolesnika (22). Kod ratnih veterana Zaljevskog rata, godinu nakon izloženosti ratnom stresu, utvrđena je veća zastupljenost mentalnih poremećaja (23). Nadalje, anksiozni poremećaj je razvila1/5 osoba koje boluju od PTSP-a. Ostala komorbiditetna stanja, koja se često navode, nisu ispitivana u ovom istraživanju (panični poremećaj, poremećaj ličnosti), ili nije utvrđena statistički značajna razlika u odnosu na kontrolnu skupinu (alkoholizam i ovisnosti o psihoaktivnim tvarima).

Kada se promatra broj udruženih psihičkih poremećaja rezultati pokazuju statistički značajnu razliku između branitelja i kontrolne skupine. Među braniteljima je najveći udio onih koji boluju od jednog ili dva psihička poremećaja. Tek ¼ nema nijedan psihički poremećaj a slijede branitelji s tri, odnosno četiri udružena psihička poremećaja. Ovi rezultati poklapaju se s rezultatima longitudinalnog praćenja ratnih veterana i komorbiditeta povezanog s PTSP-em (24,25).

Većina ispitanika iz kontrolne skupine ne boluje od psihičkih poremećaja, dok manje od 1/5 boluje od jednog. U prilog navedenom ide i podatak o redovitijem uzimanju lijekova kod branitelja gdje također postoji značajna razlika. Iako među ispitanicima nije bilo pokušaja suicida, uz PTSP veže se suicidalnost oboljelih na što upućuje istraživanje ovog problema u nas i u svijetu (26-28).

Zanimljiv rezultat dobiven je na pitanje o redovnoj fizičkoj aktivnosti. Naime, branitelji se značajno češće redovno bave fizičkom aktivnošću, što je vjerojatno rezultat organizirane aktivnosti u okviru braniteljskih udruga.

Dosadašnja istraživanja pokazuju povezanost PTSP-a s konzumacijom alkohola (29, 30). Dobiveni rezultati ovog istraživanja pokazuju nešto veći udio branitelja koji konzumiraju alkohol svaki dan ili povremeno u odnosu na kontrolnu skupinu, ali ta razlika nije značajna. Slične rezultate pokazuje i pušenje cigareta. Nešto je veći udio branitelja koji puše svaki dan, premda branitelji dnevno popuše više cigareta. Istraživanje među ratnim veteranima iz Vijetnama bilježi visok udio pušača - čak 60 % (31). Prema odgovorima koji se odnose na upotrebu opijata većina ispitanika ne konzumira ih nikada, te među njima nema razlike. U tom pogledu postoje razlike u odnosu na rezultate u svijetu. Kod 20 % američkih veterana iz Vijetnama, Iraka i Afganistana kod kojih je utvrđena neka od psihijatrijskih dijagnoza utvrđeno je konzumiranje opijata (32). Jedna od najčešćih poteškoća koje se vežu uz dijagnozu PTSP-a su problemi sa spavanjem. Prema nekim istraživanjima čak 70-87 % osoba s dijagnozom PTSP-a pati od poremećaja spavanja (33). Poremećaji spavanja odnose se na smetnje pri uspavljivanju, spavanju, duljini sna, noćne more ili hodanje u snu (34). Prema ranijem istraživanju na uzorku od 375 hrvatskih ratnih stradalnika, komorbiditetna bolest se javila u 85,3 % slučajeva; najčešće anksioznost (46,9 %) i depresivni poremećaj (32,5 %) (30). U drugom istraživanju na uzorku od 292 muškaraca s iskustvom borbe i ratnog stresa u 47 % slučajeva nađen je PTSP i komorbiditetni poremećaj (35).

U ovom istraživanju utvrđena je značajna razlika između branitelja i kontrolne skupine u pogledu poremećaja spavanja. Među braniteljima je pet puta veći udio onih koji često imaju probleme s nesanicom. Probleme s nesanicom navodi manje branitelja u odnosu na ispitanike iz kontrolne skupine (1 : 3,5).

Kada je riječ o terapiji bolesnika koji pate od nesanice mišljenja kliničara su podijeljena(35-40).

Zbog brojnih socijalnih i psihičkih problema oboljeli branitelji iz Domovinskog rata u Republici Hrvatskoj imaju dobro razrađenu integralnu skrb (8,31).

Kao nedostatak istraživanja može se navesti relativno mali broj ispitanika i primjena nevalidiranog anketnog upitnika. Ipak, rezultati potvrđuju dosadašnja saznanja o brojnim zdravstvenim tegobama s kojima se ratni veterani nose i danas, mnogo godina nakon završetka rata, te ukazuju na potrebu daljnjeg istraživanja ovog problema na znatno većem broju ispitanika. Rezultati bi trebali pomoći u poboljšanju Nacionalnog programa psihosocijalne i zdravstvene pomoći sudionicima i stradalnicima Domovinskog rata.

ZAKLJUČAK

Ovim istraživanjem je utvrđena značajna razlika u strukturi morbiditeta i komorbiditeta kod osoba koje su aktivno sudjelovale u ratu i bile izložene ratnim zbivanjima u odnosu na osobe koje nisu sudjelovale izravno u borbi. Razlika između ovih dviju skupina ponajviše se očitovala u učestalosti psihičkih i komorbiditetnih poremećaja. Radi se o velikom broju oboljelih branitelja od PTSP-a uz koji se nerijetko u komorbiditetu javljaju depresija, anksiozni poremećaj te poremećaji spavanja. Uz to je utvrđena razlika u povećanom obolijevanju branitelja od bolesti srca. Kada je riječ o braniteljima komorbiditetna stanja se smatraju pravilom a ne iznimkom, što je potvrđeno i u ovom istraživanju.

Unatoč očekivanoj razlici u skladu s dosadašnjim istraživanjima, u ovom istraživanju nije se potvrdila statistički značajna razlika u broju osoba koje konzumiraju alkohol, cigarete ili opijate, te narušenim obiteljskim odnosima. Iako prema istraživanju pate od većeg broja bolesti i tegoba, osobito onih psihičkih, zanimljivo je da se branitelji značajno češće bave fizičkom aktivnošću, što može biti rezultat pozitivnog utjecaja udruživanja u braniteljske udruge koje organizirano pomažu svojim članovima.

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SUMMARY

CONNECTIONS OF WAR EVENTS WITH THE STRUCTURE OF MORBIDITY AND COMORBIDITY IN HOMELAND WAR VETERANS FROM THE VUKOVAR AREA

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Aim: **The aim of the study was to examine the impact of war events on the structure of morbidity and comorbidity in Homeland War veterans.** ***Respondents and Methods:*** **The survey was conducted using a questionnaire consisting of 20 questions. The study included 60 veterans and 51 age- and gender-matched subjects that had not participated actively in combat activities, all from the Vukovar area.** ***Results:*** **A statistically significant difference was found, primarily in the incidence of psychiatric disorders and subsequently in heart disease. Veterans were more likely to suffer from post-traumatic stress disorder (PTSD) (χ2=52.486; p=0.000), depression (χ2=7.150; p=0.007), anxiety disorder (χ2=6.678; p=0.010), sleep disorders (χ2=6.678; p=0.010) and heart disease (χ2=5.409; p=0.020). At the same time, there was a greater number of psychological problems in the veterans than in the control group.** ***Conclusion:*** **A large proportion of veterans suffer from PTSD, with depression, anxiety and sleep disorders as often comorbidities. In addition, heart diseases were more common among the veterans.**

Key words: **war veterans, morbidity, comorbidity**

THE ROLE OF HEAT AND MOISTURE EXCHANGER IN POSTLARYNGECTOMY QUALITY OF LIFE

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Aim: The aim of this study was to investigate the effect of heat and moisture exchanger use on everyday problems and quality of life aspects in laryngectomized patients. ***Methods:*** Seventy laryngectomized patients were included and divided into a control group that used no device, and a group equipped with a heat and moisture exchanger. The effect of the heat and moisture exchanger was evaluated by means of a specially designed questionnaire. Medical records were reviewed to collect demographic, health, behavior, tumor and surgical data. Assessment of the benefits and drawbacks of the device was made by statistical comparison of the control group and the group using the device. ***Results:*** the group using the device scored significantly better on the questions about verbal communication, social interaction, paying attention and concentration. ***Discussion:*** The results of this study suggest that the use of heat and moisture exchanger can effectively reduce psychosocial and physical problems after total laryngectomy. A review of medical literature and comparison of the results of this study with the literature data available shows that the use of heat and moisture exchanger influences particular aspects of the quality of life of laryngectomized persons. ***Conclusion:*** the heat and moisture exchanger cannot fully restore physiological functions of the upper respiratory tract, but it plays an important role in the prevention of symptoms and in pulmonary and psychosocial rehabilitation after laryngectomy.

Key words: heat and moisture exchanger, laryngectomy, rehabilitation, quality of life

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INTRODUCTION

Laryngeal cancer and its treatment change some of the most important and vital functions such as oral communication, breathing, feeding, and social interaction. Total laryngectomy is still the treatment of choice for advanced laryngeal carcinoma. Complete removal of the larynx results in complete disconnection of the upper and lower respiratory tract, the voice organ is lost, and breathing through the tracheostoma leads to chronic lung problems. In addition, laryngectomees complain of a reduced sense of taste and smell, swallowing problems, fatigue, sleeping problems, anxiety and depression (1). These lifelong functional and psychosocial consequences have a devastating effect on patients and their families, and significantly influence the quality of life (QOL) of these patients. Rehabilitation of these patients has long been a major challenge, but in the last three decades restoration of function and QOL has become as important as cure and survival (2). Voice rehabilitation is individual and, in the past, included two methods, i.e. esophageal and electrolaryngeal speech. For the last 30 years, tracheoesophageal speech using voice prosthesis has become the most preferred method in voice restoration following total laryngectomy (3-5). Different techniques have been developed for improvement of olfaction in laryngectomees (6). At present, the only effective

non-pharmaceutical method of pulmonary rehabilitation following total laryngectomy is regular use of heat and moisture exchangers (HME). These devices are designed to help laryngectomees regain some of the lost functions, a role normally played by the upper respiratory tract (7). Daily consecutive use of an HME contributes to a healthier respiratory tract, restores airway resistance, and helps maintain optimal lung ventilation (8). The HME that are available to our patients are synthetic open-cell foam discs, impregnated with hygroscopic salt in order to increase its humidifying power, and antibacterial substance. Filters are placed over the tracheostoma by peristomal adhesion, in a special holder, and should be replaced at least once a day. These devices have a triple function, i.e. warming and humidifying the inspired air, and removing particles. The filter also increases airway resistance (9).

THE AIM OF STUDY

The main objectives of the research were to describe the problems of patients who had undergone total laryngectomy as a treatment for laryngeal cancer, and to investigate the effect of HME use on some factors influencing the QOL in laryngectomized patients.

METHODS

Testing was conducted on a sample of 70 totally laryngectomized patients of both genders. Thirty-five of them were regular users of HME (experimental group to test the HME, HME group) from two manufacturers whose cassettes are available in Croatia (Blom-Singer HME Cartridge and Provox HME Cassette) and 35 of them were non-users (no-treatment, control group). According to composition, the main part of the HME consists of a porous foamy substance that acts as a condensation and absorption surface, and is impregnated with hygroscopic salts and bactericidal solution. The Blom-Singer HME cartridge consists of a foam filter impregnated with chlorhexidine and lithium chloride. Provox HME cassettes also consist of a foam filter impregnated with calcium chloride and an antibacterial substance. Regular users had been using HME for at least one year. All of them had undergone total laryngectomy for laryngeal carcinoma combined with neck dissection at least one year before. All patients received radiotherapy postoperatively. Speech rehabilitation was conducted in all of them, and they are good alaryngeal speakers. They had been heavy smokers but none of them continued smoking following laryngectomy. Patients with a history of chronic lung disease before laryngectomy were excluded from the trial. None of the patients exhibited clear signs of active pulmonary infection. The state of general health was good in all study patients. All patients were informed about the aims of the study and all volunteered to take part in it. They were asked to complete a questionnaire to obtain their clinical history. Data were requested concerning current and previous lung diseases and other diseases related to pulmonary function, as well as on previous smoking habits. The experimental group evaluated the HME effectiveness. Medical records were reviewed to collect demographic, health, tumor and surgical data. The effect of HME was evaluated by means of a self-designed questionnaire. The first group of questions was a simple symptom score questionnaire. It contains ten questions intended to assess the impact of specific symptoms on daily life (1 – insufficient, 2 – sufficient, 3 – good, 4 – very good, 5 – excellent). The second group of questions evaluated some psychosocial problems and their frequency, as well as their impact on QOL (never, sometimes, always).

The benefits and drawbacks of the device were assessed by statistical comparison between the control group and the group using the device.

RESULTS

The study included 70 laryngectomized patients, nine (12.86%) of them women and 61 (87.14%) men, randomized to the HME (n=35) or control (n=35) group. The mean age of the HME group was 63.69±8.64 years, and of the control group 63.43±7.20 (median 62 min. 51, max. 89 **vs**. median 61 min. 50, max. 79, z=-0.100, p=0.920). There was no statistically significant age difference between the HME and control group. All patients had been heavy smokers, with a mean tobacco consumption of 38.17±12.51 years in the HME group and 38.15±8.91 years in the control group. We found no statistically significant between-group difference in the time elapsed from total laryngectomy. The mean time elapsed from the surgery was 5.37±3.81 years in the HME group and 5.31±4.68 in the control group (median 5, min. 1, max. 14 **vs**. median 5, min. 1, max. 28, z=-0.118, p=0.906) (Table 1). Voice rehabilitation of respondents from both groups was analyzed. Of the total number of respondents, 48 (69%) were speaking tracheoesophageally, 17 (24%) esophageally and 5 (7%) by electrolarynx. HME cassettes were statistically significantly more often used by those speaking tracheoesophageally (χ^2=13.226; p<0.001); there was no statistically significant difference between the groups for other methods of speech rehabilitation.

Table 2 shows patient rating of their problems and symptoms. Both groups equally evaluated the examined symptoms. They had no major problems with pain, dry mouth, breathing, nasal secretion, swallow-

ing and speech, but had problems with smell and taste, coughing and expectoration. Contrary to expectations, there was no significant between - group difference for most of the examined parameters in the perceived problems and symptoms. A statistically significant difference between the two groups was recorded in pain (χ^2=8.400; p=0.021) and taste (χ^2=11.076; p=0.020), i.e. results were significantly better in the HME group.

In the second group of questions, respondents evaluated the prevalence of certain parameters related to daily functioning (oral communication, social interaction, concentration and attention, sleeping, fatigue and weakness, loss of appetite, concern about health, depression and sadness). The majority of patients reported that they had never had any problems with sleeping (64.29%), appetite (81.43%), depression (72.86%), and concentration and attention (62.86%). Statistically significantly better results were recorded for oral communication (χ^2=10.809; p=0.004), social interaction (χ^2=16.533; p=0.001), and concentration and attention (χ^2=6.513; p=0,030) in the HME group. Overall, all HME users were very positive about the HME effects. Twenty of them (57.14%) rated it as excellent, 12 (34.29%) as very good, and three (8.57%) as good.

DISCUSSION

Obviously, treatment outcomes and overall survival remain the key issues in the evaluation of therapy effectiveness and QOL assessment is needed to put the loss of function into perspective and to evaluate the effectiveness of specific treatments and solutions (10). Patient perception of change in the overall QOL after total laryngectomy differs from the physician's. Mohide *et al.* performed a study comparing the relative importance of various QOL dimensions as ranked by patients and health care professionals. Health care professionals ranked communication impairment as the most important dimension, and patients ranked physical consequences and social activities as the most important QOL dimensions (11). In the recent past, the main attention of postlaryngectomy rehabilitation was paid to voice rehabilitation, while relatively little attention was paid to pulmonary rehabilitation according to the literature. The loss of normal voice was the predominating problem after total laryngectomy (12). However, it is clear that total laryngectomy has a profound impact on the patient daily living in many ways. Proper function of the upper airway is known to be highly important because it has the role of protecting the lungs, humidifying and conditioning the air before reaching the trachea, preventing dehydration of secretions, and facilitating mobilization (13).

In this study, less expected was the finding that olfactory deterioration was a major problem in all subjects. This fact has important implications for future efforts to improve rehabilitation of smell after total laryngectomy. Statistical comparisons failed to detect any significant differences between the HME and control groups in respiratory symptoms, speech, swallowing and nasal secretion, but HME group had significantly better results in the sense of taste and pain. However, in a study by Gonzalez *et al.,* an increase in humidity was observed after one hour of wearing the HME cassette. In all subjects, the HME cassette provided hydration >37 mg H_2O/L and patency of the endotracheal tube; however, it should be noted that their study included only 10 respondents (14). In this study, HME group also showed significantly better results in some parameters related to daily functioning, i.e. oral communication, social interaction, and concentration and attention. Some patients reported that they used to cover their tracheostoma because of aesthetic and hygienic reasons.

CONCLUSION

Results of this study suggest that the use of fan HME can effectively reduce some psychosocial and physical problems following total laryngectomy. HME cannot completely restore physiological functions of the upper airway, but plays an important role not only in pulmonary rehabilitation but also in psychosocial rehabilitation, as well as returning to normal life after total laryngectomy. This study also highlighted the functional and psychological difficulties, stimulating healthcare professionals to develop improved standards of care for patients after total laryngectomy.

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SAŽETAK

ULOGA KAZETA ZA ODRŽAVANJE VLAŽNOSTI I TEMPERATURE ZRAKA U KVALITETI ŽIVOTA NAKON LARINGEKTOMIJE

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Cilj: **Ispitati ulogu kazeta za održavanje vlažnosti i temperature zraka u smanjenju svakodnevnih problema i u nekim aspektima kvalitete života laringektomiranih bolesnika.** ***Metode:*** **Sedamdeset laringektomiranih bolesnika uključenih u istraživanje podijeljeni su u kontrolnu skupinu koja ne rabi kazete za održavanje vlažnosti i temperature zraka i skupinu ispitanika koja ih rabi. Uloga kazeta za održavanje vlažnosti i temperature zraka procijenjena je pomoću posebno osmišljenog upitnika. Pregledana je medicinska dokumentacija te su dobiveni demografski i zdravstveni podatci, podatci o navikama te podatci o tumoru i liječenju. Procjena prednosti i nedostataka ovog pomagala učinjena je statističkom usporedbom kontrolne skupine i skupine ispitanika.** ***Rezultati:*** **Ispitivana skupina je statistički značajno bolje ocijenila verbalnu komunikaciju, društvenu interakciju, pozornost i koncentraciju.** ***Rasprava:*** **Rezultati ovoga istraživanja ukazuju na to da upotreba kazeta za održavanje vlažnosti i temperature zraka može učinkovito smanjiti psihosocijalne i fizičke probleme nakon totalne laringektomije. Pretraživanje medicinske literature i usporedba rezultata ovoga istraživanja s dostupnim publiciranim podatcima pokazuje da upotreba kazeta za održavanje vlažnosti i temperature zraka utječe na određene aspekte kvalitete života laringektomiranih osoba.** ***Zaključak:*** **Kazeta za održavanje vlažnosti i temperature zraka ne može u potpunosti obnoviti fiziološke funkcije gornjeg dišnog puta, ali ima važnu ulogu u prevenciji simptoma te u plućnoj i psihosocijalnoj rehabilitaciji nakon laringektomije.**

Ključne riječi: **kazeta za održavanje vlažnosti i temperature zraka, kvaliteta života, laringektomija, rehabilitacija**

POREMEĆAJ REGULACIJE MAGNEZIJA U BOLESNIKA S KRONIČNOM BUBREŽNOM BOLESTI

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Magnezij je važan unutarstanični kation koji sudjeluje kao kofaktor u više od šest stotina biokemijskih reakcija. Raspon koncentracije magnezija strogo je reguliran apsorpcijom u crijevu, izlučivanjem putem bubrega te puferiranjem u stanicama i koštanom tkivu zbog čega određivanje isključivo koncentracije magnezija u serumu često nije dostatno za cjelovitu procjenu razine magnezija u organizmu. Napredovanjem kronične bubrežne bolesti (KBB) dolazi do smanjenja glomerularne filtracije što nerijetko dovodi do nastanka hipermagnezemije. Cilj ovog rada je povećati svijest o poremećaju homeostaze magnezija u bolesnika s KBB i mogućim posljedicama poremećaja njegove ravnoteže. Pri provođenju hemodijalize treba pažljivo odabrati koncentraciju magnezija u dijalizatu. Korištenjem vode za dijalizu bez magnezija često dolazi do razvoja hipomagnezemije, a korištenjem otopine s višim koncentracijama magnezija nuspojave su blaže. U bolesnika na dijalizi češća je hipermagnezemija, dok hipomagnezemija najčešće nastaje zbog smanjene apsorpcije u jejunumu. Povezanost peritonejske dijalize i hipomagnezemije još nije dovoljno istražena. U bolesnika s transplantiranim bubregom hipomagnezemija je česta. Uočeno je više mehanizama kojima niska koncentracija magnezija u serumu povisuje stopu smrtnosti u bolesnika s KBB-om; neki od njih su ubrzana kalcifikacija krvnih žila, dijabetogeni učinak, poticanje razvoja dislipidemije te metaboličkog sindroma. Nadalje, teška hipomagnezemija može izazvati nastanak smrtonosnih srčanih aritmija. Ne postoji usuglašeno mišljenje treba li se provoditi nadoknada magnezija u bolesnika s KBB-om, iako su neke studije pokazale da se na taj način mogu prevenirati dugoročne komplikacije i srčanožilni incidenti.

Ključne riječi: magnezij, kronična bubrežna bolest, dijaliza, transplantacija bubrega

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UVOD

MAGNEZIJ

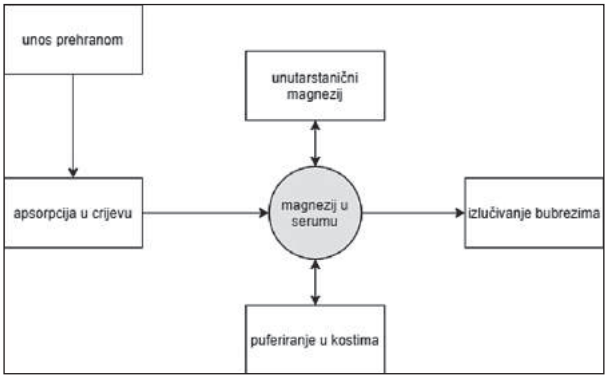
Magnezij je drugi najbrojniji unutarstanični kation (1), a njegova uloga prepoznata je u normalnom funkcioniranju mnogobrojnih bioloških procesa (2): Ima ulogu kofaktora u više od šest stotina enzimskih reakcija u vitalnim metaboličkim putevima, uključujući sintezu nukleinskih kiselina, proteina i visokoenergijskih spojeva (ATP-a) (1,3). Nužan je u procesu glikolize i oksidativne fosforilacije, za aktivaciju vitamina D, te za normalan rad Na^+/K^+-ATP-aze (1,3,4). Iako je održavanje homeostaze magnezija od vitalne važnosti za organizam, status magnezija u kliničkom radu nerijetko je zapostavljen (5). Cilj ovog preglednog rada je povećati svijest o važnosti prepoznavanja i ispravljanja poremećaja statusa magnezija, posebice u bolesnika s kroničnom bubrežnom bolesti.

Regulacija magnezija u organizmu

U ljudskome organizmu, manje od 1 % magnezija nalazi se u izvanstaničnom obliku, ostatak se većinom nalazi u kostima (60 %), pretežno u obliku koštanih minerala ili unutar stanica (6,7). Koncentracija magnezija u plazmi strogo je i usko regulirana (5) te je najčešće u rasponu između 0,7 i 1 mmol/L (2,8) od čega se 63 % nalazi u slobodnom (ioniziranom) obliku, 7 % u obliku difuzibilnih kompleksa, a ostatak je

vezan za proteine plazme – dakle, oko 70 % magnezija podliježe glomerularnoj filtraciji (7,9).

Homeostaza magnezija regulira se na tri glavne razine: apsorpcijom u crijevima, izlučivanjem bubrezima te puferiranjem magnezija u stanicama i koštanom tkivu (6,10,11). Regulacija magnezija u serumu shematski je prikazana na sl. 1.



Sl. 1. *Shematski prikaz regulacije koncentracije magnezija u serumu*

Dnevna potreba magnezija u zdravih osoba iznosi 300-400 mg (12). Crijevom se apsorbira oko 30-50 % magnezija unesenog hranom i to dvama mehanizmima – paracelularnim i transcelularnim (6). Paracelularni put apsorpcije je jednostavna elektrokemijska difuzija, a ovisna je o izraženosti različitih kaludina – proteina koji se nalaze u području čvrstih veza (tzv. „*zonulae occludentes*"). Ovaj je put odgovoran za apsorpciju većine magnezija pri unosu uobičajenih količina, a najaktivniji je u području jejunuma i ileuma. Transcelularna apsorpcija značajna je prilikom unosa većih količina magnezija, a odvija se putem ionskih kanala za dvovalentne katione - TRPM6 i TRPM7 (od engl. *transient receptor potential melastatin*) (6,10). Stupanj apsorpcije ovisi i o unosu druge hrane koja je unesena uz magnezij – laktoza, fruktoza i glukoza pojačavaju, a oksalati, fitati, slobodne masne kiseline te cink ju koče (6). Hrana bogata magnezijem uključuje grahorice, špinat, orašaste plodove te sjemenke bundeve (2).

Najveći dio magnezija izlučuje se urinom, a pri intenzivnom vježbanju mogući su i značajniji gubitci znojenjem (2,4). Tijekom jednog dana, profiltrira se otprilike desetina sveukupnog magnezija u organizmu (13). U proksimalnom tubulu reapsorbira se oko 15 % filtriranog magnezija, u uzlaznom kraku Henleove petlje reapsorbira se 70 % filtriranog magnezija, a 10 % u distalnom tubulu. Oko 5 % filtriranog magnezija izluči se urinom (9). Zbog velike reapsorpcije natrija i vode u proksimalnom tubulu koncentracija magnezija u proksimalnom tubulu se dvostruko poveća što uzrokuje povećanje kemijskog gradijenta i omogućava paracelularni transport magnezija (7,9,13). U uzlaznom kraku Henlejeve petlje, gdje se reapsorbira većina filtriranog magnezija, najvažniju ulogu ima električni gradijent koji nastaje zbog aktivnosti elektrogenog Na^+-K^+-Cl^- kotransportera (NKCC) koji zbog stvaranja pozitivnog naboja u lumenu tubula potiče paracelularnu difuziju magnezija (7,9,13). Furosemid, blokator NKCC kotranportera, može dovesti do hipomagnezemije (14). Magnezij se u distalnom tubulu reapsorbira transcelularno, putem TRPM6 ionskih kanala, a ključni pokretač difuzije u ovom segmentu je negativni membranski potencijal stanice tubula (7,9). Epidermalni čimbenik rasta (EGF) potencira reapsorpciju magnezija djelujući na TRPM6 kanal. Inhibitor EGF receptora kao što je cetuksimab također može dovesti do hipomagnezemije (7,14). PTH, kalcitonin i glukagon potiču reapsorpciju magnezija u Henleovoj petlji i distalnom tubulu, a metabolička acidoza, kalipenija i deplecija fosfata ju smanjuju i time potiču ekskreciju (9).

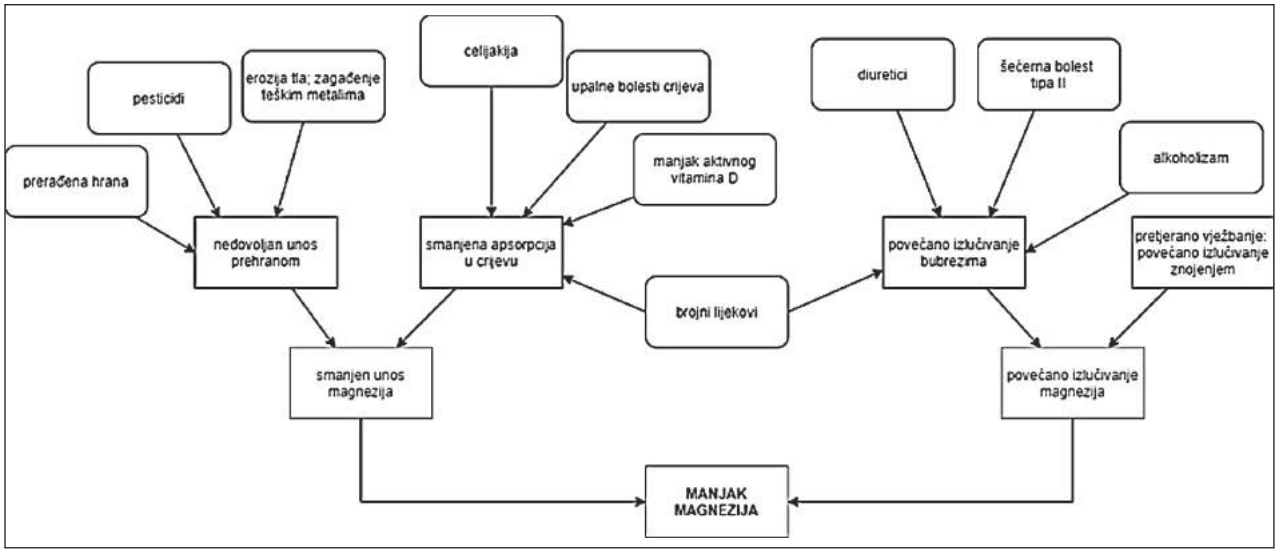
Procjena statusa magnezija

Ne postoji jedinstveni laboratorijski ili klinički parametar za primjerenu procjenu statusa magnezija (15). U kliničkoj se praksi najčešće koristi koncentracija ukupnog magnezija u serumu (15). Naime, razine magnezija u serumu dobro su puferirane prethodno navedenim regulacijskim mehanizmima koji koncentraciju magnezija održavaju u strogom rasponu (3,15). Tek pri značajnom nedostatku ili preopterećenju magnezijem dolazi i do značajnijih promjena serumske koncentracije (15). Uz to, moguće je da referentni raspon koncentracije magnezija u serumu koji iznosi 0,75 – 0,95 mmol/L, a postavljen je 1974., više nije mjerodavan prikaz populacije 21. stoljeća. Naime, zbog promjena načina života i prehrambenih navika dnevni unos magnezija hranom se smanjio u odnosu na vrijeme kada je određen referentni raspon (15). Još jedan problem je i činjenica da donje granice normalnog raspona koncentracije magnezija u serumu (*0,75 – 0,85 mmol/L*) (15) mogu biti praćene teškim intracelularnim manjkom magnezija (12), a ova se pojava označava kao kronični latentni manjak magnezija (3,12,15).

Ostale mogućnosti procjene statusa magnezija uključuju mjerenje ionizirane koncentracije magnezija u serumu, koncentracija magnezija u eritrocitima, procjena unosa magnezija hranom, te mjerenje koncentracije magnezija u 24-satnom urinu (15). Iako je to teško provedivo u rutinskom liječničkom radu, preporuča se kombiniranje više pretraga za adekvatnu procjenu statusa magnezija (15).

Manjak magnezija

Hipomagnezemija je relativno čest poremećaj elektrolita u kliničkoj praksi, no često prolazi nezamijećeno budući da se status magnezija relativno rijetko procjenjuje (16). Čimbenici koji utječu na manjak magnezija u tijelu prikazani su na sl. 2.



Sl. 2. *Grafički prikaz čimbenika koji mogu dovesti do nedostatka magnezija*

Kronični latentni manjak magnezija

Kronični latentni manjak magnezija pojam je koji se odnosi na supklinički smanjene razine magnezija unutar stanica i u kostima, dok je koncentracija magnezija u serumu održana unutar referentnog raspona (11,16). Novija istraživanja upućuju na to da čak 10 do 30 % populacije pati od latentnog manjka magnezija (16,19). Velika prevalencija najvjerojatnije je posljedica promjena životnih i prehrambenih navika – povećan unos rafinirane hrane siromašne magnezijem, a korištenje pesticida u uzgoju te termička obrada hrane također smanjuju udio magnezija u hrani (6,12). Uz to, manjak vitamina D te mnogi često korišteni lijekovi mogu uzrokovati manjak magnezija; takvi lijekovi često korišteni u kliničkoj praksi prikazani su u tablici 1 (4,14). Kronični latentni manjak magnezija povezuje se s razvojem brojnih kroničnih bolesti, a posebice šećerne bolesti (*diabetes mellitus* tipa II, DM2), metaboličkog sindroma te bolesti srca i krvnih žila (20–23).

Tablica 1.
Prikaz odabranih lijekova koji dovode do manjka magnezija i često se prepisuju u liječničkoj praksi

Skupina lijekova	Primjeri iz skupine
Antiaritmici	Amiodaron, sotalol, kvinidin
Antibiotici	Azitromicin, amoksicilin, ciprofloksacin, trimetorpim – sulfametoksazol
Diuretici	Furosemid, klortalidon, klorotiazid, indapamid
Imunosupresivi	Ciklosporini, takrolimus
Inhibitori protonske pumpe (IPP)	Pantoprazol, esomeprazol
Kortikosteroidi	Deksametazon, betametazon, flutikazon

Manifestna hipomagnezijemija

Manifestna hipomagnezijemija najčešće se javlja tek kad koncentracija magnezija u serumu padne ispod 0,5 mmol/L (24). Simptomi uključuju mišićnu tetaniju, tremor, konvulzije, mišićnu slabost, nistagmus, depresiju, delirij i psihozu. Uz to, hipomagnezijemija može uzrokovati i promjene u EKG-u koje uključuju produljenje PR i QT intervala, inverziju T valova (24) te poremećaje srčanog ritma, sinus tahikardiju, fibrilaciju atrija te ventrikularne aritmije; moguća je pojava polimorfnih ventrikularnih tahikardija (*torsades de pointes*) za koje je prva linija terapije magnezijev sulfat (20,24).

Blaga hipomagnezijemija može se liječiti peroralnom nadoknadom magnezija, a izraženije hipomagnezijemije liječe se intravenskim davanjem magnezijeva klorida ($MgCl_2$) uz praćenje serumskih koncentracija magnezija (24). Intravenska primjena $MgSO_4$ za ovu indikaciju nije preporučena – injekcije su bolne, a sulfati mogu vezati kalcij u serumu i urinu te uzrokovati (ili pogoršati postojeću) hipokalcijemiju (24).

Hipermagnezijemija

Hipermagnezijemija je stanje u kojem je razina magnezija veća od 1,25 mmol/L i rijedak je elektrolitski poremećaj u bolesnika s normalnom bubrežnom funkcijom (24,25). Osim zatajivanjem bubrežne funkcije može biti uzrokovana unosom velikih količina magnezija te stanjima koja uzrokuju nekrozu tkiva te otpuštanje magnezija u izvanstaničnu tekućinu kao što su trauma, šok, sepsa, opekline ili srčani arest (24).

Česti simptomi hipermagnezijemije su proljev i povraćanje (25). Kod izraženijih hipermagnezijemija (>2

mmol/L) može doći i do vazodilatacije s refrakternom hipotenzijom te do pojave neuroloških simptoma koji uključuju oslabljene tetivne reflekse, mišićnu slabost s progresijom do zatajenja disanja te komu(24,26). Moguć je i razvoj paralitičkog ileusa (24,26). Kardiološki simptomi uključuju pojavu paradoksne bradikardije i razvoj malignih aritmija (25).

Liječenje hipermagnezijemije uključuje prestanak unosa magnezija, administraciju laksativa (koji nisu na bazi magnezija) ili klizmi te obilnu intravensku hidraciju. Hemodijaliza je učinkovita mjera, posebice u bolesnika s kroničnom bubrežnom bolesti (24,27).

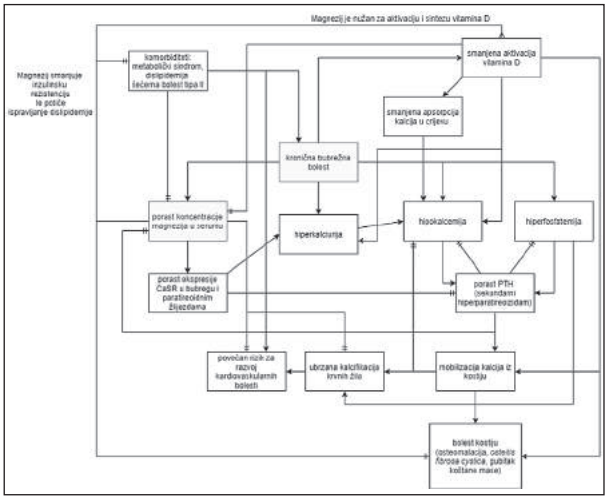
KRONIČNA BUBREŽNA BOLEST

Kronična bubrežna bolest (KBB) uključuje spektar patofizioloških procesa koji su povezani s poremećajem funkcije bubrega te s padom stupnja glomerularne filtracije (GF) (27). Najčešće bolesti koje dovode do razvoja KBB su dijabetička nefropatija, glomerulonefritis, hipertenzija, autosomno dominantna policistična bolest bubrega te cistične i tubulointersticijske nefropatije (27). Čimbenici rizika za razvoj KBB uključuju nisku porođajnu masu, pretilost u djetinjstvu, hipertenziju, šećernu bolest, prethodno preboljelo akutno oštećenje bubrega, proteinuriju te abnormalnost urotrakta (27). Prema procijenjenoj glomerularnoj filtraciji *(pGF)*, bolesnici s KBB mogu se podijeliti u pet skupina, odnosno pet stadija. Bolesnici prve dvije skupine, s pGF >60 mL/min/1,73 m^2 većinom su bez simptoma, a njihovo se prepoznavanje temelji na laboratorijskoj dijagnostici (27,28). Napredovanjem bolesti do trećeg i četvrtog stadija, pGF >15 mL/min/1,73 m^2 dolazi do očiglednih poremećaja drugih organskih sustava te nastanka simptoma anemije, gubitka apetita, poremećaja homeostaze kalcija, fosfora te kalcitriola i PTH (27). Peti stadij, pGF <15 mL/min/1,73 m^2, naziva se i *završni stadij KBB* (ZSKBB*)* – pojam koji označava činjenicu da bolesnik ne može preživjeti bez nadomjesnog bubrežnog liječenja (NBL) koje uključuje neki oblik dijalize ili transplantaciju bubrega (27,28).

POREMEĆAJ HOMEOSTAZE MAGNEZIJA U KRONIČNOJ BUBREŽNOJ BOLESTI

PATOGENETSKA VEZA MAGNEZIJA I KRONIČNE BUBREŽNE BOLESTI

Bubreg zdravog čovjeka ima veliku sposobnost izlučivanja magnezija, čak 250 mmol tijekom jednog dana (24,27). Hipermagnezijemija se zbog tog najčešće javlja u kontekstu kronične bubrežne bolesti, no čak i u bolesnika u ZSKBB većinom je blagog intenziteta (24,27,29). Patofiziološka povezanost povišenih koncentracija magnezija i kronične bubrežne bolesti vrlo je kompleksna (29), a pojednostavljeno je prikazana na sl. 3.



Sl. 3. *Grafički pojednostavljeni prikaz složenog međudjelovanja koncentracije magnezija i posljedica kronične bubrežne bolesti. Koncentracija magnezija prikazana je iz perspektive hipermagnezemije. (Relativni doprinos učinka je varijabilan; učinci su ovisni o dozi)*

Poznato je da magnezij može modulirati izraženost receptora osjetljivog na kalcij (engl. *calcium sensitive receptor*, CaSR) te posljedično uzrokovati hiperkalciuriju, a istim mehanizmom dovodi i do smanjenja koncentracije PTH; ovim učincima magnezij može uzrokovati hipokalcemiju (27). Poticanjem redukcije koncentracije PTH ostvaruje i svoje blagotvorne učinke: usporava kalcifikaciju krvnih žila te bolest kostiju koja nastaje zbog KBB (29). Pitanje ispravljanja blage hipermagnezemije je kontroverzno zbog njezinih protektivnih učinaka. No, Azem i sur. su u studiji objavljenoj 2020. godine uočili povećanu stopu smrtnosti u bolesnika s hipermagnezemijom u 3. i 4. stadiju KBB (30). Nije opažena razlika u godišnjem padu razina pGF u bolesnika s hipermagnezemijom u odnosu na one s normalnim koncentracijama (30). Uz to su uočili kako i hipomagnezemija u serumu dovodi do povećane smrtnosti u odnosu na bolesnike s normomagnezemijom (30). Navedeni rezultati upućuju na važnost održavanja koncentracije magnezija unutar referentnog raspona.

STATUS MAGNEZIJA U BOLESNIKA NA DIJALIZI

Za održavanje života bolesnika sa ZSKBB, a koji nemaju transplantirani bubreg, potrebno je bubrežnu funkciju nadomjestiti hemodijalizom ili peritonejskom dijalizom (31).

Hemodijalizom se preko sintetske, polupropusne membrane odstranjuju ioni, voda i toksini (31).

Peritonejska dijaliza je rjeđe korištena metoda dijalize koja se može provoditi od kuće (32), a polupropusnu membranu čini izrazito vaskulariziran sloj peritoneja, a intraperitonejskim davanjem hiperosmolarne otopine glukoze stvara se transmembranski osmotski i difuzijski gradijent kojim se olakšava prijenos tvari (31). Srednje preživljenje bolesnika na peritonejskoj dijalizi jednako je kao i u onih na hemodijalizi, ali je peritonejska pogodnija za bolesnike s manje pridruženih bolesti i one koji su tek počeli s nadomještanjem bubrežne funkcije (32). Međutim, ograničenja koja se javljaju kod ovakvog oblika dijalize ovise o dugovječnosti peritonejske membrane i hipoalbuminemiji (32).

Dijalizibilnost magnezija

Dijalizom se iz seruma može ukloniti dijalizibilni magnezij, tj. magnezij koji nije vezan za serumske proteine, a to uključuje slobodni magnezij u ionskom obliku, koji je ujedno i metabolički aktivan oblik magnezija, te magnezij u kompleksu s bikarbonatima, fosfatima i citratima (5,33–35). Koncentracija dijalizibilnog magnezija može varirati ovisno o količini albumina te neproteinskih aniona na koje se magnezij može vezati, no najčešće iznosi oko 70 % ukupne serumske koncentracije. Dva glavna čimbenika koja utječu na difuziju magnezija tijekom dijalize su koncentracijski gradijent duž dijalizne membrane i Gibbs-Donnanov efekt – fenomen u kojem na transport iona utječe nejednaka raspodjela proteina između plazme i vode za dijalizu (34). Odlučujući čimbenik difuzije magnezija u hemodijalizi je koncentracijski gradijent između plazme i vode za dijalizu (34). Tijekom hemodijalize dolazi do brze uspostave ravnoteže između dijalizibilnog magnezija u krvi i magnezija u vodi. Zato treba voditi računa o nekoliko stvari pri odabiru koncentracije magnezija (33) - korištenjem vode bez magnezija primijećena je velika učestalost pojave hipomagnezijemije, a pri nižim koncentracijama magnezija u vodi za dijalizu češće dolazi do nastanka mišićnih grčeva i hipotenzije tijekom dijalize. Više koncentracije magnezija u vodi za dijalizu izazivaju manje nuspojava, iako je opisan slučaj svrbeža induciranog hipermagnezemijom koji se povukao nakon što je koncentracija magnezija u vodi spuštena s 1 mmol/L na 0.2 mmol/L (33,34). U hemodijalizi se najčešće koriste koncentracije magnezija od 0,375, 0,5 ili 0,75 mmol/L (33).

Ultrafiltracija osmolita u peritonejskoj dijalizi povećava se korištenjem otopine s višim udjelom glukoze (34) čime se povećava i prelazak magnezija u dijalizat (34). Do sniženja serumskih razina magnezija dolazi i zbog upale i neuhranjenosti (33). Koncentracija magnezija u urinu bolesnika na peritonejskoj dijalizi veća je nego u zdravih osoba, međutim, smatra se kako to nije posljedica zaostale, održane bubrežne funkcije već smanjenog volumena urina u takvih osoba (33).

Poremećaji statusa magnezija u bolesnika na dijalizi

Bolesnicima koji se liječe hemodijalizom, a koji bubrezima mogu izlučiti zanemarivo malo magnezija, njegova razina u serumu određena je unosom magnezija na usta, intestinalnom apsorpcijom, te koncentracijom magnezija u vodi za dijalizu (5). Odabirom odgovarajuće razine magnezija u vodi za dijalizu moguće je održavati urednu serumsku koncentraciju magnezija usprkos unosu hrane s malo magnezija (5,33).

Kronična bubrežna bolest najvažniji je rizični čimbenik za razvoj hipermagnezemije (33). Bolesnicina dijalizi češće imaju više razine magnezija nego zdrava populacija, a do toga najčešće dolazi povišenjem koncentracije magnezija u vodi za dijalizu (33). Povećani oralni unos magnezija ne smatra se dovoljno značajnim za razvoj hipermagnezemije u bolesnika na dijalizi (5), iako do povećanja može doći uporabom kelatora fosfata na bazi magnezija (5,33). Pokazano je kako su u bolesnika na dijalizi povećane koncentracije ukupnog serumskog magnezija praćene sniženim ili čak normalnim (5) koncentracijama ioniziranog magnezija u serumu (5,33) zbog povećanog stvaranja kompleksa fosfata i drugih nakupljenih aniona s magnezijem, ali važnost toga još je uvijek nepoznata (5,33). Jedna od pretpostavki je da se povišenom razinom ukupnog serumskog magnezija nastoji održati razina ioniziranog magnezija u normalnim rasponima (5).

Hipomagnezemija u bolesnika na dijalizi može se razviti zbog nedovoljne apsorpcije magnezija u jejunumu, što se djelomično događa i zbog nedostatka D vitamina (5). Također, korištenje inhibitora protonske pumpe (IPP) dovodi do hipomagnezemije inhibicijom intestinalne apsorpcije magnezija (5,34). U hemodijaliziranih bolesnika hipomagnezemija je povezana s povećanim rizikom smrtnosti (18). Povezanost hipomagnezemije i peritonejske dijalize nije toliko istražena (33). Čini se da je njezin nastanak kompleksniji u usporedbi s hemodijalizom i povezuje se s pothranjenosti i hipoalbuminemijom, no patogenetski mehanizmi koji povezuju peritonejsku dijalizu i hipomagnezemiju nisu u potpunosti razjašnjeni (18,33). Postoje studije koje upućuju na to da je hipomagnezemija u bolesnika na peritonejskoj dijalizi neovisan rizični čimbenik za nastanak srčanožilnih bolesti, a takva korelacija posebice je izražena u žena (18).

Učinak poremećaja statusa magnezija u bolesnika na dijalizi na srčanožilni sustav

Srčanožilne bolesti zastupljene su deseterostruko do dvadeseterostruko puta više u bolesnika na dijalizi nego u općoj populaciji (33). Iako još ne postoji direktna poveznica između poremećene ravnoteže magnezija i nastanka aritmija, pokazano je da magnezij ima složene učinke na ione u miokardu (34). Manjak magnezija dovodi po poremećaja rada Na^+/K^+-ATPaze te posljedično do sniženja intracelularne koncentracije kalija i depolarizacije stanične membrane što povećava sklonost razvoju aritmija (20,34). Dobar pretkazatelj razvoja srčanožilnih bolesti u općoj populaciji je debljina intima-medije u karotidnim žilama (engl. *carotid artery intima-media thickness*, cIMT) (33,34). U studiji provedenoj na 93 bolesnika na hemodijalizi snižena unutar- i izvanstanična koncentracija magnezija bila je povezana s povećanom vrijednošću cIMT-a te povećanim srčanožilnim rizikom (33). Uz to, istraživanja su pokazala kako se nadomještanjem magnezija vrijednosti cIMT-a snižavaju (33,35). Snižena razina magnezija u bolesnika na dijalizi u korelaciji je i s drugim srčanožilnim rizičnim čimbenicima poput pulsa, tlaka, indeksa mase lijevog ventrikula te vaskularnim i valvularnim kalcifikacijama (5,33). Zbog ovog elektrolitskog disbalansa može doći do pojave iznenadne srčane smrti, a u hemodijaliziranih bolesnika iznenadna srčana smrt uzrokuje 20 % smrti povezanih s hemodijalizom te je najveći samostalni uzrok smrtnosti ove populacije (33).

Hipermagnezijemija također pokazuje negativne učinke na srčanožilni sustav (34). Teška hipermagnezemija (vrijednosti iznad 1,65-2 mmol/L) pokazuje učinke na provodni sustav srca u smislu bradiaritmija i potpunog srčanog bloka. Osim toga zahvaća i neuromuskularni sustav izazivajući gubitak dubokih tetivnih refleksa i slabost mišića (35). Međutim, blaža hipermagnezemija bi dugoročno mogla dovesti do zaštitnih učinaka na srčanožilni sustav zbog inhibicije kalcifikacije žila (5,33). U hemodijaliziranih bolesnika na usta primijenjen magnezijev karbonat kao kelator fosfata usporava kalcificiranje arterija (34).

Učinak magnezija na koštano tkivo u bolesnika na dijalizi

Magnezij je esencijalni mineral u kostima (5). Kosti reguliraju koncentraciju magnezija u serumu puferiranjem – otpuštanjem i vezivanjem magnezija (5). Hipermagnezemija u bolesnika na dijalizi povezana je s osteomalacijom (34). Uočeno je da u bolesnika koji razviju osteomalaciju, sniženjem koncentracije magnezija u vodi za dijalizu s 0,5 na 0,25 mmol/L, dolazi do normalizacije koncentracije magnezija u serumu, te do poboljšanja osteomalacije u razdoblju od jedne godine (33). U bolesnika na peritonejskoj dijalizi provedeno je manje studija nego u hemodijaliziranih, no uočeno je postojanje negativne korelacije između koncentracije magnezija u serumu i PTH u tih bolesnika (33,34). Studijom iz 2018. godine kojom je ispitivana povezanost između prijeloma kuka i serumskih razina magnezija u bolesnika na hemodijalizi u Japanu pokazano je da nema dokaza da visoke serumske razine magnezija dovode do povećane učestalosti prijeloma (5). Štoviše, rizik od prijeloma linearno se smanjuje nakon što koncentracija magnezija u serumu dosegne vrijednost od 1,65 mmol/L (5). Ova povezanost nije ovisila o PTH, ali magnezij može pokazivati pozitivan učinak na koštani metabolizam jer potiskuje aktivnost PTH osobito kod niskih do normalnih vrijednosti kalcija (5). Stoga vjerojatno postoje drugi mehanizmi kojima magnezij utječe na frakture, ali nisu još dokazani (5). Eksperimentalne su studije pokazale da magnezij direktno utječe na koštanu snagu i inhibira aktivnost osteoklasta (5).

Nadoknada magnezija u bolesnika na dijalizi

S obzirom da postoji mnogo različitih čimbenika koji utječu na razinu magnezija u serumu kod bolesnika na dijalizi postavlja se pitanje potrebe za njegovom nadoknadom u svrhu održavanja odgovarajuće koncentracije te smanjivanja posljedica poremećene ravnoteže (36). Treba naglasiti kako ne postoje studije koje bi opravdale uvođenje nadoknade magnezija kao standardne terapije u liječenju KBB (5,34). Dnevna potreba za magnezijem u bolesnika na hemodijalizi niža je nego u zdravih te iznosi 200-300 mg (5). Ona je dostatna da se spriječi hipermagnezemija, a ako se i javi najčešće je asimptomatska (5). Postoji nekoliko mogućnosti nadoknade magnezijem: jedna od mogućnosti je konzumacija hrane bogate magnezijem, no bolesnici na dijalizi slabije apsorbiraju magnezij u usporedbi sa zdravim pojedincima što je najvjerojatnije posljedica manjka vitamina D (5,35). Drugi način suplementacije je korištenje preparata magnezijevih soli - karbonata ili hidroksida. Uz to, mogu se prekinuti lijekovi koji blokiraju apsorpciju magnezija. Naposljetku, magnezij se može održavati odgovarajućim odabirom njegove koncentracije u vodi za dijalizu - u bolesnika na peritonejskoj dijalizi ona iznosi 0,5 mmol/L (5).

STATUS MAGNEZIJA U BOLESNIKA S TRANSPLANTIRANIM BUBREGOM

Transplantacija bubrega je terapija izbora u ZSKBB. Bolesnici s transplantiranim bubregom imaju duži očekivani životni vijek od bolesnika kojima se bubrežna funkcija nadomješta dijalizom (27).

Hipomagnezijemija je česta pojava u bolesnika s transplantiranim bubregom. Izvješća o prevalenciji variraju

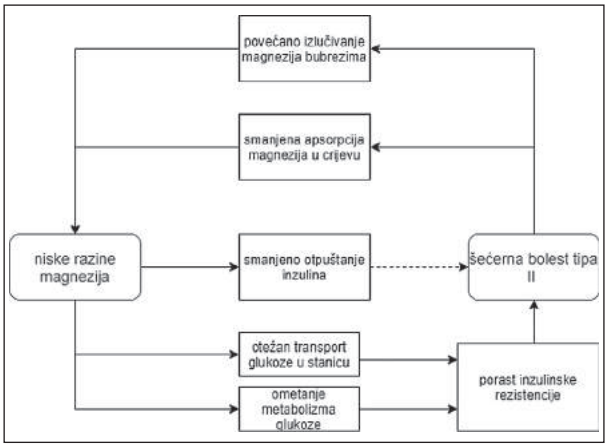
između 5 i 40 % (36,37). Snižene koncentracije magnezija u serumu uglavnom se mogu zabilježiti već u prvim posttransplantacijskim tjednima, a takvo stanje može zaostati i po nekoliko godina nakon zahvata(36). Metabolička acidoza, inzulinska rezistencija, smanjena apsorpcija magnezija u crijevima te uzimanje diuretika uočeni su kao dodatni važni čimbenici razvoja hipomagnezemije (36). Pokazano je da profilaktičko davanje magnezija u posttransplantacijskom razdoblju značajno smanjuje rizik dugoročnih komplikacija povezanih s hipomagnezemijom – ubrzani razvoj ateroskleroze, dislipidemija, nastanak kroničnih fibrotičnih lezija bubrega, razvoj šećerne bolesti i srčanožilnih incidenata (20,36,38).

Inhibitori kalcineurina

Povećana pojavnost hipomagnezemije u bolesnika s transplantiranim bubregom posebice se pronalazi u bolesnika koji su kao imunosupresivnu terapiju primali inhibitore kalcineurina (CNI). Naime, zamijećeno je da CNI uzrokuju smanjenu izraženost molekula epidermalnog čimbenika rasta (EGF), te kationskih kanala TRPM6 i TRPV5 u distalnom sabirnom tubulu nefrona čime se reapsorpcija magnezija smanjuje, a odstranjivanje urinom posljedično povećava (36,39). Takrolimus i ciklosporin ne pokazuju bitne razlike u težini hipomagnezemije koju uzrokuju (36,37). U bolesnika koji uzimaju CNI uočen je negativan odnos između razine GF te koncentracije magnezija u serumu što znači da je hipomagnezemija izraženija u bolesnika s višim GF (37). Uz navedeno, Holzmaher i sur. su retrospektivnom analizom uočili da su niske koncentracije magnezija u bolesnika s transplantiranim bubregom kojima je ujedno dijagnosticirana i nefrotoksičnost uzrokovana ciklosporinom A povezane s kraćim životnim vijekom presatka (40).

Novonastala šećerna bolest nakon transplantacije

Novonastala šećerna bolest nakon transplantacije *(New-Onset Diabetes Mellitus after Transplantation*, NODAT) razvija se u čak 10 do 30 % bolesnika nakon transplantacije bubrega. Etiopatogeneza NODAT-a složena je i još uvijek nije potpuno razjašnjena. Starija životna dob, muški spol, visok indeks tjelesne mase (BMI), akutno odbacivanje presatka te visoke doze takrolimusa i hipomagnezemija neki su od prepoznatih čimbenika rizika za razvoj NODAT-a (36), dok je kao jedan od važnijih prediktivnih čimbenika za nastanak ovog poremećaja uočena upravo posttransplantacijski snižena razina magnezija u serumu (38). Smatra se da hipomagnezemija pogoduje razvoju NODAT-a ometajući transmembranski prijenos te metabolizam glukoze, smanjuje izlučivanje inzulina iz gušterače te interferira sa signalnim putom inzulina u stanici (38), no zaštitni utjecaj terapijskog ispravljanja koncentracije magnezija u serumu nije jednoznačno uočen (36). Uz to, patofiziološki mehanizam dijabetogenog učinka takrolimusa također se tumači deplecijom magnezija (41). S druge strane, šećerna bolest tipa 2 dovodi do povećanog bubrežnog izlučivanja magnezija te do smanjene intestinalne apsorpcije čime dovodi do deplecije magnezija (sl. 4)(38) te se time *začarani krug* zatvara.



Sl. 4. *Grafički prikaz patogenetske veze hipomagnezemije i šećerne bolesti tipa II.*

KOMPLIKACIJE MANJKA MAGNEZIJA U KONTEKSTU KRONIČNE BUBREŽNE BOLESTI

Istraživanja su pokazala da kronični bubrežni bolesnici s nižim koncentracijama magnezija u serumu imaju veću stopu pomora u usporedbi s onima bez hipomagnezemije (36). Magnezij je neophodan za modulaciju srčanog ritma, a uključen je i u regulaciju funkcije endotelnih stanica i tonusa krvnih žila te u agregaciju trombocita zbog čega njegov nedostatak može rezultirati češćim i bržim nastupom srčanožilnih bolesti (20,42). Hipomagnezijemija može biti poticajni čimbenik za nastanak metaboličkog sindroma što dodatno povećava vjerojatnost srčanožilnih oštećenja (42).

Utjecaj dugoročnog manjka magnezija na koštano tkivo

Kosti kao velika skladišta magnezija u tijelu jedna su od najzahvaćenijih tkiva pri kronično sniženim koncentracijama tog minerala (43,44). Oko 30 % od magnezija u kostima nalazi se na površini same kosti i koristi se za brzu regulaciju koncentracije magnezija unutar i izvan stanice (43). Manjak magnezija rezultira smanjenjem funkcije osteoblasta, a uz to i povećanjem osteoklastične aktivnosti što dovodi do redukcije koštane mase (43). U istraživanjima provedenim na glodavcima koji su primali hranu sa sniženim koncentracijama magnezija tijekom duljeg vremena razvila se

osteopenija, a uočena je i povećana sklonost razvoju osteoporoze te usporenje rasta u životinja u razvoju (43,44).

Hipomagnezijemija i bolesti srca i krvnih žila u bolesnika s kroničnom bubrežnom bolesti

Srčanožilne bolesti, kao glavni uzrok smrti u svijetu posljednjih godina, posljedica su brojnih štetnih čimbenika koji povećavaju rizik njihovog nastajanja (20). Nekoliko je studija pokazalo da je kao jedan od takvih čimbenika prepoznata hipomagnezijemija. Naime, uočena je povezanost između niske koncentracije magnezija u serumu u sklopu ZSKBB i povećane smrtnosti od srčanožilnih bolesti, a koju su prouzrokovali ubrzani razvoj ateroskleroze, koronarne bolesti srca, aritmije i srčani zastoj (20,36). Također, hipomagnezemija je prepoznata i kao važan rizični čimbenik za formiranje kalcifikacija stijenki krvnih žila jer je izmjerena kod velikog dijela bolesnika s tom vrstom vaskularnog poremećaja (36). Dvije su glavne teorije kojima magnezij ometa kalcifikaciju krvnih žila. Jedna pretpostavlja da magnezij inhibira interakciju kalcija i fosfata vežući fosfat na sebe i time smanjuje formiranje hidroksiapatita te njegovo taloženje u stijenkama arterija (42). Druga teorija uzima u obzir sposobnost modulacije prokalcificirajućih čimbenika magnezijem (42). Uz to, magnezij smanjuje izlučivanje PTH stimulirajući receptore osjetljive na kalcij (CaSR) paratireoidne žlijezde te time smanjuje proaterosklerotske učinke PTH (42). Koronarne arterije posebno su sklone kalcifikaciji u bolesnika kod kojih kronična bubrežna bolest izaziva visoku koncentraciju fosfata u serumu (20). Niske koncentracije magnezija u serumu povezane su s povećanim rizikom za razvoj metaboličkog sindroma te dislipidemije (visoki trigliceridi, nizak HDL) vjerojatno zato što magnezij povećava aktivnost lipoprotein lipaze koja je zaslužna za pretvorbu triglicerida u HDL-kolesterol. DM2 još je jedna u nizu komplikacija niskih koncentracija magnezija do koje dolazi zbog promjena u regulaciji metabolizma glukoze u stanici te utjecaja magnezija na izlučivanje inzulina u gušterači putem interakcije s unutarstaničnom homeostazom kalcija (46). Metabolički sindrom i DM2 dodatno pridonose razvoju koronarne bolesti srca (20).

Podražljivost srčanog mišića ovisi i o magneziju koji regulira ionske kanale za kalij i kalcij te Na^+/K^+-ATPazne crpke na stanicama provodnog i radnog srčanog mišićja (20). Prirodni antagonistički utjecaj magnezija na kalcij pri vezanju za troponin C i kalmodulin uzrokuje otežanu aktivaciju mikrofilamenata i kontrakciju kardiomiocita, a to dovodi do produljenog QT intervala koji je česta pojava na EKG-u osoba s niskim, ali i visokim koncentracijama magnezija u serumu (20). Produljeni QT interval često je okidač za razvoj fatalnih srčanih aritmija. Jedna od takvih aritmija je *torsades de pointes* u čijoj se terapiji kao prva linija primjenjuje magnezijev sulfat čak i kod pacijenata s normalnom koncentracijom magnezija u serumu (20). Profilaktičko davanje magnezija u nekim istraživanjima pokazalo se učinkovito u smanjenju postinfarktnih aritmija, a u drugim neefikasno pa se potreba nadoknade u tu svrhu još razmatra, no uočeno je da se aritmije uzrokovane toksičnim dozama digitalisa mogu u nekim slučajevima uspješno poništiti davanjem magnezija (20).

Utjecaj nadoknade magnezija na srčani zastoj predmet je brojnih istraživanja i danas (20). LIMIT-2 istraživanje pokazalo je 25 % smanjenja ranog zastoja lijevog ventrikula kod bolesnika s akutnim infarktom miokarda koji su bili na intravenskoj terapiji magnezijem, a kasnijom studijom MAGIC pokazano je da davanje magnezija u bolesnika sa srčanim zastojem nema nikakvog učinka (46,47). Zbog različitih zaključaka nadomjesna terapija magnezijem ne preporuča se u bolesnika sa zastojem srca (20).

ZAKLJUČAK

Procjena statusa magnezija u kliničkom se radu često zapostavlja (48). U ovom je radu izložena važnost procjene statusa magnezija te posljedice poremećaja ravnoteže ovog elektrolita, s posebnim naglaskom na bolesnike na nadomjesnom bubrežnom liječenju.

U bolesnika s KBB često se javlja hipermagnezijemija (24,27). Još nije provedeno dovoljno istraživanja koja bi upućivala na jednoznačnu povezanost između postupaka dijalize i razine magnezija. Međutim, utvrđeno je da je za održavanje normalne koncentracije magnezija u serumu, najvažnije odabrati odgovarajuću koncentraciju u vodi za dijalizu (5,33). Individualnim pristupom svakom bolesniku moguće je izbjeći stanje hipo- ili hipermagnezijemije, a samim time i njihove posljedice na zdravlje bolesnika (33). Bolesnike s transplantiranim bubregom najčešće prati hipomagnezijemija, koja je posebice povezana s razvojem srčanožilnih bolesti (36). No, nadoknada magnezija u ovoj skupini nije dovoljno istražena te nije dio standardnog liječenja (11).

Održavanje i briga o homeostazi magnezija nadilazi mjerenje koncentracije magnezija u serumu već uključuje i razmišljanje o intracelularnim i intraosealnim zalihama ovog kationa (49). Svrhovitost korekcije statusa magnezija u ovih pacijenata nije dovoljno istražena, a za definitivni dokaz nužno je provoditi dvostruko-slijepa nasumična klinička istraživanja na većem broju ispitanika (50).

Poremećaji statusa magnezija bili su i predmet istraživanja hrvatskih znanstvenika. Ratković-Gusić i sur. predstavili su pregled hipomagnezijemije 2003. godine (51), a Kes i sur. su opisali simptomatsku hipomagnezijemiju koja je (uz hipokalcemiju i hipokalemiju) uslijedila nakon terapije gentamicinom te pronašli pozitivnu povezanost između kumulativne doze gentamicina i gubitka magnezija bubregom (52).

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SUMMARY

MAGNESIUM HOMEOSTASIS DISORDER IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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Magnesium is an important intracellular cation that acts as a cofactor in over 600 biochemical reactions. Concentration range of magnesium is strictly regulated by intestinal absorption, renal excretion and via cellular and bone buffering; thus determining magnesium concentration in serum may not be sufficient to fully assess magnesium levels in the body. Chronic kidney disease (CKD) progression leads to a decrease in glomerular filtration resulting in hypermagnesemia. The aim of this article is to increase the awareness of magnesium homeostasis disorders in CKD and possible repercussions of magnesium imbalance. Concentration of magnesium in dialysis fluid should be determined very carefully during hemodialysis. Hypomagnesemia often occurs when dialysis fluid without magnesium is used, while using dialysis fluid with higher magnesium concentrations has been reported to have less side effects. Patients on dialysis often have hypermagnesemia, while hypomagnesemia is connected with lower absorption in jejunum. Connection between peritoneal dialysis and hypomagnesemia is not fully investigated. Hypomagnesemia is common in patients with kidney transplant. There are many mechanisms through which hypomagnesemia increases mortality rate in patients with CKD, including increased rate of blood vessel calcification, pro-diabetic effects, increasing the risk of dyslipidemia and metabolic syndrome. Furthermore, severe hypomagnesemia can cause fatal heart arrhythmias. A consensus regarding magnesium supplementation in patients with CKD has not been reached, although some studies have shown that it might prevent long-term complications and cardiovascular incidents.

Key words: magnesium, chronic kidney disease, dialysis, kidney transplantation

THE DIAGNOSTICS AND TREATMENT OF CERVICAL CANCER

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Cervical cancer is the second most commonly diagnosed cancer among women in less developed countries with the incidence of about half million new cases and a quarter million deaths worldwide. Croatian cervical cancer epidemiological data lie in the European average and reflect current social characteristics of the society. Important key is that about 40% of targeted population do not respond to the national strategies proposed for prevention and early detection of cervical cancer. Traditional, well established Croatian preventive programs provide appropriate ground to detect preinvasive and early stages of cervical cancer, which should be regularly updated and refreshed with new discoveries and modern guidelines. Special strategies to motivate and encourage women to use preventive measures should be created and aggressively advertised in all aspects of social life. The objective of this review is to compare several current international guidelines for diagnosis and treatment of cervical cancer, and to present the homogenized management of these patients.

Key words: cervical cancer, guidelines, cervix, surgery, chemotherapy, radiotherapy

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INTRODUCTION

In 2014, cervical cancer accounted for about 3% of all malignancies in Croatia, representing a major public health problem with estimated 310 new cervical intraepithelial neoplasia (CIN III) cases and 307 new cervical cancer cases annually. In the same year, there were 130 cervical cancer related deaths, placing Croatia in the middle of the European five-year relative survival rate (1) . The average European survival rate shows sustainable geographic variations due to remarkable differences in the prevalence of human papillomavirus (HPV) infection, and availability of screening and HPV vaccination among European countries (2). The connection of HPV chronic infection with development of cervical cancer is well documented. History of smoking, parity, oral contraceptive use, early age at onset of sexual activity, numerous sexual partners, history of sexually transmitted disease, certain autoimmune diseases, and chronic immunosuppression are other possible epidemiological risk factors associated with cervical cancer (3). Squamous cell carcinoma accounts for approximately 80% and adenocarcinoma for approximately 20% of all cervical cancers (4). Globally, about 80% of women experience HPV infection during life span, but the infection has a subclinical course in about 75% of infected women (5). The peak incidence of HPV infection in young women is observed between age 20 and 25. In 80% of previously infected women, after one year the virus cannot be detected with biomolecular tests available (6) (Table 1).

Table 1.
Biomolecular tests for HPV detection

Test name	Methodology	HPV type
Hybrid capture test	HPV DNA-hybridization	13 high-risk viral types and additional 5 low-risk types
Cobas 4800 test	DNA-PCR	14 high-risk types of HPV, special accent on types 16 and 18

Persistent HPV infection presents a ground for development of cervical cancer. After discovery of the HPV role in cervical cancer oncogenesis, emphasis was put on systematic prevention. Active immunization is performed with vaccines consisting of several types of dead viruses prepared by biotechnology in order to prevent HPV infection and subsequent development of genital condylomas and cervical neoplasia (2) (Table 2).

Table 2.
HPV vaccination modalities

Vaccine	HPV types	Vaccination schedule
Cervarix	16,18	0, 1, 6 months i.m.
Gardasil	6,11,16 and 18	9-14 years: 0, 4-5 months (if second dose delayed after 5 months, 3rd dose mandatory) Older than 15: 0, 2, 6 months
Gardasil 9	6, 11, 16, 18, 31, 33, 46, 52, 58	9-14 years: 0, 4-5 months (if second dose delayed after 5 months, 3rd dose mandatory) Older than 15: 0, 2, 6 months

Current approach is to vaccinate children of both sexes to achieve the best immunity status prior to the onset of sexual maturity (7). The Croatian national cervical cancer screening program offers Papanicolaou (PAP) cervical smears each three years. However, recent statistics show that in Croatia only about 40% of targeted population are really covered with the program, responding to the proposed screening recommendations, which affects national statistics (8). On the other hand, it is also clear that PAP smear alone has important limitations due to its rather low sensitivity (about 51%). Its accuracy can be affected by errors in sampling (proper sampling from transformational zone), subjectivity of the cytologist interpretation of the smear, effect of fatigue, and objective technical appropriateness of the smear (9). Adding HPV-DNA typing besides PAP smear improves the accuracy up to 70%, making it highly recommendable, especially in women with epidemiological risks, mainly those older than 30 years (10). Abnormal cervical cytology mandates further evaluation following the protocol presented in Figure 1.

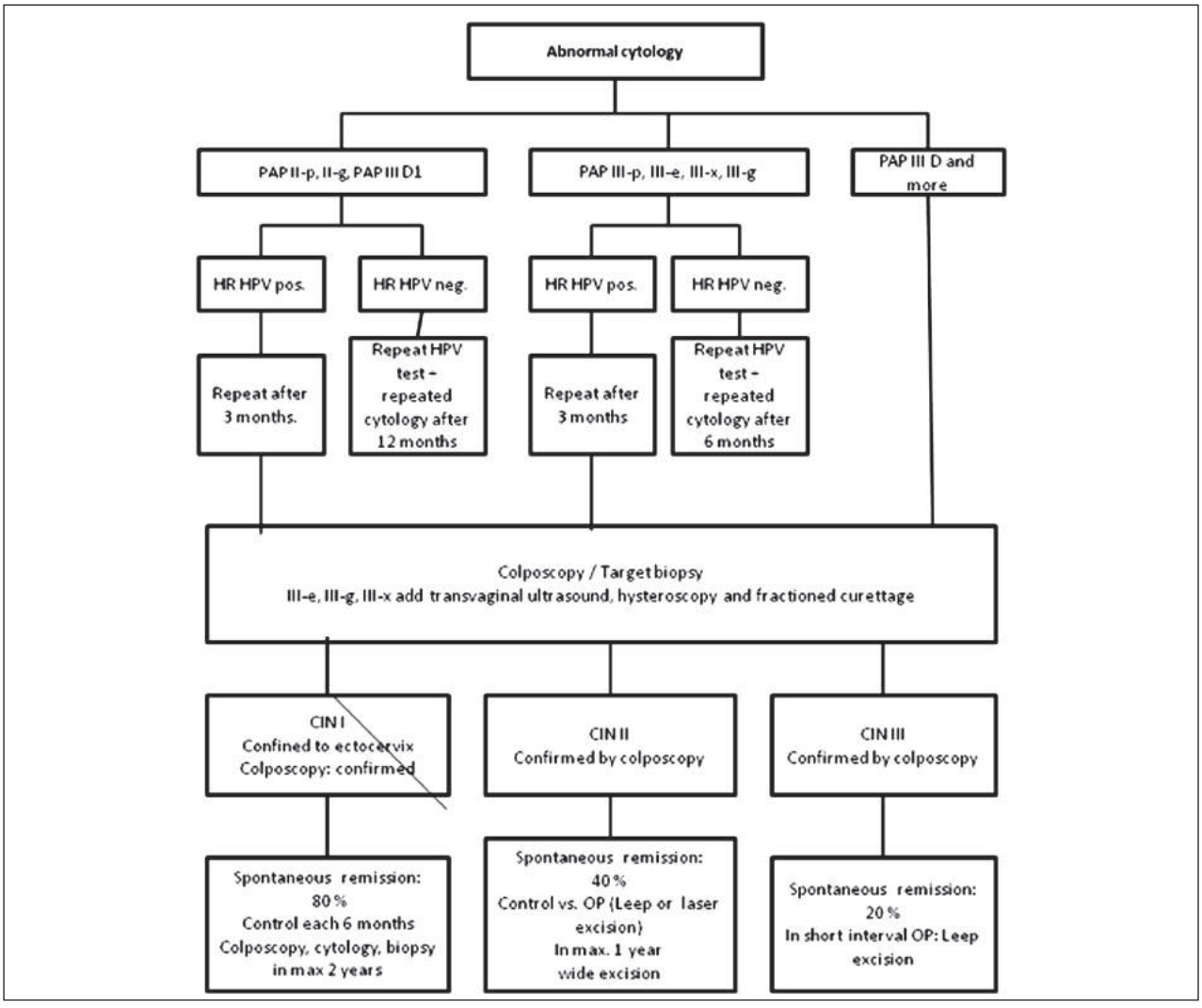

Fig. 1. *Management flow chart of cervical intraepithelial neoplasia – CIN I-III.*

Cervical cancer accounts for about 30% of gynecologic malignancies, holding the third position after endometrial and ovarian cancer. It is the second most common cancer in young women (25-29 age group), just after breast cancer (8). The apparent rising trend in the incidence of cervical cancer in this age group is of high importance. Although it is observed that cervical cancer in younger women has better prognosis and better survival indices (10), it remarkably affects the quality of life and eventual fertility wishes of the patient. Special concern is paid to the treatment of cervical neoplasia in pregnancy. Numerous obstetricians still have doubts regarding accurate strategy of pregnancy management and treatment of cervical malignancies when conjoined. The increasing trends of cervical cancer incidence in younger women of generative age warrant clear and reasonable rules for the management of cervical pathology in reproductive age and in pregnancy. Besides classic guidelines for the management of cervical cancer, we have also presented a segment of fertility sparing therapy (11), which enables safe preservation of fertility and successful family planning in selected patients.

Vaccination

The anti-HPV vaccination is usually provided by public health services for children aged 9-14 with two doses five months apart. If the second dose is applied after five months, the third dose must be administered. After the age 15, three doses are necessary, administered according to the following schedule: at 0, 2 and 6 months apart (12). The vaccination is recommendable for all women, especially younger population. It has been observed that the cumulative risk of fresh HPV infection declines with advancing age. In women above 45 years, the risk is about 15% (13). The vaccine was originally designed for girls. However, recently, it has been demonstrated that achievement of HPV immunity in communities which vaccinate both boys and girls leads to remarkable drop in the incidence of cervical cancer, and shows its maximal effects three years after vaccination (14). Permanent HPV infection in unvaccinated young men presents a threat of horizontal spread of the infection. Furthermore, sexual contact with infected partner carries the risk of re-infection for the women who have already been treated due to HPV-related pathology. After cervical conization, the gynecologist should offer HPV vaccination. In vaccinated patients, the risk of recurrent disease in the next ten years declines by 80% (15). Pregnancy and existing CIN both present contraindications for HPV vaccination.

Cervical intraepithelial neoplasia in pregnancy

The prevalence of suspicious smears in pregnancy is 2%-5%. The incidence of CIN in pregnant women does not differ from the one in non-pregnant age-matched population and ranges between 0.2% and 0.4% (16). Invasive cervical cancer in pregnancy appears in 0.01%-0.05% of cases. Pregnancy does not enhance progression of cervical dysplasia (8). All inconclusive and suspicious cytologic smears in pregnancy require colposcopy and targeted biopsy. Generally, biopsy can be performed throughout pregnancy, but the most suitable period for it falls between the 16th and 20th week of pregnancy. Endocervical curettage is contraindicated throughout pregnancy. Clinical and colposcopic follow-ups should be repeated each 8 weeks up to 36th week of pregnancy. Histologic re-evaluation should be performed in any suspicion of the progress (17).

If dysplasia is histologically confirmed and cervical cancer excluded, surgical procedure should be delayed until postpartum. Still, due to the high incidence of complications and increased mortality rate in every case with potential malignancy that cannot be excluded by histology (or in overt histologic evidence of microinvasive cancer), it must be individually decided if the intervention can be postponed until delivery.

Cervical intraepithelial neoplasia presents no contraindication for spontaneous vaginal delivery. In patients with cervical cancer in pregnancy, it is advised to terminate pregnancy by cesarean section. Puerperae with CIN diagnosed during pregnancy should be re-evaluated 6-8 weeks after delivery; cytologic smears, colposcopy and repeated biopsy should be performed. Remission of HPV infection after delivery is experienced by 25%-70% of patients (16).

Diagnostics of cervical cancer

In these patients, meticulous social history should be retrieved, and patient independence status, occupation and care should be clarified. It is important to determine duration of the disease and identify contact person or legal guardian of the patient (if present). The patient should be informed in detail about the disease and therapeutic options (surgical procedures, conization). The issues of partnership and sexuality should be discussed in detail. Gynecologic history should provide all the necessary data regarding patient reproduction, menarche, menopause, pregnancies, deliveries, lactation, contraception, conception wishes, and history of regular/irregular vaginal bleeding. Previous morbidities should be discussed with special reference to the history of radiotherapy or/and other concomitant neoplasia. In a previously irradiated patient, effort should be made to retrieve the irradiation plan performed. Patients with previous surgical interventions should be asked when and why was the last abdominal surgical procedure. Thorough insight into the previous operative and histology reports is mandatory. It is

important to determine the status of HPV infection and vaccination. The presence of herpes simplex virus (HSV), human immunodeficiency virus (HIV), chlamydial adnexitis, and condylomas must be determined (18). Detailed history of medication and possible allergies should be obtained as well. Description of patient symptoms should be in the center of our interest, as follows: When pain, bleeding, micturition appeared? For how long does it last? Is there any pattern?

The information regarding previous check-ups should be gathered, as follows: regular PAP smear? When was the last one? HPV-DNA typing? Biopsy/histology? It is of utmost importance to retrieve cytology and histology results from the referring physician (16). Abbreviations of the often used terms are listed in Table Supplement 1.

Table – Supplement 1.
Acronyms and abbreviations

AChRT	adjuvant chemoradiotherapy
ARH	abdominal radical hysterectomy
ART	adjuvant radiotherapy
BRT	brachytherapy
CBC	complete blood count
CCIP	cervical cancer in pregnancy
CCRT	concurrent chemoradiotherapy
ChT	chemotherapy
CIN	cervical intraepithelial neoplasia
CKC	cold knife conization
CRS	conventional radical surgery
CS	cesarean section
CT	computed tomography
DVT	deep venous thrombosis
EBRT	external beam radiotherapy
ESGO	European Society of GynaecologicalOncology
ESMO	European Society of Medical Oncology
ESP	European Society of Pathology
ESTRO	European Society of Radiotherapy and Oncology
EVGF	epithelial vascular growth factor
FIGO	Fédération internationale de gynecologie et d'obstétrique
FSS	fertility sparing surgery
FST	fertility sparing treatment
GIT	gastrointestinal tract
HDR	high-dose rate
HE	hysterectomy
H&E	hematoxylin and eosin
HIV	human immunodeficiency viru
HPV	human papillomavirus
HSV	herpes simplex virus
ICG	indocyanine green
IGABT	image guided adaptive brachytherapy
IGRT	image guided radiotherapy
IMRT	intensity modulated radiotherapy
LACC	locally advanced cervical cancer
LARVH	laparoscopic-assisted radical vaginal hysterectomy
LDR	low-dose rate
LEEP	loop electrosurgical excision procedure
LH	laparoscopic hysterectomy
LLETZ	large loop excision of the transformation zone
LN	lymph node
LN+	positive lymph nodes
LND	lymph node dissection
LVSI	lymphovascular space involvement
MDR	medium-dose rate
MRI	magnetic resonance imaging
NAChT	neoadjuvant chemotherapy
NART	neoadjuvant radiotherapy
OS	overall survival
OT	ovarian transposition
PAP	Papanicolaou smear
PALN	para-aortic lymph node
PALND	para-aortic lymph node dissection
PET	positron emission tomography
PET-CT	positron emission tomography-computed tomography

PLN	pelvic lymph node
PLND	pelvic lymph node dissection
pPROM	preterm spontaneous rupture of membranes
PROM	premature rupture of membranes
RH	radical hysterectomy
RT	radiation therapy
SCC	squamous cell carcinoma
SH	simple hysterectomy
SLN	sentinel lymph node
SLNB	sentinel lymph node biopsy
SLND	sentinel lymph node dissection
Tru-cut (core cut)	capture of high-quality biopsy tissue samples with minimal trauma to the patient

Examination

Examination of a patient with suspicion of cervical cancer should follow these steps (19):

- general health assessment
- laboratory analyses: complete blood count (CBC), liver and renal tests
- gynecologic examination: bimanual, rectovaginal left and right pelvic examination
- axillary, supraclavicular and inguinal lymph node check-up
- differential colposcopy with histologic examination of targeted biopsy samples
- sonography: vaginal (sonomorphology of the cervix) + abdominal (parametria, kidneys)
- radiography: thoracic x-ray or thorax computed tomography (CT) scan with upper thoracic aperture (scalene lymph nodes) for higher *Federation Internationale de Gynecologie et d'Obstetrique* (FIGO) stages
- abdominal magnetic resonance imaging (MRI) or CT scan, pelvic MRI
- if symptoms are present, skeletal scintigraphy and x-ray should be added
- examination in anesthesia
- cystoscopy/rectoscopy (in suspicion of bladder/bowel extension), possibly hysteroscopy with abrasion or biopsy
- in selected cases, positron emission tomography-computed tomography (PET CT) scan (suspicion of locally advanced and spread disease)
- HIV test

A combination of these clinical and radiological results leads to final clinical diagnosis and FIGO stage of cervical cancer (Table 3).

Table 3.
T-classification and FIGO staging (2018)

T category	FIGO stage	Definition
TX	/	Primary tumor cannot be assessed
T0	/	No evidence for primary tumor
T1	I	Cervical carcinoma strictly confined to the uterus (extension to corpus should be disregarded)
T1a	IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion less than 5.0 mm measured from the base of the epithelium: horizontal spread, vascular space involvement, venous or lymphatic, does not affect classification
T1a1	IA1	Measured stromal invasion <3.0 mm
T1a2	IA2	Measured stromal invasion of more than 3.0 mm and not more than 5.0 mm
T1b	IB	Clinically visible invasive lesion confined to the cervix or microscopic lesion greater than T1a2/IA2. Includes all macroscopically visible lesions, even those with superficial invasion. Lesions limited to the cervix
T1b1	IB1	Invasive carcinoma with 5 mm or more deep stromal invasion, less than 2 cm in greatest dimension
T1b2	IB2	Lesion greater than 2 cm but smaller than 4.0 cm in greatest dimension
T1b3	IB3	Invasive carcinoma bigger than 4 cm in greatest dimension
T2	II	Cervical carcinoma invading beyond the uterus but not to the pelvic wall or to the lower third of the vagina
T2a	IIA	Involvement limited to the upper 2/3 of vagina, without parametrial invasion
T2a1	II A1	Clinically visible lesion of 4.0 cm or less in greatest dimension
T2a2	IIA2	Clinically visible lesion of more than 4.0 cm in greatest dimension
T2b	IIB	Tumor with parametrial invasion, but not up to the pelvic wall
T3	III	Tumor extending to the pelvic sidewall* and/or involving the lower third of the vagina and/or causing hydronephrosis or nonfunctioning kidney, and/or involves PLN or PaLN
T3a	IIIA	Tumor involving the lower third of the vagina but not extending to the pelvic wall
T3b	IIIB	Tumor extending to the pelvic wall and/or causing hydronephrosis or nonfunctional kidney
T3c	III C	Involvement of PLN and/or PaLN, irrespective of tumor size and extent
T3c1	III C1	PLN metastasis only
T3c2	IIIC2	PaLN metastasis
T4	IV	Tumor outside the true pelvis, or affection of the rectum/bladder mucosa
T4a	IVA	Tumor invading the mucosa of the bladder or rectum and/or extending beyond the true pelvis (bullous edema is not sufficient to classify a tumor as T4)
T4b	IVB	Tumor invading distant organs (including extrapelvic lymph nodes)

*The pelvic sidewall is defined as the muscle, fascia, neurovascular structures and skeletal portions of the bony pelvis

The only exception is FIGO stage IA: pT1a1/1a2 (in which the diagnosis/stage is based on the histopathology report), All patients should be advised on smoking cessation. Young women with reproductive wishes should be referred to reproductive health center to determine the possibilities of fertility sparing treatment (20).

Cervical cancer staging

The diagnosis of cervical cancer and cervical cancer stage is reached by summing the results of clinical and radiological tools, and further corrected by histopathology (additional data are obtained after surgical procedure). Clinical staging is based on the following:

- tumor size
- vaginal/parametrial involvement
- bladder/rectum extension
- presence of distant metastases

The tumor is classified according to FIGO criteria and Union for International Cancer Control TNM classification, 8th edition (21,22).

Relevant diagnostics for FIGO classification:

- bimanual pelvic and bilateral rectovaginal examination under general anesthesia
- endoscopies (colpo-, hystero-, cysto- and rectoscopy)
- thoracic x-ray, IV urography
- biopsy/curettage

Helpful but irrelevant for FIGO classification:

- MRI
- sonography
- lymphangiography
- angiography
- laparoscopy as a staging procedure (can eventually serve for the para-aortic lymph node (PLN) assessment)

Nodal/distant metastatic diagnostic workup:

- In early stage (T1a, T1b1, T2a1), surgical/pathologic staging of PLNs is the criterion standard to assess the prognosis and guide treatment (except for T1a1 and no LVSI).
- In LACC (T1b2 and higher, except for T2a1), or in early-stage disease with suspicious LNs on imaging, PET-CT, or chest/abdomen CT is recommended for assessment of nodal and distant disease.
- PET-CT is the preferred option for treatment planning before chemoradiotherapy with curative intent (20).
- PALN dissection, at least up to inferior mesenteric artery, may be considered in LACC with negative PALNs on imaging for staging purposes.
- Equivocal extrauterine disease is to be considered for biopsy to confirm or rule out metastatic disease and to avoid inappropriate treatment. Tru-Cut (core-cut) biopsy is the option preferred to fine-needle aspiration biopsy because it allows histologic assessment of the tissue (20).

Tumor risk assessment

- Tumor size
- Tumor stage
- Depth of invasion
- LN status
- LVSI
- Histologic subtype of the tumor

Presence or absence of positive LN is the most important prognostic factor. Histologic type is of high importance; adenocarcinomas have worse prognosis than squamous cell carcinomas with 10%-20% (23) worse results on 5-year overall survival, microcellular and neurocrine carcinomas even more. Patients with pathologic risk factors (e.g., positive LNs, tumor-positive surgical margins, depth of invasion, vascular thrombosis, interstitial infiltration depth, higher tumor stage, and tumor differentiation) have a higher frequency of recurrence when compared to patients without these factors (24). At the same time, especially recent studies have found that the size of tumors over 2 cm may also be a poor prognostic factor (25).

Primary therapy

Types of primary therapy:

- primary surgical therapy, possibly in combination with AChT
- staging surgery, possibly with RChT
- primary RChT, possibly followed by ChT
- surgery after NAChT
- surgery to treat symptoms, before palliative therapy, i.e. repair of fistulas

The optimal therapeutic sequence should be chosen. Risk factors should be taken into account in decision process (Table 4).

Table 4.
Risk factors for disease progression (require higher order of radicality in therapeutic approach)

Risk factors
Lymph node status positive
Resection status R1, R2
Parametria positive
Tumor diameter >4 cm
Distant lymphangiosis (satellite LVSI) or hemangiosis
Malignancy grade G3
Up-staging (TNM>FIGO) after the surgery

It should be considered and decided if they define the necessary therapeutic mode (for instance, to decide on RChT). RChT and surgery are proven to be equally effective in the treatment of early stages of cervical carcinoma. However, surgery (up to FIGO II A) is proven as a better solution due to the decreased rate of morbidities (10). Trimodal therapy (surgery with ChT and irradiation, all three together) should be avoided if possible because it does not improve overall survival and exhibits increased toxicity (20).

A) Surgical therapy

The first-line treatment of cervical cancer, if possible, is surgical (9). However, there are several therapeutic strategies in cervical cancer treatment, depending on the disease stage, histologic characteristics of the tumor, patient preferences and general health condition (26). In surgical approach, the first step is to decide whether there is an indication for surgical procedure. There are several types of surgical procedures, defined by their goals:

- staging surgical procedures
- curative surgery
- fertility-preservation surgery
- palliative surgery (i.e. urine and stool derivation procedures)

Decision should be made on what surgical procedure and which technique to use. Furthermore, the degree of radicality must be defined, e.g., staging lymphadenectomy, SH or RH (Tables 5 and 6).

Table 5.
Operative therapy classification

Querleu/Morrow (Q/M) radical hysterectomy classification					
	Mobilization of ureters	Dissection of lateral parametria	Vagina	Sacrouterine ligaments	Vesicouterine ligaments
A Extrafascial HE	Mobilization of ureters	Near the cervix	Minimal resection	Dissection near the cervix	Dissection near the cervix
B Modified radical HE	Partial	Medial from the tunnel of the ureter	>10 mm	Partial resection	Partial resection
C** Classical radical HE	Partial resection	Partial resection	15-20 mm	Dissection near the rectum, after preparation of the plexus of the hypogastric artery	Remove near the bladder, with preservation of neural structures
D Laterally widened dissection	Complete	Resection of the branch of the internal iliac artery, dissection of the root of the ischiadic nerve			
** **C 1**: surgical procedure with dissected and spared nerves; **C2** nerves cannot be dissected and spared					
Classification of lymphadenectomy according to Querleu/Morrow (Q/M) classification					
Level 1 Level 2 Level 3 Level 4	Internal and external iliac arteries Common iliac artery Aorta below the upper mesenteric artery Aorta below the renal vein				

Table 6.
Suggested type(s) of radical hysterectomy according to prognostic factors and risk groups

Risk group	Tumor size	LVSI	Stromal invasion	Type of RH*
Low risk	<2 cm	Negative	Inner 1/3	B1 (A)
Intermediate risk	≥2 cm <2 cm	Negative Positive	Any Any	B2 (C1)
High risk	≥2 cm	Positive	Any	C1(C2)

*According to Querleu-Morrow classification

Preparation for the procedure starts with blood type screen (to order two units of blood). Physical preoperative preparation consists of thromboprophylactic pneumatic stockings and operative field shaving). Perioperative antibiotic prophylaxis should be administered, i.e. cefuroxime + metronidazole. The potential complications of the procedure should be clarified in detail to the patient, i.e. the need to insert the suprapubic catheter, drainage, infusions, development of lymphedema/thrombosis (embolism), the need for blood transfusions. The risk of infection, effects of the procedure on fertility, difficulties of wound healing, scarring, development of hernias should also be discussed.

A1. Surgical procedures

Prior to surgery, after meticulous consideration of tumor staging, patient general health, wishes and risk factors, proper surgical strategy is chosen. Every surgical procedure starts with exploration of the operative site and reconsideration of the indication for surgical procedure. For cervical cancer treatment, metastatic spread is the key point, so every procedure begins with checking the LN status, as follows:

1. Clinically unsuspicious lymph nodes, SND as the only test has its place in bilateral demarcation with ICG or demarcation with patent blue and radioactive tracer (27)
2. If the SN does not mark and the tumor is smaller than 2 cm, systematic pelvic lymphadenectomy should follow, with *ex tempore* histopathology. The procedure should follow the histopathology results
3. In tumors smaller than 2 cm, the SND is convenient as a single procedure, and it can be optimally offered for tumors up to 4 cm (28)
4. If *ex tempore* histopathology is negative, the procedure should be continued with SH, RH, or radical trachelectomy
5. Perioperative/intraoperative conspicuous LN (PLN/PALN)
6. Targeted extirpation of the tumor with *ex tempore* examination
7. Systemic pelvic LND and *ex tempore* histopathology
8. If *ex tempore* histopathology is positive, PALND without SH, RH, or radical trachelectomy
9. Cancellation of the procedure, or its modification should follow after intraoperative up-standing
10. In case of debulking, LND and clip demarcation of the highest cranially positioned positive LN, not RH l
11. In planned irradiation, ovariopexy (29) with clip marking, or bilateral adnexectomy, depending on menstrual status
12. In cervical adenocarcinoma >4 cm, check the potentially suspicious ovaries (ovarian cancer often has the same histopathology as cervical adenocarcinoma) (16)

Exception

Microcellular cervical carcinoma: NAChT followed by modified radical surgery and lymphadenectomy

A2. Surgical procedure reporting

Documentation

Patient list should contain the type of procedure, special remarks, type of drainage
OP report: preoperative OP site, surgical procedure description, post OP site
Tumor FIGO stage
Tumor histopathology

Minimally invasive procedures

- Intraoperative staging using conventional, robotically assisted laparoscopy
- Combined vaginal operations + laparoscopy (LARVH, laparoscopically assisted radical vaginal hysterectomy)
- TLH

A3. Fertility sparing treatment (FST)

- Before starting FST, consultation at a fertility center is recommended
- Available for selected patients with stages T1a or T1b with tumor ≤2 cm in the largest diameter
- The patient should be counselled about the possibility of FST abandonment if there are positive margins or LN involvement, and to be informed regarding oncologic and obstetric risks related to this type of management
- Conization and simple trachelectomy are appropriate fertility sparing procedures for stages T1a1 and T1a2, LN-negative, LVSI-negative patients
- FST should not be recommended for rare histologic subtypes of cervical cancer including neuroendocrine carcinomas, microcellular cancer, adenocarcinomas with minimal deviation (malignant adenoma) and non-HPV-related adenocarcinomas, which tend to exhibit aggressive behavior
- Negative PLN status is a precondition for any FST. Therefore, PLN (SLN) staging should always be the first step in each FST procedure
- Radical trachelectomy (type A) can be considered for stages T1a1 and T1a2, LN-negative, LVSI positive
- Radical trachelectomy (type B) should be performed in patients with cervical cancer stage T1b1 ≤2 cm in the largest diameter, LN-negative, LVSI±
- Intraoperative placement of permanent cerclage should be performed during simple or radical trachelectomy
- Therapy without fertility preservation in patients with neuroendocrine tumors or in extended surgical procedures (i.e. adnexectomies, para-aortic LN dissections (type Q/M 2-4), partial colpectomy, inguinal/supraclavicular LN dissections, and kidney and bowel derivation surgical procedures)
- Any pregnancy following FST should be considered as a high-risk pregnancy, and delivery should be performed in a perinatal center. Following simple or radical trachelectomy with its inherent

placement of a permanent cerclage, delivery can be performed only by cesarean section
- Routine hysterectomy after finishing fertility plans is not necessary (20)

B) Non-surgical treatment

B1. Primary radiochemotherapy (RChT)

Radiochemotherapy is used in the treatment of LACC for bulky tumors from stages FIGO IB2 to IVA. FIGO III stage is always an indication for primary RChT. In alternation to surgery, it can be used in FIGO IIB-IV A and every N1, and as primary or postoperative treatment for FIGO IB2 and IIA stage patients with risk factors. In patients with stage FIGO IA, FIGO IB1 RChT can be applied if there are contraindications for surgery (10,30,31). After an indication has been established, the next step is to make a plan with irradiation therapist.

Principles of radiotherapy (RT)

EBRT before surgery to reduce tumor volume, NART after surgery to destroy the metastases ART. EBRT, radioactive source out of the body, 80-100 cm away, exposure to 1.6-2 Gy daily/5X weekly, in combination with cisplatin standard RChT/6-7 weeks, ART.

BRT, intracavitary therapy, uterine cavity and vaginal fornices, afterloading LDR (low dose rate) 2 Gy/h; MDR 2-12 Gy/h; HDR >12 Gy/h. The goal is to deliver 80-85 Gy to point A in 6-8 weeks (32).Technical advances in imaging/RT planning have facilitated precision in BRT and enabled dose escalation with reduction of toxicity to the surrounding normal tissue (bladder, rectum, vagina, GIT) (24).

Definitive RChT and brachytherapy (BRT) consist of concomitant pelvic platinum based chemoradiotherapy and brachytherapy or pelvic external beam RT (EBRT) alone and BRT. Overall treatment time for definitive treatment should not exceed 7 to 8 weeks, while it is estimated that every day of extension lowers disease control by 0.5% to 1% (19).

Procedure:
1. if possible, once a week RChT with cisplatin
2. combination of percutaneous (EBRT) and BRT (HDR, afterloading), followed by two cycles of cisplatin/gemcitabine (33)
3. the curative therapeutic approach without BRT is impossible (the necessary cumulative dose on the tumor cannot be reached)
   Stereotactic procedures are not adequate substitutes
   Total duration of therapy should not exceed 8 weeks

Exceptions:
1. Primary combined irradiation only in selected cases with contraindications to cisplatin application
2. In patients with inability to probe cervical canal (extremely rare), only percutaneous irradiation with adequate boost (final decision is reached on examination after application of 50% of external radiotherapy)

B2. Neoadjuvant chemotherapy (NAChT):
- Reduces the primary tumor size allowing operability
- Eradicates micrometastases
- Increases tumor vascularization and diminishes the number of hypoxic cells
- Followed by radical surgery
- Decreases mortality rate by about 35% (10)
- NAChT + radical surgery proven better than RChT alone (34)
- Reduces the need for ART after radical surgery
- FIGO stage IB2 and II B, if radiotherapy is impossible, in pregnancy wish, or fertility-sparing surgical procedure

Procedure:
1. Perform pelvic MRI, abdominal CT scan/thoracic x-ray with the upper aperture before therapeutic plan
2. In positive LNs on preoperative radiologic staging, laparoscopic staging:
   - LNs negative, NAChT
   - LNs positive, R(Ch)T
3. Clinical control of therapeutic effect before every cycle
4. 2-4 cycles of carboplatin/paclitaxel weekly
5. In limited general health condition alternative TC weekly
6. In progression under NAChT-RChT or irradiation

B3. Adjuvant radiochemotherapy (ARChT) (35,36):
- Presence of one high-risk factor
- Affection of lymph nodes
- Affection of parametria
- *Non in sano* – resection
- Adequate lymphadenectomy has not been performed
- Presence of three or more intermediary risk factors
- Lymphangiosis carcinomatosa
- Hemangiosis carcinomatosa
- Tumor greater than 4 cm in diameter
- Stromal invasion deeper than 2/3
- Presence of one or two risk factors except for G3: individual evaluation (16)

Performance

- If possible as RChT with cisplatin weekly

Exceptions:

- Only radiotherapy in cisplatin contraindications
- Radiation after neoadjuvant therapy
- Special cases

Management of cervical carcinoma – detailed clinical guidelines

Overall management of cervical cancer is graphically presented in Figures 2 and 3.

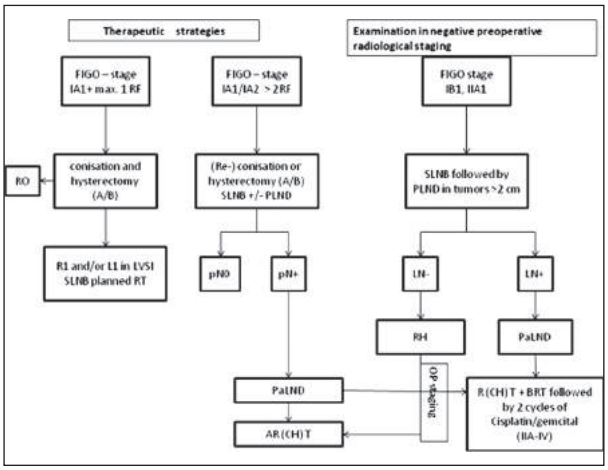

Fig. 2. *Treatment algorithm for cervical cancer.*

RO – negative surgical margins; R1 – positive surgical margins; L1 – positive LVSI; pNO – no nodal metastasis in histopathology report: pN+ – nodal metastasis present; A/B – A and B type of RH according to Querleu-Morrow classification

1) Management of stage T1a (T1a1 and T1a2)

Diagnosis of T1a cancer is reached through examination of the specimen obtained by conization by an expert pathologist. The report must contain accurate measures of horizontal spread and depth of invasion, as well as status of surgical margins. Special stress should be put on the reliable status of the lymphovascular space invasion (LVSI), which is the main predictor of local recurrence and growth of distant metastases after surgical treatment for early-stage cervical cancer (37). LVSI is defined as the presence of malignant cells within small lymphatics and small vascular spaces (blood vessels). Metastatic ability of cervical carcinoma is associated with the lymphovascular spread. During invasion of the interstitium, tumor cells exfoliate into the vascular system and form tumor thrombi. The deeper the stromal infiltration, the more LVSI will appear. Tumor thrombi spread to various tissues and organs of the body causing metastatic growth. When tumor differentiation is worse, the rate of cancer malignancy is higher and LVSI is more likely to occur (38).

Conization is the main diagnostic and therapeutic procedure. CKC is preferred by the pathologists due to clear surgical margins, without thermal artifacts. Loop or laser conization is preferable to CKC in women desiring fertility preservation (39). Surgical margins of the cone specimen should be clear of both invasive and preinvasive disease. Intraoperative staining of the cervix with Lugol solution may be helpful (40).

The management of T1a1 stage depends on age, desire for fertility preservation, and LVSI status. In case

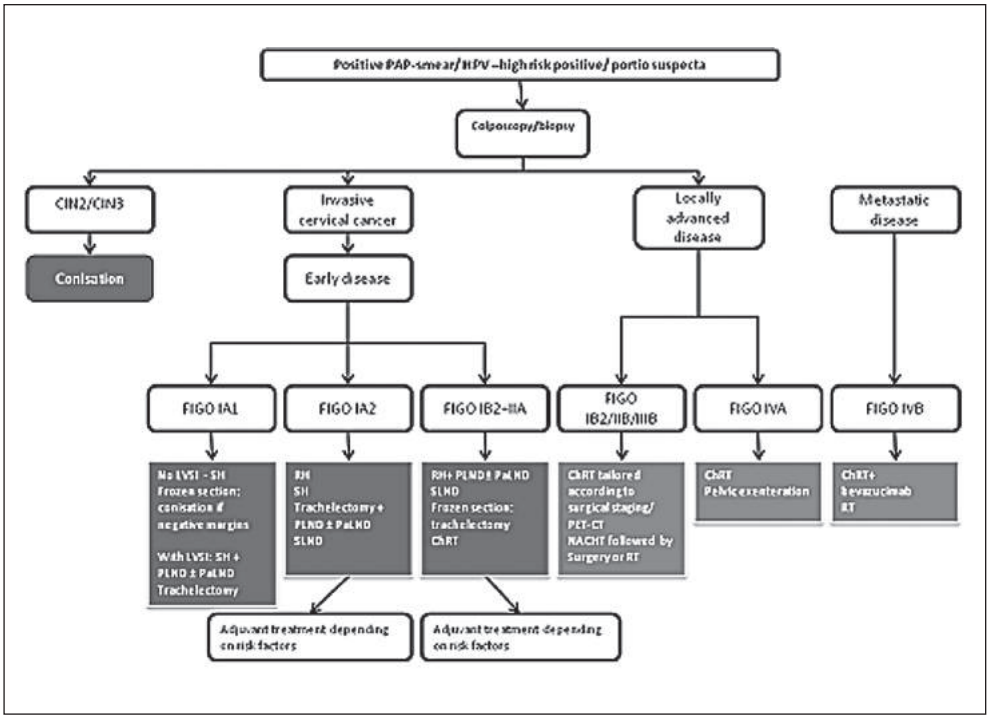

Fig. 3. *Treatment algorithm for cervical cancer (modified according to Marth C, Landoni F, Mahner S, McCormack M, Gonzalez-Martin A, Colombo N; ESMO Guidelines Committee. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(Suppl_4):iv72-iv83. doi: 10.1093/annonc/mdx220. Erratum in: Ann Oncol. 2018 Oct 1;29(Suppl 4):iv262).*

of positive margins (except for preinvasive disease in ectocervix), repeat conization should be performed to rule out more extensive invasive disease. In LVSI-negative patients LN staging is not indicated, but it can be considered in T1a1 LVSI positive patients. SLN biopsy (without additional PLN dissection) is an acceptable method of LN staging. There is no need for simple or radical hysterectomy or parametrectomy because they do not improve the outcome, and represent overtreatment for patients with T1a1 disease. The management of stage T1a2 disease is similar, i.e. conization or simple hysterectomy is an appropriate treatment option. There is no need for parametrial resection. LN staging is positioned one step higher than in T1a1 stage; it may be considered in LVSI-negative patients but should always be performed in LVSI-positive patients. SLN biopsy alone (without additional PLN dissection) seems to be an acceptable method of LN staging (20).

2) Management of T1b1/T2a1 stages

Therapeutic strategy mainly depends on radiological staging. Patients with negative lymph nodes on preoperative radiological staging are preferably treated by radical surgery. At this stage, good patient selection is of utmost importance. It is generally recommended to avoid combination of radical surgery and RT because of the highest morbidity after combined treatment. If surgical option is elected, minimally invasive approach is favored. The procedure begins with LN staging in the form of systematic PLND. SN biopsy before pelvic lymphadenectomy is preferable using demarcation with blue dye with radiocolloid or (better) indocyanine green dye (41). Intraoperative LN frozen section assessment should be performed, i.e. bilateral pelvic SNs and all suspicious LNs. If intraoperative LN assessment reveals no positive LNs, the procedure continues with PLND (removal of lymphatic tissue from the regions with the most frequent occurrence of positive LNs including obturator fossa, external iliac regions, common iliac regions bilaterally, and presacral region). Distal external iliac LNs (circumflex iliac LNs) should be spared if they are not macroscopically suspicious (42). Subsequent radicality of surgical procedure is guided by preoperative assessment of the potential risk factors. Tumor size, maximum stromal invasion, and LVSI divide patients into high-, intermediate- and low-risk category of treatment failure. The 2017 modification of the Querleu-Morrow classification presents the extent of parametrial resection recommended for different risk combinations. Ovarian preservation with bilateral salpingectomy should be offered to premenopausal patients with squamous cell carcinoma and HPV-related adenocarcinoma (43) (Table 6). Adjuvant RT should be considered in the presence of a combination of risk factors at final pathology, such as tumor size, LVSI, and depth of stromal invasion. After primary radical surgery, ARChT is indicated in patients with metastatic involvement of PLNs, parametrial involvement, and patients with positive surgical margins (vagina/parametria) in whom BRT boost may be considered (44).

If intraoperative LN assessment reveals positive LNs (including macrometastases or micrometastases), further PLND and radical hysterectomy should be avoided. Patients should be referred for definitive RChT. PALND, at least up to the inferior mesenteric artery, may be considered for staging purposes. If the risk factors are known at diagnosis and mandate adjuvant therapy, surgical treatment may be abandoned and the patient treated solely with RChT and BRT. PLN dissection should be avoided. PALN dissection, at least up to the inferior mesenteric artery, may be considered in patients with negative PALN on imaging. NAChT followed by surgery is not recommended (20). Patients with positive lymph nodes on preoperative radiological staging are preferably treated by definitive RChT. As above, PALN dissection, at least up to the inferior mesenteric artery, may be considered in patients with negative PALN on imaging. Debulking of suspicious PLNs may be considered (20).

3) Management of locally advanced cervical cancer (LACC)

Stage T1b2/T2a2

Generally, patients with negative lymph nodes on radiological staging should be treated with definitive platinum-based RChT and BRT. The main goal is to avoid the combination of radical surgery and postoperative EBRT as this combination does not improve survival and leads to serious morbidity. PALN dissection prior to RT can be considered. PLN dissection is of no value (45). In selected patients with low-risk status, radical surgery (type C2) may be an alternative option. The principle is the same as above, i.e. if intraoperative assessment of LNs reveals no positive LNs, the procedure continues with systematic dissection of PNS and radical hysterectomy, but if it does, surgery is abandoned and treatment switched to platinum-based RChT and BRT. Patients with positive lymph nodes on radiological staging should be treated with definitive platinum-based RChT and BRT. An additional radiation boost to the involved LNs should be applied. PALN dissection, at least up to the inferior mesenteric artery, may be considered before treatment for staging purposes in patients with negative PALN on imaging. Debulking of suspicious PLNs may be considered (20).

Stage T2b, T3a/b, T4a

Therapeutic strategy is the same as for patients with T1b2/T2a2 stage with positive lymph nodes on radio-

logical staging. Pelvic exenteration is an option in selected cases with stage T4 N0 M0 disease (46).

4) Distant metastatic disease at presentation – 4b stage

Patients with widespread distant metastatic disease at presentation (visceral +/- nodal)

- Confirm the histologic stage FIGO IVB, and then
- Primary ChT- cisplatin-paclitaxel or cisplatin-topotecan or platin mono in contraindications to platin-combinations
- Addition of bevacizumab to standard chemotherapy is recommended in patients with good performance status and where the risk of significant gastrointestinal/genitourinary toxicity has been carefully assessed and discussed with the patient; if no contraindication: cisplatin-paclitaxel or topotecan-paclitaxel in combination with bevacizumab (cave! risk of fistulization 8%) (47)

In response to distant metastases (partial remission, complete remission)

- local operative sanitation, or
- local therapy with RChT of the pelvis, or
- local therapy of singular or local distant metastases
- patients with supraclavicular LN as the only site of distant disease can be considered for RChT with curative intent. Treatment algorithm may include additional ChT
- AChT may be considered in cases carrying a high risk of recurrence such as positive margins, positive LN, or LVSI-positive tumors
- oligometastatic disease with only nodal metastasis in PLN, PALN – high dose RT- long term disease control with prolonged progression free interval

If distant metastases ***do not respond***

- second line/supportive therapy – individually-adapting palliative therapy
- derivation of the urine/stool (fistulas)
- modified radiation/BRT (bleeding)

5) Local recurrence

Treatment of recurrent disease with curative intent requires referring patients with recurrence for treatment to highly specialized units. Patients with multiple nodal/distant metastases or multifocal local disease with extensive pelvic wall involvement are usually not considered as candidates for curative treatment. The prognostic factors should be carefully evaluated and balanced in relation to major morbidity caused by the treatment. Patient should be carefully counseled regarding not only treatment options but also the involved risks and consequences. A full diagnostic package consisting of relevant imaging is recommended to establish the status of the disease locally, regionally, and systemically. RChT in curative dosage is the treatment of choice if the patient was not previously irradiated:

- In central pelvic recurrence after primary surgery – definitive RChT combined with image guided adaptive BRT is the treatment of choice
- For BRT, small superficial lesions (<5-mm thickness) in the vagina may be treated using a vaginal cylinder, ovoids, or mold, whereas other lesions usually require combined intracavitary-interstitial techniques
- In pelvic sidewall recurrence, after primary surgery definitive RChT is the preferred option. Definitive RT or RChT followed by stereotactic ablative boost/image guided interstitial BRT/ particle beam therapy is an emerging option
- In central pelvic or pelvic sidewall recurrence, after RT or RChT pelvic exenteration is recommended if there is no involvement of the pelvic sidewall and extrapelvic nodes
- Laterally extended endopelvic resection may be considered for a recurrence that extends close to or involves the pelvic sidewall
- Alternatively, in patients unfit for or refusing exenteration surgery reirradiation with image guided adaptive BRT for central recurrences
- In nodal and oligometastatic recurrences (localized para-aortic, mediastinal, and/or periclavicular recurrences above the previously irradiated fields) may be treated by radical EBRT, if possible, in combination with concomitant chemotherapy. It is recommended to electively irradiate the immediate regional nodal stations below and upstream

Indications for surgical procedure in selected cases:

- Presumptions: good general health, patient's wish
- Depends on localization and previous therapies
- After exclusion of distant metastases
- Exenteration procedures or extended resection of the pelvic wall
- Cooperation with radiotherapist to insert the applicator for brachytherapy (20)

When the surgery or irradiation are not the option:

- Complex ChT regimens
- Cisplatin/carboplatin-paclitaxel or topotecan-paclitaxel in combination with bevacizumab
- Addition of bevacizumab prevents tumor angiogenesis (blocks EVGF) but causes rise in hypertension, DVT risk and fistulization (48)

Recurrence out of the pelvis/distant metastases

- If there was no platin therapy, cisplatin, paclitaxel or topotecan-paclitaxel + bevacizumab or cisplatin-topotecan
- After cisplatin therapy, if there are no contraindication: cis- or carboplatin-paclitaxel or topotecan-paclitaxel in combination with bevacizumab
  - monotherapy (topotecan, paclitaxel, vinorelbin, ifosfamide)
  - pembrolizumab

Individual adaptative palliative treatment

- Palliative ChT – classic monotherapy cisplatin 50 mg/m^2 every 3 weeks/low response rate
  - cisplatin based doublets/cisplatin + topotecan or paclitaxel
  - TIP/paclitaxel-ifosfamide-cisplatin/acceptable toxicity
- urine/stool derivation procedures (fistulas)
- modified irradiation/brachytherapy (bleeding)
- pain therapy

6) Invasive cervical cancer in pregnancy (CCIP)

The main principle: multidisciplinary approach (obstetrics, neonatology, radiotherapy, psycho-oncology, pelvic care nurse). Primary aims of recommended treatment plan are oncologic safety of the pregnant woman, as well as survival without additional morbidity of the fetus. Preferred imaging modalities for clinical staging in patients with CCIP include MRI or expert ultrasound. Because of limited experience and inherent radioactivity, PET-CT (PET-MRI) should be indicated only under very selected circumstances (20).

Tumor involvement of suspicious nodes should be verified histologically because of its prognostic significance and the impact on the management up to 24th week of gestation (fetal viability), preferably by minimally invasive approach. Factors important for decision: gestational age, tumor stage, histopathology, family planning wish of the patient (49). The issue of pregnancy termination does not depend on tumor characteristics, but on patient preferences after thorough counseling. Depending on tumor stage and gestational week, the following treatment options have to be discussed with the patient including risks and benefits of individual approaches:

- Adapted surgery including removal of the tumor: conization, trachelectomy, and LN staging according to the stage of the disease with the intent to preserve pregnancy.
- Radical surgery or definitive RChT as recommended for the stage of the disease without preservation of pregnancy, with or without previous pregnancy termination.
- Delay of oncologic treatment until fetal maturity (if possible >32 weeks of gestation) and beginning of cancer-specific treatment immediately after delivery by cesarean section.
- ChT until fetal maturity and beginning of cancer specific treatment immediately after delivery by cesarean section. Treatment after delivery must consider application of previous ChT. In patients with locally advanced stage or with residual tumor after conization that cannot be completely excised (risk of premature rupture of membranes (PROM) and/or cervical insufficiency), platinum-based chemotherapy can be considered starting at 14 weeks of gestation at the earliest.
- Spontaneous delivery seems to have negative prognostic impact in patients with CCIP. Thus, cesarean section after 32nd week of gestation (if possible) is the recommended mode of delivery. At the time of or following cesarean section, definitive stage-adjusted oncologic therapy has to be performed corresponding to that of nonpregnant women, taking into account therapy that has already been administered during pregnancy (20).

7) Follow-up

- Primary goals of follow-up in patients with cervical cancer are early detection of recurrent disease and patient education and support (50).
- Follow-up intervals of 3 to 4 months for the first 2 years and then 6 to 12 months for up to 5 years are recommended.
- At each visit, patient general condition, appearance of new symptoms or late treatment side effects should be evaluated, together with physical examination. Patient should be educated or referred to appropriate expert for counseling and treatment.
- Imaging and laboratory tests should be performed based on symptoms or findings suggestive of recurrence or morbidity. In symptomatic women, MRI or CT should be considered to assess the potential clinical recurrence; PET-CT can be added if necessary. Pathologic confirmation of any persistent or recurrent tumor should be considered.
- Following FST, all women remain at risk of tumor recurrence and must be carefully followed up. Follow-up should include HPV testing (with or without cytology). Colposcopy in combination with HPV testing in parallel performed by an experienced colposcopist is an option. The incorporation of high-risk HPV testing at 6, 12, and 24 months after treatment is advocated. If HPV testing is negative, then every 3 to 5 years as long as the follow-up is indicated.

- Follow-up after definitive RChT should use the same imaging method for evaluation of tumor response as was used at baseline. Imaging should be performed not earlier than 3 months following completion of treatment. In dubious cases, re-evaluation should be performed not before 8 weeks thereafter. For re-evaluation purposes, the optimal diagnostic workup for local extent is pelvic MRI, and for distant spread, it is chest/abdomen CT or PET-CT. Cytology is not recommended in these patients.
- Providers should inform and educate patients about sexual and vaginal health because vaginal stenosis and dryness may occur. Vaginal dilation should be offered, as well as vaginal lubricants and local estrogen (20,51).

CONCLUSION

Cervical cancer presents today as a preventable and easily detectable disease in the societies which encourage vaccination and public early-stage screening programs. However, when diagnosed, the disease mandates expert treatment and follow-up according to updated clinical guidelines. The best results are achieved in specialized departments where patients are managed by multidisciplinary teams in close cooperation of different specialties.

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SAŽETAK

DIJAGNOSTIKA I LIJEČENJE RAKA VRATA MATERNICE

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Rak vrata maternice drugi je najčešći oblik raka među ženama iz nerazvijenih zemalja. Diljem svijeta od njega svake godine oboli oko pola milijuna, a od njega umre četvrt milijuna žena. Hrvatska se prema epidemiološkim parametrima povezanima s rakom cerviksa nalazi u sredini europske ljestvice, što je u skladu sa slojevitom strukturom hrvatskog društva. Važan parametar je slab odaziv žena u Hrvatskoj na nacionalne preventivne programe i mjere ranog otkrivanja ovog raka. Iako tradicionalni preventivni programi u Hrvatskoj u pravilu nude dobar temelj za otkrivanje i liječenje preinvazivnih i ranih stadija raka vrata maternice, potrebno ih je osuvremenjivati i dopunjavati novim saznanjima u skladu s aktualnim svjetskim smjernicama. Poseban je zadatak iznalaženje odgovarajućih mjera za motivaciju žena na korištenje nacionalnih preventivnih mjera i rane dijagnostike, što bi trebalo intenzivno promovirati u svim segmentima društvenog života. Cilj ovog pregleda je usporedba domaćih i aktualnih inozemnih smjernica za dijagnostiku i liječenje raka vrata maternice te prezentacija homogeniziranog stava i prijedloga modernog pristupa liječenju ove bolesti.

Ključne riječi: **rak vrata maternice, smjernice, cerviks, kirurgija, kemoterapija, radioterapija**

FETALNI KARDIOLOŠKI PROBIR U ZAŠTITI PERINATALNOG MORTALITETA I MORBIDITETA - NOVA, VRLO VAŽNA ULOGA FETALNE EHOKARDIOGRAFIJE U PORODNIŠTVU I PEDIJATRIJSKOJ KARDIOLOGIJI

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Cilj: Osnovni je cilj ovog pregleda istaknuti vrijednost fetalnog kardiološkog probira (FKP) u zaštiti perinatalnog morbiditeta i mortaliteta uzevši u obzir suvremene dijagnostičke i terapijske mogućnosti i nova znanstvena otkrića. Istaknute su indikacije za FKP prema stupnju rizika, kako tablično tako i u opsežnoj raspravi koja uvažava timski rad i interpretira nalaz uzimanjem u obzir klasičnih smjernica stručnih društava (engl. *Classical of recommendations* - COR) i rasprave o bolesniku zasnovane na dokazima (engl. *Level of evidence* - LOE). ***Metode i rezultati*** izvedeni su proučavanjem smjernica stručnih društava za fetalnu pedijatrijsku kardiologiju: *American Heart Association* – AHA, *Asociation of European Pediatric Cardiology* – AEPC), *International Society of Ultrasound in Obstetrics and Ginecology* – ISOUG) te druge opsežne novije literature. Ističu se interesi fetalne kardiološke medicine uključujući dijagnozu prirođenih srčanih bolesti i aritmija, procjenu funkcije fetalnog kardiovaskularnog sustava (KVS) i raspoložive metode intrauterinog liječenja, kao i moguću potrebu neposredne ili vrlo rane intervencije nakon porođaja. Opsežnom raspravom uz brojne literaturne citate i tabličnim prikazom istaknute su referalne indikacije za FKP, čimbenici koji povećavaju rizik od prirođenih srčanih grješaka (PSG) i drugih srčanih bolesti (aritmije i kardiomiopatije) te populacijski pregled ekstrakardijalnih anomalija (EKA) koje imaju visok posljedični rizik za pridruženu srčanu bolest. Tekstu je uz tablice priloženo nekoliko važnih crteža ili ehokardiografskih prikaza koji na svoj način prožimaju zajedničke nalaze opstetričara i pedijatrijskog kardiologa-fetologa. Na kraju su istaknuta istraživanja koja dokazuju kako primjena i uvažavanje fetalnog kardiološkog probira pozitivno utječe na smanjenje perinatalnog morbiditeta i mortaliteta, posebno na primjeru složenih PSG. ***Zaključak:*** U posljednjih 20 godina fetalna kardiološka medicina je tako uznapredovala u dijagnostičkom i terapijskom smislu da značajno utječe na ukupni perinatalni morbiditet i mortalitet, osobito stoga što su PSG najčešće kongenitalne anomalije. Precizna kardiološka fetalna dijagnostika, sve brojniji terapijski pristupi u fetalno srce, kako medikamentni tako i intervencijski te dinamičan razvoj novih tehnologija doveli su fetalnu kardiološku medicinu do razine bez koje se više ne može zamisliti suvremena medicina u jednoj zemlji.

Ključne riječi: kardiologija, pedijatrija, fetus, fetalna ehokardiografija, prirođene srčane bolesti, perinatalni morbiditet i mortalitet

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UVOD

Istraživanje fetalnog srca i cijelog kardiovaskularnog sustava doživljava svoj procvat u posljednja dva desetljeća ponajprije zbog napretka tehnologije slikovnih metoda. Prije se dijagnoza postavljala s određenom vjerojatnošću, ali bez prepoznatljivih detalja, a nisu postojale ni intrauterine mogućnosti liječenja. Zbog toga su opstetričari smatrali trudnoću u kojoj se naslućivala srčana bolest intrauterino rizičnom, a eventualni postporođajni problemi ovisili su o snalažljivosti neonatologa kojem se obraćalo za djecu sa sumnjom na srčanu bolest. S najnovijim spoznajama o morfologiji, etiologiji, etiopatogenezi i genetici srčanih bolesti u djece, razvoju intervencijske kardiologije i rane kardijalne kirurgije, odličnog postnatalnog zbrinjavanja te otvaranja mogućnosti prenatalne terapije na više razina, današnje stanje u fetalnoj kardiologiji je od primarnog značenja za poboljšanje perinatalnog mortaliteta i morbiditeta. Uz spomenute teorijske i praktične čimbenike ovdje je od presudnog značenja razvoj sofisticiranih tehnoloških mogućnosti u prenatalnoj dijagnostici patologije fetalnoga srca. Dodamo li tome veliki napredak u ritmologiji i liječenju fetalne srčane disfunkcije i mogućnosti prenatalne medikamentne i intervencijske terapije, fetalna je kardiologija postala dio svakodnevice bez koje se suvremena pedijatrija ne može više zamisliti. Ovaj tekst pišemo s namjerom da se osvijesti ovaj važan problem koji se naziva fetalna medicina u kardiologiji, a uključuje dijagnozu srčanih bolesti, ocjenu srčane i cjelokupne kardiovaskularne funkcije te raspoložive terapijske mogućnosti. Detaljan opis fetalnog ehokardiograma uključuje opis srčane anatomije te procjenu funkcije i ritma. S daljnjim tehnološkim napretkom kao što su fetalna magnetska rezonancija (fMRI), fetalna elektrokardiografija i fetalna magnetokardiografija (fMCG) moguće je i detaljno dijagnosticiranje srčanih aritmija M-prikazom i doplerskom analizom. Nameću se i drugi dijagnostički i terapijski problemi kao što su feto-fetalna transfuzija, problem jednojajčanih dvojaka i višeplodne trudnoće, plućnih masa, vaskularnih tumora, hijatalne hernije. Sve spomenuto utječe na pripremu za porođaj, daljnje neonatološko zbrinjavanje, transport i druge čimbenike koji značajno utječu na perinatalni mortalitet i morbiditet. U literaturnom smo se pregledu služili smjernicama stručnih društava, u prvom redu AHA, FWG/AEPC, ISUOG, ali i drugih. U prikazu na prvom mjestu ističemo potrebu uvažavanja dogovorenih smjernica na visokoj razini i nasušnu potrebu rasprave o pacijentu uz uvažavanje vidljivih argumenata. Kako se ova načela provlače čitavim prikazom, započinjemo s tabličnim prikazom klasifikacije i preporuka na osnovi principa COR i LOE (tablica 1).

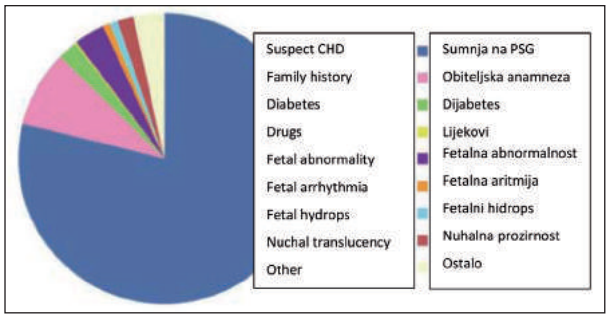
Tablica 1.
Klasifikacijske smjernice i preporuka na osnovi stupnja dokazivosti.

Razina preporuke na osnovi suglasnosti o dokazivosti bolesti	
Razina preporuke	**Definicija**
I	Dokaz i/ili opća suglasnost da je primijenjena terapija ili dijagnostički postupak blagotvoran, koristan i djelotvoran
II	Sporni dokaz i/ili različitost u mišljenju o blagotvornosti/ djelotvornosti date terapije ili postupka
II a	Sporan dokaz/mišljenje idu u korist blagotvornosti/djelotvornosti
II b	Blagotvornost/djelotvornost su slabije etablirani od dokazivosti/mišljenja
III	Dokaz i opća suglasnost da primijenjena terapija ili postupak nisu korisni/djelotvorni, a u nekim slučajevima mogu biti i štetni
Supanj dokazivosti bolesti prema raspoloživim metodama dokazivanja	
Stupanj dokazivosti	**Raspoloživa metoda dokazivanja**
A	Podatci izvedeni iz multicentričnih, randomiziranih kliničkih studija ili metaanaliza
B	Podatci izvedeni iz pojedinačnih randomiziranih kliničkih studija ili velikih nerandomiziranih studija
C	Suglasje u mišljenju od eksperata i/ili malih studija, retrospektivnih studija, registara i kliničkog iskustva

Referalne indikacije za fetalni kardiološki pregled

Incidencija PSG procjenjuje se na 6-12 promila prema različitim studijama (1-4) uključujući i hrvatske epidemiološke studije prema kojima je incidencija 7,8 i 8 promila (5,6). S obzirom na 30-godišnja izvješća iz recentne literature (od 1985. do 2015.) podatci su vrlo vjerodostojni. No, jedna belgijska studija (7) pokazuje značajno veću incidenciju PSG kod živorođene ili mrtvorođene djece gestacijske dobi do 26 tjedana, bez kromosomnih anomalija. Ocjena incidencije u ranoj gestacijskoj dobi remećena je ipak spontanim i elektivnim (svjesnim) prekidima trudnoće, pa je egzaktne vrijednosti teško utvrditi. Mnogobrojni čimbenici povećavaju rizik od pojave PSG-a, neovisno jesu li obiteljske, majčinske ili fetalne etiopatogeneze. Nema

sumnje da je vodeća indikacija za fetalni kardiološki pregled upravo sumnja opstetričara na strukturnu srčanu grješku i ona iznosi > 50 % indikacija, što je osobito dobro prikazano u velikoj epidemiološkoj Evelin studiji G. Saarland (8) (sl. 1), a nešto manje od 40 % indikacija bilježimo u vlastitom istraživanju kod hrvatskih opstetričara (9).



Sl. 1. *Razlozi za pregled fetalnom ehokardiografijom na zahtjev opstetričara za 4 000 dijagnosticiranih PSG u Evelin studiji između 1980-2010. godine (8)*

Druga indikacija po redu su majčine metaboličke bolesti jer nose rizik od pojave PSG od 5 do 10 %. Opće je pravilo u svijetu da se indikacija za FKP stječe ako je prisutan čimbenik s rizikom većim od 2 %. Ako je rizik od pojave srčane bolesti manji od 1 %, fetalna ehokardiografija (FE) nije potrebna, što je i logično, jer ulazimo u razinu kontinuirano očekivane incidencije. Neophodno je naglasiti da se FE očekuje od educiranog fetalnog kardiologa prema smjernicama krovnih stručnih društava (npr., FWG/AEPC, 2006). Ovdje navodimo stanja s ocjenom rizika pojavnosti fetalne srčane bolesti koje prihvaća većina priznatih stručnih društava pa se nazivaju klasičnim preporukama (engl. *Classical of recommendations* - COR).To se primjerice odnosi na preporuke AHA i FWG/AEPC (10,11). Sve su preporuke navedene na osnovi argumentiranih preporuka stručnih društava (COR) i rasprave o pacijentu (LOE). Način ocjenjivanja sustava LOE prikazan je u tablici 1, a isti se model danas u suvremenom timskom radu koristi i u većini drugih stručnih društava. Stoga ovdje i navodimo referalne indikacije sa stupnjem rizika većim od 2 %, tako da je uz spomenuto stanje u zagradi naveden stupanj rizika izražen u postotcima, a u drugoj se zagradi nalaze navodi iz literature. U daljnjem su tekstu opisana ta stanja s opširnijim osvrtom na pojedine indikacije (tablica 2).

Tablica 2.
Čimbenici koji povećavaju rizik od PSG (navedeni su samo oni s rizikom većim od 2 %)

Stanje	Apsolutni rizik (%)	COR/LOE	Vrijeme/učestalost pregleda	Komentar
MATERIJALNI ČIMBENICI				
- **pregestacijski dijabetes**; prekoncepcijski ili utvrđen u prvom tromjesečju[61-64]	3-5	I/A	18-22 gestacijski tjedan (gt,) ponoviti u 3. trimestru (tr.)	DM - visok stupanj rizika za heterotaksiju (6.22), TAC (4,72), TGA (2,85), SV (18,24). Nekontrolirani DM-hipertrofija. stijenki LV (3.tr.)
- **fenilketonurija**[12,13,65]	12-14	I/A	18-22 gt.	Samo ako je prekoncepcijska razina fenilalanina > 10 mg/dL
- **SLE i SS** s poz. anti - SSA/SSB protutijelima. (> rizik kod hipotireoze ili manjka vit .D, a kod prethodne trudnoće CHB ili NLE [14-20, 66-69]	1-5 11-19	IIa/B I/B	<15 tj., jednom tjedno do 28. gt. <15.gt, do 28. gt. Svaki tjedan	antiSSA>50/U/mL predstavlja veći rizik. Pregled u 3. trimestru zbog mogućnosti fibroelastoze lijeve klijetke (restrikcijska kardiomiopatija)
IZLOŽENOST LIJEKOVIMA				
- ACEi[22]	2,9	IIa/B	18-22 gt.	
- Retinoična kiselina[21,76,77]	8-20	I/B	18-22 gt.	
- NSAIDs[23-25,59,86] - manjak folne kiseline[78-80,86] - paroksiten[73]	1-2 za PSG 5-50 % za duktalnu konstrikciju 3,3	IIb/B prvi tr. I/A Treći tr. /	18-22 gt. Od trenutka davanja NSAIDa Dnevni pregled /	 Preporuka za ukidanje NSAIDa /
MATERNALNE INFEKCIJE[87,88,89]	1-2	I/A rubeola III/C drugi virusi	17-22 gt.	Samo rubela je rizična za PSG. Virusi: parvo, *coxsackie*, adeno i *cytomegalo* - fetalni miokarditis
REPRODUKTIVNE TEHNOLOGIJE[56-58, 89]	1,1-3,3	IIa/A	18-22 gt.	Isti rizik za IVF i ICSI
OBITELJSKA ANAMNEZA				

- Majčine strukturne srčane bolesti [29-31, 59, 90-92]	3–7 (za sve) 10–14AVSD 13–18 (AS) <3TOF,TGA	I/B	18-22gt.	
- Očeve strukturne srčane bolesti[26-31,, 93, 94]	Oko 2-3	I/B	18-22	Prema nekima 7,5 % (uključeni mali ASD i VSD)
- Blizanci s PSG[55, 110-112]	za sve 3-8 za HLHS 55	I/B	18-22 gt.	Prema nekim autorima veća učestalost
- Srčana bolest ili sindrom s mendelskim tipom nasljeđivanja[59 93]	>50 %	I/C	18-22 gt.	Ima malo prenatalnih podataka jer se odnosi na interrupcije (Marphan, asimetr. HKM, Ehler-Danlos sy.
FETALNI ČIMBENICI				
- Opstetrička sumnja na srčanu bolest[97-100, 105, 106]	>40 %	I/B	Kod sumnje	Ponavljani pregled
POREMEĆAJI RITMA[101, 103] - tahikardija - bradikardija - iregularni ritam	 1 kod PSG 50-55 2 (izolirano)	 I/C I/C IIa/C >1-2tj.	 Kod pojave Kod pojave Od pojave 2 tj.	Uz FKP ocijeniti vrstu aritmije i isključiti PSG ili KMP te pratiti redovito (kod iregularnog ritma najmanje 2 tjedna.
NEKARDIJALNE ANOMALIJE	20-45	I/B	Od otkrića	Ovisno o anomaliji (tbl.4)
KROMOSOMNE ANOMALIJE	>90 %	I/C	18-22 gt.	Vidjeti rizik od EKA (tbl. 4)
POVEĆANA FNP[44-47, 104-109] - 3-3,4 - >3,5 - >6 - >8,5	 3 6 24 >60	 IIa/A I/A I/B I/B	 18-22 12-14 i 18-22	
ANOMALIJA PUPKOVINE PLACENTE I ABD. VENA[49,105]	3,9	IIb/C	18-22 gt.	Značajna sklonost
MONOKORIONSKI BLIZANCI[110-112]	2-10	I/A	12-14 i 18-22, dalje ovisno o nalazu	
HIDROPS FETALIS [54,113]	15-25	I/B	od dijagnoze nadalje	

Legenda: CO – classical of recommendation, LOE – level of evidence, DM – diabetes mellitus, SLE sistemni eritemski lupus, TAC zajednički arterijski trunkus, d-TGA – jednostavna transpozicija velikih krvnih žila, SV-single ventricle, NLE – neonatalni lupusni sindrom, ACEi - inhibitori angiotenzin konvertiajućeg enzima, IVF – in vitro fertilizacija, ICSI – intracitoplazmatska injekcija spermija, HLHS – sindrom hipoplastičnoga lijevog srca, ASD – atrijski septumski defekt, VSD – ventrikulski septumski defekt, HKM – hipetrofična kardiomiopatija, FKP – fetalni kardiološki probir, EKA – ekstrakardijalna anomalija.

Od metaboličkih se bolesti navodi dijabetes melitus (3-5 %) (7-11*)* i fenilketonurija (12-15 %), ako je perikoncepcijska razina fenilalanina > 10 mg/dl (12,13). Od sistemnih bolesti vezivnog tkiva navodi se SLE (sistemni eritemski lupus) i SjS (Sjögrenov sindrom) (1-5 %), a osobito ako je prethodno dijete imalo CCAVB (kompletni kongenitalni AV blok) (11-19 %). Kada je razina anti SSA/SSB protutijela > 50 U/mL moguć je razvoj i restrikcijske kardiomiopatije (KMP) lijeve klijetke u trećem tromjesečju (14-20*)*. Od teratogenih čimbenika navodi se primjena retinoične kiseline (8-20 %) (21)*,* inhibitori angiotenzin konvertirajućeg enzima (ACEi) (2,9 %) (22) i NSAID (nesteroidni antiflogistički lijekovi) u trećem trimestru (5-50 %) zbog prematurnog zatvaranja arterijskog duktusa (23-25*)*. Rizik veći od 2 % su i majčine strukturne srčane bolesti (3-7 %), a posebno je izračunat rizik za AVSD (atrioventrikulski septumski defekt) (10-14 %), AS (aortalna stenoza) (13-18 %), TOF (tetralogija Fallot) i d-TGA (d- transpozicija velikih krvnih žila) (<3 %) (26-29). Poznato je da je manji rizik kod očevih strukturnih srčanih grješaka (ukupno 2-3 %) (30-32*)*. Ako su u obitelji poznate sindromne bolesti s mendelskim nasljeđivanjem uz pridružene strukturne srčane bolesti (hipertrofična KMP, Ehlers-Danlosov sindrom, Marfanov sindrom) rizik iznosi >50 %, iako je većinom riječ o interrupcijama (32). Izrazito visok rizik nalazimo ako opstetričar sumnja na srčanu anomaliju (40-50 %) (8, 9,33) ili ako je riječ o bradikardiji s PSG (50-55 %) (34). Pojava tahikardija i iregularan ritam imaju nizak rizik od PSG (2 %) (35*)*. Znatno veći rizik od PSG ima nalaz nekardijalnih anomalija (20-45 %) (36-41), a osobito kromosomne abnormalnosti (>90 %) (42,43). Rizik od PSG ovisno o veličini fetalne nuhalne prozirnosti (FNP) (engl. *fetal nuchal translucency* - FNT) povećava se kako slijedi i: 3-3,4 mm (3 %), >3,5 mm (6 %), >6 mm (24 %), >8,5 mm (66 %) *(*44-48). Također nalazimo visoki rizik kod abnormalnosti pupkovine, placente i intraabdominalne venske anomalije (39 %) (42,49,50), monokorionskih dvojaka (2-10 %) (51,52) i fetalnog hidropsa (15-25 %) (53,54). Postoje različita izvješća u literaturi o riziku nakon potpomognute oplodnje (1,1-3,5 %) koji je još uvijek predmet istraživanja, ali se čini da nije visok (55-58). Sve ostale, često spominjane indikacije, imaju stupanj rizika manji od 2 % (gestacijski dijabetes melitus - GDM), neki teratoge-

ni kao što je vitamin K, NSAID, maternalne infekcije, tahikardija) pa prema ovim kriterijima nisu indikacija za FKP. Iz ovih se podataka izvode glavne indikacije za FKP prema stupnju rizika, kako je navedeno u tablici 3. Većina kriterija izvedena je do travnja 2014. i objavljena u oglednim časopisima (10,11). Samo godinu dana kasnije objavljeni su argumentirani podatci o drugim važnim negenetičkim čimbenicima s rizikom za srčane bolesti >2 %. Navodi se multigraviditet (2,5 %), prekomjerna tjelesna težina (2 %), stres (2,7 %), hiperkolesterolemija (2,9 %), epilepsija (2,7 %), infekcije gornjeg respiracijskog trakta (5,9 %), genitourinarne infekcije (2,1 %), korištenje bronhodilatatora (2,2 %), kombinacije dehidrofolat reduktaza inhibitora sa sulfonamidima (2,3-3,0 %), beta blokatora (2,6 %), naproksena 3,0 % i kokaina (3,7-9,4 %). Svi su ovi podatci izvedeni iz velikih studija *European surveillance of congenital anomalies* (EUROCAT), *Baltimore-Washington Infant Study* (BWIS), *Atlanta Birth Defects Risk Factors, Shandong Penisula, China* i drugih (59). Slijedi opširniji opis nekih važnijih čimbenika.

Tablica 3.
Referalne indikacije za fetalnu ehokardiografiju

Indikacije s visokim profilom rizika (prema procjeni >2 % - apsolutni rizik)
Maternalni pregestacijski dijabetes melitus
Dijabetes melitus dijagnosticiran u prvom tromjesečju
Maternalna fenilketonurija (nekontrolirana)
Maternalna protutijela (anti-SSA/SSB+)
Maternalni medikamenti (ACE inhibitori, retinoična kiselina, NSAID u trećem tromjesečju)
Maternalne infekcija rubeolom u prvom tromjesečju
Maternalne infekcije sa sumnjom na kardiotropne viruse (miokarditis)
Asistirana reproduktivna tehnologija
PSG u prvom koljenu obitelji (majka, otac ili blizanac s PSG)
Prvo i drugo koljeno prema fetusu s poremećajem mendelskog nasljeđivanja udruženog s PSG
Fetalna srčana abnormalnost sumnjiva na osnovi opstetričkog ultrazvučnog nalaza.
Fetalna ekstrakardijalna abnormalnost sumnjiva na osnovi opstetričkog ultrazvuka
Fetalna kariotipska abnormalnost
Fetalna tahikardija ili bradikardija ili perzistirajući fetalni iregularni srčani ritam
Fetalno povećana nuhalna prozirnost FNP(T) >95 % (≥3 mm)
Monokorinski dvojci
Fetalni hidrops ili izljevi
Indikacije s niskim profilom rizika (procijenjeno >1 % i <2 % apsolutnog rizika))
Maternalne indikacije (antikonvulzivi, litij, vitamin A, SSRIs (samo paroksiten), NSAIDs u prvom/drugom tromjesečju)
PSG u drugom i trećem koljenu prema fetusu
Fetalne abnormalnosti pupkovine ili placente
Fetalne intraabdominalne venske anomalije
Nema indikacija (<1 %)
Maternalni gestacijski dijabetes s HbA_{1c} <6 %
Maternalna medikacija (SSRIs osim paroksitena, antagonisti vitamina K – Coumadin)
Maternalna infekcija drugim virusima osim rubeolom i kardiotropnim virusima
Izolirana PSG u prvom i drugom koljenu u odnosu na fetus

ACEi, inhibitori angiotenzin-konvertirajućeg enzima; PSG, prirođena srčana grješka; HbA_{1c}, hemoglobin HbA_{1c}; NSAID, nesteroidni antiflogistički lijekovi; SSRIs, selektivni inhibitori reapsorpcije serotonina.

MAJČINSKI (MATERNALNI) ČIMBENICI

Diabetes mellitus (DM) je najvažniji majčinski čimbenik s rizikom od 3 do 10 % za pojavu srčane bolesti u fetusu. Smatra se da čak 20 % trudnica u kojih se dijagnosticira GDM ima i pregestacijski DM (PDM) (ili 1 % od svih trudnih žena). To je gotovo peterostruka vrijednost (3-5 %) u usporedbi s očekivanom incidencijom PSG, pa se smatra da je PDM rizik za pojavu heterotaksije (6,22 %), zajedničkog arterijskog debla (TAC) (4,27 %), d-TGA (2,85 %) i SV (engl. *single ventricle*) (18,24 %) (7,9). Neke studije prekoncepcijske glikemije pokazuju evidentno povećanje glikoziliranog hemoglobina (HbA1c) kod 8,5 % trudnoća u prvom tromjesečju, što je udruženo s većim postotkom svih malformacija ako se ne nastavi kontrola glikemije, a ako je ona dobro kontrolirana, rizik se smanjuje kao kod nedijabetičke populacije (7,60, 61,63). Studije u tri različite dijabetičke populacije kod kojih je vrijednost HbA1c bila lagano iznad normalnih vrijednosti pokazale su značajan rizik od pojave srčanih malformacija u 2,5 % do 6,1 % potomaka (60, 61). Shodno tome još je veći rizik ako je HbA1c >8,5 % kod svih majki s PDM. Na osnovi tih podataka FKP bi trebalo učiniti u svih žena s PDM. Čini se da inzulin rezistentni DM ne povećava rizik od PSG u fetusa, pa stoga FE nije indicirana kod tih trudnica. U slučaju loše kontrole PDM i GDM fetus može u kasnijoj gestacijskoj dobi razviti hipertrofiju ventrikula, a stupanj hipertrofije je u korelaciji s visinom glikemije. Fetalni kardiolog je u tom slučaju dužan mjeriti indeks ventrikularne učinkovitosti (Tei indeks) (62). Kod žena s razinom HbA1c <6 % učinak promjena na srcu je minimalan i tada nije indicirana FE. Ipak, ako je razina HbA1c >6 % u trećem trimestru, valja učiniti FE zbog moguće hipertrofije septuma i stražnje stijenke (63). Iako mehanizam nastanka PSG kod žena s GD nije jasan, čini se da su hiperglikemijske krize tijekom embrionalnog razdoblja uzrok srčanih malformacija. Ovo mišljenje potkrijepljeno je spoznajom da je prevelik otklon od naravne ravnoteže svih čimbenika koji sudjeluju u embrionalnom razvoju djeteta logičan razlog poremećaja u morfološkom razvoju organa, pa tako i srca. Ovaj primjer pokazuje da većina egzogenih čimbenika ostavlja posljedice u embrionalnom razvoju srca dok se posljedice nekontroliranog dijabetesa u obliku sekundarnog zadebljanja srčanih stijenki očituju tek u trećem tromjesečju trudnoće pa se mogu smatrati fetopatijom (62-64).

Fenilketonurija: Ako se ne liječi, maternalna fenilketonurija uzrokuje fetalni zastoj u rastu (FZR) (engl. *intrauterine growth retardation/restriction*-IUGR), mikrocefaliju, postnatalni zaostatak u rastu i razvoju, mentalnu retardaciju i PSG kod potomaka (12,62,65). Povišena razina fenilalanina (>15 mg/dl) ima 10-15 puta veću opasnost od razvoja PSG (12,13). Rizik kod

kontroliranih pacijentica je 12 % u odnosu na kontrolnu skupinu, pa je kod tih trudnoća indiciran rani FKP. Kod dobre perikoncepcijske dijetalne kontrole rizik se može smanjiti. U prospektivnoj studiji 576 trudnoća kod žena s fenilketonurijom i 101 žena kontrolne skupine s kriterijem da je fenilalanin < 6 mg/dl prije koncepcije i za vrijeme organogeneze (12), utvrđeno je da FE nije potrebna u žena s dobro kontroliranom fenilketonurijom u prvom tromjesečju pri čemu se očekuje razina fenilalanina u serumu <10 mg/dl.

Autoimune bolesti i pozitivna autoprotutijela: Poznato je da SLE, SjS i neke druge sistemske bolesti vezivnog tkiva (MCTD) mogu biti razlogom FZR (66). Fetus može biti zahvaćen kod majki s evidentnom bolešću ili samo s pozitivnim nalazom protutijela (anti-Ro/SSA i anti La/SSB). U prospektivnim studijama majki s pozitivnim protutijelima kod kojih prvo dijete nije razvilo KAVB, rizik pojave KAVB u drugog djeteta je 1-5 %, ali se povećava na 11 %-19 % ako ga je razvilo prethodno dijete. K tome, majke koje imaju oba protutijela pozitivna i još hipotireozu izlažu se deveterostrukom riziku u odnosu na one koje imaju samo prisutna anti-SSA ili samo anti SSB protutijela (18). Nadalje, uz poremećaj u provodnom sustavu, 10-15 % trudnoća s pozitivnim anti-SSA protutijelima razvije upalu miokarda u kasnijoj trudnoći s posljedičnom restrikcijskom KMP (fibroeleastoza miokarda) ili/i s disfunkcijom atrioventrikularnog valvularnog (u prvom redu mitralnog) aparata (67). Zbog spoznaje o ranom razvoju posljedica na srce kod žena s pozitivnim protutijelima SSA/SSB, FE pregled indiciran je prije navršenog 15. tjedna trudnoće (najkasnije 16.-18. tj.) (14-19). Kod svih spomenutih stanja potrebno je nakon navršenog 15-tog tjedna gestacije uključiti deksametazon i bez obzira na moguće neželjene pojave za dijete (povećana tjelesna težina), očekuje se povoljan utjecaj te terapije. Prema većini autora vrijeme davanja deksametazona (4 mg/dan) traje od navršenog 15-tog do konca 20-tog tjedna gestacije (20). Prikaz neonatalnog lupusnog sindroma (NLE) i razvoj KAVB-a kao posljedicu istraživali smo i u domaćoj literaturi (68).

Maternalni stres: U referentnim indikacijama AHA i AEPC-a (10,11) ne spominje se maternalni stres kao visokorizični čimbenik, ali se u nekim studijama (Shandog Penisula, China) on navodi s rizikom od 2,7 % (69). U maternalnim stresu povećava se izlučivanje kortikosteroida, a tome je pridružena i hiperinzulinemija s rezistencijom na inzulin, što u cijelosti dovodi do poremećaja ravnoteže glikemije u obliku hiperglikemijske krize kao kod PDM-a (60-63). Kortikosteroidi izazivaju smanjeni protok krvi kroz posteljicu s posljedičnom hipoksijom. Razvojem metode za mjerenje intrauterinog stresa (70) moguće je da će se značenje ovog rizičnog čimbenika povećati.

IZLAGANJE MEDIKAMENTIMA

Unatoč uvriježenom mišljenju o mogućem teratogenom utjecaju brojnih medikamenata na razvoj PSG, danas se rizičnima smatraju neki antikonvulzivi, litij, ACEi, retinoična kiselina, selektivni inhibitori serotoninske resorpcije (SSRIs) i nesteroidni antiinflamacijski lijekovi (NSAIDs).

Antikonvulzivi koji se koriste u trudnoći su karbamazepini, difenilhidantoin i valproati. U meta-analizi studije koja je obuhvaćala 1208 trudnica koje su uzimale karbamazepin povećan je rizik za PSG u 1,8 % u odnosu na kontrolnu skupinu neliječenih trudnica s epilepsijom. Ta je proporcija bila ista neovisno o kombinaciji s drugim antiepilepticima (71). Unatoč tome, neke velike studije (*Canadian Institute for Health Information*) iz 2013. navode čimbenik rizika od 2,7 % (72). Neovisno o nesuglasju oko rizičnosti antiepileptika i mišljenju referentnih indikacija AHA/AEPC (10,11) kako viši rizik od 3 % ima samo liječenje depresije Paroxetinom (73), postoji mišljenje da i neki psihotici i neuroleptici povisuju rizik od PSG >3 %, u prvom redu zbog interferencije s metabolizmom folne kiseline (74).

Litij se u nekim studijama povezuje s pojavom PSG kod 8 % trudnica koje su ga uzimale (75). Međutim, kasnije studije i analize pokazale su da je rizik manji nego se u početku mislilo. Prema izloženom, FE se može učiniti, ali on nije obvezan (22).

Inhibitori angiotenzin konvertirajućeg enzima (ACEi): Izlaganje fetusa ACEi u prvom tromjesečju nosi rizik od 3,72 % za PSG u odnosu na očekivani rizik u općoj populaciji od 0,78 % (22). Najčešće se navodi FZR i perzistirajući DA.

Retinoična i folna kiselina: Retinoična kiselina (analog vitamina A) je dokazano teratogena na životinjskim modelima (76,77) i kontraindicirana je u trudnoći. U 8 % fetusa čije majke koriste retinoičnu kiselinu opisuju se PSG tipa konotrunkusnih anomalija s predominacijom anomalija aortalnog luka, a s vremenom se povećao broj slučajeva ukazujući na rizik od 20 % (12 do 54 %) pa je kod uzimanja retinoične kiseline potrebno učiniti rani FKP (21). Retinoična kiselina je oksidirani oblik vitamina A, a naziv retinoidi obuhvaća sve njegove derivate. Retinoidi su signalne molekule koje sudjeluju u diferencijaciji stanica i njihovoj proliferaciji, pa prema tome i u morfogenezi. Posebni geni reagiraju na signale retinoida depresijom ili indukcijom transkripcijskih čimbenika odgovornih za sintezu tkiva. Zato u suvišku retinoična kiselina djeluje kao opasan teratogen. U medicinu je uvedena 1982. godine u SAD pod nazivom Accutan za liječenje akni i bila je vrlo proširena lijek. Postupno se spoznalo

da ima teške teratogene posljedice. Već 1985. Lammer sa suradnicima dokazuje teratogenost retinoične kiseline na animalnim modelima jer Accutan generira retinoid izotretionin (76). Njegov je utjecaj ispitan u 154 trudnice koje su njime liječile cistične akne. Utvrđen je visok rizik za pojavu malformacija, a među njima se ističu kraniofacijalne, srčane i timusne anomalije te anomalije središnjeg živčanog sustava, odnosno rascjep neuralnog grebena (78). Ovaj trijas simptoma pripada i konotrunkusnim anomalijama (KTA) koje su prema Clarkovoj etiopatogenetskoj osnovi uzrokom nastanka PSG-a zbog poremećaja migracije stanica neuralnog grebena u mezenhimnu osnovu za srce (78). I nehotice se kod poznavalaca etiopatogeneze ovdje nameće sukladnost simptoma koji se u velikom broju radova opisuju kao KTA. Iako jedan dio tih anomalija ima genetičku osnovu u genomopatiji (22q11.2 delecijski sindrom - diGeorgeov sindrom – DGS1, 10p13 delecija – DGS2), iste se anomalije mogu razviti i u djeteta s normalnim genotipom kao posljedica nedostatka folne kiseline i poremećaja u sintezi DNA. Premda je nedostatak folne kiseline posebno poglavlje, smatra se da upravo derivati retinoida, alkohol i antiepileptici izazivaju disfunkciju folne kiseline, a retinoična kiselina smatra se uzrokom 30 % negenetički uzrokovanih KTA. Retinoidi oštećuju vrlo osjetljive stanice neuralnog grebena zbog nedostatka enzima superoksid dismutaze i katalaze koji su odgovorni za otklanjanje slobodnih radikala. KTA anomalije spadaju u najteže srčane grješke, a redovito su udružene s anomalijama timusa (deficit specifične celularne imunosti), lica (sindrom srce-lice), i rascjepa neuralnog grebena. U KTA spadaju: 1. defekti septacije konotrunkusa (subaortalni VSD, DORV, TF, PAsV-SD-om, AO-PA prozor, TAC), 2. abnormalna pozicija konotrunkusnih jastučića (d-TGA), 3. defekti faringealnih (škržnih) lukova (osobito prekid aortalnog luka, desni aortalni luk, dvostruki aortalni luk) (79). Ovom smo problemu dali toliko prostora zbog činjenice da se unatoč svim dokazima o štetnosti analoga vitamina A reklamira velik broj lijekova u obliku krema i to ne samo za liječenje akni, već i za njegu, pomlađivanje i slično (Tretinoin, Retinol, Renova, Eucerin retinol, Vitacid, Airol).

Selektivni inhibitor serotoninske reapsorpcije (SSRIs): U nekoliko je studija ispitivan utjecaj SSRIs-a na trudnoću odnosno fetus (73). Već je navedeno da je rizik od pojave PSG povećan kada se uzima antidepresiv paroksetin (Seroxat) iako i kod drugih antidepresiva postoji češći zahtjev za FKP-om. Studija koja je istraživala 10 000 djece čije su majke uzimale druge antidepresive pokazuje nizak i teško dokaziv rizik od 1,2 %, a kod uzimanja paroksetina je nađeno da se može razvijati opstrukcijska lezija izlaznoga trakta desne klijetke s rizikom od 3,3 %, pa je razumno trudnicu uputiti na FE (80).

MAJČINSKI NEGENETIČKI I NETERAPIJSKI ČIMBENICI

Iako ih referalne indikacije i najutjecajnijih međunarodnih kardioloških društava ne uvrštavaju u visokorizične čimbenike, postoje podatci da se valja osvrnuti na alkohol, pušenje i kokain.

Alkohol postaje visokorizični čimbenik za pojavu strukturnih srčanih grješaka ako trudnica u embrionalnom razdoblju uzima više od 5 pića/dan i tada to odgovara riziku od 1,5 do 7,5 % (81). U našim uvjetima smo istraživali alkoholne fetopatije u vremenu kada se fetalnoj kardiologiji nije obraćalo ovakvu pozornost (82). Bilo bi interesantno učiniti distinkciju između utjecaja alkohola i drugih negenetičkih vanjskih čimbenika na embrij i fetus posebno, jer nije nemoguće da su etablirana obilježja alkoholne fetopatije posljedica embriopatije. ***Pušenje*** je sigurno uzrok FZR-a, ali nema relevantnih podataka da uzrokuje PSG. No, izvjesno je da pušenje izaziva fetalnu hipoksiju te time i poremećaj ravnoteže esencijalnih nutrijenata s direktnim teratogenim djelovanjem s pretpostavkom o poremećaju sinteze DNA (83). Stoga je razuman savjet o zabrani pušenja prije i tijekom trudnoće. Možda i na ovom mjestu nema jasne distinkcije između embriopatija i fetopatija, kao i kod alkohola.

Kokain se spominje u istraživanju s rizikom za pojavu PSG od 3,7 %, ako se uživa tijekom embrionalnog života. Smatra se da ima direktan toksični učinak na fetalne miocite. Toksični kokainski metaboliti razaraju stanice miocita u razvoju s posljedičnim razvojem strukturnih anomalija (84).

Antagonisti vitamina K: Warfarin i drugi kumadinski preparati koji se koriste u prvom tromjesečju trudnoće smatraju se teratogenim agensima. Iako postoji povećan rizik za druge prirođene defekte, novije prospektivne studije na više od 600 izloženih trudnica i 1 000 kontrolnih pokazuju podjenaku učestalost PSG, pa prema tome nema ni indikacije za FE (78,85).

Nesteroidni antiinflamacijski lijekovi (NSAID): NSAID se ponekad koriste za tokolizu i liječenje polihidramnija. Evidentna konstrikcija duktusa doplerskom analizom nastaje u 25-50 % trudnica koje koriste indometacin u drugom i trećem tromjesečju trudnoće, ali se proces konstrikcije može prekinuti ako se spomenuti lijek ukine. Rizik od konstrikcije duktusa se povećava, ako se Indometacin daje nakon 32. tjedna i duže od 48 sati. Poznato je da duktalnu konstrikciju mogu učiniti i drugi NSAID jer djeluju kao antagonisti prostaglandina, pa ih ne treba davati u drugom i trećem tromjesečju trudnoće. Čini se da je rizik od istih lijekova zanemariv u ranoj gestaciji. Prema tome, FE je indicirana u pacijentica koje uzimaju NSAID na-

kon prvog tromjesečja (23-25). Čini se da rizik veći od 2 %, prema nekim istraživanjima, imaju i ibuprofen i naproksen (59,86).

Infekcije: Učinak nespecifičnih maternalnih infekcija (osim s virusom rubeole) teško je analizirati, jer se uz bolest daju i različiti lijekovi uključujući i antipiretike. U jednoj populacijskoj studiji koja je istraživala febrilna stanja u trudnoći rizik za PSG bio je 1,8 % (87). Zbog toga je u prvom tromjesečju potrebno učiniti FE kod trudnica inficiranih virusom rubeole, dok kod drugih virusnih infekcija ne očekujemo veću vjerojatnost pojave PSG (88). No, to je potrebno učiniti onda kada se kod fetusa nalazi hidrops ili drugi izljevi. Serološki nalazi nisu indikacije za FE, ako nije riječ o kardiotropnim virusima koji mogu biti razlogom razvoja mioperikarditisa. Ako tijekom trudnoće nalazimo morfološke elemente dilatacijske kardiomiopatije s mogućim razvojem hidropsa ili/i srčane slabosti, valja posumnjati na fetalni miokarditis. U toj situaciji treba učiniti testove na kardiotropne viruse (parvo-B19, *coxackie* A i B, ECHO viruse, influenzu, polio, mumps, adenoviruse, EBV, citomegalovirus, HIV1 virus). Takav slijed događaja može se češće naći kod majki koje rade u stacionarnim ustanovama (vrtić, škola). Stupanj rizika nije studiran u literaturi. U našem smo radu izvijestili o PSG koja je bila posljedica rubeolarne embriopatije (Greggov sindrom) u djeteta čija majka nije cijepljena MoPaRu cjepivom (89). Ovaj primjer ilustrira koliko infekcija može utjecati na razvoj ploda, a ujedno ističe važnost anamneze tijekom suradnje opstetričara i pedijatrijskog kardiologa.

OBITELJSKA ANAMNEZA

Majčine srčane bolesti: Rizik ponavljanja nesindromnih, nekromosomnih PSG je dvostruko veći ako je pogođena majka, a ne otac (90,91). Rizik varira sa specifičnim maternalnim dijagnozama, a najveći je ako majka ima AVSD (oko 10 %) ili aortalnu stenozu (oko 13-18 %) (29-31,92). Za većinu maternalnih srčanih bolesti rizik je 3-7 %. Ponavljanje tetralogije Fallot (TOF) i d-TGA je manje od 3 %. Na osnovi iznesenog FE je potreban kod trudnica koje imaju u anamnezi PSG, hiperpirektični sindrom u embrionalnoj fazi, hiperhomocistinemiju ili hiperkolesterolemiju (59).

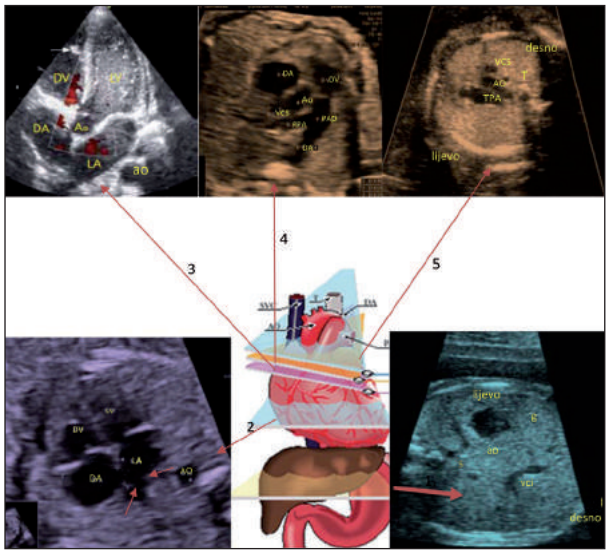
Očeve srčane bolesti **s**u manji rizik od majčinih, a za nesindromne PSG rizik je 2-3 % (26-31). Veći je rizik za AS, poglavito u populaciji bikuspidne aortalne valvule (BAV) (30,93,94). FE je, dakle, indicirana i kod očevih srčanih bolesti, premda je očekivani rizik manji nego kod majčinskih. BAV se u literaturi adultne kardiologije spominje kao sindrom BAV, a u dječjoj dobi još nije dobio taj naziv. Međutim, s obzirom na činjenicu da je aortalni zalistak u središtu zbivanja više patoloških morfoloških promjena koje se događaju u različitim razdobljima života (stenoza i/ili insuficijencija same valvule, dilatacija tubularne i/ili luka aorte, koarktacija, subaortalna stenoza, stenoza mitralne valvule, Shone sindrom) treba ga smatrati rizičnim čimbenikom neovisno o tome što se može razvrstati i u skupinu bolesti koje nazivamo interrupcijama, jer se klinički očituju u kasnijem životu, iako su genetički uvjetovane (Marfanov sindrom, Ehlers-Danlosov sindrom ili hipertrofična KMP). Za razliku od njih malformacije su posljedica poremećene morfogeneze u embrionalnom razvoju srca, a deformacije se smatraju poremećenjem protoka (94).

Bolesti, poremećaji i sindromi s mendelskim tipom nasljeđivanja: U obitelji gdje postoji bolest s autosomno recesivnim ili dominantnim nasljeđivanjem i u kojoj jedan od roditelja ima autosomno-dominantnu genetičku bolest ili u trudnoćama s delecijskim sindromom (npr. 22q11.2 delecija, Alagille sindrom, 7q11.23 delecijski sindrom - Williams-Beurenov sindrom WBs), rizik za PSG je vrlo visok. U njih je svakako indicirana FE uz pretpostavku da se poznaje moguća ekspresivnost samog poremećaja (93). Uz dosada spomenute delecijske sindrome (7q11.23 delecijski sindrom - Williams-Beurenov sindrom , 22q11.2 delecijski sindrom., DiGeorgeov sindrom) i interrupcije (Ehlers-Danlosov, Marfanov sindrom, HKMP), u pedijatrijskoj se praksi sve temeljitije promatraju takozvane RASopatije u koje se ubrajaju Noonanov sindrom, sindrom nalik Noonanovu sindromu, Noonanov sindrom s multiplom lentiginozom (NSML), kardiofaciokutani sindrom (CFC), Costellov sindrom, Legiusov sindrom, neurofibromatoza tipa 1 te sindrom nalik Noonaninom (*Noonan syndrome with Loose Anagen Hair* – NSLH) koji se opisuju u publikacijama o molekularnoj genetici (59,95). Sudjelovali smo u istraživanju molekularno-genetičkih uzroka Holt Oramova sindroma gdje smo dokazali u našeg pacijenta novu heterozigotnu mutaciju *TBX5* koji kodira transkripcijski čimbenik regulacije razvojnih procesa (96). U poremećaje s mendelskim nasljeđivanjem spada i CHARGE sindrom te heterotaksije, a u okviru heterotaksičnih sindroma opisuju se takozvane ciliopatije koje se teorijski mogu smatrati uzrokom kako heterotaksije i izomerizma tako i Kartagenerova sindroma (59). U našem kliničkom radu istraživali smo genetiku Noonanova sindroma kod monokorionskih dvojaka (97).

FETALNI ČIMBENICI

Sumnja na srčane anomalije na osnovi opstetričkog ultrazvuka: Od svih indikacija za FE brojne studije su pokazale da ih se više od 40 % postavlja nakon standardnog opstetričkog ultrazvuka s presjekom kroz če-

tiri srčane šupljine (4 chv) (9,97,98). Ako je opstetričar savladao i određivanje odnosa velikih krvnih žila prema srcu (3VV), povećava se opravdana indikacija na čak 52 % (97). Studije koje uključuju 3VV s trahejom (3VVT) pokazuju da se u opstetričkom probiru dodatno povećava indikacija za FKP (105,106,114). Navedena istraživanja ukazuju da je nakon suspektnog nalaza opstetričkog ultrazvuka neophodan pregled pedijatrijskog kardiologa (sl. 1) (8). Vlastita istraživanja također ukazuju u prilog ovakvom načinu razmišljanja (9). I dinamika tehnološkog razvoja podsticala je povećanu potrebu za FKP. Sredinom osamdesetih godina 20. stoljeća postoji tek rutinski opstetrički pregled u gestacijskoj dobi od 18. do 22. tjedna, tako da je još u razdoblju od 1993. do 1995. u UK senzitivnost pretrage bila samo 25 % (4chv). Uvođenjem obveze prikaza izlaznog trakta velikih krvnih žila (3VV) senzitivnost se povećava na 45 %, a uvođenjem pet osnovnih osi i 3VVT (prikaz tri krvne žile i traheje) senzitivnost se povećava na >95 % u dobro educiranih pedijatrijskih kardiologa-fetologa (sl. 2) (99). No, i dalje postoje ograničenja uzrokovana smještajem fetusa i srca, multiplih trudnoća, prematurnog zatvaranja ovalnog otvora i arterijskog duktusa, dijagnoze TAPVR, koarktacije aorte, progresivne stenoze aortalnog ušća te heterotaksije s izomerizmom ili bez njega (100).



Sl. 2. *Pet osnovnih ECHO(presjeka) neophodnih za postizanje visokog stupnja senzitivnosti (>95 %). 1.najniži presjek; fetalni želudac (g), abdominalna aorta (ao), kralješnica (s) i jetra (l), 2. pogled u četiri šupljine, FO+..+, pulmonalne vene (strjelice), aorta, 3. „pogled u pet šupljina" - aortalni korijen, obje klijetke i pretklijetke i ortogradni presjek kroz descendentnu aortu, 4. pulmonalne arterije s bifurkacijom i obadvije grane, arterijski duktus (DA) te presjek kroz ascendentnu i descendentnu aortu, 5. Presjek kroz tri krvne žile i traheju; trunkus plućne arterije, proksimalna aorta, DA, distalna aorta, gornja šuplja vena i traheja (T).*

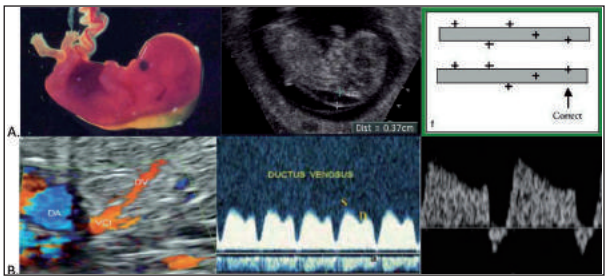
Sumnja na abnormalnosti srčane frekvencije i srčanog ritma: Fetalna tahikardija je rijedak nalaz kod PSG. Nasuprot tome, fetalna bradikardija koja je rezultat abnormalnog AV-provođenja navodi se u 50-55 % slučajeva s kompleksnim PSG (34) ili ona pripada imunološkim promjenama kod sistemskih bolesti majke s pozitivnim anti-SSA/SSB protutijelima (SLE, SS, MCTD). Fetalna bradikardija može biti i posljedica produženog QT-intervala (LQTS) i očituje se blagom bradikardijom s A-V blokom 2:1 (101.02). FE treba učiniti u svih trudnica sa sumnjivim tahiaritmijama ili bradiaritmijama da bi se isključila moguća pridružena patologija. Iregularan fetalni ritam uzrokovan atrijskom ekstrasistolijom, bez bradikardije ili tahikardije ima vrlo nizak stupanj rizika, ali ako perzistira, može postati izvor malignijih aritmija, pa je potrebna kontrola. U fetusa s prematurnim atrijskim kontrakcijama i učestalim ektopičnim ritmom (bigeminija, trigeminija) treba isključiti moguće morfološke promjene srca, kardiomiopatske obrasce te upale ili tumore (35). Prema opsežnim epidemiološkim istraživanjima srčane su aritmije rijetki problemi fetalnog kardiologa (vidjeti sliku 1 – studija Saarland- Evelin) (8). Ipak valja naglasiti da su paroksizmalne tahikardije s undulacijom (fibrilacijom) atrija ili bez nje stanja koja se mogu dobro liječiti intrauterino, osobito ako se otkriju prije pojave hidropsa koji je siguran znak stečene srčane insuficijencije (103).

Nekardijalne abnormalnosti: Ekstrakardijalne anomalije mogu imati pridružene PSG unatoč normalnom kariotipu. Incidencija PSG s pridruženom ekstrakardijalnom anomalijom iznosi 20-45 %, ovisno o populacijskoj studiji, vrsti malformacije, gestacijskoj dobi i o kvaliteti ultrazvučnog probira (36-41). Srčana malformacija nalazi se u 30 % djece s omfalokelom, 20 % s duodenalnom atrezijom, 30 % s dijafragmalnom hernijom, 15 % s anomalijama središnjeg živčanog sustava i više od 31 % s urogenitalnim anomalijama (tablica 4). Velike razlike u ishodu studija uvjetovane su jamačno vremenom istraživanja, tehnološkim napretkom i nozološkim spoznajama samih liječnika. Postoje i izolirane anomalije kod kojih se ne zna točno pridruženost PSG-a, ali i kod njih (ventrikulomegalija, unilateralni rascjep usnice) valja učiniti FE unatoč urednom 4chv i 3VVT.

Tablica 4.
Populacijski pregled ekstrakardijalnih anomalija i posljedični rizik za srčanu bolest

Ekstrakardijalne anomalije, % / Sustav	Greenwood i sur.[38]	Gallo i sur.[39]	Walgreen i sur.[40]	Miller i sur.[41]
CNS	6,9	3,2	6,0	23,2
Respiracijski	3,8	8,0	5,2	10,5
Gastrointestinalni	4,2	….	15,5	25,2
Genitourinarni	5,3	….	13,1	23,1
Muskularni	8,8	4,5	16,1	35,0
Ukupno	25,2	32,9	43,9	28,6
Ukupan broj uključene djece	1566	1354	1 000	7984

Povećana nuhalna prozirnost u prvom tromjesečju: Tranzitorno nakupljanje tekućine u nuhalnoj regiji humanog fetusa vidi se od 10. do 14. tjedna gestacije i naziva se fetalna nuhalna prozirnost (FNP) (engl. *Fetal nuchal translucency* - FNT), a pobuđuje sumnju na aneuploidiju i druge anomalije (104). Uzroci ove pojave su spekulativni, a studije srčane funkcije u toj gestacijskoj dobi ukazuju da one vjerojatno nisu posljedica srčane insuficijencije (105,106). K tome, centilne vrijednosti cijele populacije ovise o antropometrijskim svojstvima populacije, pa se normalnom smatra širina FNP do 3 mm, ako se računa prema 95. centili (2SD), a 3,5 mm ako se računa prema 97. centili (3SD). Koja se centilna vrijednost uzima u obzir ovisi o odluci opstetričara koji na osnovi zadanih kriterija mjeri odnos tjeme-trtica fetusa između 11. i 13. tjedna gestacije (45,48). Iako većina centara u rutinskom radu smatra normalnom širinu FNP do 3,5 mm, ponavljamo prethodno navedene izračunate rizike za pojavu PSG (rizici navedeni u zagradi); FNP >3-3,4 mm (3 %), > 5 mm (6 %), >6 mm (24 %), >8,6 mm (66 %) (44-48). Pridruženost PSG povećanim vrijednostima FNP priznata je od 1996. godine, ali je i dalje predmetom brojnih studija (46). Također je vrlo važno naglasiti ispravno mjerenje FNP (106). Uz brojna istraživanja povezanosti ove pojave s pojavom PSG, može se reći da rizik od aneuploidijskih grješaka raste također eksponencijalno s porastom FNP (46,47). No, danas se uz ispravno mjerenje FNP savjetuje snimiti i doplerski obrazac venoznog duktusa. Smatra se da je patološka FNP uzrokovana srčanom insuficijencijom, ako je prisutan i patološki doplerski obrazac venoznog duktusa (44-47). U nekim meta-analizama porast FNP i abnormalni doplerski obrazac DV navješćuju srčanu malformaciju s rizikom 15 – 20 %. Mogli bismo ipak reći da u praksi svaki porast FNP >3 mm treba popratiti i snimkom doplerskog obrasca DV-a. Fetalni ehokardiogram nije indiciran ako je FNP <3 mm, ali je indiciran u slučaju abnormalnog doplerskog obrasca DV-a koji svjedoći o postojanju srčane insuficijencije više nego širina FNP-a. Zato se uvijek uz FNP treba gledati i obrazac DV (107). I dalje se o ovom fenomenu vode opsežne rasprave (45, 48)(sl. 3).



Sl. 3. *Prikaz FNP i DV-a u gestacijskoj dobi 11-15 tjedana. Patološki nalaz FNP smatra se posljedicom srčane insuficijencije samo ako postoji i patološki nalaz doplerskog obrasca venoznog duktusa* ***A****. Fetalna nuhalna prozirnost graničnih vrijednosti; nativni nalaz, 2D ehokardiografski nalaz i prikaz točnog mjerenja FNP (106).* ***B****. Prikaz venoznog duktusa (dvodimenzijski), pulsni dopler - normalni nalazi PWD patološkog nalaza (reverzni a val) (113)*

Abnormalnosti pupkovine i abdominalnog venskog sustava: Postojanje samo jedne umbilikalne arterije - SUA-e (engl. *single umbilical artery*) rizik za PSG iznosi do 3,9 %, a prema nekim autorima dvostruko je veći u odnosu na fetuse s obje arterije (42). Fetalne anomalije venskog sustava su sporadične, a mogu se očitovati i kao ageneza DV(108). Kod nepostojanja DV javlja se neovisni povratni protok krvi u posteljicu, jer se pupčana vena drenira alternativnim putem. To može uzrokovati volumno opterećenje desnog srca i posljedičnu srčanu insuficijenciju (109). Ukratko, u tijeku su rasprave o odnosu anomalija krvnih žila i pojave PSG, a zaključci se donose u prvom redu na osnovi opstetričkih analiza.

Primjena potpomognute oplodnje. Broj trudnoća iz ovih postupaka još 2005. u SAD je iznosio 1% neovisno je li se radilo o klasičnoj *in vitro* fertilizaciji (IVF) ili postupku intracitoplazmatske injekcije spermija (ICSI) (89). Čini se da je povećan rizik za PSG kod blizanačkih trudnoća. dok za jednoplodne trudnoće nema takvih dokaza. Veća učestalost PSG može biti zbog starije životne dobi žena i zbog većeg rizika za monozigotne blizance (56-58). Preporuča se sve trudnice koje su začele potpomognutom oplodnjom uputiti na FE. Najveći problem u probiru svakako su monokorionski dvojci (blizanci) .

Monokorionski dvojci. Kad se oplođena zigota podijeli unutar prvih triju dana nastaju monozigotni bikorionski dvojci, a ako se podijeli između 4. i 8. dana nastaju monokorionski dvojci. Učestalost blizanaca je približno 3-4 na 1000 živorođenih; jedna trećina svih blizanaca su monozigotni, a dvije trećine monozigotnih dvojaka su monokorionski. Kod svih monokorionskih dvojaka indicirana je FE s obzirom da je rizik za PSG povišen od 2 do 9 % (55,110,111). Prema najnovijim stavovima postoje dva etiološka čimbenika odgovorna za promjene na srcu fetusa: 1. primarne strukturne anomalije i 2. stečene abnormalnosti zbog

TTTS sindroma (engl. *tween to tween transfusion syndrome*). Primarne su uvjetovane okolišnim i genetičkim čimbenicima. Sekundarne osobine srčanih promjena posljedica su TTTS-a koje se u prvom redu očituju kod primaoca sa sljedećim promjenama: biventrikularna hipetrofija, opstrukcija izlaznog trakta desne klijetke, pulmonalna stenoza/atrezija, atrioventrikularna regurgitacija (TV i MV), povratni protok u DV, pulsacije u umbilikalnoj veni i fetalni hidrops. Srce donora je obično normalno (ako nema primarnu strukturnu grješku) (112).

Neimuni fetalni hidrops s izljevima: Fetalnim hidropsom smatra se nakupljanje tekućine u dva ili više fetalna odvojena prostora (pleura, perikard, abdominalna šupljina, peritonej ili placenta). Mehanizam nastanka hidropsa u fetusa je kombinacija povišenog hidrostatskog tlaka, smanjenog onkotskog tlaka i rijetkog poremećaja limfne drenaže. Približno 15-25 % fetusa s neimunim hidropsom ima srčanu insuficijenciju ili aritmije. Abnormalnosti se očituju povišenim venskim tlakom zbog volumnog opterećenja zbog valvularne regurgitacije, povišenim biventrikularnim tlakom i smanjenim dijastoličkim punjenjem za vrijeme tahikardije (54,113). Uz to 10 % fetusa s hidropsom ima visok srčani izbačaj uzrokovan fetalnom anemijom, sakrokokcigealnim teratomom ili fetalnim placentnim anomalijama. Stoga je FE indicirana u svih fetusa s neimunim hidropsom.

OPSTETRIČKI PROBIR

Poznato je da se najviše PSG otkriva patološkim nalazom na razini četiriju srčanih šupljina, a ako se ispita i izlazni trakt prema velikim krvnim žilama, senzitivnost se povećava na 90 % u populaciji s niskim rizikom za pojavu PSG (114). S obzirom na ipak niski postotak dijagnosticiranih PSG od ginekologa (10-26 %) sumnjive nalaze treba uputiti fetalnom kardiologu. Od 90 do 95 % sumnji na PSG u opstetričkim nalazima stvarna se grješka u srednjoj gestacijskoj dobi potvrđuje u 54 % slučajeva, a ako se uključi i analiza 3VVT senzitivnost se povećava na 90 % u istom razdoblju pretraživanja (115). S obzirom da preostaje još 10 %-tni rizik preporučuje se u rizičnim skupinama ispitati obiteljsku, osobito majčinsku anamnezu te uzeti u obzir sve rizične fetalne čimbenike kako bi senzitivnost bila što veća. Najnovije studije u SAD pokazuju da se opstetričkim ultrazvukom dijagnosticira oko 30 % PSG (116,117). Ti rezultati ovise o edukaciji i uopće informiranosti opstetričara o važnosti fetalne kardiologije, pa je u tom smislu neophodno unaprjeđivanje njihova znanja u ovom području (118).

Dokazi o vrijednosti fetalne kardiologije u zaštiti perinatalnog morbiditeta i mortaliteta i stratifikacijski (uvjetovani) rizik

Mnoga djeca s kompleksnim PSG u bliskoj prošlosti umirala su prije dolaska u tercijarni kardiološki centar (119). Stanje se počelo popravljati s centralizacijom pedijatrijske kardiološke službe i spoznajom ukupnog stratifikacijskog rizika zbog ekstremne heterogenosti srčanih anomalija. Ovi rizici uključuju vrijeme i mjesto porođaja koji utječu na brzinu dolaska u kompetentni tercijarni centar te neposredno neonatalno zbrinjavanje (120). Samo tako prenatalna dijagnoza dopušta potpuni angažman multidisciplinskog tima koji uključuje opstetričare, pedijatrijske kardiologe, neonatologe, genetičare, a potom i kardijalne kirurge, osobito educirane anesteziologe, medicinske tehničare i druge (121). Od posebnog je pak značenja dobra organizacija transporta djece, ako se moraju liječiti u zemljopisno udaljenim centrima. Sve su to čimbenici, kao i mnogi drugi, koji bez daljnjega poboljšavaju perinatalni morbiditet i mortalitet. Prepoznavanje ekstrakardijalnih anomalija i genetičkih abnormalnosti ima krucijalno značenje za krajnji ishod bolesti (121). Najbolji dokaz o smanjenju perinatalnog morbiditeta i mortaliteta nalazimo u studiji Bonneta i sur. na primjeru d-TGA (122), potom na tečaju iz fetalne kardiologije 2003. godine u Amsterdamu *(Outcome an effect of prenatal diagnosis of structural lesions, AEPC, Amsterdam, May 2003*), a kasnije je studija proširena sudjelovanjem drugih centara i autora (123).Prikazana je velika razlika u tijeku bolesti kod d-TGA, ovisno o prenatalnoj u odnosu na postnatalnu dijagnozu (68/250 pts.) u nekoliko ključnih točaka: 1. vrijeme transporta od rađaonice do tercijarnog centra: 68 pts. (2 ± 2,8 sati) *vs*. 250 pts. (73 ± 210 sati) (p=0,01), 2. kritično stanje kod prijma: 5/60 pts. *vs*. 37/250 pts. p<0,01), 3. preoperacijski mortalitet: 0/68 pts. *vs*. 15/250 (8 prehospitalnih, 7 nakon prijma) (p<0,01), 4. postoperacijski mortalitet: 0/68 pts. *vs*. 20/235 pts. (p< 0,01). Nije bilo razlike u rizičnim čimbenicima (pridružene grješke, koronarni obrazac, trajanje EKC-a). Vidljivo je da je nesrazmjerna razlika u svim mjerenim kriterijima, a od osobitog je značenja podatak da nema smrtnosti u prenatalno dijagnosticiranih bolesnika s d-TGA. Statistički značajna razlika zabilježena je u vremenu prijma (2,2 : 73 sata), trajanju mehaničke ventilacije (12 : 95 sati), metaboličkoj acidozi (8: 56 pts.), preoperacijskom mortalitetu (0:15 pts), postoperacijskom mortalitetu (0 : 20 pts) i trajanju hospitalizacije (24:30 dana). Osnovna je poruka iz tog istraživanja da prenatalna dijagnoza d-TGA smanjuje učestalost perioperacijske metaboličke acidoze sa svim posljedicama uključujući i učestalost akutnog neurološkog oštećenja. Prikazan je i napredak u dijagnosticiranju i liječenju d-TGA i HLHS-a u razdoblju od 1983. do 2000. godine (126-128). U razdoblju od

1983. godine (kada je fetalna kardiologija počela tek dobivati na značenju, a senzitivnost je bila izrazito niska) do 2000. godine (kada je senzitivnost prenatalne dijagnoze porasla na 95 %), sabrana su istraživanja nekoliko centara na okolnost ishoda liječenja d-TGA i HLHS-a, a impresivni rezultati prikazani su u tablici 5.

Tablica 5.
Prenatalna dijagnoza, završetak trudnoće, perinatalni i rani neonatalni mortalitet za izoliranu skupinu kompleksnih PSG.

	1983.-1988. (%)	**1989.-1994.** (%)	**1995.-2000.** (%)	p
TGA				
Prenatalna dijagnoza	12,5	48,1	72,5	0,001
Prekid trudnoće	0	7,4	0	0,62
Smrtnost u 1. tjednu	18,8	8,3	2,6	0,04
Perinatalni mortalitet	23,5	12,0	5,0	0,02
HLHS				
Prenatalna dijagnoza	31,8	82,8	88,9	<0,001
Prekid trudnoće	13,6	72,4	63,0	<0,001
Smrtnost u 1. tjednu	83,3	75,0	50,0	0,12
Perinatalni mortalitet	84,2	75,0	50,0	0,10

Uz detaljno prikazan pozitivan učinak prenatalne dijagnoze na ishod bolesti jasno se prikazuje pozitivan učinak kod već spomenutih hitnih stanja koja se očituju kao o duktusu ovisne grješke (TAPVR s opstrukcijskim lezijama i HHLS), d-TGA s restiktivnim interatrijskim septumom i CCAVC niske frekvencije. Rana infuzija PGE_1 i što je moguća ranija atrioseptostomija (ili septektomija) onemogućuju razvoj progredirajuće acidoze i smanjuju mogućnost trajnog neurološkog oštećenja. Samo u rijetkim slučajevima (4 %) rana intervencija ne popravlja stanje (ako se radi o perzistirajućoj neonatalnoj pulmonalnoj hipertenziji). Ako se ispravno postupi, npr. kod HLHS-a, moguć je i transport u specijalni centar koji može hitno učiniti operaciju Norwood I ili K-D-S (Kaye-Damus-Stansel). To smo pokazali i na vlasitom istraživanju ishoda HLHS-a pri čemu su bolesnici dijagnosticirani prenatalno upućeni u inozemne centre na prvu palijaciju, a smrtnost i krajnji ishod se ne razlikuju od ishoda u tercijarnim centrima koji nemaju potrebe za udaljenim transportom (124). Isto tako publiciran je podatak da je smrtnost nula od 50 djece zbrinute u našem tercijarnom centru (i rođeno nakon fetalne dijagnoze u pridruženom tercijarnom opstetričkom centru) te je nakon urednog inicijalnog zbrinjavanja transportirano u inozemstvo na anatomsku operaciju (ukrižanje velikih krvnih žila, *switch*) (6). Nedostatak iskustva u procjeni hitne potrebe za atrioseptostomijom razlog je neuspjeha kod d-TGA i HLHS-a s teškim posljedicama na neurološki status djeteta ako preživi, a kod HLHS-a i razlogom za kasnu komplikaciju koja se očituje razvojem sekundarnih pulmonalnih limfangiektazija (*nutmeg lung* – muškatni oraščić) kao uzrok plastičnog bronhitisa (125). Nije uvijek samo hitnost razlog za ispravnu prenatalnu dijagnozu PSG, već i poznavanje njezine hemodinamike, morfologije i genetičke pozadine. Npr. kod CCAVC-a važno je prepoznati heterogenu fenotipsku ekspresiju, moguću pridruženost aneuploidije (50-60 %), odrediti adekvatnu prenatalnu genetičku ekspertizu, a potom dati roditeljima kompletnu prenatalnu informaciju i pripremiti se za operaciju (palijativna – ovisno o fenotipskoj ekpresiji) ili moguće kompletna korekcija u odsustvu plućne arterijske hipertenzije (PAH) s previsokim plućnim vaskularnim otporom (PVR). Bez prenatalne dijagnoze i svih prednosti takvog pristupa, postpartalni razvoj događaja može biti mukotrpan i manje uspješan od prenatalne dijagnoze, a iznad svega granično etičan. Slično stanje se može opisati i kod kompleksnih PSG koje se mogu prikazati sa zajedničkom dijagnozom (TF-PA+VSD+MAPCAs intra- ili ekstraperikardijski). Ovdje je postpartalni tretman različit, a ovisi o fenotipskoj ekspresiji i vrsti „TF“, vremenu i vrsti palijacije ili moguće kompletne korekcije, prethodne medikamentne terapije (beta-blokatori), moguće interventne ili samo dijagnostičke kateterizacije srca, a potom i moguće genetičke podloge razvoju CHD-a (delecija 22q11.2), što uključuje potencijalnu imunodeficijenciju, moguću hipokalcemiju i mentalni komorbiditet. Jasno je da fetalni kardiolog u prvom redu mora biti temeljno obrazovan pedijatrijski kardiolog da bi zajedno s opstetričarem mogao suvislo odgovoriti na niz pitanja koja se postavljaju za vrijeme trudnoće od roditelja i drugih sudionika u liječenju ove i sličnih anomalija. Stratifikacijski rizik ogleda se na poseban način kod koarktacije aorte iz nekoliko razloga; nerijetko nije moguće postaviti dijagnozu s dovoljno visokim stupnjem senzitivnosti, pa ju je neophodno rano postpartalno potvrditi. Pri tome valja uzeti u obzir i činjenicu da se definicija mijenja od gradijenta 30 mm Hg, na gradijent 20 mm Hg, ali i spoznaju da koarktacija može postpartalno progredirati. Prenatalno se dijagnoza postavlja na osnovi 3VV longitudinalnog presjeka kroz cirkulaciju, a ako to nije moguće, postoje indirektni znaci koji se očituju dominacijom desne klijetke i hipertrofijom stijenke lijeve klijetke sa smanjenim dimenzijama već u prvom trimestru. Takav obrazac, međutim, može imati i TAPVR, perzistirajuća LVCS te prematurno zatvaranje arterijskog duktusa, pa se u toj diferencijalnoj dijagnozi treba očitovati i senzitivnost pretraživača. Poznato je također da se dijagnoza koarktacije postavlja s višim stupnjem vjerojatnosti kod kompleksnih PSG nego izoliranih koarktacija. Svaka pogrješka ili presmiona odluka kod sumnje na koarktaciju ima za posljedicu moguću iznenadnu smrt ili povećanje komorbiditeta kod preživljavanja komplikacija (acidoza), što se trajno očituju u poremećenom neurorazvoju. Zbog toga u slučaju sumnje na CoAo dijete treba ispratiti iz rodilišta uz primjenu prostaglandina i uz ultrazvučnu kontrolu. K tome valja dodati da dijete kojem je postavljena sum-

nja na koarktaciju u fetalnom životu treba redovito kontrolirati tijekom cijele prve godine života kako bi se isključila njezina evolucija. Primjer kako prenatalna dijagnoza pozitivno utječe na ishod bolesti opsežno je prikazan i u vlastitoj publikaciji koja se odnosi na manjkavu pulmonalnu valvulu i anomaliju Botallova duktusa (129).

Suvremeni pristup fetalnoj kardiologiji i nezaobilaznom kardio-opstetričkom prožimanju započeo je u Hrvatskoj unazad jednog desetljeća (130).

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SUMMARY

FETAL CARDIAC SCREENING IN PROTECTION FROM PERINATAL MORTALITY AND MORBIDITY – THE NEW, VERY IMPORTANT ROLE OF FETAL ECHOCARDIOGRAPHY IN OBSTETRICS AND PEDIATRIC CARDIOLOGY

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Objective: The main objective of this review is to highlight the value of fetal cardiac screening in the protection from perinatal morbidity and mortality by respecting modern scientific, diagnostic and therapeutic possibilities. Indications for fetal cardiac screening according to the level of risk are highlighted, both tabularly and in an extensive discussion that takes into account teamwork and interprets findings by taking into account Class of Recommendation (COR) and evidence-based patient discussions, Level of Evidence (LOE). ***Methods and results*** are derived from studying the guidelines of the American Heart Association (AHA), Association of European Pediatric Cardiology (AEPC), International Society of Ultrasound in Obstetrics and Gynecology (ISOUG), and other extensive recent literature. ***The aim*** is to highlight the interests of fetal cardiac medicine, including the diagnosis of congenital heart disease (CHD) and arrhythmias, assessment of fetal cardiovascular function and available methods of intrauterine treatment, as well as of immediate or early postnatal intervention. Extensive discussion with numerous literature citations and tabular presentation highlights the referral indications for fetal cardiac screening (FCS), factors that increase the risk of CHD and other heart diseases (arrhythmias and cardiomyopathies), and a population overview of extracardiac abnormalities associated with heart diseases. Along with the inevitable tables, the text is accompanied by several important drawings or echocardiographic representations that in their own way permeate the joint findings of obstetricians and pediatric cardiologists-fetologists. Research confirming that the application and consideration of fetal cardiac screening has a positive effect on reducing perinatal morbidity and mortality, especially in the case of complex heart defects, is presented at the end. ***Conclusion:*** In the last 20 years, fetal cardiac medicine has advanced so much in diagnostic and therapeutic terms that it significantly affects overall perinatal morbidity and mortality, especially because CHDs are the most common congenital anomalies. Accurate cardiac fetal diagnosis, increasing therapeutic approaches to the fetal heart, both medical and interventional, and dynamic development of new technologies have brought fetal cardiac medicine to a level without which modern medicine in any country can no longer be imagined.

Key words: cardiology, pediatric, fetus, fetal echocardiography, congenital heart disease, perinatal morbidity and mortality

UTJECAJ OŠTEĆENJA SLUHA NA RAZVOJ ZDRAVSTVENIH I KOGNITIVNIH POTEŠKOĆA U OSOBA TREĆE ŽIVOTNE DOBI: PREGLED LITERATURE I SMJER JAVNOZDRAVSTVENOG DJELOVANJA

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Oštećenje sluha ima negativne učinke na kvalitetu života, osobito u socijalnoj i emocionalnoj domeni kvalitete komuniciranja. To izrazito dolazi do izražaja u starijoj životnoj dobi, kada je slabljenje kognitivnih sposobnosti najviše izraženo. Osim toga, starije osobe oštećenog sluha, koje su još uvijek radno aktivne, shvaćaju da je održavanje dobrog sluha od presudnog značenja za učinkovitost na radnom mjestu. S obzirom na značajnu prevalenciju starijih osoba s oštećenjem sluha koje ne koriste slušno pomagalo, kako u populaciji neverificiranih, tako i u audiološki verificiranoj populaciji, od ključne je važnosti učiniti dodatne napore da se takvim osobama povećaju spoznaje o prednostima i koristima upotrebe slušnih pomagala. Kako bi se ostvario ovaj cilj, nužan je multidisciplinaran javnozdravstveni pristup u rješavanju ovog zapostavljenog problema. Jedan od smjerova djelovanja bio bi pojačani audiološki probir populacije u domeni primarne zdravstvene zaštite. Drugi smjer djelovanja bio bi da se u sustavu i mreži javnog zdravstva osmisli nacionalni program ranog otkrivanja osoba oštećenog sluha u populaciji starijoj od 50 godina. Program bi trebao putem edukativnih sadržaja podizati svijest o potrebi liječenja i rehabilitacije nagluhih osoba. Treći smjer djelovanja bio bi provođenje randomiziranih kontroliranih studija kojima bi cilj bio ne samo prikupljati podatke povezane s prihvaćanjem, nošenjem i zadovoljstvom sa slušnim pomagalom, već ispitati i parametre koji su pokazatelji poboljšanja općeg zdravlja, kao što su emocionalno i socijalno funkcioniranje, komunikacijske sposobnosti te kognitivne mogućnosti.

Ključne riječi: **starije osobe, gubitak sluha, slušna pomagala, audiologija, javno zdravstvo**

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UVOD

Prema podatcima Svjetske zdravstvene organizacije (SZO) procjenjuje se da u svijetu ima oko 278 milijuna osoba s blagom do umjerenom nagluhošću (1) od kojih je samo u Sjedinjenim Američkim Državama 28-32 milijuna u svim dobnim skupinama (2,3). Međutim, evidentno je da prevalencija broja osoba, kao i jačina oštećenja sluha, drastično raste s dobi (1).

Kako se životni vijek produžuje, tako će u populaciji i udio osoba s nagluhošću porasti, prema predviđanjima sa sadašnjih 15 % na oko 20 % do 2030. godine (4). To potvrđuju i recentna istraživanja prevalencije osoba s oštećenjem sluha provedena u Europi i SAD-u, koja pokazuju da je oštećenje sluha prisutno u 25 % populacije u dobnoj skupini 51-65 godina, 10-33 % populacije u dobnoj skupini 65-75 godina, 25-60 % u dobnoj skupini 76-85 godina te 50-80 % u dobnoj skupini starijih od 85 godina (5). Ovako visoka prevalencija oštećenja sluha u starijoj životnoj dobi glavni je razlog da je ta prevalencija na trećem mjestu najčešćih bolesti u starijoj životnoj dobi – odmah iza hipertenzije i artritisa (2,6).

U Republici Hrvatskoj je prema popisu stanovništva iz 2011. godine bilo 758.633 stanovnika, tj. 17,7 % uku-

pnog stanovništva starijeg od 65 godina (7). Unutar te skupine procjenjuje se da ima između 30 i 50 % bitno nagluhih osoba (incidencija prema studijama provedenim u SAD-u). Međutim, unazad više od 10 godina u Hrvatskoj nije objavljena ni jedna epidemiološka studija prevalencije nagluhosti u populaciji starijih osoba.

Ipak, treba uzeti u obzir da podatci o rasprostranjenosti i jačini oštećenja sluha mogu međusobno varirati, ovisno o načinu i metodama prikupljanja podataka. Naime, neke studije rađene su putem probira telefonom. U tim studijama podatci su prikupljeni na osnovi izjave sudionika je li im sluh oslabio ili nije, dok je u drugima učinjena kompletna audiološka obrada (tonska i govorna audiometrija) uz prethodno ispitanu anamnezu i učinjenu otoskopiju. Ako je ispitivanje temeljeno na izjavi pojedinaca, njihovoj subjektivnoj procjeni o većem ili manjem oštećenju sluha, to može biti razlogom da rezultati procjene prevalencije budu veći odnosno manji u odnosu na rezultate dobivene audiološkom obradom. Iz dosad navedenih studija vidimo da starije osobe s oštećenjem sluha svoj slabiji sluh pripisuju godinama života. Budući da imaju reduciranu radnu aktivnost, imaju za razliku od mlađih osoba imaju i smanjenu potrebu za dobrim sluhom.

PROCJENA SLUŠNE OSJETLJIVOSTI

Procjena slušne osjetljivosti odnosno praga sluha određuje se tonskom audiometrijom (8). Ispitivanje se radi u tihoj prostoriji, kako bi dobiveni podatci bili što vjerodostojniji. Pri tome se ispituje na kojoj jačini (u decibelima; dB) osoba čuje čisti ton za svaku određenu frekvenciju (u hercima; Hz). Tu jačinu nazivamo prag sluha za svaku određenu frekvenciju, a vrijednosti se prikazuju grafički. Grafički prikaz praga sluha za pojedine čiste tonove nazivamo tonalni audiogram. On nam pokazuje mogućnosti percepcije zvukova neke osobe u tihoj prostoriji (8).

U svim je studijama gotovo podjednako graduirano oštećenje sluha na način da je u tonskoj audiometriji prag uredno čujećeg uha, po frekvencijama 0,5, 1, 2 i 4 kHz, na 0-25 dB. Prag blage nagluhosti je na 25-40 dB, umjerene na 40-55 dB, premda se u nekim studijama već prag nagluhosti veći od 35 dB tretira kao umjerena nagluhost. Umjereno teška nagluhost je na 55-70 dB, teška na 70-90 dB i jako teška s pragom većim od 90 dB, što je zapravo već klinički značajna gluhoća (9,10).

Govoreći o nagluhosti treba razlikovati tri osnovne vrste: provodnu, zamjedbenu i mješovitu (11). O provodnom oštećenju sluha govorimo ako je zapreka dovođenja zvuka u području vanjskog i srednjeg uha (zvukovoda i bubnjića), a o zamjedbenoj nagluhosti ako je oštećenje u području unutarnjeg uha i/ili slušnog živca. Međutim, govorimo li o nagluhosti u starijoj životnoj dobi, tada ponajprije mislimo na staračku nagluhost ili prezbiakuziju, koja je u prvom redu zamjedbenog tipa. Naime, nagluhost u toj dobi može biti i neke druge naravi kao posljedica brojnih drugih bolesti koje uzrokuju bilo provodna, bilo mješovita oštećenja sluha (12).

Upravo oštećenje sluha zamjedbenog tipa svojstveno je starijoj životnoj dobi (13). Prevalencija oštećenja sluha udvostručuje se svakom narednom dekadom života, tako da dvije trećine osoba starijih od 70 godina imaju klinički značajno oštećenje sluha koje znatno utječe na njihovu mogućnost komunikacije (13). Naime, u starijih osoba dolazi do slabljenja sluha u prvom redu zbog sporog i postupnog oštećenja slušnih stanica u pužnici (*organum Corti*), zaduženih za konverziju zvučnih signala u neurološke impulse, ali i slušnog živca, kojim se neurološki impulsi dalje prenose do slušnih centara u mozgu (11,14). Navedeno rezultira smanjenom slušnom osjetljivošću, što dovodi do podizanja praga sluha u tonskom audiogramu (8). To znači da će jačina zvuka morati biti pojačana da bi ju starija osoba mogla čuti. Ove promjene vezane uz proces starenja prvo zahvaćaju više frekvencije, one iznad 3 kHz, gdje vidimo značajno povišene pragove sluha, dok su niske i srednje frekvencije (0, 5, 1, 2, 3 kHz) u granicama normale (12).

Osobe s ovom vrstom oštećenja sluha subjektivno ne moraju imati osjećaj nagluhosti, ali imaju poteškoće slušanja suglasnika visokih frekvencija (14). Oni su pak važni za razumijevanje govora i mogućnosti razlikovanja riječi kao što su npr. „taj“ ili „daj“ . Upravo je gubitak sluha u visokim frekvencijama razlogom da osoba može krivo shvatiti što je bilo rečeno. Osobe će vjerojatno ispravno čuti samoglasnik zbog čega će svoj problem sa slušanjem pripisati nerazgovjetnom govoru sugovornika. Radije će tvrditi da drugi mrmljaju, odnosno dobro ne artikuliraju, nego da u tome prepoznaju karakteristični oblik vlastite nagluhosti. Poteškoće s razumijevanjem govora pojačavaju se u bučnom okruženju, koje često još više zasjeni zvukove visokih frekvencija. Kako progresija gubitka sluha napreduje, tako je sve veći gubitak sluha i u nižim frekvencijama, što rezultira sve većim poteškoćama razumijevanja govora, čak i u tišem okruženju.

Za točniju procjenu kolika je sposobnosti slušanja i razumijevanja govora, osim tonske audiometrije potrebno je učiniti i govornu, tijekom koje se osobi čitaju određene riječi na pojedinim jačinama u dB i traži se da te riječi ponovi (15). Ako uspije točno ponoviti određeni broj riječi u 50 % vremena, smatra se da može razumjeti govor. Međutim, iako se ispitivanje uglavnom obavlja u tihoj sredini, trebalo bi ga provesti

u uvjetima pozadinske buke (16), budući da se razgovori često vode u sredinama gdje je žamor, odnosno gdje više ljudi govori u isto vrijeme.

Gubitak sluha utječe i na međuodnos liječnik-pacijent (17), kada tijekom ispitivanja anamneze pacijent ne može jasno razumjeti postavljena pitanja, što onda dovodi do pogrešnog percipiranja liječnikovih savjeta. To može biti i opasno, jer ograničava pacijentovu mogućnost razumijevanja njegove dijagnoze ili preporučene terapije (17).

U konačnici, gubitak sluha je povezan i s većim rizikom za razvoj drugih bolesti kao npr. demencije, koja može biti pogrešno klasificirana u osoba s neotkrivenim ili nerehabilitiranim gubitkom sluha (2). Međutim, kako sluh postupno slabi tijekom godina, osobi ga nije lako prepoznati, budući da ga može kompenzirati verbalnom i neverbalnom, više ili manje, prilagođenom komunikacijom (18). To je razlogom da mnogi nisu svjesni svoje nagluhosti. Naime, u osoba koje uredno čuju, oslabljeni zvučni signali u mozgu se kompenzacijski popravljaju i dopunjuju uključivanjem drugih regija mozga, što rezultira boljim kontekstualnim razumijevanjem (19). Međutim, svako popratno kognitivno oštećenje dodatno pogađa kvalitetu slušne komunikacije, jer centralno dekodiranje zvuka u mozgu baš ovisi o mogućnosti korištenja dodatnih kognitivnih resursa. Radi toga se kod velikog broja starijih osoba, u pokušaju što bolje verbalne komunikacije, javlja dvostruka zapreka: oštećenja u području pužnice s jedne strane i otežanog dekodiranja zvuka u području mozga. Kod potonjeg se inače uključuju i druge moždane regije, no sada zbog određenih kognitivnih oštećenja ta potpora izostaje.

I podatci istraživanja u SAD-u, objavljeni 2014. godine, pokazuju da se prevalencija gubitka sluha u visokim frekvencijama (3, 4 i 6 kHz) kreće od 36 % u dobi 50-59 godina, do 59 % u dobi 60-69 godina, a u dobi od 70 i više godina još je i veća (20,21). Nadalje, uočena je niža prevalencija uz niže pragove sluha u Afroamerikanaca, nego u bijelaca i Latinoamerikanaca (20-22). Za ovu rasnu razliku nema za sada znanstvenog tumačenja. Međutim, jedna od hipoteza je da je ta razlika nastala zbog pigmentacije melaninom koji daje zaštitu osjetnim stanicama pužnice (23,24), dok je druga hipoteza da je to zbog različite dužine vremena izloženosti buci ili nekim drugim čimbenicima okoline (25). Nadalje, genetska su istraživanja otkrila čimbenike koji kontroliraju na molekularnoj razini putove između osjetnih stanica unutarnjeg uha i slušnog živca (14). Međutim, do koje razine su povezani genetski faktori i rasa, odnosno etnička pripadnost vezano uz prevalenciju slabljenja sluha, još je nepoznato.

BOLESTI POVEZANE S OŠTEĆENJEM SLUHA

Pozitivnu korelaciju oštećenja sluha vidimo, osim već ranije navedenih uzroka, također i kod nižeg stupnja edukacije, prethodne vojne službe, izloženosti buci na radnom mjestu, kod alkoholizma, šećerne i kardiovaskularne bolesti (26-28), loše prehrane i pušenja duhana (29,30), ali i uz socioekonomski status pojedinca. Osobe s nižim stupnjem obrazovanja i nižim materijalnim prihodima imaju veću vjerojatnost za nastanak oštećenja sluha. To potvrđuju i studije iz Norveške i Australije (20,21,31,32). To je naročito bilo vidljivo u starijih osoba nižeg stupnja obrazovanja, bijelaca i Latinoamerikanaca. Spomenute studije su pokazale da su subjektivne procjene jačine nagluhosti osoba oštećenog sluha bile potpuno različite od one koju su imali članovi njihove obitelji. Nadalje, istraživanje iz 2005. godine na 2169 osoba pokazalo je da je samo 45 % osoba oslabljenog sluha o tome razgovaralo sa svojim obiteljskim liječnikom (33). Očito je da je u starijoj populaciji još uvijek velik broj znatno nagluhih koji ne traže liječničku pomoć. Međutim, u osoba koje su prema tvrdnji obitelji imale poteškoće u komunikaciji, audiometrijski je bila ustanovljena tek blaga nagluhost. To ukazuje da je audiometrijski utvrđeni stupanj nagluhosti nedovoljan pokazatelj stvarne kvalitete sluha i mogućnosti kvalitetnog slušanja. Ovaj podatak nam ukazuje da čak i audiometrijski blaga oštećenja sluha imaju potencijal za stvaranje funkcionalnih teškoća i zbog toga potencijal da umanje kvalitetu života, što dodatno kompliciraju otegotni čimbenici koji prate starenje poput smanjenja viših kognitivnih funkcija.

Brojne do danas provedene studije potvrđuju upravo tu vezu koja vjerojatno nije jednosmjerna, već dvosmjerna.

Istraživanja provedena unazad 35-40 godina pokazala su da u dobnoj skupini osoba treće životne dobi nagluhost dovodi do bitnog oštećenja zdravlja budući da dolazi do slabljenja kognitivnih funkcija, mentalnog, psihosocijalnog i fizičkog zdravlja (34-36). Također, registrirana je i veća pojavnost depresije, anksioznosti, paranoje, psihoza, kao i povećani rizik za razvoj nesigurnosti, socijalne izolacije i nesuglasica u obitelji (37-39). Starije osobe oslabljenog sluha imaju i povećane probleme u obavljanju dnevnih i instrumentalnih aktivnosti te veći rizik od nastanka demencije (40,41).

Oštećenje sluha značajno je povezano s manjom samosvijesti o slabijoj fizičkoj funkcionalnosti koja zbog toga može doprinijeti većem gubitku samostalnosti. To je potvrđeno u više provedenih istraživanja u kojima je ispitivano ima li određeni stupanj oštećenja sluha, koji je audiometrijski dokazan, utjecaja na umanjene dnevne aktivnosti poput oblačenja, hranjenja, kupanja, kao i instrumentalne aktivnosti svakodnev-

nog života poput upotrebe telefona, obavljanja lakših kućanskih poslova, snalaženja u kućnim financijama i pranja rublja (42).

Utjecaj oštećenja sluha na kvalitetu života bio je ispitivan do sada u nekoliko studija koristeći različite parametre procjene. Međutim, bilo da se procjena oštećenja sluha temeljila na audiometrijskom nalazu ili samoprocjeni, i u jednoj i u drugoj skupini pokazao se utjecaj oštećenja sluha na fizičku aktivnost i komunikacijsku i socio-emocionalnu kvalitetu života (43). U studijima provedenim na ispitanicima prosječne dobi 67 godina, prema izjavama ispitanika, oštećenje sluha je imalo najveći utjecaj na njihovu fizičku aktivnost i komunikacijsku i socio-emocionalnu kvalitetu života, nego što su imale bolesti poput dijabetesa, hipertenzije, angine pektoris i išijasa (44,45).

Oštećenje sluha bilo je na trećem mjestu prema jačini negativnog utjecaja na tjelesnu komponentu zdravlja, nakon respiratornih bolesti i artritisa, te na drugom mjestu (odmah iza digestivnih smetnji) po utjecaju na mentalnu komponentu ocjene zdravlja (44,45). Osobe oštećenog sluha u dobi od 55 godina imale su niže vrijednosti specifičnih pokazatelja kvalitete života u području tjelesnog i mentalnog zdravlja (46).

Novija istraživanja su potvrdila, nakon praćenja tijekom proteklih pet godina, pozitivnu korelaciju između jačine oštećenja sluha i opsega kognitivnih oštećenja, što znači da veće oštećenje sluha rezultira smanjenjem opsega kognitivnih funkcija (47-50). Buduća istraživanja trebala bi objasniti koji je biološki mehanizam u podlozi ove povezanosti. Poteškoće u komunikaciji osoba oštećenog sluha negativno utječu kako na nagluhu osobu, tako i na članove obitelji, osobito ako žive u zajedničkom kućanstvu (51). Manifestacije tih poremećaja mogu u osoba slabijeg sluha utjecati na njihov život uzrokujući stres i gubitak socijalne interakcije, koja se u obliku frustracija manifestira povlačenjem iz socijalnih odnosa, izbjegavanja određenih društvenih događanja, što onda može voditi u depresiju. Zatim, često dolazi i do razvoja promijenjenih, poremećenih kućnih odnosa kao posljedica npr. pojačanih zvukova radija ili televizora. Neka istraživanja su ukazala na negativni utjecaj osoba oštećenog sluha na svog partnera, odnosno suprugu/supruga, koji češće pokazuju slabije fizičko funkcioniranje, što se očituje smanjenjem tjelesne energije, a osim toga pokazuju znakove depresije ili se ne osjećaju sretnim. Međutim, ovi poremećaji u komunikaciji su češće izraženi u obiteljima osoba koje imaju poteškoća u slušnoj komunikaciji, a nisu audiometrijski obrađene i ne prihvaćaju činjenicu da imaju poteškoće sa slušanjem, što onda rezultira frustracijama partnera i članova obitelji (52).

Generalno govoreći, slabljenje sluha, odnosno oslabljeni sluh, kod svake osobe dovodi do smanjene kvalitete života, a više provedenih studija potvrdilo je kako postoji pozitivna korelacija između socijalne podrške i subjektivnih doživljaja kvalitete života (53).

U studiji iz 2011. godine u Hrvatskoj, na 155 članova udruge slijepih i teško nagluhih, ispitivano je u kakvom su odnosu subjektivna procjena kvalitete života i doživljaja socijalne podrške ovisno o upotrebi ili neupotrebi slušnih pomagala (54). Osobe koje su koristile slušno pomagalo imale su statistički značajno veće vrijednosti izražene na ljestvici ocjene subjektivnog doživljaja kvalitete života (QOL), kao i u ocjeni kvalitete zdravlja, životnog zadovoljstva, doživljaju socijalne potpore i bliskih odnosa u obitelji. Studija je pokazala kako korištenje slušnih pomagala rezultira većom percepcijom socijalne podrške, koja je najjači prediktor sveukupne kvalitete života (QOL) (54). Međutim, usprkos ovim činjenicama, prihvaćanje i nošenje slušnih pomagala je relativno rijetko u odnosu na ukupan broj osoba koji su izjavile da imaju poteškoće sa slušanjem (55,56).

U procjeni ovih učinaka od velike je važnosti odabir parametara po kojima će se procjenjivati.

Tako će na procjenu kvalitete života upotrebom, npr. probirnog testa kojim se ispituju hendikepi starijih osoba oslabljenog sluha (HHIE-s), a koji je specifičan za starije nagluhe osobe, dobiveni rezultati najvjerojatnije pokazati puno veći utjecaj nagluhosti na kvalitetu života, nego što bi to bilo vidljivo iz nekog testa za općenitu procjenu kvalitete života (HHIE-čitavi upitnik), koji je manje osjetljiv za ocjenu utjecaja slušnog pomagala na kvalitetu života, vezano uz komunikaciju (57,58).

Nagluhost kao posljedica starenja je progresivna i za nju trenutno nema lijeka. Međutim, mogućnosti zbrinjavanja su dobre, mada u pojedinim državama, ovisno o vrstama zdravstvenog osiguranja mogu biti skupe za pojedinca.

SLUŠNA POMAGALA U REHABILITACIJI SLUHA

Novije studije u kojima je ocjenjivana učinkovitost više vrsta slušnih pomagala, kao što su standardna slušna pomagala, programibilna slušna pomagala, koja se mogu podesiti za slušanje u različitim slušnim okruženjima, kao i razni uređaji za pomoć slušanju, kao npr. ALDs (engl. *assistive listening devices)* samo su potvrdili ranije dobivene rezultate o pozitivnom učinku slušnih pomagala na sposobnost slušanja. Novije studije, u kojima je ocjenjivana učinkovitost standardnih i programibilnih slušnih pomagala (koja se

mogu podesiti za slušanje u različitim slušnim okruženjima) te raznih uređaja za pomoć kod slušanja kao što su ALDs, samo su potvrdila ranije navode o pozitivnom učinku tih uređaja na komunikaciju, a time i na socijalnu i emocionalnu dobrobit njihovih korisnika (59). Uspoređujući prevalencije osoba treće životne dobi, koje su koristile slušno pomagalo, tijekom dvaju vremenskih razdoblja u proteklih 15 godina, pokazalo se da se nije povećala incidencija osoba koje koriste slušna pomagala – unatoč tehnološkom napretku tih pomagala (60,61). U dvije recentne studije, provedene u SAD-u i Australiji, u zajednicama u kojima je nošenje slušnih pomagala slabo zastupljeno, ispitano je zašto osobe oslabljenog sluha ne prihvaćaju korištenje slušnih pomagala (62,63). Neki od navedenih razloga bili su: materijalni troškovi, različiti problemi vezani uz nošenje aparata poput otežanog postavljanja i skidanja, ugađanja glasnoće i zamjena baterija, nadalje loše iskustvo osoba koje već imaju ili su imale slušno pomagalo, kao i vlastiti osjećaj da im pomagalo ne treba (62,63).

U anketi provedenoj *on line* i telefonom tijekom 2011. u SAD-u na 2232 osobe starije životne dobi cilj je bio saznati koje probleme imaju vezano uz nagluhost, koliko su ih svjesni, odnosno koliko ih doživljavaju kao problem i kakvi su im stavovi vezani uz potrebu za slušnim pomagalom (64). Anketa je pokazala da su osobe starije životne dobi daleko sklonije učiniti npr. kontrolu krvnog tlaka, kolesterola i kontrolu vida, nego testiranje sluha.

Možemo zaključiti da starije osobe i članovi njihovih obitelji često ne pridaju prioritet problemima povezanima uz gubitak sluha, budući da se on postupno razvija, rekli bismo „podmuklo". Može se pretpostaviti da, kad bi uz gubitak sluha bila povezana i bol, tada bi vjerojatno ranije i brže takve osobe poduzele određene korake. Ponekad članovi obitelji nastoje kompenzirati slabiji sluh voljene osobe tako da preuzimaju konverzaciju tijekom posjeta liječniku ili tijekom nekih drugih susreta (17). Članovi obitelji trebali bi se prestati tako ponašati i shvatiti kako time doprinose tome da voljena osoba nikada ne zatraži stručnu pomoć glede oslabljenog sluha. Tako se gubi svaka inicijativa za slušnom rehabilitacijom, budući da drugi ljudi slušaju umjesto njih samih.

Istraživanja su pokazala da je samo 43 % ispitanika u proteklih 5 godina pristupilo testiranju sluha, dok ih je nasuprot tomu 85 % kontroliralo krvni tlak, 81 % razine kolesterola, a 88 % testiralo vid. Mamografija i pregledi prostate također su bili zastupljeniji od kontrole sluha (64).

U studiji na populaciji od 2956 osoba prosječne dobi 67,4 godine u Australiji, tijekom 5 godina, ispitana je prevalencija osoba s oslabljenim sluhom, čimbenici povezani s odlukom o nošenju/nenošenju slušnog pomagala i postotak onih koji su prihvatili upotrebu slušnog pomagala (65). Prag sluha bio je određen audiometrijski, uz prethodnu kompletnu obradu audiologa koja je uključivala i pitanja o slušnim pomagalima (65). Iz rezultata je bilo vidljivo da 33 % ispitanika ima oštećenje sluha; ali ih je samo 11 % imalo slušno pomagalo, od kojih ga je 4,4 % upotrebljavalo tijekom proteklih 12 mjeseci, dok ga 24 % nikada nije koristilo (65). Od onih koji su ga koristili 8,5 % koristilo ga je tijekom manje od 1 godine, 46 % tijekom 1-5 godina, 18,9 % tijekom 6-10 godina i 26,4 % dulje od 10 godina. Od svih ispitanika s oštećenjem sluha samo ih se jedan od troje odlučio prihvatiti slušno pomagalo, a samo jedan od četvero ga je i koristio (65).

Većina (60,5 %) osoba koje su nosile i koristile slušno pomagalo koristilo ga je samo 1 sat/dan, a 24,1 % 8 sati/dan (65). Slični podatci navedeni su i u ranijim studijama provedenim u Australiji (66,67), a vezano uz 8-satno korištenje slušnih pomagala (25 % odnosno 26,5 %).

Interesantni su i odgovori na pitanje zašto nisu koristili slušno pomagalo koje su imali: 30 % izjavilo je: „nije mi pomoglo", 28 %: „previše mi je bilo bučno", 28 %: „bilo mi je neudobno", 8,4 %: "slušno pomagalo je zviždalo", 2,8 %: „nismo ga mogli postaviti", 1,4 %: „baterije su preskupe" a 1,4 % izjavilo je: „nije radio" (65). Zanimljivo je kako nitko nije izjavio da slušno pomagalo nije koristio zbog estetskih razloga ili stigme. Ne iznenađuje podatak da je novac bio nekima zapreka za nabavku slušnog aparata. Naime, 28 % izjavilo je da njihovo zdravstveno osiguranje ne pokriva u dovoljnoj mjeri troškove vezane uz njegovu nabavku, 27 % misli da su slušni aparati preskupi, dok ih oko 8 % nema zdravstveno osiguranje. Čak trećina ispitanika izjavila je da im je lakše živjeti sa slabijim sluhom nego ići tražiti tretman, jer nošenje slušnog pomagala ionako, prema njihovom mišljenju, ne rješava sve probleme vezane uz nagluhost (64).

Danas na tržištu postoji veliki izbor slušnih pomagala koja se međusobno znatno razlikuju po cijeni i tehničkim karakteristikama (68). Kvalitetnija slušna pomagala mogu selektivno pojačati određene frekvencije, glasnoću ili smjer iz kojega zvuk dolazi, unutar kompleksnog zvučnog signala (68).

Osobama s oštećenim sluhom mora biti jasno da slušna pomagala ne obnavljaju postojeća oštećenja senzo-neuralnog sustava, ali mogu osigurati bolju jačinu zvuka i razumljivost govora u različitim uvjetima slušanja. Međutim, većini osoba potrebno je određeno razdoblje adaptacije prije nego uspiju u potpunosti ostvariti korist od slušnih pomagala (69).

Budući da su jedno vrijeme živjeli u tišem okruženju jer su slabije čuli, nakon što počnu koristiti slušno pomagalo mozak se mora ponovo prilagoditi na zvukove koje nije čuo dulje vrijeme pa stoga korisnici slušnih pomagala moraju biti upoznati s tim procesima (69).

U osoba s urednim sluhom u bučnom okruženju mozak automatski profiltrira i procesuira zvuk koji je osobi važan, dok se drugi zvukovi zanemaruju (68). Međutim, kada se u istom okruženju nalazi osoba oštećenog sluha, njoj je ta mogućnost smanjena zbog slabe mogućnosti pužnice za neuralno enkodiranje zvuka. U toj situaciji pojačanje zvuka putem slušnog pomagala samo joj djelomično pomaže ublažiti taj nedostatak, jer i najbolje slušno pomagalo ima ograničene mogućnosti selektivnog pojačanja zvukova (68).

Korist od upotrebe slušnog pomagala može tada biti upitna, budući da je u prostorima u kojima je jaki žamor (kao npr. u restoranima) glasnoća željenog zvuka stišana, a okolna buka visoka. Međutim, u takvom slušnom okruženju, pomoćni uređaj za slušanje (ALDs) može poboljšati kvalitetu zvuka, budući da zvuk hvata u blizini njegovog izvora i prenosi ga bežično do slušnog pomagala ili nekog posrednog '*strimer*' uređaja. Danas takvi uređaji mogu poboljšati kod upotrebe slušnih pomagala omjer zvuka i buke, čime se poboljšava razumljivost i kvaliteta slušanja putem slušnog pomagala**.**

OSJEĆAJ HENDIKEPA ZBOG NAGLUHOSTI

Audiometrijom utvrđena jačina oštećenja sluha nije uvijek u skladu sa stupnjem poteškoća koju će ta osoba iskusiti tijekom komunikacije. Primjerice, osobe s blažim oštećenjem sluha ne trebaju nužno uvijek i u svim prilikama koristiti slušno pomagalo. Međutim, osobe s teškom nagluhošću i gluhoćom imaju općenito veće poteškoće u komunikaciji pa bi im uporaba slušnih pomagala vjerojatno češće koristila, pogotovo u komunikacijski povoljnim situacijama (npr. poput tihog okruženja, razgovora 1-na-1 i slično) (70). Radi toga, trebalo bi se više usredotočiti upravo na tu skupinu osoba, kako bismo bolje spoznali razloge radi kojih se nisu odlučili potražiti liječničku pomoć, odnosno nisu zatražili slušno pomagalo (65,70).

Također se pokazalo kako je upotreba slušnih pomagala bila u pozitivnoj korelaciji s dobi ispitanika, jačinom nagluhosti i samopercepcijom invalidnosti povezane s nagluhošću (65). Unatoč tome što su dosadašnja istraživanja pokazala da je upotreba slušnog pomagala povezana s poboljšanom sposobnošću komuniciranja (71) i boljom kvalitetom života (72), boljom mentalnom sposobnošću (73) i manjom usamljenošću (74). U Finskoj, u populaciji osoba starijih od 80 godina s pragom iznad 35 dB HL, čak 75 % ne nosi slušno pomagalo (75), a u Velikoj Britaniji manje od polovice osoba starijih od 60 godina s teškom nagluhošću (prag sluha iznad 75 dB HL) upotrebljava slušno pomagalo (76). U Engleskoj je među starijom populacijom gotovo polovica onih koji su sami primijetili da imaju poteškoće sa sluhom, a da o tome nisu razgovarali sa zdravstvenim djelatnicima tako da nisu bili audiološki obrađeni.

Rezultati nisu ohrabrujući budući da pokazuju kako je u starijoj populaciji malo osoba koje imaju slušno pomagalo, a još manji broj onih koji ga koriste (65). Ispitanici su izjavili da bi vjerojatno u većoj mjeri zatražili pomoć audiologa kada bi vjerovali da će im to poboljšati kvalitetu života, odnosno kada bi osjećali da im je njihova nagluhost ograničavajući faktor u komunikaciji sa članovima obitelji i prijateljima. Naglasili su da bi prihvatili nositi slušno pomagalo kada bi im, primjerice, voljena osoba ili unučad to preporučila, jer jako žele biti povezani sa svojom unučadi, barem putem mobilnih uređaja ako već ne mogu uživo (65).

Velik broj ispitanika izjavio je da bi vjerojatno nešto poduzeli povezano s njihovom nagluhosti da su imali saznanje kako bi to poboljšalo njihovu mentalnu i fizičku sposobnost (64). Članovi obitelji trebali bi prema voljenim osobama oslabljenog sluha biti manje kritičko-osuđujući nastrojeni, a više otvoreni i iskreni. Primjer takvog ponašanja bio bi kada bi roditelju: mami/tati npr. rekli: "Bila/bio si ovih dana vrlo šutljiva/šutljiv tijekom obiteljskog ručka/večere", ili primjerice kada bi rekli: „Tata/mama, primijetio sam da te onaj vic nije nasmijao".

Međutim, starije osobe koje su još uvijek radno aktivne shvaćaju da nagluhost nije samo problem vezan uz starenje. Održavanje dobrog sluha, od presudnog je značenja za dobru učinkovitost na radnom mjestu, osobito ako žele maksimalno produžiti svoj radni vijek u svjetlu nadolazeće ekonomske nesigurnosti (77).

Istraživanja su pokazala kako se kod osoba koje su prihvatile nositi slušno pomagalo to očitovalo u većem samopoštovanju, većoj samostalnosti, zdravijem međuodnosu i poboljšanom mentalnom zdravlju. Poboljšanje u osoba sa slušnim pomagalom dokumentirano je rezultatima dobivenim tijekom provođenja probirne verzije testa vezanog uz saslušanja hendikepa zbog gubitka sluha (HHIE-S) (78). Osim toga i mjerenje parametra kao što je kvaliteta života također može ukazivati na poboljšanje funkcioniranja (79).

CILJANE PREPORUKE I PREPORUČENI SMJEROVI DJELOVANJA

S obzirom na znatnu prevalenciju starijih osoba oštećenog sluha, koje ne koriste slušno pomagalo, kako u populaciji neverificiranih, tako i u audiološki verificiranoj starijoj populaciji, bilo bi od velike važnosti učiniti dodatne napore da se starijim osobama oslabljenog sluha povećaju saznanja o prednostima i koristima upotrebe slušnih pomagala. Jednako tako i mogućim posljedicama i problemima vezanim uz njegovo nekorištenje s ciljem prevencije nepotrebnog morbiditeta. Na taj način vjerujemo da bi znatno veći broj osoba oštećenog sluha bio potaknut na odluku za upotrebu slušnog pomagala.

Svakako da su potrebna daljnja istraživanja kako bismo mogli bolje razumjeli zašto neke osobe traže pomoć, a druge ne. Saznali bismo i koji su to ključni čimbenici koji dovode do odluke da netko zatraži slušno pomagalo. Potrebno nam je postaviti si za cilj povećati u populaciji broj audiološki obrađenih, ponajprije starijih osoba, a za ostvarenje tog cilja trebalo bi istovremeno učinkovitije djelovati u više smjerova.

1) Probir sluha u ordinacijama obiteljske medicine

Jedan od smjerova bio bi započeti audiološki probir populacije u domeni primarne zdravstvene zaštite u svrhu otkrivanja potencijalnih kandidata za slušnu rehabilitaciju. Djelatnici primarne zdravstvene zaštite mogu u tome doprinijeti da uoče osobe kojima bi koristilo nošenje slušnog pomagala, informirati ih o realnim mogućnostima i očekivanjima glede korištenja slušnih pomagala te ih kontinuirano pratiti tijekom korištenja slušnog pomagala.

Budući da probirni testovi i dijagnostika nisu teški za pacijente, pitanje je samo koje testove koristiti za probir i na kojoj populaciji, kako bi se optimizirala njihova učinkovitost (80). Algoritam za njegovo provođenje u ordinacijama obiteljske medicine mogao bi biti: 1. postaviti pitanje: "Imate li bilo kakve poteškoće sa slušanjem"; 2. učiniti test šaptanjem (za upotrebu testa šapatom, trebalo bi napraviti standardizaciju); 3. za pacijente koji su izjavili da nemaju poteškoća sa slušanjem učiniti test audiootoskopom. U slučaju pozitivnog nalaza pacijenta uputiti na detaljnu audiološku obradu unutar koje bi se učinila tonska i govorna audiometrija. Međutim, vidjeli smo iz učinjenih studija da sam probir nagluhosti neće povećati odluku o upotrebi slušnog pomagala u populaciji s oštećenim sluhom (65). Vjerojatno starije osobe još uvijek imaju u sjećanju sliku svojih starijih članova obitelji koji su se "borili" s ondašnjim starim modelima slušnih pomagala, koji su daleko zaostajali za današnjom tehnologijom.

Audiolozi iz SAD-a naglašavaju kako nije dovoljno pacijentu samo odrediti i postaviti slušno pomagalo. To znači da bi s pacijentom, koji je dobio slušno pomagalo, bilo potrebno provesti slušne vježbe. (64). Međutim, iz vlastitog iskustva možemo posvjedočiti da se slušne vježbe provode samo na našim klinikama. U županijskim i gradskim bolnicama slušne aparate propisuju naši otorinolaringolozi (koji nemaju subspecijalizaciju iz audiologije), a nakon što pacijent preuzme slušni aparat, logoped ne provodi slušne vježbe, jer te bolnice nisu za to opremljene.

Iz provedenih studija je jasno kako su ispitanici izjavili da bi vjerojatno u većoj mjeri zatražili stručnu pomoć, kada bi bili uvjerenja da će im to poboljšati kvalitetu života. Međutim, izazov koji stoji pred nama je postignuće stalnog nošenja odabranog slušnog pomagala nakon što je dijagnoza potvrđena, unatoč njegove cijene, percipirane stigme i percipiranoj svijesti o njegovoj maloj koristi.

Informacije o svim tim mogućnostima trebalo bi na sve moguće načine podjednako usmjeriti kako prema liječnicima obiteljske medicine, tako i korisnicima domova umirovljenika i raznim religijskim zajednicama, a s ciljem podizanja svijesti o važnosti slušne rehabilitacije za sveukupno zdravlje osoba s oštećenjem sluha.

2) Nacionalni program ranog otkrivanja nagluhosti

Drugi smjer u kojem bi trebalo djelovati je da se sustavom i mrežom javnog zdravstva osmisli jedan nacionalni program ranog otkrivanja gubitka sluha u populaciji starijoj od 50 godina, koji će putem edukativnih programa podizati svijest o potrebi liječenja i rehabilitacije nagluhih osoba. To bi svakako pridonijelo skidanju stigme s tih osoba u društvu, ali i boljem odazivu za prihvaćanje nošenja slušnih pomagala. Za postizanje potonjeg cilja bi svakako trebalo poraditi i na što većoj dostupnosti slušnih pomagala (81).

S ciljem podizanja učinkovitosti ovih napora trebalo bi i smanjiti troškove oko nabavka slušnih pomagala, povećati njihovu učinkovitost i poraditi na povećanju svijesti o važnosti rehabilitacije sluha. Različiti probirni testovi pokazali su dobru prihvaćenost kod pacijenata, pouzdanost i točnost uz relativno male troškove (9).

Mišljenje američkih audiologa iz ASHA (*American Speech-Language-Hearing Association*) je da bi razne inicijative i edukacije povezane sa značenjem gubitka sluha trebale biti usmjerene na pojašnjenje kako oštećenje sluha nije hendikep sam po sebi, već da je ono u pozitivnoj korelaciji s mogućnošću da osoba zadrži svoju razinu komunikacije, odnosno povezanosti **što** je ključno za održanje dobrog zdravlja u starijoj životnoj dobi. (82).

3) Provođenje randomiziranih studija

Treći smjer djelovanja bio bi provođenje randomiziranih kontroliranih studija koje bi imale za ciljeve ne samo ispitivati i prikupljati podatke povezane s prihvaćanjem, nošenjem i zadovoljstvom sa slušnim pomagalom, već ispitivati i parametre koji su pokazatelji poboljšanja zdravlja kao što su npr. emocionalno i socijalno funkcioniranje, komunikacijske sposobnosti te kognitivne mogućnosti.

Buduće analize trebale bi simultano istražiti relativne učinke uzročnih čimbenika kao što su čimbenici životnih stilova, psihološki aspekti, znanje o zdravlju, faktori okoliša i zdravog načina ponašanja. Naime, poznato je da socioekonomski čimbenici kao što su stupanj obrazovanja i visina materijalnih prihoda utječu na odluku o upotrebi slušnog aparata (83,84). Rješavanje ovih izazova povećat će vjerojatnost da se zadovolje potrebe starije populacije oko brige kako održati dobru razinu sluha i osnaže osobe oštećenog sluha na upotrebu slušnih pomagala, a sve kako bi i nadalje ostali zdravi i aktivni članovi unutar svoje obitelji i društva u cjelini.

ZAKLJUČAK

Ovih nekoliko navedenih studija pokazuje da oslabljen sluh može imati negativne učinke na kvalitetu života, glede zdravlja općenito, a osobito u domeni socijalne i emocionalne razine komuniciranja. Možemo zaključiti da upotreba slušnih pomagala može poboljšati ove komunikacijske tegobe i time poboljšati kvalitetu života. Neki od dobivenih podataka iz provedenih istraživanja potvrđuju da je slabljenje kognitivnih sposobnosti povezano sa slabljenjem sluha, no radi se o fenomenu koji nije samo medicinske naravi, već za sobom povlači čitav niz drugih posljedica. Shodno tome nužan je multidisciplinaran javnozdravstveni pristup u rješavanju ovog zapostavljenog problema.

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SUMMARY

THE IMPACT OF HEARING IMPAIRMENT ON THE DEVELOPMENT OF HEALTH AND COGNITIVE DIFFICULTIES IN THE ELDERLY: A REVIEW OF THE LITERATURE AND THE PROPOSED DIRECTION OF PUBLIC HEALTH ACTION

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Hearing loss is associated with negative effects on the quality of life, especially in the domain of social and emotional communication aptness, with the problem being particularly conspicuous in old age when it can also be linked to cognitive impairment. In addition, elderly individuals who are still working realize that hearing loss is not just an aging problem, since maintaining good hearing is indispensable for workplace effectiveness. Given the substantial prevalence of hearing-impaired, non-rehabilitated individuals, both in the unverified and audiologically verified elderly population, it is pivotal to make additional efforts in order to increase the awareness of the benefits of hearing aids. Consequently, a multidisciplinary public health approach is warranted to address this highly neglected issue. One of the salient directions to tackle this problem would be increased audiological screening of the population within the primary health care arena, in order to identify the potential candidates for hearing rehabilitation. Another direction is to design a national program for early detection of hearing loss in the population over the age of 50 by utilizing available public health system and network, which will subsequently (i.e., with the use of educational programs) raise awareness regarding the treatment and rehabilitation of hearing-impaired individuals. The third line of action would be to conduct randomized controlled studies aimed not only towards hearing aid acceptance, wearing and satisfaction data gathering, but also to examine the parameters that are indicators of overall health improvement, such as emotional and social functioning, communication skills and cognitive abilities.

Key words: **elderly, hearing loss, hearing aids, audiology, public health**

SINDROM UKOČENE OSOBE I TORAKALNA HIDROMIJELIJA

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Prikazujemo prvi slučaj pacijentice sa sindromom ukočene osobe i pridruženom torakalnom hidromijelijom s pozitivnim antitijelima na glutamatdekarboksilazu. U literaturi je do sada opisan samo slučaj sindroma ukočenog psa s pozitivnim antitijelima na glutamatdekarboksilazu te cervikalnom siringomijelijom zbog Arnold-Chiarijeve malformacije. Glutamatdekarboksilaza je enzim nužan za sintezu gama-aminomaslačne kiseline, inhibicijskog neurotransmitera. Manjak gama-aminomaslačne kiseline dovodi do poremećaja ravnoteže ekscitacijskih i inhibicijskih utjecaja na alfa-motoneurone prednjih rogova kralježnične moždine te posljedične kontinuirane stimulacije mišića što se klinički prezentira rigiditetom i nekontroliranim mišićnim spazmima. Hidromijelija hipotetski izaziva oštećenje i gubitak GABAergičkih neurona kralježnične moždine što dovodi do imunološkog odgovora na antigene enzima glutamatdekarboksilaze. Možemo pretpostaviti da je značajan broj bolesnika s ovim sindromom neprepoznat, odnosno da im je utvrđena pogrešna dijagnoza te da nisu liječeni na adekvatan način.

Ključne riječi: sindrom ukočene osobe, hidromijelija, glutamatdekarboksilaza, gama-aminomaslačna kiselina

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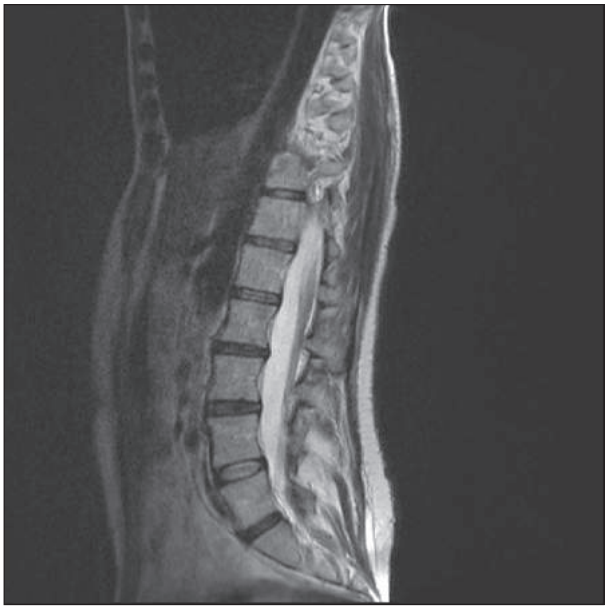
UVOD

Prikazujemo prvi slučaj pacijentice sa sindromom ukočene osobe („stiff person syndrome"; Moersch-Woltman; SPS) i pridruženom torakalnom hidromijelijom. SPS je rijedak neurološki entitet koji obuhvaća skupinu autoimunih poremećaja koji se prema kliničkoj slici klasificiraju na: klasični SPS, paraneoplastički SPS, SPS varijante (fokalna ili segmentna), SPS s mioklonizmima, SPS-plus i progresivni encefalomijelitis s rigiditetom i mioklonizmima) (1,2). Kod pacijenata sa SPS-om utvrđene su sljedeće vrste antitijela: antitijela na glutamatdekarboksilazu (GAD), presinaptički protein amfifizin, postsinaptički protein gefirin, glicinski alfa-1 ili GABA receptor (2). Sindrom je rijetko povezan s drugim neurološkim poremećajima, ali se kao komorbiditeti mogu javiti brojne autoimune bolesti. Prvi opis SPS-a potječe iz 1956. godine, kada su Moersch i Woltman u Mayo klinici opisali 14 bolesnika (3).

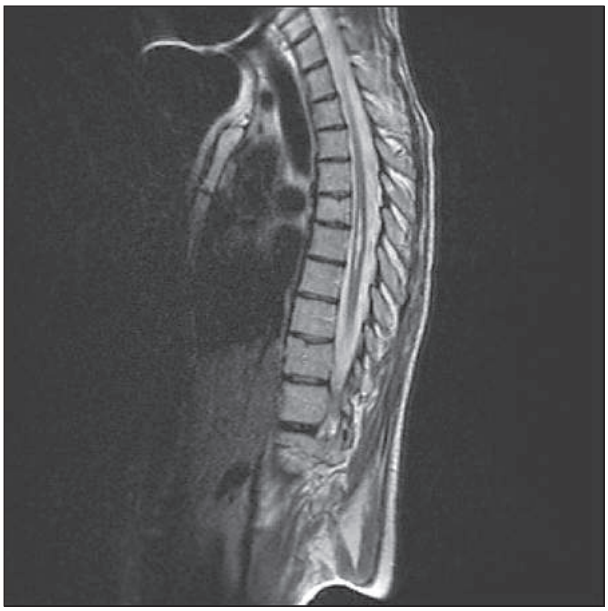
PRIKAZ BOLESNICE

Tridesetdevetgodišnja pacijentica hospitalizirana je na Odjelu neurologije zbog višemjesečnih smetnji u obliku bolova u donjem dijelu leđa s propagacijom u obje noge te zbog povremenih grčeva u mišićima potkoljenica i stopala. Ranije joj je dijagnosticiran Hashimotov tireoiditis. Pri prijmu se neurološkim pregledom utvrdi sljedeće: uredna funkcija kranijskih živaca, meningealni znakovi su negativni, bez šumova nad karotidnim arterijama. Motorika, tonus i osjet na rukama su uredni. Miotatski refleksi na rukama su simetrični, srednjeg inteziteta. Noge osciliraju u položaju po Mingazziniju uz facilitirane miotatske reflekse i obostrano pozitivan Babinskijev refleks. Tonus na nogama je spastički povišen. Lasegueov znak je negativan. Koordinacija i kontrola sfinktera su uredni. Ne registrira se siringomijelički tip disocijacije osjeta na trupu i nogama. Hod pacijentice je spastičko-paraparetičan. Prisutna je lumbalna hiperlordoza i torakalna dek-

strokonveksna skoliza (sl. 1). Tijekom pregleda pacijentica signalizira povremene bolne spazme mišića stopala. S obzirom na tip kliničkih tegoba na početku dijagnostičke obrade napravi se elektromioneurografija (EMNG). Elektroneurografska obrada pokazala je uredne motorne i senzorne brzine provodljivosti. Elektromiografskom obradom registrirano je izbijanje akcijskih potencijala motoričke jedinice (MUAPs; engl. *motor unit action potentials*; potencijali motoričke jedinice) uredne morfologije, u mirovanju, u antagonističkim mišićnim skupinama, bez miotonih izbijanja, uz pozitivan odgovor na i. v. aplikaciju diazepama (pozitivan diazepamski test, odnosno prestanak izbijanja MUAPs nakon aplikacije). Nalaz je osobito izražen u torakalnoj paravertebralnoj muskulaturi. S obzirom da su navedene anamnestičke tegobe, klinička slika i nalaz EMNG obrade ponajprije suspektni na SPS, napravi se dodatna ekstenzivna obrada s ciljem dijagnosticiranja SPS-a te isključenja ev. paraneoplastičke varijante ovog poremećaja. Nalazi laboratorijske obrade (hematologija, koagulogram, reumatski testovi, imunologija) su uredni. Uredna je i većina biokemijskih testova osim CK 210 U/L (<177). Uredni su i nalazi hematološke i biokemijske obrade likvora. Oligoklonske IgG vrpce u likvoru su negativne. Analiza seruma i likvora na neurotropne uzročnike je negativna. Uredni su nalazi hormona štitnjače i tumorskih biljega (CEA, CA 125, CA 19-9, CA 15-3, CYFRA 21-1, AFP). Antitijela na amfifizin su negativna. Nalazi EEG-a, MSCT-a toraksa, abdomena i zdjelice, MR-a mozga, vratne i lumbosakralne kralježnice, te nalazi ginekologa, mamografije i ultrazvuka dojki su u granicama normale. Pozitivan je nalaz anti-GAD antitijela u serumu, a MR torakalne kralježnice pokazuje hidromijeliju od visine trupa kralješka Th5 do gornjeg ruba trupa kralješka Th8, centralnog položaja i maksimalnog promjera od 3,5 mm (sl. 2). Praćenje vrijednosti anti-GAD antitijela pokazalo je sljedeće rezultate: anti-GAD 3283 IU/mL (11/2017.), >2000 IU/mL (02/2018.), >2000 IU/mL (09/2018.), 2929 IU/mL (02/2019.), 2929 IU/mL (08/2019.), 2345 IU/mL (02/2020.), >2000 IU/mL (02/2021.). Tijekom razdoblja 2017.-2021. kod pacijentice kontrolnim pretragama nismo dokazali postojanje malignog tumora. U navedenom razdoblju liječena je u dva navrata plazmaferezom, i.v. imunoglobulinima (svakih 6 mjeseci) te simptomatskom terapijom diazepamom, baklofenom i nesteroidnim antireumaticima uz gastroprotekciju. Uz ovu terapiju u navedenom se razdoblju ne registrira značajnije pogoršanje neurološkog statusa. Pacijentica trenutno uzima 40 mg diazepama (20 mg + 10 mg + 10 mg) i 15 mg baklofena (3x5 mg) i terapiju dobro podnosi.



Sl. 1. *MR lumbosakralne kralježnice – sagitalni presjek na T2 mjerenoj slici – lumbalna hiperlordoza*



Sl. 2. *MR torakalne kralježnice – sagitalni presjek na T2 mjerenoj slici - hidromijelija*

RASPRAVA

Opisani slučaj je klasični oblik SPS-a s pozitivnim anti-GAD antitijelima (pozitivna su u 60–90 % slučajeva klasičnog oblika SPS-a) te ujedno prvi slučaj SPS s pridruženom torakalnom hidromijelijom. U literaturi je do sada opisan samo slučaj anti-GAD pozitivnog sindroma ukočenog psa s pridruženom vratnom siringomijelijom zbog Arnold-Chiarijeve malformacije (4). SPS se najčešće javlja u 3. do 5. desetljeću života

i kao većina autoimunih bolesti dva je puta češći kod žena što se može vidjeti i u ovom slučaju. Često dolazi u kombinaciji s drugim autoimunim bolestima – u ovom slučaju to je Hashimotov tireoiditis. GAD je enzim nužan za sintezu GABA-e, inhibicijskog neurotransmitera. Manjak GABA-e dovodi do poremećaja ravnoteže ekscitacijskih i inhibicijskih utjecaja na alfa-motoneurone prednjih rogova kralježnične moždine. Kada je funkcija GAD značajno reducirana, snižena je razina GABA-e, a mišići su kontinuirano stimulirani impulsima iz motoneurona što rezultira rigiditetom i nekontroliranim mišićnim spazmima (1). Moguće je da hidromijelija izaziva oštećenje i gubitak GABA-ergičkih neurona kralježnične moždine što dovodi do imunološkog odgovora na antigene enzima GAD smještenog u sinaptičkim završetcima (4). Dijagnostički kriteriji za SPS uključuju: 1. rigiditet aksijalne muskulature (rana faza), 2. rigiditet proksimalne muskulature ekstremiteta (kasna faza), 3. lumbalnu hiperlordozu, 4. „startle" fenomene – mišićni spazmi provocirani pokretom, stresom, taktilnim, zvučnim ili svjetlosnim podražajima, 5. izostanak znakova i simptoma lezije gornjeg i donjeg motornog neurona, ekstrapiramidnog sustava, uredna kontrola sfinktera, uredna kognicija i osjet, 6. karakterističan nalaz EMNG obrade (opisan u prikazu slučaja), 7. visok titar antitijela na GAD ili amfifizin (5). Naša pacijentica zadovoljava sve dijagnostičke kriterije osim 5. kriterija jer su zbog torakalne hidromijelije prisutni znakovi lezije gornjeg motoričkog neurona. Diferencijalno dijagnostički pri sumnji na SPS potrebno je isključiti sljedeće bolesti: latentni autoimuni dijabetes odraslih, „spinalnu" multiplu sklerozu, hiperekpleksiju, tetanus, konverzivnu neurozu i histeriju, mioklonu epilepsiju, distoniju, neuromiotoniju (Isaacov sindrom), Schwartz-Jampelov sindrom, otrovanje strihninom, paraneoplastički mijelitis i spinalnu arterio-vensku malformaciju (6). Inicijalno liječenje uključuje primjenu benzodiazepina (diazepam ili klonazepam) ili baklofena zbog njihovog agonističkog djelovanja na GABA-A, odnosno GABA-B receptore (7,8). U liječenju se koriste i.v. imunoglobulini (u ukupnoj dozi od 2 g/kg, i to na dva načina: 0,4 g/kg i. v. tijekom 5 dana ili 1 g/kg tijekom dva dana), plazmafereza (obično 5 plazmafereza svaki drugi dan, ali se mogu rabiti i kraći, kao i duži protokoli, ovisno o kliničkoj slici), kortikosteroidi (prednizon u dozi 0,75-1,5 mg/kg/dan tijekom 2 tjedna, potom jednaka doza svaki drugi dan 2-4 mjeseca), azatioprin, ciklofosfamid, rituksimab, tinazidin, gabapentin, botulinus toksin tip A, dantrolen, vigabatrin, propofol, natrijev valproat, levetiracetam, tiagabin, analgetici, fizikalna terapija, psihijatrijsko liječenje (9).

ZAKLJUČAK

Zaključno, može se reći da iako rijedak, SPS je klinički važan, osobito uzevši u obzir postojanje paraneoplastičke varijante bolesti. Dijagnosticiranje ovog sindroma često je dugotrajan proces pri kojemu je potrebno isključiti brojne kliničke entitete koji diferencijalno-dijagnostički dolaze u obzir. Možemo pretpostaviti da je značajan broj bolesnika s ovim sindromom neprepoznat, odnosno da im je utvrđena pogrešna dijagnoza te da nisu liječeni na adekvatan način.

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SUMMARY

STIFF PERSON SYNDROME AND THORACIC HYDROMYELIA

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Here we present for the first time a case of a patient with stiff person syndrome and associated thoracic hydromyelia and positive antibodies to glutamate decarboxylase. To our knowledge, only one case of antiglutamate decarboxylase positive stiff dog syndrome with associated cervical syringomyelia due to Arnold-Chiari malformation has been described in the literature so far. Glutamate decarboxylase is an enzyme necessary for the synthesis of gamma-aminobutyric acid, an inhibitory neurotransmitter. Gamma-aminobutyric acid deficiency leads to disturbance of the equilibrium of excitatory and inhibitory effects on the anterior horn alpha-motoneurons at the level of spinal cord and consequent continuous muscle stimulation, which is clinically presented by rigidity and uncontrolled muscle spasms. Hydromyelia hypothetically may cause damage to and loss of GABA-ergic neurons of the spinal cord leading to an immune response to the newly exposed glutamate decarboxylase antigens. We can assume that a number of patients with stiff person syndrome have not received complete diagnosis and therefore are not optimally treated.

Key words: **stiff person syndrome, hydromyelia, glutamic acid decarboxylase, gamma aminobutyric acid**

IS EVEROLIMUS INVOLVED IN THE PATHOGENESIS OF IMMUNOTHROMBOCYTOPENIA IN A RENAL TRANSPLANT RECIPIENT WITH RENAL ADENOCARCINOMA?

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DEAR EDITOR,

Thrombocytopenia is frequent in renal transplant recipients and is most commonly caused by suppression of the bone marrow, especially in the early stage of transplantation (1). Paraneoplastic syndromes are a group of malignancy-associated disorders that occur due to immune response to the tumor or hormones produced by tumor itself. Some cases can present as immune-mediated hematological diseases, such as immune thrombocytopenia (ITP) (2). These can present prior to the cancer diagnosis, concurrent with cancer or in a period of complete remission. Recent meta analysis showed that autoantibody testing in ITP patients has a high specificity but low sensitivity, and concluded that a positive autoantibody test can be useful for ruling in ITP, but a negative test does not rule out ITP (3). Paraneoplastic ITP associated with renal cancer after renal transplantation has not been reported. A 43-year-old male patient with end-stage renal failure due to sepsis after the war-injury had replaced his renal function with hemodialysis from 1996 until 2003 when he received a renal allograft from a deceased donor. Immunosuppressive regiment included cyclosporine, mycophenolatemofetil and steroid, with no other concomitant drugs. The posttransplant course was uneventful until 2019 when his right native kidney was removed due to finding of a complicated Bosniak type IV cystin his native kidney on routine examination. Eventually, patohistology verified the mass to be a clear cell renal carcinoma, staged pT3aN0R0. Postoperatively, cyclosporine was replaced with everolimus. Three months later, patient had developed petechial rash on lower extremities. Laboratory examination verified severe thrombocytopenia [$10x10^9$/L] with stable allograft function and normal findings of other laboratory parameters. Hematologic workup revealed positive IgG anti-human platelet antibodies on glycoprotein Ia/IIa complex (GP Ia/IIa) in serum, thus implying of possible immune etiology of thrombocytopenia. Patient responded well to 3 days of therapy with 6-methilprednisone pulses (125 mg each) and platelet count increased to $60x10^9$/L. However, in the further follow-ups, patient's platelet count decreased to $34x10^9$/L, thus therapy with eltrombopag has been introduced (1x50 mg per day) what resulted with increase of platelet count to $110x10^9$/L and their stabilization at this level.Rituximab was not used in order to avoid further immunosuppression in the context of malignancy but also due to the beginning of the COVID-19 pandemic. After 12 months of follow-up our patient has no residual or recurrent cancer as determined by computerized tomography.

Paraneoplastic ITP most commonly occurs in patients with lung and breast cancer and, although rare, there had been some published cases of this phenomenon in renal cell cancer. In most patients, it responded well to steroids (4).

The only change in medications in our patient was replacement of cyclosporine with everolimus. Everolimus is approved for use in kidney and liver transplant patients, and is used for prophylaxis for organ rejection. Some patients who had undergone this therapy showed increased rate of thrombocytopenia (5). In the context of positive antithrombocyte antibodies, the most probable cause of thrombocytopenia is paraneoplastic syndrome. However, everolimus, although reported to improve paraneoplastic immunothrombocytopenia (6) may contribute to development of immunothrombocytopenia by decreased suppression of antibody production in general. Namely, everolimus was suspected initially to be associated with an increased risk of donor specific antibody production (7), what neither was not case in our patient, nor was found in large studies including the TRANSFORM study (8). GPIIb/IIIa antibodies were reported in a patient with renal cancer (9), and were negative in our patient. Possible explanation for positive GP Ia/IIa but not GPIIb/IIIa might be performance characteristics of autoantibody testing especially with low number of platelets as was present in our patient (3).

In conclusion, patients with thrombocytopenia after renal transplantation should undergo careful diagnostic evaluation and paraneoplastic origin of symptoms should be considered in the differential diagnosis. Everolimus may be involed in development of immunothrombocytopenia by allowing antibodies production.

We declare that this manuscript is original and has not been published before or currently being considered for publication elsewhere.

We know of no conflicts of interest associated with this case report and declare any financial support.

We submit this case report with consent given by a case patient.

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Guluyer AY, ur. Health indicators. An international study for the European Science Foundation. Oxford: M. Robertson, 1983.

Poglavlje u knjizi

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Terauchi Y, Takamoto I, Kubota N. Glucokinase and IRS-2 are required for compensatory beta cell hyperplasia in response to high-fat diet-induced insulin resistance. J Clin Invest [Internet]. 2007;117. [cited 2007 Aug 12]. Available from: http://www.jci.org/cgi/content/full/117/1/246

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The Journal of the Academy of Medical Sciences of Croatia

Acta Med. Croatica • Vol. 75 (1) • pp 1-108 • Zagreb, March 2021.

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