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CHRONIC KIDNEY DISEASE
KRONIČNA BOLEST BUBREGA

Papers presented at 12th BANTAO (The Balkan Cities Association of Nephrology,Dialysis, Transplantation and Artificial Organs) Congress, Opatija, Croatia, October 15th - 18th, 2015

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EDITORIAL

The Balkan Cities Association of Nephrology, Dialysis, Transplantation and Artificial Organs (BANTAO) was born in Ohrid on October 9, 1993. The war in former Yugoslavia negatively affected the development of nephrology and also the connections among nephrologists from the Balkans. However, there was willingness for further collaboration among nephrologists from the Balkans. The war in Yugoslavia created hate among people and the newly established countries, and there were problems with recognition of the names of the new countries; so, the nephrologists decided to apply the ancient principle of using the names of cities instead of countries as founders of the Association. The main goal of BANTAO is to promote scientific and technical cooperation in the fields of renal disease and artificial organs between the regions on the Balkan Peninsula and the world, to give an opportunity for exchange of experience and knowledge among experts in the area, and to engage in collaborative projects in order to demonstrate that cooperation is possible even on the turbulent Balkan Peninsula. The first BANTAO congress was held in Varna, 1995 (President, D. Nenov, Varna). The second congress of BANTAO was held in Struga, 1997 (President, M. Polenaković, Skopje). The third BANTAO congress was held in Belgrade, 1998 (President, Lj. Djukanović, Belgrade). The fourth congress of BANTAO was held in Izmir, 1999 (President, A. Akcicek, Izmir). The fifth congress of BANTAO was held in Thessaloniki, 2001 (President, P. Stathakis, Athens). The sixth congress of BANTAO was held for the second time in Varna, 2003 (President, D. Nenov, Varna). The seventh congress of BANTAO was held in Ohrid, 2005 (President, - M. Polenaković, Skopje). The eighth BANTAO congress was held in Belgrade, 2007 (President, V. Nešić, Belgrade). The ninth BANTAO congress was held in Antalya, 2009 (President, A. Basci, Izmir). The tenth BANTAO congress was held in Chalkidiki, 2011 (President, D. Tsakiris, Thessaloniki). The eleventh BANTAO congress was held in Timisoara, 2013 (President, A. Schiller, Timisoara). At the seventh BANTAO Congress, a CME Course was organized for the first time by ERA/EDTA and ISN/COMGAN entitled Frontiers in Nephrology, with seven distinguished speakers. A very important event in the existence of BANTAO was the appearance of the BANTAO Journal in 2003. The BANTAO Journal has been published biannually since 2003. Editors of the Journal were as follows: D. Nenov, 2003-2005; A. Basci, 2005-2009; and G. Spasovski, 2009-to the present.

The BANTAO Congress was established as the major scientific and institutional forum for Balkan nephrologists, with its own journal, indicating our will to communicate, to collaborate, to get to know each other, and to share our difficulties. More than just a professional event, the BANTAO Congress has become a cultural phenomenon, through which we have discovered that we have many more things in common than we previously thought, and that now we must take every advantage to live and communicate in a world without political boundaries.

At present, the BANTAO Council has managed, in the spirit of peace, friendship and collaboration, to continuously strengthen this association, and moreover, to make it a reputable partner to the European and international associations. It is obvious that the BANTAO Council has succeeded in its initial targets. It is essential that nephrologists must come to know each other better. Now, more than ever, we have to learn what unites us, to tone down and even forget what divides us, to renew old and make new friendships, and to strengthen our peaceful relations, keeping in mind that we all work under the same oath of Hippocrates. It is in this 'BANTAO spirit', a spirit not only of local but also of global importance that could provide the basis for a peaceful world. Hence, we can achieve our goals only by joining together in our common beliefs and by collaborating and acting toward these objectives. In this way, we can live in a 'world without boundaries', a peaceful and prosperous one, even though confronted with the numerous boundaries that have been placed.

After the First BANTAO Congress, F. Valderrábano, then Chairman of the EDTA/ERA Registry, wrote in Nephrology Dialysis Transplantation (1996;11:740): "Nephrologists of the Balkan countries meet across political frontiers and war fronts – an example to politicians!"

Prof. Petar Kes, MD, PhD
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CORRELATION BETWEEN ATTITUDES AND EATING HABITS AND SERUM LEVEL OF PHOSHPATES IN HEMODIALYSIS PATIENTS

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Nutritional problems in hemodialysis (HD) patients are frequently associated with poor control of serum phosphorus what may lead to chronic kidney disease-metabolic bone disease. Hyperphosphatemia is an important risk factor for extraskeletal and vascular calcifications and is associated with cardiovascular morbidity and mortality. Increased ingestion of phosphorus is an important factor in development of hyperphosphatemia.

We investigated nutritional habits and attitudes of HD patients and determined their correlation with serum phosphate levels in 57 patients treated in Clinical centre Montenegro. Twenty-two patients were male (38.6%), with average age 57 (range, 30-73 years). Statistically significant correlation was found between red meat or milk ingestion and serum phosphate, as well as between educational level and serum phosphate. In our population, socioeconomic level was directly correlated with serum phosphate. Conclusion: a serum phosphate level is determined by socioeconomic level, ingestion of red meat and milk, and depends on educational level in HD population of the capital of Montenegro.

Key words: end-stage renal disease; hemodialyisis; hyperphosphatemia; nutritional status

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INTRODUCTION

Hyperphosphatemia is an significant and common disorder in patients with chronic kidney disease and occurs as a result of reduced renal elimination of phosphates and disordered bone remodeling, with simultaneous continuous intestinal absorption of phosphate and it is often associated with poor clinical outcome[(1)]. Hormonal regulation of serum phosphate includes activation of 1.25 dihydroxy vitamin D(1,25(OH)^2 vitamin D), fibroblast growth factor 23 (FGF-23), with the cofactor Klotho, and parathyroid hormone (PTH)[(2)]. The system of FGF-23 Klotho has a significant role in the regulation of homeostasis of phosphate. Klotho is a co-receptor for phosphatiuric hormone FGF-23. FGF-23 is secreted by osteocytes and osteoblasts in response to increased oral intake of phosphate and increased serum levels of 1,25 (OH)^{2}D3. Phosphate retention is a critical moment in the pathophysiology of chronic kidney disease (CKD). Hyperphosphatemia occurs early in the third stage of CKD, and it's evidenced by increased serum FGF-23, which precedes the increased concentration of PTH and serum phosphate concentration[(3)].

There is correlation between hyperphosphatemia and increased risk of CKD and mortality in the general population, and an increased risk of mortality in patients with CKD who are undergoing chronic intermittent hemodialysis. Hyperphosphatemia is an independent risk factor for increased mortality in patients with CKD, whether

they are on chronic dialysis programme or not[4]. The high rate of mortality in patients with CKD is associated with cardiovascular disorders (CVD), which are responsible for over 50% of deaths among patients in the terminal stage of CKD. Sudden cardiac death, heart failure, ischemic heart disease and peripheral artery disease are the primary cause of cardiovascular mortality in those patients[5]. Those cardiovascular diseases are directly associated with vascular calcifications, which are pathological disorder that occurs as a result of hyperphosphatemia. The main characteristic of vascular calcification is the deposition of calcium phosphate in the form of hydroxyapatite in arteries, myocardium and heart valves. Calcification of blood vessels is an active process regulated by inhibitors and promoters of calcification[6]. Hyperphosphatemia leads to worsening of CKD-MBD (bone mineral disorder in chronic kidney disease). Continuous stimulation of the parathyroid glands with increased concentrations of extracellular phosphate, especially when it is associated with a reduced extracellular concentrations of ionized calcium and significantly reduced serum concentrations of calcitriol leads to increased production of PTH. As a result of all this pathophysiologycal mechanisms polyclonal diffuse hyperplasia of parathyroid glands accompanied by monoclonal nodular hyperplasia is common in those patients. Severe form of secondary hyperparathyroidism may exacerbate hyperphosphatemia by turning out phosphorus from the bones. In some cases, the PTH-induced bone changes can progress to Brown's tumors, which are a product of the rapid destruction of bone reabsorption, with the bleeding and replacement of the normal bone tissue, with granulation tissue[7]. Increased serum phosphate level is also associated with endothelial dysfunction and elevated FGF-23, what contribute to left ventricular hypertrophy as an independent risk factor for mortality in CKD[8].

Phosphate intake from food is an important factor which contributes to the development of hyperphosphatemia, but its bioavailability depends on various factors such as the origin of food (animal or plant) and the types of food (organic or inorganic phosphates). The organic phosphates are generally found in food rich in proteins, including animal and vegetarian sources of proteins and dairy products[9]. Inorganic phosphates are used as feed additives in the form of additives that improve the color and flavor of food, and their bioavailability is almost 100%[10]. The organic phosphates from dairy products, meat, poultry and fish can become easily available as inorganic phosphates after a many hydrolytic processes what is reason why diet rich in animal protein associated with the development of hyperphosphatemia in patients with CKD. On the other hand phosphates plant origins are in the form of phytic acid or phytate and because there is no human form of the enzyme phytase bioavailability of this source of phosphate is low (20-40%)[11]. Group of foods that are rich in phosphates include: red meat, milk and dairy products (cheese, goat's milk, sheep's milk), grains (wheat germ, bran, soybean meal, rice), soups made with additives that are rich in phosphate, mushrooms, fish, mainly sea fish, a moderate proportion of phosphate containing chocolate, ice cream, carbonated beverages, pasta, snacks[12].

Man with weight 70 kg contains 700 g of phosphorus , of which 85% goes to the bones and teeth , 14% of the soft tissues, and 1% in the blood and extracellular fluids. 40-80% of phosphate entered by nutrition will be absorbed in the digestive tract. During hemodialysis, can be removed and 600 mg of phosphorus. According to the recommendations of the European Renal Best Practice (ERBP) daily protein intake must be at 1.1 g/kg "dry" weight[13].

Modern therapeutic approaches in controlling of hyperphosphatemia in patients who are on chronic hemodialysis programme include multiple modalities: 1. Regulation of phosphate intake through nutrition, which involves reducing intake of foods rich in phosphates. This type of regulation of phosphate homeostasis in recent times is in the focus of interests[14], 2. More intensive dialysis processes, which require longer and more frequent dialysis improves phosphate homeostasis[15], 3. Usage a phosphate binder can also contribute to the regulation of serum phosphate concentration. Studies have shown that the usage of a phosphate binders is associated with a substantial reduction in the risk of mortality in the multivariate analyzes[16]. The benefits are related to the basic values of serum phosphate and lowering the concentration of FGF-23 which has been increased up to 100 times in patients with untreated form of hyperphosphatemia, who are undergoing hemodialysis programme[17]. Applicable KDIGO (Kidney disease-Improving Global Outcome) guidelines recommend the use of phosphate binder for the treatment of hyperphosphatemia of III-V stages of CKD[18].

However, a reduced intake of protein foods rich in phosphates may disturb the nutritional status by type PEW (protein-energy malnutrition) which represents a significant risk factor for increased mortality in these patients. PEW is the "short term killer" in those patients[19]. Inflammation and oxidative stress are important factors that lead to protein-energy malnutrition, which consecutively leads to increased mortality of these patients[20].

Nephrologists have a key role, who in team with a nutritionist and medical technicians should participate in the education of patients with CKD treated with hemodialysis about the types of foods that can be consumed, eating habits in order to achieve an adequate intake of foods rich in phosphates and consecutive better regulation of serum phosphate levels[21].

AIM

The aim of this study was to investigate attitudes and eating habits of patients who has been treated by the hemodialysis and to determine the correlation between attitudes and habits of patients on chronic hemodialysis, and serum phosphorus in those patients.

PATIENTS AND METHODS

The survey was conducted in March 2015. It was conducted among the patients at the Center for hemodialysis, Clinic for Urology and nephrology, Clinical Center of Montenegro. The study incuded patients who are on chronic hemodialysis programme, two to three times a week, lasting 4 hours or 4.5h. The subjects were informed about the objectives of the research, after which they voluntarily agreed to participate. The sample included 57 patients who were at the time of the survey the chronic hemodialysis program at the Center for Hemodialysis, Clinical Center of Montenegro. Eight patients (12.30%) were refused participation in the study. The rate of inclusion of the patients was 87.69%.

The survey instrument was a questionnaire. The questionnaire consists of 31 questions. It contains basic socio-demographic information about patients, data on nutritional habits, attitudes and knowledge about nutrition, information on physical activity and other habits. The survey was anonymous and there were no issues that would be used for identification purposes. The response rate to the questions amounted to 99.79%.

Also, in this study we used the laboratory data on serum levels of phosphorus, which is under regular control laboratory findings do several times a month. Laboratory analyzes are conducted at the Center for Clinical Laboratory Diagnostics, Clinical Center of Montenegro.

The data were processed in the software program SPSS (Statistical Package for Social Science) version 20.

RESULTS

The study included 57 patients undergoing chronic intermittent hemodialysis in Center for haemodialysis , Clinical Center of Montenegro. The parameters of reasarch are presented in Table 1 (age and serum phosphorus (PO_4)), while the distribution of values in relation to the categories is presented in Table 2 (gender, level of education and informing patients about the specifics of diet on hemodialysis. Also , the distribution of serum phosphate (PO_4) is listed in Table 2 and causes of terminal stage of CKD in those group of patients (Fig. 1).

Table 1.

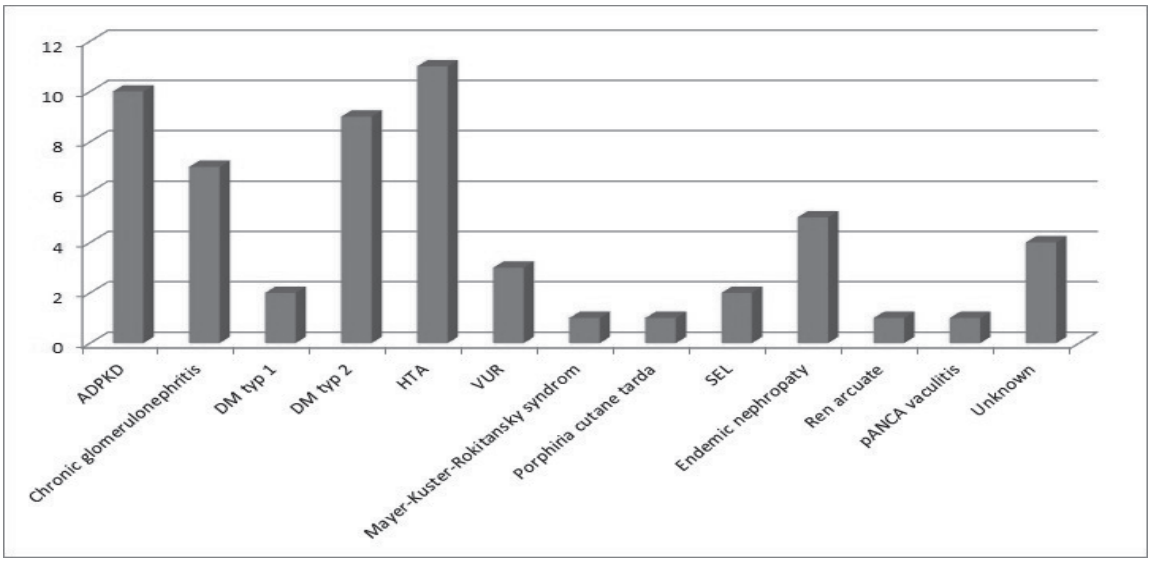
Parameter	**Mean** (std.dev.) minimum - maximum
Age	**57.07** (9.71) 30 - 73
PO_4	**2.18** (0.61) 1.22 - 3.77

Table 2.

Parameter	Category	Number of patients (%)
Gender	Male	21 (37.50%)
	Female	35 (62.50%)
Level of education	Elementary school	13 (23.64%)
	Secondary school	31 (56.36%)
	Higher education	4 (7.27%)
	Faculty	7 (12.73%)
Awareness about special food treatments	Yes	34 (59.65%)
	No	1 (1.75%)
	Partially	22 (38.59%)
Serum level of phosphate (PO_4)	Normal	11 (19.29%)
	Cat1	23 (40.35%)
	Cat2	20 (35.09%)
	Cat3	3 (5.26%)

Figure 1.

Causes of terminal stage of CKD

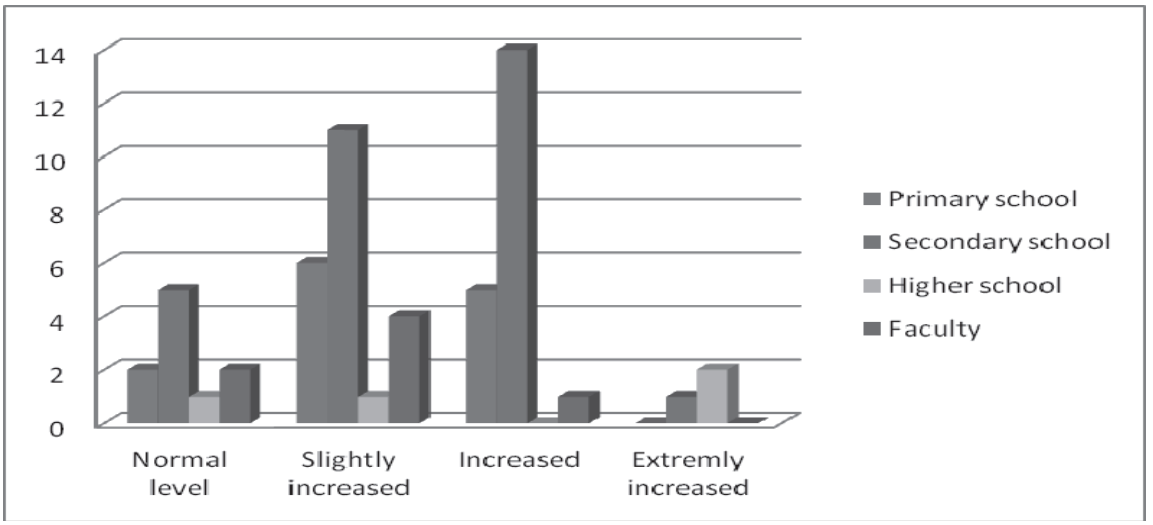


Below are the results of an analysis comparing the differences between the groups in relation to the category of serum phosphate (PO_4).

χ^2 test showed that there is a statistically significant difference between the serum levels of phosphate and education of patients (χ^2 (9,55) = 20.569, p = 0.014 <0.005). Among the patients with normal serum levels of phosphate most of them has finished secondary school while those with extremely elevated serum phosphate values are mostly in category with higher education (Fig. 2).

Figure 2.

Level of education and serum level of phosphate



Regarding the consumption of red meat χ^2 test results show that there is a statistically significant difference in the values of the increased serum level of phosphate (χ^2 (9,55) = 18.703, p = 0.036 <0.05). Among the patients with extremely elevated serum levels of phosphate most of them used to consume red meat more than five times a week (Fig. 3).

χ^2 test results show that there is a statistically significant difference in the values of the extreme values of serum phosphate regarding to consumption of milk and milk products (χ^2 (9,50) = 16.019, p = 0.05 $\leq$0.05). Among patients with extremely elevated serum phosphate most of them used to consume milk and dairy products more than five times a week (Fig. 4).

Figure 3.

Red meat and serum level of phosphates

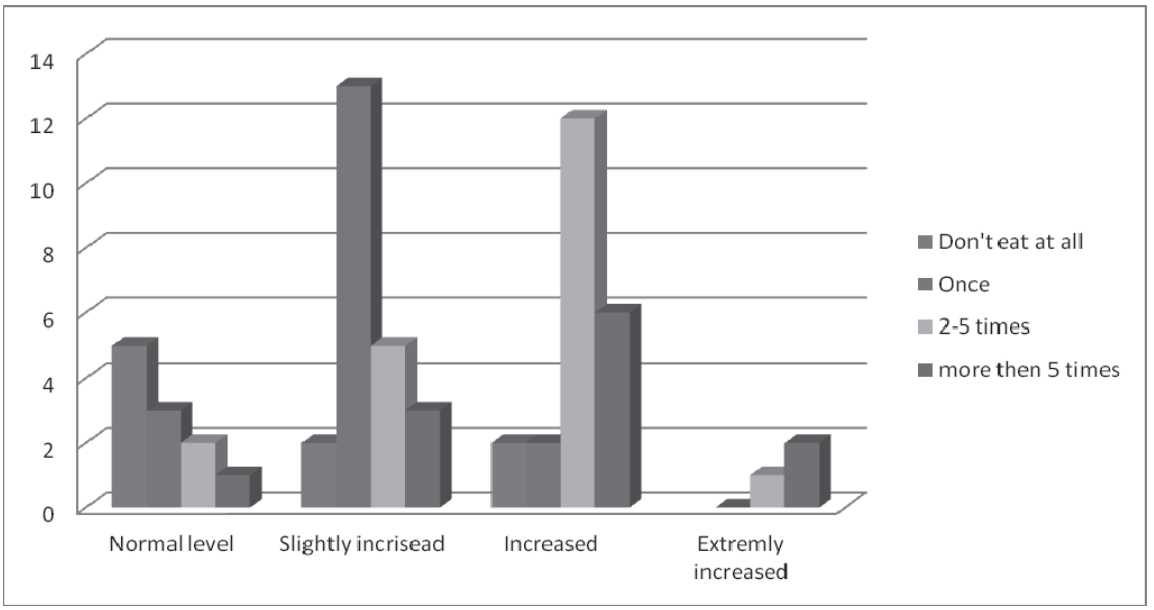
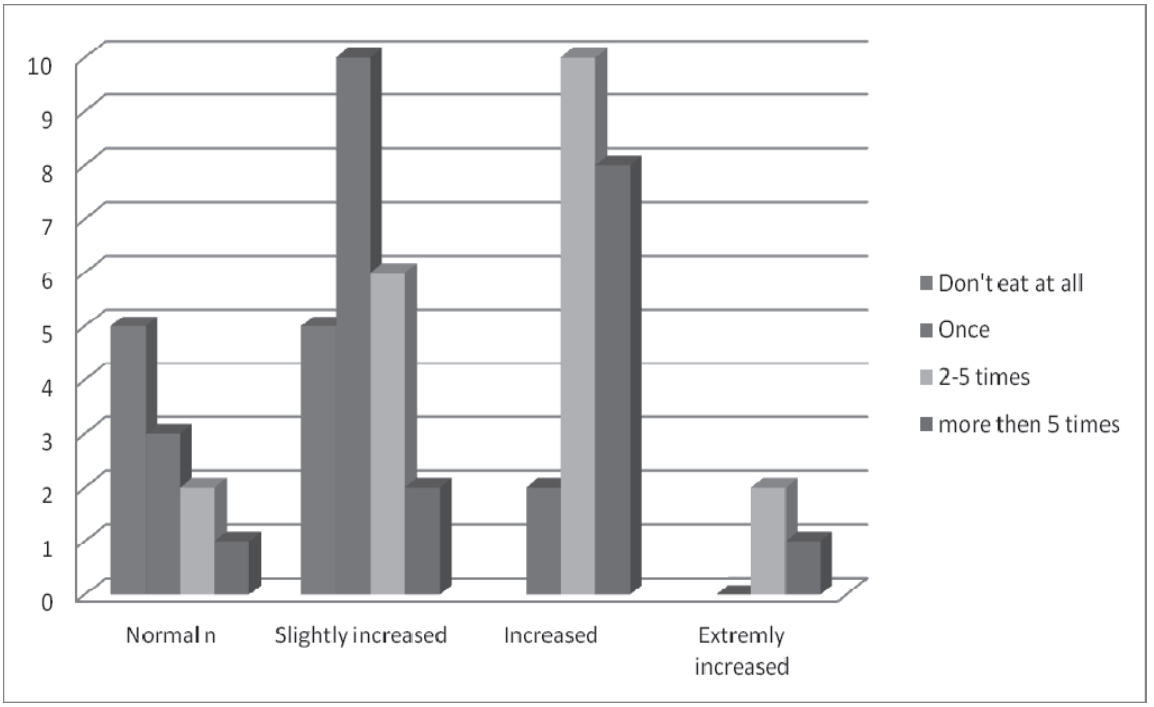


Figure 4.

Consumption of milk and milk products and serum level of phosphates



χ^2 test results show that there is a statistically significant difference in the values of the extreme values of serum phosphate in subjects with respect to the consumption of carbonated drinks (χ^2 (9,55) = 23.000, p = 0.001 <0.05). Among patients with extremely elevated serum phosphate most of those who consume soft drinks more than five times a week (Fig. 5).

χ^2 test results show that there is a statistically significant difference between the extreme values of serum phosphorus in patients in relation to the place of food consumption among 19 patients who had previously responded to have meals outside the home (χ^2 (6,19) = 13.242 , p = 0.039 <0,05). Among patients with extremely elevated serum phosphorus values most of them used to eat in bakeries,

while a slightly lower value of serum phosphate concentration is found in those patients who eat in restaurants and fast food markets. Respondents with normal serum concentrations of phosphate used to eat exclusively in restaurants (Fig. 6).

Figure 5.

Carbonated drinks and serum level of phoshates

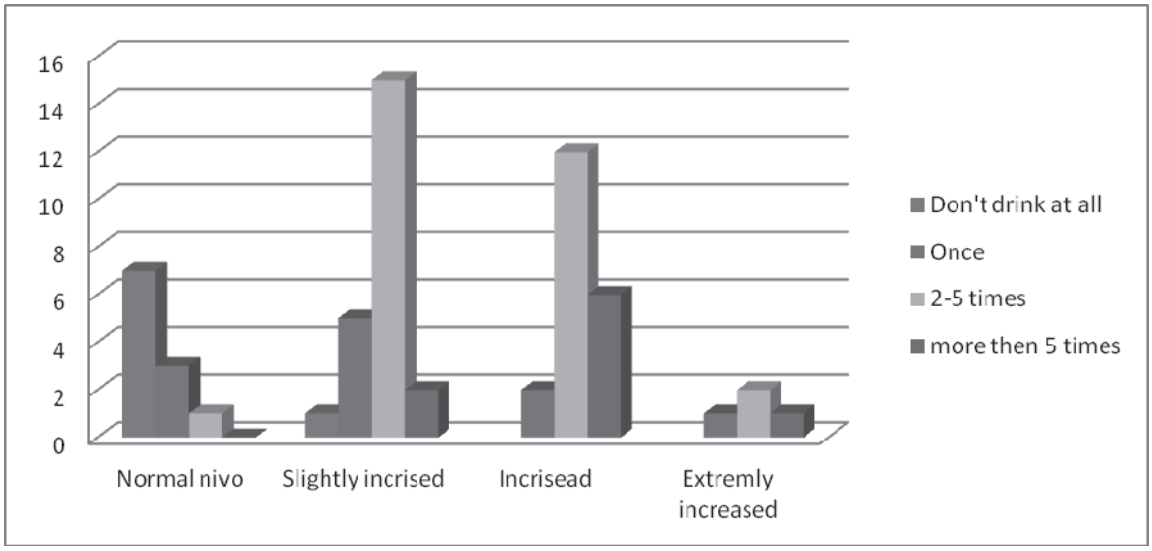
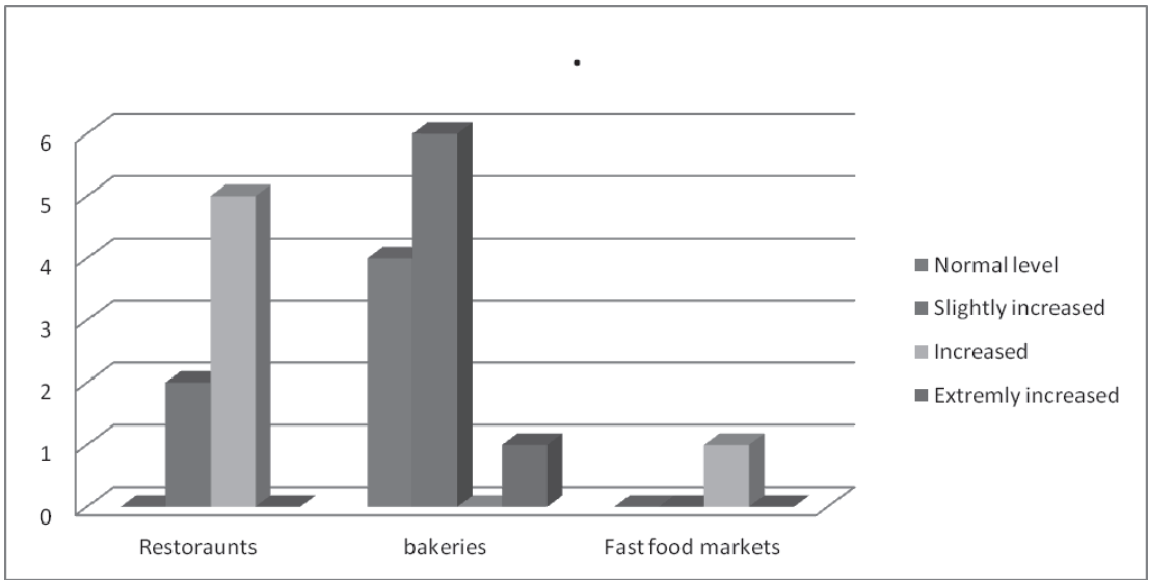


Figure 6.

Places for eating food and serum level of phoshates



DISCUSSION

The conducted study was based on determining the relationship of nutritional attitudes and habits , education level in patients undergoing chronic intermittent hemodialysis and their influence on serum phosphate levels. There are many studies that find a correlation between hyperphosphatemia with increased mortality in patients with advanced renal failure or who are undergoing chronic hemodialysis. In one study published in 2004 which included 40.538 patients it was found that high serum level of phosphate are directly associated with increased mortality[22].

Numerous studies dealing with the examination of the most appropriate mechanism for the correction of hy-

perphosphatemia in patients with chronic kidney disease and in patients who are undergoing chronic intermittent hemodialysis. The last few years in the research focus placed phosphate binders and various dialysis modalities that can directly affect the correction of serum phosphate. A small number of studies have examined the eating habits as a significant factor that can influence the regulation of serum phosphate.

The significance of our study is that it demonstrates the enormous influence of the nutrition, with the direct analysis of individual foods on serum level of phosphate, and that the intervention procedures on changing eating habits, can significantly affect the regulation of serum phosphate and the reduction of morbidity and mortality in those patients, what consecutively occurring as a result of the hyperphosphatemia. This fairly simple, affordable and less expensive interventional procedure can reach respectable result in long-term outcome and treatment of these patients. It is a modern and innovative concept that is primarily related to patient education about the specifics of diet in patients with chronic renal failure and chronic dialysis, and the importance of this concept is often curtailed in relation to the application of phosphate binder and adequate dialysis modalities.

Restriction diet for the control of serum phosphorus is generally associated with a reduced daily intake of foods rich in proteins. Decreased intake of foods rich in proteins can, on the other hand, lead to protein-energy malnutrition (PEW) and decreased survival of patients on chronic hemodialysis programme.

Study Sullivan et al. in 2010 showed that education of patients about the specifics of nutrition on chronic hemodialysis is primarily related to the reduction in the intake of foods rich in phosphate, what leads to a statistically significant improvement in serum phosphate[23].

Results of this study showed that 59.6% of respondents, and 34 were well educated about the special food treatmans. The study Poduval et al. from 2003, which was conducted among 117 patients on chronic hemodialysis programme showed that 74% of them did not know to identify foods that are rich in phosphorus, while 61% of respondents did not know the potential clinical complications related to hyperphosphatemia, and the results of this study shows that patients are not educated enough regarding the specifics of nutrition of patients on chronic hemodialysis program, which differs from the results of studies conducted in our patients[24].

The results of this study have shown that excessive consumption of foods rich in phosphates, primarily of red meat and dairy products is directly linked to the extreme increase in serum phosphate. The study Moa and his associates conducted in 2010 among patients of stage 3-5 CKD were monitored serum levels of phosphate in patients who have taken the meat in the diet foods and in patients who were predominantly on a vegetarian diet. The results of this study showed that in patients who were exclusively fed food containing meat there is a significant increase in serum concentration of the phosphate relative to those who had been on a vegetarian diet[25].

In this study it was found that the increasing level of education of respondents is directly connected with increased level of serum phosphate, and is found in patients with university degrees most of those with extremely elevated serum phosphate values. This does not coincide with the results of other studies. In the study of Gutiérrez and al. From 2010, which included 2.879 patients with chronic kidney disease, it was found that a lower level of education of the patient is directly associated with elevated serum phosphate concentrations (26). This can be explained by the fact that most patients who are on chronic dialysis, and have a high school education are mainly employed and have a wider range of social activities, and despite knowing the specifics of diet in patients undergoing chronic hemodialysis are not able to act in accordance with it.

The research found that the majority of patients with elevated serum levels of phosphate in the food bakeries and fast food shops, where it offers the greatest number of foods rich in inorganic phosphates. These results are consistent with results of other studies. Most studies indicate that the majority of patients treated with the method of chronic renal insufficiency, lower economic status[26], and that usually buy food in places where food is cheaper and they are primarily bakeries and fast food shops and these foods are rich organic and inorganic phosphates[27].

CONCLUSIONS

Diet food rich in phosphates (red meat, milk and dairy products, foods rich in additives, saltwater fish, etc.) in patients on chronic hemodialysis programme is directly associated with increased serum levels of phosphate, which is a significant risk factor for cardiovascular disorders and mineral-bone disorders which consecutively leads to increased morbidity and mortality in these patients.

Attitudes and eating habits in these patients are directly connected with the level of education, and patient's konowladge related to nutrition can significantly affect the regulation of serum phosphate and morbidity and mortality in these patients.

An important role in the consumption of foods rich in phosphates have places where patients are taking food which is usually associated with socioeconomic status of those patients. Serum level of phosphate therefore are extremely elevated in patients who are predominantly taking food in bakeries and fast food shops, and normal serum phosphate occur in those patients who mostly consume food in restaurants.

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SAŽETAK

POVEZANOST IZMEĐU STAVOVA I NAVIKA U ISHRANI I SERUMSKOG FOSFORA U BOLESNIKA NA HEMODIJALIZI

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Poremećaj uhranjenosti bolesnika kojima se bubrežna funkcija nadomješta hemodijalizom (HD) često je povezan s lošom kontrolom serumskog fosfora, što može dovesti do poremećaja metabolizma kosti s posljedičnim razvojem sekundarnog hiperparatireoidizma i poremećajem mineralo-koštanog metabolizma. Hiperfosfatemija je značajan čimbenik rizika za razvoj kalcifikacija mekih tkiva, kao i za pobolijevanje i smrtnost od srčano-žilnih bolesti. Povećan unos hrane bogate fosforom značajan je čimbenik koji dovodi do hiperfosfatemije. Istraživanje ima za cilj ispitati prehrambene navike i stavove bolesnika liječenih HD i utvrditi njihovu povezanost s razinama serumskog fosfora. Istraživanje je provedeno u ožujku 2015. u Centru za hemodijalizu, Kliničkog centra Crne Gore. Istraživanje je provedeno na 57 bolesnika koji su na redovitom programu intermitentne hemodijalize. Muškaraca je bilo 22 (38,6 %). Prosječna dob bolesnika bila je 57 godina (raspon 30-73 godine). Pronađena je statistički značajna povezanost između vrste hrane, osobito crvenog mesa ili konzumiranja mlijeka i mliječnih proizvoda i serumske razine fosfora, kao i između razine obrazovanja ispitanika i razine serumskog fosfora. U našoj je populaciji serumska razina fosfora bila direktno povezana sa socioekonomskim statusom bolesnika. Zaključujemo da je: koncentracija fosfata u serumu određena socijalno–ekonomskom razinom društva, kao i običajem da se u prehrani koriste meso i mlijeko. Nadalje, u konkretnom slučaju vezana je uz prosvjećenost bolesnika koji se dijaliziraju u glavnom gradu Crne Gore.

*Ključne riječ*i: uremija; hemodijaliza; hiperfosfatemija; uhranjenost

ML20474 STUDY: CROATIAN EXPERIENCE IN EFFICACY AND SAFETY OF ANEMIA CORRECTION IN PREDIALYSIS PATIENTS

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We performed observational multicenter study on CKD patients in stage 3-5, with renal anemia. Key inclusion criteria were: haemoglobin level > 6.0 g/dL, age >18 years and written inform consent. Exclusion criteria were dialysis and transplanted patients and haemoglobin level > 12.0 g/dL. Study was performed from 2006.-2012. and 368 patients were included. All patients received Erythropoietin beta (Neorecormon®; Roche, Basel, Switzerland) subcutaneously in dose of 4000-6000 IU every week during the correction phase of anemia treatment or once weekly 2000-4000IU during the maintenance treatment. Iron supplementation was administrated orally in >80% patients in order to achieve serum ferritin 200-500 µg/L. From 368 patients on beginning, 246 were followed and statistically analyzed (M:F=136/110). Mean duration study period was 13.6 (Std.dev.10.36) months (max 52 months). Patients were mainly men (55.3%), age >51 years (81.3%). The median of Hb level at baseline was 9.35 g/dL and after 12 months 10.4 g/dL respectively. After 12 months, most of patients had Hb range 10.0 g/dL to 11.0 g/dL. There were no statistically significant differences between Hb in groups of patients stratified according to the primary kidney disease and age, and between sex: mean level of Hb in M at the end of study was 10.27 g/dl and in F 10.58 g/dl (p=0.051). Baseline eGFR (Cocroft Gault) values were 16.31 (range form 4.1-62.6) vs. 16.71 (range from 4.9-43.8) mL/min after 12 months. The majority of patients had reported better exercise tolerance and sleep. 47.7% of patients have started after predialysis education with dialysis and in 2 patients preemptive transplantation was performed. The results of this multicenter observational study in Croatia suggest that the use of erythropoietin beta is effective and safe in correction of anemia in pre-dialysis CKD patients.

Key words: anemia, non-dialysis chronic kidney disease

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INTRODUCTION

Anemia is a common complication of patients with chronic kidney disease (CKD), which lowers their quality of life and causes cardiovascular diseases such as congestive heart failure and coronary heart disease, and accelerates the progression of kidney dysfunction[1-2]. Anemia is a decrease in the effective circulating volume of red blood cells and is measured by serum hemoglobin (Hb). The World Health Organization (WHO) defines anemia as Hb <13.0 g/dl in adult men and non-menstruating women and <12.0 g/dl in menstruating women[3]. The data from the US Renal Data System (USRDS) have shown that the prevalence of anemia is 4.3% in the general population, while patients with a glomerular filtration rate (GFR) <60ml/minute showed an average prevalence of 14.2%, with escalating prevalence of anemia with progression through stages of CKD: 6.2% in stages

1 and 2, 11.9% at stage 3, and from 47.8% to 95% in stages 4 and 5[4,5]. Symptoms generally occur when the Hb level is less than 10.0 g/dl and become more pronounced as Hb continues to decline[6-9]. The cause of anemia in CKD is often multifactorial, with the most common etiology being ineffective erythropoietin (EPO) production by the diseased kidneys, often complicated by iron deficiency[10]. There are other factors contributing to anemia in patients with CKD, such as acute and chronic inflammation and the accumulation of uremic toxins, but will not be the focus of this article. Recombinant human erythropoietin was introduced in the 1980s in the treatment of anemia associated with CKD. The majoritiy of the trials and evidence for use of ESAs in the CKD population was with patients on hemodialysis and have documented an improved QoL and functional status, as well as relief of symptoms associated with anemia[11-13]. Pre-dialyzed patients in Croatia can not afford the treatment with erythropoietin. Purpose of this Study was to evaluate efficacy and safety of erythropoietin administration subcutaneously once weekly for correcting anemia in the patients in Croatia with chronic kidney disease (CKD), not on dialysis.

PATIENTS AND METHODS

Study Design and Patients

This retrospective observational study was conducted in pre-dialyzed Croatian nephrology centers for follow-up of patient records. Records of CKD pre-dialyzed patients who were included in the ML20474 STUDY database between May 2006 and February 2012 were analyzed if they had at least one Hb value per month over a period of at least two months. Key inclusion criteria were: haemoglobin level > 6.0 g/dL, age >18 years and written inform consent. Exclusion criteria were dialysis and transplanted patients and haemoglobin level >12.0 g/dL, patients with cancer, chronic infectious disease (such as hepatitis B, C or HIV infection). On beginning 368 patients were included. All patients received Erythropoietin beta (Neorecormon®; Roche, Basel, Switzerland) subcutaneously in dose of 4000-6000 IU every week during the correction phase of anemia treatment (Hb value above 9.0-10.0 g/dL) or once weekly 2000-4000 IU during the maintenance treatment. Oral iron supplementation was administrated in patients in order to achieve serum ferritin 200-500 mg/L. Other medical treatment and diagnostic monitoring were left to the Centers' discretion following their routine practice.

The main objective of the study was the description of the therapeutic anemia management in pre-dialyzed patients in Croatia. Secondary objectives included a description of the used treatment strategies in comparison to national and international guidelines compared to target Hb levels.

Data collection

Anonymized data on sex, height, weight, underlying disease causing chronic kidney disease, glomerular filtration rate, co-morbidities (diabetes, hypertension), laboratory tests for anemia (complete blood count, Hb, serum ferritin, serum iron, transferrin saturation), C-reactive protein, serum albumin, serum creatinine, urea, potassium, treatments of anemia (transfusions, ESA, iron) and significant events such as hospitalizations and death were extracted from the database for 246 CKD pre-dialysis patients.

Statistical Analysis

No formal statistical hypothesis was tested. The statistical analysis was essentially descriptive (percentages, mean and standard deviation [SD], median range). Groups were compared using Student's t-test for quantitative variables and Chi-2 test for qualitative variables. All tests were considered statistically significant if $p < 0.05$. Statistical analysis was performed using STATISTICA 10, 2011 software (Stat Soft Inc., USA).

RESULTS

Primary purpose of this Study was to evaluate efficacy and safety of erythropoietin administration subcutaneously once weekly for correcting anemia in the patients in Croatia with chronic kidney disease (CKD), not on dialysis. This study in a cohort of 246 CKD pre-dialyzed patients (M:F=136/110) showed that 55.3% (M=136) of evaluable patients were male. The median age was 65.5, ranging from 19-91 years. The majority of patients (51.6%, 127 of 246) were in the age group of 51-75 years. Patients older than 75 years accounted for a significant proportion (29.7%, 73 of 246). Mean duration study period was 13.6 (SD 10.36) months (max 52 months).

The most common causes of primary renal disease were hypertensive renal disease (hypertensive nephrosclerosis in 31.3%, 77 pt) and diabetic nephropathy (27.6%, 68 pt), whereas chronic pyelonephritis and glomerulonephritis have been causes of primary renal disease in 48 (19, 5%) and 28 (11.4%) patients. Other causes of CKD accounted for 8.5%. It lacked data on underlying disease in 1.6% (4 patients). The largest number of patients (54.1%) had 3 or more concurrent diseases, while 45.9% had 2 or more accompanying diseases such as hypertension, diabetes and atrial fibrillation.

The median of Hb level at baseline was 9.35 g/dL (SD 10.76) and after 12 months 10.4 g/dL respectively. After 12 months, most of patients had Hb range above 10.0 g/dL. There were no statistically significant differences between Hb in groups of patients stratified according to the primary kidney disease and age, and between sex: mean level of Hb in M at the end of study was 10.27 g/dl and in F 10.58 g/dl (p=0.051).

The majority of patients prior to study entry did not treat anemia. Only 18.3% of patients received an oral iron therapy (100 mg). During the study 80% of patients were treated with oral iron (ferrous sulfate tablets 200 mg) with ESA supplemented and this was the most frequently used anemia treatment option.

Average iron value was 8.94 umol/L, (range 2-24.9), and the average ferritin value (only the part of the patient that is determined by ferritin) was 285.7 mg/L. Most patients were within 3/4 CKD stage (81.5%). The levels of hemoglobin (Hb) less than 9.0 g/dL had 35% of patients at baseline, while at the end of the study only 10.6%. At the end of the study 89.4% of patients achieved a level of hemoglobin (Hb) above 9.0 g/dL.

Weekly doses of NeoRecormon varied at the start and at the end of treatment: at baseline over 50% of patients required a week of dose administration of 4000-6000 IU sc. Theere were about 17% requiring a higher dose of 6000 IU sc. weekly. At the end of follow-up only 6.5% of patients required a dose higher than 6000 IU sc (2.5 x times less than at the beginning of the study). At the end of the study there was an increase in the number of patients with application of a lower doses of 4000 IU sc. weekly. Analysis of variance (ANOVA) showed that the values of Hb at baseline were statistically significantly lower than the value at the end of the Hb monitoring for all weekly dosage ($p<0,05$) (Figure 1).

Table 1.
Characteristic of parameters of the cohort

Descriptive Statistics					
Variables	Valid N	Mean	Minimum	Maximum	Std.Dev.
Hb beginning (month1)	243	93.50	61.0	123.0	10.757
Hb end (month 12)	239	104.23	59.0	134.0	12.037
Fe beginning	202	8.94	2.0	24.9	3.775
Creatinine (month 1)	243	383.33	107.0	1300.0	171.302
Creatinine (month 12)	113	377.99	141.0	820.0	171.164
GFR (month 1)	235	16,31	4,1	62,6	8,638
GFR (month 12)	112	16,71	4,9	43,8	9,042

Hb=hemoglobin value (g/L), Fe= iron (umol/L),
creatinine = serum value (IDMS standardization, umol/l)
GFR=glomerular filtration rate (CG/Cockroft-Gault, ml/min),
Values are expressed as mean standard deviation (SD). Other data are presented as number

Secondary endpoint of study was evaluation of impact of anemia on improvement of kidney function: Renal function after 6 months of treatment of anemia remains stable. Baseline eGFR (Cockroft-Gault) values were 16.31 (range from 4.1-62.6) vs. 16.71 (range from 4.9-43.8) mL/min after 12 months and statistically proven to improve renal function compared to baseline after 6 months ($p <0.05$) (Table 1). During the study 9 patients (3.7%) died and 2 (1F/1M) received a preemptive kidney transplant. We do not consider 9 deaths related to administration of NeoRecormon. After predialysis education 47.7% of patients have started with dialysis.

DISCUSSION

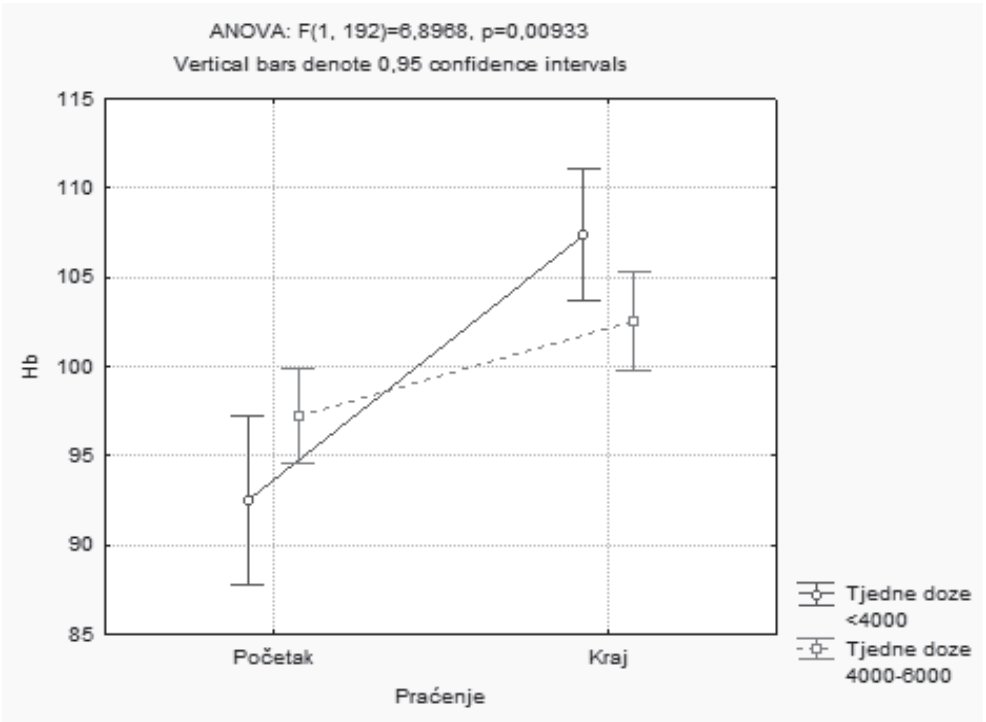
Chronic kidney disease (CKD) is a major global health problem and anemia is a frequent complication. Anemia may, if there is no proteinuria, be the first sign of kidney disease. In all patients with anemia and CKD diagnostic evaluation is required. Prior to diagnose a renal anemia, it is necessary to eliminate possible other causes. The cause of anemia is often multifactorial in patients with CKD. After controversy about the optimal (upper) limit of Hb levels based on three studies in patients with CKD not on dialysis, comparing ESA treatment with high Hb target levels (≥13 g/dL) vs. low Hb targets (~11 g/dL) or placebo (CHOIR, CREATE and TREAT study), European guidelines for ESA-treated dialysis and non-dialysis patients recommend Hb target levels in the range of 10–12 g/dL[6,12]. The guidelines provided by KDIGO recommended Hb target from 9.5 to 11.5 g/dL[8]. Hb levels should not exceed 12 g/dL, particularly in patients with severe cardiovascular disease or diabetes and concurrent peripheral vascular disease[8,12].

Croatian Society of Nephrology, Dialysis and Transplantation (HDNDT) has already published its own guidelines based on the recommendations and the positive experience of European and international professional societies, as well as on own experience.

To the best of our knowledge, this is the first multicentar report of beneficial treatment in CKD pre-dialyzed patient in Croatia. However, our data show additional effect of anemia treatment in slowing natural progression of CKD. As expected, most patients of our study were treated with an ESA and/or iron to control anemia. In the majority of patients Hb levels were in the novel Hb target range of 10–11 g/dL and was within the acceptable today target range according to European guidelines.

Further research documenting the frequency and investigating the mechanisms of those effects reported in CKD pre-dialysed patients with long lasting is necessary, as treatment of anamia in pre-dialysed patients may constitute an effective treatment option to reduce cardiovascular risk and kidney failure progression and prepare patients for preemptive kidney transplantation.

Figure 1.
Levels of Hemoglobin and EPO doses during the study



Hb = hemoglobin value (g/L)
EPO = Erythropoietin beta doses therapy
(<4000 IU sc, 4000-6000 IUsc) on begining and the end of study

CONCLUSIONS

Anemia is independent risk factor for kidney disease progression and recognition of the appropriate treatment is essential for providing renoprotection.

The results of this multicenter observational study in Croatia suggest that the use of erythropoietin beta is effective and safe in correction of anemia in pre-dialysis CKD patients.

Conflict of Interest: None to declare.

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SAŽETAK

STUDIJA ML20474 PRIMJENE ERITROPOETINA BETA (NEORECORMON) U LIJEČENJU ANEMIJE PREDIJALIZNIH BOLESNIKA – HRVATSKO ISKUSTVO

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Prikazano je prospektivno, neintervencijsko, opservacijsko praćenje učinkovitosti i podnošljivosti eritropoetina beta (NeoRecormon®) u liječenju anemije u bolesnika s kroničnom bubrežnom bolesti (KBB) koji još nisu podvrgnuti nadomjestnom bubrežnom liječenju u Hrvatskoj. U studiji ML20474 uključeno je ukupno 368 bolesnika u 3 do 5. stadiju KBB s anemijom u kojih je bilo indicirana primjena lijekova koji stimuliraju eritropoezu (LSE). Svi su bolesnici primili eritropoetin beta (Neorecormon) supkutano u dozi od 4000 do 6000 IU jednom tjedno u razdoblju do korekcije anemije ili porasta Hb za 10 g/L a potom jednom tjedno u reduciranoj dozi od 50% u odnosu na početnu. Bolesnici su praćeni u razdoblju od 3 do maksimalno 52 mjeseca, prosječno 13.6 (Std.dev.10,36) mjeseci. Većina bolesnika bili su muškarci (55,3%), dob preko 51 godina (81,3%). Medijan vrijednosti razine hemoglobina iznosio je 93.5 g/L na početku studije a nakon 12 mjeseci 104,23 g/L. Nije bilo statistički značajne razlike u razini Hb ovisno o uzroku osnovne bubrežne bolesti i dobi bolesnika. Na kraju praćenja većina je bolesnika navela bolje podnošenje napora, bolje spavanje i manju razdražljivost. Nuspojave primjene terapije eritropoetinom beta nismo uočili. Rezultati pokazuju da je primjena učinkovita i sigurna u liječenju anemije u bolesnika s KBB koji nisu započeli liječenje nadomještanjem bubrežne funkcije.

Ključne riječi: anemija, kronična bolest bubrega

INFLAMMATORY BOWEL DISEASE AND KIDNEY – IS THERE A CONNECTION?

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The aim of the present study was to investigate whether patients with inflammatory bowel disease (IBD) have some degree of renal involvement. Furthermore, we investigated whether this connection is related to active bowel disease. In this cross-sectional study, 50 patients diagnosed with IBD, mean age 47.1±16.5 years, were recruited from September 2012 to September 2013. The diagnosis of IBD was based on clinical history, endoscopic, histological and radiological findings. Disease activity was assessed using the UC activity index (UCAI) for ulcerative colitis (UC) and Crohn's disease activity index (CDAI) for Crohn's disease (CD). There were 38% of UC patients and 62% of CD patients. The prevalence of abnormal albuminuria in UC and CD patients was 21.1% and 29%, respectively. There was a high negative correlation between duration of bowel disease and 24-h albuminuria in UC patients, as well as a high correlation between albumin-creatinine ratio (ACR) and UCAI score in UC patients, but these correlations were not statistically significant, probably due to the small number of UC patients. On the other hand, estimated glomerular filtration rate (eGFR) showed negative correlation with disease activity in CD patients (r=-0.569; p=0.05), while there was no statistically significant correlation between active UC and eGFR (r=0.343; p=NS). In conclusion, abnormal albuminuria is quite frequent in patients with IBD. It seems that patients with IBD have some degree of glomerular damage, mainly those with CD. Collaborative, prospective studies conducted by gastroenterologists and nephrologists are needed to investigate this association.

Key words: inflammatory bowel disease, extraintestinal manifestation, kidney

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INTRODUCTION

Inflammatory bowel diseases (IBD) comprise two types of chronic intestinal disorders: Crohn's disease (CD) and ulcerative colitis (UC). CD involves the ileum and colon, but it can affect any region of the intestine, often discontinuously. UC involves the rectum and may affect part of the colon or the entire colon (pancolitis) in an uninterrupted pattern. In CD, the inflammation is often transmural, whereas in UC the inflammation is typically confined to the mucosa[(1)].

The extraintestinal manifestations of IBD are common and may occur in 25%-40% of patients. Inflammatory manifestations in the skin, eyes, liver and joints are considered primary manifestations. Development of primary extraintestinal manifestation appears to increase the risk of developing a second extraintestinal manifestation. Most IBD patients with extraintestinal manifestations have colonic inflammation, although some patients develop them prior to the onset of colonic symptoms. Extraintestinal manifestations are usually present at the time of active phase of IBD[(2)].

In recent years, there have been reports on renal and urologic complications of IBD. They were mostly found to be related to ureteral obstruction by oxalate stones, cystitis, acute tubular necrosis due to volume depletion and AA amyloidosis. Nephrolithiasis and obstructive uropathy are especially seen with small bowel dysfunction[3-5]. In a great proportion of IBD patients, ureteral obstruction is not caused by stones. This noncalculus obstruction can occur in 50%-73% of CD patients and 50% of UC patients, and is usually caused by retroperitoneal local inflammation or by surgical complication (sutures) or colon cancer[6].

There have also been reports of interstitial nephritis, mainly due to applied anti-inflammatory therapy, such as 5-aminosalicylic acid (5-ASA). Serious renal impairment is reported to occur in 1 of 500 patients treated with 5-ASA derivative. On the other hand, there are some reports that renal tubular damage is an extraintestinal manifestation of IBD and not a toxic side effect of anti-inflammatory therapy using 5-ASA or sulfasalazine[7-10].

Furthermore, renal failure due to glomerulonephritis (GN) caused by the immune complex has been reported in several cases as an extraintestinal manifestation of IBD. The types of immune complex GN that have been described due to IBD are membranoproliferative GN, mesangial proliferative GN, membranous nephropathy, IgA nephropathy, IgM nephropathy, minimal-change disease and antiglomerular basement membrane GN. Renal disease occurred in a setting of active IBD in many of reported cases. However, the question is whether renal disease occurs only related to active IBD[6, 11].

According to these observations, the association between IBD and kidney remains unclear and has to be investigated. The aim of the present study was to investigate whether patients with IBD (CD and UC) have some degree of renal involvement. Furthermore, we investigated whether this connection is related to active bowel disease and occurs due to the duration of bowel disease.

PATIENTS AND METHODS

In this cross-sectional study, 50 patients diagnosed with IBD were recruited from September 2012 to September 2013. The diagnosis of IBD was based on clinical history, endoscopic, histological and radiological findings. There were 31 (62%) patients with CD and 19 (38%) patients with UC. Disease activity was assessed using standardized questionnaires. The activity of UC was quantified using the UC activity index (UCAI) introduced by Rachmilewitz. A score ≥6 was considered to be suggestive of active UC. Furthermore, endoscopic activity of UC was also evaluated according to the reliable endoscopic index established by other researchers. The activity of CD was estimated according to the Best CD activity index (CDAI).

Patients with signs of urinary tract infection, known renal disease, hypertension, diabetes mellitus, and use of nonsteroidal anti-inflammatory drugs (NSAIDs) or other nephrotoxic drugs, patients with a current or recent pregnancy were excluded from this analysis. Furthermore, patients who had morphological changes of kidney (proven by ultrasound) were also excluded from the study. Extraintestinal manifestations were recorded in nine IBD patients. The most common extraintestinal manifestation was arthritis.

Blood samples were analyzed for routine hematological and biochemical indices including burn, serum creatinine, liver tests (AST, ALT, GGT and ALP), serum iron and ferritin, C-reactive protein (CRP), serum complement C3 and C4, as well as immunoglobulin levels by standard clinical chemistry techniques. Estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease (MDRD) formula. Additionally, patients provided 24-h urine collection which was used for estimation of albuminuria, sodium, potassium, burn and creatinine clearance. In all patients, cytological analysis of urine was also performed. Urinary albumin concentrations were expressed in mg/24h. Albumin-creatinine ratio (ACR) was expressed in mg/mmol. Clinical and laboratory data were collected at the time of study initiation.

For this analysis, patients were stratified into two groups according to type of IBD into UC and CB groups.

Statistical analysis of data was performed using descriptive statistics (mean and standard deviation). Categorical variables were tested by χ^2-test or Fisher test. Testing of the importance of difference between two independent groups was performed using t-test or ANOVA. Pearson or Spearman correlation coefficient was used to express correlations between variables. The level of statistical significance was set at $p < 0.05$. Statistical analysis was performed using MedCalc statistical software package, version 10 (MedCalc, Mariakerke, Belgium).

RESULTS

There were 31 patients with CD and 19 patients with UC. Of the patients with CD, five had colonic disease, eight had ileal disease, and 18 had small and large bowel disease. Of the patients with UC, six had pancolitis, five had left-sided colitis and eight had procto-sigmoiditis.

Thirty-one IBD patients had an active bowel disease. The mean age of our patients (34 male and 16 female) was 47.1±16.5 years and the mean duration of disease 141±153.4 months.

First, we were interested to analyze whether there is any difference in demographic, clinical and laboratory data of our patients with respect to the type of IBD. For this analysis, patients were stratified into two groups according to the type of IBD: UC and CB groups. Demographic and clinical characteristics of the 50 patients according to the type of IBD are shown in Table 1A. There was no significant between-group difference according to age, sex or duration of bowel disease.

Table 1A

Patient characterisities according to type od inflammatory bowel disease (UC or CD)

Characteristic	UC (n=19)	CD (n=31)	p
Age (yrs) (X±SD)	45.4±10.6	43.4±16.7	NS
Sex:			
Male, n (%)	11 (57.9)	23 (74.2)	NS
Female, n (%)	8 (42.1)	8 (25.8)	NS
CDAI, n (%)	/	123.8±51.4	
UCAI (Mayo score), n (%)	5.9±3.4	/	
Duration of disease (months), n (%)	144.2±173.9	135.8±121.2	NS
Therapy			
5-ASA, n (%)	8 (42.1)	11 (35.5)	
Corticosteroid, n (%)	7 (36.8)	10 (32.3)	
Azathioprine, n (%)	4 (21.1)	15 (48.4)	
Biological therapy, n (%)	5 (26.3)	11 (35.5)	

CD = Crohn's disease; UC = ulcerative colitis; CDAI = Best CD activity index;
UCAI = UC activity index; 5-ASA = 5-aminosalicylic acid derivative; NS = nonsignificant

Laboratory data of our patients are shown in Table 1B. The prevalence of albuminuria in UC and CD patients was 21.1% and 29%, respectively. Although CD patients had higher 24-h albuminuria and ACR, these differences were not statistically significant (Table 1B).

In the next step, we were interested to investigate correlation among various renal tests and clinical data in IBD patients. There was a high negative correlation between duration of bowel disease and 24-h albuminuria in UC patients, but this correlation was not statistically significant, probably due to the small number of UC patients (Table 2A). Table 2B shows correlation between ACR and clinical data in UC and CD patients. There was a high correlation (r=0.737) between ACR and MCS score in UC patients, although it was not statistically significant (p=0.09), probably due to the small number of patients. On the other hand, eGFR showed a statistically significantly negative correlation with disease activity in CD patients (r=-0.569; p=0.05). Also, statistical significance was almost reached in the correlation between eGFR and duration of bowel disease in CD patients (r=-0.391; p=0.09) (Table 2C).

DISCUSSION

Extraintestinal manifestations of IBD are common and probably reflect systemic inflammation, autoimmune susceptibility, metabolic and nutritional derangement, or drug-related toxicity[12,13]. In our study, there was a high negative correlation between duration of bowel disease and 24-h albuminuria in UC patients, as well as high correlation between ACR and MCS score in UC patients, but these correlations were not statistically significant, probably due to the small number of UC patients. Also, eGFR showed a statistically significant negative correlation with disease activity in CD patients. Statistical significance was almost reached in the correlation between eGFR and duration of bowel disease in CD patients. We suppose that by increasing the number of UC and CD patients, all these correlations would reach statistical significance.

The first two reports of glomerulonephritis in association with IBD appeared in the European literature in 1976[14,15]. Kidney disease as a complication of IBD has been the subject of case reports until recently. In 2014, Ambruzs *et*

al.[12] published a case series examining IBD and kidney disease. This was the largest clinicopathologic series to date on this topic. They evaluated a large series of kidney biopsy specimens from patients with IBD (45 CD cases and 38 UC cases). The most common indication for kidney biopsy in their analysis was acute or chronic kidney failure and nephrotic-range proteinuria. IgA nephropathy was the most common diagnosis, followed by interstitial nephritis, arterionephrosclerosis, acute tubular injury, proliferative GN and minimal-change disease.

Table 1B

Laboratory data according to type od inflammatory bowel disease (UC or CD)

Characteristic	UC (n=19)	CD (n=31)	p
CRP (mg/L)	49.3±67.8	48.6±87.3	NS
Complement C3	1±0.2	1±0.3	NS
Complement C4	0.2±0.1	0.3±0.1	NS
IgA	3.1±1	3.1±1.3	NS
IgM	1.5±0.8	1.2±0.5	NS
IgG	14±3.7	12.6±4.8	NS
Serum creatinine (μmol/L)	77.5±22.2	74.1±16.9	NS
Urea (mmol/L)	3.9±1.4	4.4±1.7	NS
eGFR (ml/min/1.73 m^2)	95.3±30.2	95.2±31.5	NS
Creatinine clearence (mL/min)	93.4±29.6	104.9±46.2	NS
Urinary albumin (mg/24 h)	0.1±0.1	0.171±0.2	NS
ACR (mg/mmol)	7.8±4.7	12.5±16.2	NS

CD = Crohn's disease; UC = ulcerative colitis; CRP = C-reactive protein;
eGFR = estimated glomerular filtration rate; ACR = albumin-creatinine ratio;
NS = nonsignificant; data are presented as X±SD

Table 2A

Correlation between 24-h albuminuria and clinical data in UC and CD patients

	UC (n=19)		CD (n=31)	
	r	p	r	p
UCAI	0.304	NS	/	/
CDAI	/	/	0.171	NS
Duration of bowel disease (months)	-0.509	NS	-0.125	NS

CD = Crohn's disease; UC = ulcerative colitis; CDAI = Best CD activity index; UCAI = UC activity index;
NS = nonsignificant

Table 2B

Correlation between albumin-creatine ratio and clinical data in UC and CD patients

	UC (n=19)		CD (n=31)	
	r	p	r	p
UCAI	0.737	0.09	/	/
CDAI	/	/	-0.093	NS
Duration of bowel disease (months)	-0.221	NS	-0.051	NS

CD = Crohn's disease; UC = ulcerative colitis; CDAI = Best CD activity index; UCAI = UC activity index;
NS = nonsignificant

Table 2C

Correlation between estimated glomerular filtration rate and clinical data in UC nad CD patients

	UC (n=19)		CD (n=31)	
	r	p	r	p
UCAI	0.165	NS	/	/
CDAI	/	/	-0.569	0.05
Duration of bowel disease (months)	-0.315	NS	-0.391	0.09

CD = Crohn's disease; UC = ulcerative colitis; CDAI = Best CD activity index; UCAI = UC activity index; NS = nonsignificant

The exact mechanism linking IBD and kidney is still poor understood. Recent investigations have highlighted the close relationship between the kidney and gastrointestinal (GI) tract, a term frequently referred to as the kidney-gut axis in patients with chronic kidney disease. According to data, two important pathophysiological concepts have evolved. The first refers to the production and accumulation of toxic end-products derived from increased bacterial fermentation of protein and other nitrogen-containing substances in the GI tract. The second refers to translocation of endotoxins and live bacteria from gut lumen into the bloodstream due to damage to the intestinal epithelial barrier and quantitative/qualitative alterations of the intestinal microbiota associated with the uremic milieu. In both cases, these gut-centered alterations may have relevant systemic consequences in chronic kidney disease patients, since they are able to trigger chronic inflammation[16]. Some animal and human studies suggest that prebiotics and probiotics may have therapeutic roles in maintaining a metabolically-balanced gut microbiota and reducing progression of chronic kidney disease and uremia-associated complication in these patients[17]. Additionally, an increasing number of reports have associated mucosal inflammation or infection with IgA nephropathy. Thus, IgA nephropathy in IBD probably represents a complex interplay of mucosal inflammation, loss of antigenic exclusion, and tolerance, chronic immune stimulation, and dysregulated IgA production and transport[12, 18]. On the other hand, there is growing evidence related to genetics, intestinal microbiota composition, and the immune system factors such as precursors for the initiation and progression of intestinal conditions. The use of certain probiotic microorganisms has been touted as a possible and promising therapeutic approach in reducing the risk of IBD, specifically UC[19, 20]. According to these observations, immune mechanism and gut microbiota are probably the pathogenic links between IBD and glomerulonephritis, but further studies are warranted on this topic.

Tubulointerstitial injury can also result from an indirect response through the induction of systemic inflammatory or immune reactions. Some animal and human studies support the role of immune-mediated mechanisms in tubulointerstitial nephritis[9]. 5-ASA is currently the treatment of choice for IBD patients. It can be administered as sulfasalazine (5-ASA+sulfapyridine) or mesalazine (5-ASA+gel resins)[6]. Most reported cases of tubulointerstitial nephritis in IBD occurred in patients treated with 5-ASA derivatives, which have known nephrotoxic effects. The exact mechanism is not fully understood, but some authors support the idea that it probably represents an idiosyncratic, delayed-type hypersensitivity that is independent of dose and duration of exposure[17]. However, there are some reports that renal tubular damage is an extraintestinal manifestation of IBD rather than a toxic side effect of anti-inflammatory therapy using 5-ASA or sulfasalazine. This appears to be more common in CD than in UC. According to these studies, it is possible that interstitial nephritis as an extraintestinal manifestation of IBD is maybe secondary to systemic immune dysregulation and cytokine activation[6-10, 17].

Although our study had several limitations such as observational study design, relatively small number of patients, absence of kidney biopsy, and the fact that patient and renal disease outcomes were not examined, it still raised a number of unanswered questions related to kidney function monitoring and outcome in patients with UC and CD. First, what is the exact risk of developing renal complications in IBD patients? Second, what kidney function markers correlate best with IBD activity or what patient clinical data would help us better identify those IBD patients that are at a higher risk of developing kidney complications, including drug-related nephrotoxicity? Third, how often should kidney function be monitored in patients with IBD? Are there some urinary markers which may indicate early renal impairment in IBD patients? Finally, could probiotics become a useful treatment option for kidney complications in IBD patients? Collaborative studies by gastroenterologists and nephrologists should help provide answers to these questions.

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SAŽETAK

UPALNA BOLEST CRIJEVA I BUBREG – POSTOJI LI POVEZANOST?

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Cilj ove studije bio je ispitati imaju li bolesnici s upalnom bolesti crijeva u nekoj mjeri promjene na bubregu. Štoviše, ispitivali smo odnosi li se ta povezanost na aktivnu bolest crijeva. U ovoj presječnoj studiji okupili smo od rujna 2012. do rujna 2013. godine 50 bolesnika srednje dobi od 47,1±16,5 godina s dijagnozom upalne bolesti crijeva postavljenom na osnovi anamneze, endoskopskih, histoloških i radioloških nalaza. Aktivnost bolesti procjenjivali smo indeksom aktivnosti ulceroznog kolitisa (UC activity index, UCAI) i indeksom za Crohnovu bolest (Crohn's disease index, CDAI). Bilo je 38% bolesnika s ulcertivnim kolitisom (UK) i 62% bolesnika s Crohnovom bolešću (CB). Učestalost abnormalne albuminurije bila je 21,1% u bolesnika s UK i 29% u onih s CB. Nađena je visoka negativna korelacija između trajanja bolesti crijeva i 24-h albuminurije u bolesnika s UK, kao i visoka korelacija između odnosa albumin-kreatinin (ACR) i zbira UCAI u bolesnika s UK, ali te korelacije nisu bile statistički značajne, vjerojatno zbog malog broja bolesnika s UK. S druge strane, procijenjena stopa glomerularne filtracije (estimated glomerular filtration rate, eGFR) pokazala negativnu korelaciju s aktivnošću bolesti u bolesnika s CB (r=-0,569; p=0,05), dok nije bilo statistički značajne korelacije između UK i eGFR (r=0,343; p=NS). Zaključujemo da je abnormalna albuminurija dosta česta u bolesnika s upalnom bolesti crijeva. Čini se da bolesnici s tom bolešću imaju do neke mjere oštećenje glomerula, pretežito oni s CB. Da se istraži ta povezanost potrebne su zajedničke prospektivne studije gastroenterologa i nefrologa.

Ključne riječi: upalna bolest crijeva, ekstraintestinalne manifestacije, bubreg

PLATELET AGGREGATION IN THE END-STAGE RENAL DISEASE – DIFFERENCES BETWEEN PATIENTS TREATED WITH HEMODIALYSIS and PERITONEAL DIALYSIS

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End-stage renal disease patients (ESRD) suffer from procoagulant abnormalities that lead to excessive cardiovascular events, as well as from platelet dysfunction manifesting as an increased risk of bleeding. The exact pathogenesis of complex hemostatic disorders in ESRD patients is not completely understood. The aim of our study was to investigate the possible different effects of hemodialysis (HD) and peritoneal dialysis (PD) on platelet function in patients with ESRD by using the platelet function analyzer (PFA-100) which in vitro simulates the process of aggregation and platelet activation. Tests were performed with collagen/epinephrine (COL/EPI) and collagen/adenosine-5-diphosphate (COL/ADP) cartridges. The study included 44 patients with ESRD undergoing regular HD (n=32) or PD (n=12). Although there were no significant differences in COL/EPI and COL/ADP tests, it is indicative that more than 50% of HD patients had COL/EPI test values above the upper limit. These findings correlated with a higher chance for bleeding in HD group. Additionally, patients in HD group were significantly older and had significantly lower platelet count compared to PD patients.

Key words: platelet function, end-stage renal disease, hemodialysis, peritoneal dialysis

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INTRODUCTION

Hemostatic disorders are common complications in patients with end-stage renal disease (ESRD), mainly in the form of bleeding diathesis, but also as an increased risk of thrombotic events. In terms of abnormalities of primary hemostasis, platelet dysfunction and impaired interaction between platelets and vessel wall are considered as the main factors responsible for bleeding tendencies[1-3]. Anemia and accumulation of medication due to poor clearance are also important factors in impaired hemostasis in ESRD patients[1]. On the other hand, the high mortality rate in ESRD patients is mainly due to the increased incidence of thrombotic and cardiovascular complications despite decreased platelet function[3]. Hemostatic abnormalities in ESRD, to some extent, may be affected by the choice of renal replacement therapy[4,5].

Patients on hemodialysis (HD) have an increased risk of thrombotic events, primarily due to the release of thromboxane A2 and ADP into the circulation and also platelet degranulation. Some activation of platelets occurs due to the exposure of blood to the roller pump segment[2,3,5]. On the other hand, the hemodialysis process itself may contribute to hemorrhagic tendencies1, while uremic toxins present in circulating blood can be partially responsible for platelet dysfunction which can lead to bleeding diathesis. Patients on peritoneal dialysis (PD) showed evidence of a higher degree of hypercoagulation than HD patients[2,3]. The exact pathogenesis of complex hemostatic disorders in patients with ESRD is not completely understood.

The aim of our study was to investigate the possible different effects of HD and PD on platelet function in pa-

tients with ESRD by using the platelet function analyzer (PFA-100) which *in vitro* simulates the process of aggregation and platelet activation.

PATIENTS AND METHODS

The study included patients with ESRD on two different types of renal replacement therapy (HD and continuous ambulatory peritoneal dialysis, CAPD), treated at the Department of Nephrology, Hypertension, Dialysis and Transplantation, Zagreb University Hospital Center, during a 3-month period. On regular patient visit, together with blood sampling for standard laboratory parameters, an additional 2 mL of blood was obtained from all patients that met the inclusion criteria, after providing their informed consent. Ethical approval was obtained from the Ethics Board of the Zagreb University Hospital Center. Platelet function testing was performed on a platelet function analyzer (PFA-100) which *in vitro* simulates the process of aggregation and platelet activation. The tests were performed with collagen/epinephrine (COL/EPI) and collagen/adenosine-5-diphosphate (COL/ADP) cartridges. Results are reported as the closure times in seconds for COL/EPI (increased by aspirin and nonsteroidal anti-inflammatory drugs, NSAID) and COL/ADP cartridges (variably affected by ADP receptor disorders and clopidogrel). The ranges considered normal were 85-165 s for the COL/EPI closure time and 71-118 s for the COL/ADP. Data for analysis were taken from medical records.

PATIENTS

The study was performed on 44 ESRD patients undergoing regular HD or PD. The group of patients on HD included 32 patients (19 male and 13 female, median age 62), while the PD group included 12 patients (5 male and 7 female, median age 51). The cause of ESRD was hypertension in 12, diabetic nephropathy in seven, glomerulonephritis and pyelonephritis in nine, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP) in two and congenital diseases in seven patients, whereas in seven patients the cause of renal failure was unknown. The patients included in the study received all their regular medications except for drugs that affect platelet function (aspirin, anticoagulants, nonsteroidal anti-rheumatic drugs). Statins were used by two (6.3%) patients in HD group and 9 (75%) patients in PD group. In HD group, 24 (75%) patients received erythropoietin therapy, while in CAPD group only two (16.7%) patients received erythropoietin therapy. All but two patients in HD group were administered low-molecular-weight heparin (LMWH, nadroparin or enoxaparin). Patients in PD group did not receive LMWH. All patients in both groups signed their informed consent.

IN VITRO CLOSURE TIME TEST

The Platelet Function Analyzer (PFA-100, Siemens Healthcare Diagnostics) is a tool that can detect abnormalities of primary hemostasis in small blood samples. It measures the time required for the platelet plug from citrated blood aspirated under control flow conditions through a 150-micrometer aperture to occlude the aperture (closure time). The system monitors platelet interaction on collagen-ADP (COL-ADP) or collagen-epinephrine (COL-EPI) coated membranes[3,4]. In vitro closure time was measured according to the manufacturer's instructions using 800 μL of blood for each test (COL-EPI and COL-ADP).

Results are reported as closure times in seconds for COL/EPI (increased by aspirin and NSAID) and COL/ADP cartridges (variably affected by ADP receptor disorders and clopidogrel). The ranges considered normal were 85-165 s for the COL/EPI closure time and 71-118 s for the COL/ADP[6-9].

STATISTICAL METHODS

Statistical software IBM SPSS Statistics version 21 was used in all statistical procedures. Normality of data distribution was assessed with Kolmogorov-Smirnov test; based on these results and total sample size, appropriate nonparametric test was used in following analyses. Differences between HD and CAPD groups in categorical variables were analyzed with χ^2-test and differences in quantitative variables with Mann-Whitney U test. Spearman correlation coefficients were calculated between age, duration of treatment, COL/EPI and COL/ADP levels. All p values below 0.05 were considered significant.

RESULTS

Differences between HP and PD groups in categorical patient characteristics are shown in Table 1. There were no significant differences in gender, diagnosis, EPO (erythropoietin), statin, COL/EPI and COL/ADP groups, except for LMWH prevalence in HD group that was significantly higher compared to CAPD group ($p < 0.001$).
There were no significant differences in COL/EPI and COL/ADP tests (Fig. 1).
However, more than 50% of HD patients had COL/EPI levels higher than 165 s, i.e. delayed closure time.
Differences between HP and PD groups in quantitative patient characteristics.
Differences between HD and PD groups in quantitative patient characteristics are shown in Table 2. Significant differences were noted in age (HD group was significantly older; $p=0.025$) and platelet count (higher levels in PD group; $p=0.017$).

Table 1

Differences between HD and CAPD groups in categorical patient characteristics (χ^2-test)

		Group				p
		HD N=32		CAPD N=12		
		n	%	n	%	
Gender	Male	19	59.4	5	41.7	0.293
	Female	13	40.6	7	58.3	
Dg	Hypertension	9	28.1	3	25.0	0.796
	Diabetes	6	18.8	1	8.3	
	Glom/Pye	5	15.6	4	33.3	
	HUS/TTP	2	6.3	1	8.3	
	Congenital	5	15.6	1	8.3	
	Other	5	15.6	2	16.7	
EPO	No	8	25.0	2	16.7	0.557
	Yes	24	75.0	10	83.3	
LMWH	No	2	6.3	12	100.0	<0.001
	Yes	30	93.8	0	0.0	
Statin	No	30	93.8	9	75.0	0.081
	Yes	2	6.3	3	25.0	
COL/EPI	<85 s	2	6.3	1	8.3	0.245
	85-165 s	13	40.6	8	66.7	
	>165 s	17	53.1	3	25.0	
COL/ADP	<71s	4	12.5	0	0.0	0.294
	71-118 s	17	53.1	9	75.0	
	>118 s	11	34.4	3	25.0	

Figure 1
COL/EPI

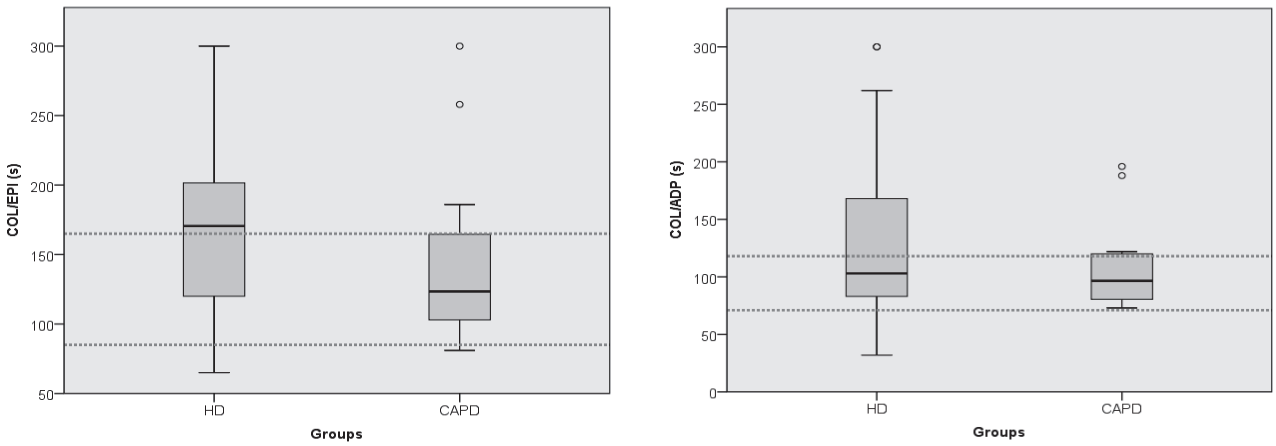

Table 2

Differences between HD and PD groups in quantitative patient characteristics (Mann-Whitney U test)

Group		n	Minimum	Maximum	Percentile 25th	Percentile 50th (Median)	Percentile 75th	p
Duration (months)	HD	32	6.00	126.00	17.25	36.50	65.00	0.094
	CAPD	12	4.00	144.00	9.50	16.00	35.75	
Age	HD	32	22.00	88.00	51.00	62.50	75.00	0.025
	CAPD	12	24.00	67.00	43.50	51.00	60.50	
TT	HD	31	41.00	94.00	56.00	64.00	71.00	0.432
	CAPD	12	42.00	95.00	54.75	68.50	75.75	
TV	HD	31	153.00	191.00	162.00	168.00	175.00	0.989
	CAPD	11	153.00	187.00	158.00	168.00	173.00	
E	HD	32	2.72	4.24	3.22	3.54	3.77	0.370
	CAPD	12	2.26	5.15	3.40	3.66	3.84	
Hgb	HD	32	76.00	127.00	104.50	111.50	119.00	0.989
	CAPD	12	87.00	139.00	97.00	113.50	118.50	
Plt	HD	32	111.00	413.00	149.00	173.00	209.00	0.017
	CAPD	12	150.00	302.00	186.75	226.50	265.00	
MPV	HD	32	6.70	12.40	7.90	8.50	9.10	0.926
	CAPD	12	6.30	9.70	7.58	8.80	9.25	
L	HD	32	2.70	12.80	5.03	6.05	7.63	0.823
	CAPD	12	3.50	12.60	4.63	5.60	7.68	
COL/EPI (s)	HD	32	65.00	300.00	119.50	170.50	201.75	0.215
	CAPD	12	81.00	300.00	100.00	123.50	175.25	
COL/ADP (s)	HD	32	32.00	300.00	81.00	103.00	171.00	0.580
	CAPD	12	73.00	196.00	80.25	96.50	121.00	

DISCUSSION

Previous studies confirmed the existence of dysfunction of primary hemostasis in patients with ESRD measured by PFA-100, a platelet function analyzer, and the ability of HD to correct some part of hemostatic disturbances[5,10]. It was also found that 60% of dialysis patients had prolonged in vitro closure time measured by PFA[10]. In our study, there was no statistical difference in platelet function measured by using the platelet function analyzer (PFA-100) and expressed as in vitro closure time between HD and PD patient groups. However, it is indicative that more than 50% of HD patients had COL/EPI test values above the upper limit. These findings could be clinically correlated with a higher chance for prolonged bleeding in HD patients. The number of patients included in the study in both groups was relatively small and this could be the possible reason for statistically nonsignificant difference in platelet function expressed as closure time. Furthermore, these findings could be correlated to the fact that hemodialysis patients received LMWH, which was not administered to PD patients. It was already observed in a clinical study that platelet dysfunction existed in approximately half of the chronic HD patients and did not improve after HD, regardless of the anticoagulation regimen used[11].

In our study, we also found a statistically significantly lower level of platelets in HD group compared to PD (p=0.017), although platelet counts were within the reference range in both groups. It is consistent with previous observations from different clinical studies, which showed that in predialysis patients, as well as in HD patients, platelet count tended to be reduced1 in the range of 175.000-180.000/mm^3 compared with 250.000/mm^3 in healthy controls. In PD patients, platelet counts have been reported to be closer to the normal range[12-14].

Another study that compared the effects of dialysis with four different heparin protocols, using either unfractionated heparin or LMWH in two different dosages, showed that decreases in platelet counts were similar

with all anticoagulation regimens used[12,15,16]. Besides the statistically significantly lower platelet level in HD group, patients in this group were also older compared to CAPD group.

CONCLUSION

In the present study, we found no statistical difference in platelet function measured by the platelet function analyzer (PFA-100) and expressed as in vitro closure time between HD and PD patient groups, but it is indicative that more than 50% of HD patients had COL/EPI test values above the upper limit, supporting the possibility of clinical correlation with a higher chance for increased or prolonged bleeding in HD patients. According to the results of this study, we can conclude that PD as a method of renal replacement therapy showed better safety profile concerning platelet function, with less reduction in platelet count and no need for LMWH. The sensitivity of the test and clinical relevance of these findings should be further investigated in a larger study with more patients included.

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SAŽETAK

AGREGACIJA TROMBOCITA U ZAVRŠNOM STADIJU ZATAJIVANJA BUBREGA – RAZLIKE IZMEĐU BOLESNIKA KOJI SU LIJEČENI HEMODIJALIZOM I PERITONEJSKOM DIJALIZOM

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Završni stadij kronične bubrežne bolesti obilježen je različitim prokoagulantnim odstupanjima koja dovode do razvoja tromboembolijskih komplikacija uz istodobno poremećenu funkciju trombocita s posljedičnim porastom rizika za nastanak krvarenja. Točna etiologija složenih hemostatskih poremećaja u završnom stadiju kronične bubrežne bolesti nije u potpunosti razjašnjena. Cilj ovoga istraživanja bio je usporediti učinak hemodijalize i peritonejske dijalize na funkciju tromobocita kod bolesnika u završnom stadiju kronične bubrežne bolesti primjenom analizatora funkcije trombocita (PFA-100) koji in vitro stimulira proces aktivacije i agregacije trombocita. Ispitivanje je provedeno na 2 testa (COL/EPI i COL/ADP) koji mjere vrijeme potrebno cirkulirajućoj krvi da okludira membranu obloženu kolagenom i adrenalinom (COL/EPI) odnosno kolagenom i ADP-om (COL/ADP). U istraživanje su bili uključeni bolesnici na hemodijalizi (n=32) odnosno peritonejskoj dijalizi (n=12). Premda nije zabilježena statistički značajna razlika između testova COL/EPI i COL/ADP, indikativno je da su u više od 50% ispitanika na hemodijalizi vrijednosti testa COL/EPI bile iznad gornje granice referentnog intervala. Ovi rezultati mogu se povezati s većom mogućnosti krvarenja u bolesnika na hemodijalizi. Uz to, bolesnici na hemodijalizi bili su značajno stariji te su imali statistički značajno niži broj trombocita u odnosu na ispitanike na peritonejskoj dijalizi.

Ključne riječi: funkcija trombocita, završni stadij kronične bubrežne bolesti, hemodijaliza, peritonejska dijaliza

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THE IMPACT OF SECONDARY HYPERPARATHYROIDISM ON ECHOCARDIOGRAPHIC PARAMETERS IN HEMODIALYSIS PATIENTS

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Cardiovascular diseases are the leading cause of mortality in hemodialysis patients. Patients are exposed to a number of risk factors for cardiovascular complications, which are the result of uremia and dialysis. Aim of our study was to examine the incidence of secondary hyperparathyroidism and left ventricular hypertrophy, the interplay between them as predictors of mortality. This prospective study included 53 patients. All patients had measured echocardiographic parameters of left ventricular hypertrophy and laboratory parameters of bone metabolism. We followed the death rate of patients over two years. Elevated levels of PTH in the serum was present in 79.24% of patients, hypertrophy of the left chamber was recorded in 81.13% of patients. The survivors had lower values of PTH and phosphate levels which were significantly lower ($p < 0.05$) in relation to deceased patients. Patients with poor outcome had higher LV mass index, lower EF and FSLV, larger diameters of interventricular septum and posterior wall ($P < 0.05$). Left ventricular hypertrophy is premature cardiovascular disorder that develops rapidly during the progression of CKD and is based of uremic cardiomyopathy. Left ventricular hypertrophy is a strong indicator of mortality in patients with ESRD.

Key words: PTH, echocardiographic parameters, cardiovascular disease, hemodialysis.

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INTRODUCTION

Patients with the end-stage renal disease (ESRD) have a high mortality rate[1,2] that far exceeds the mortality rate for the non-ESRD population[3]. Cardiovascular diseases are the leading cause of death in patients on hemodialysis (HD). The annual mortality rate from cardiovascular disease (CVD) in these patients is 9%. Cardiovascular system in HD patients is affected by a number of well-known risk factors (RF) dependent of uremia and dialysis. All these RF predisposing to atherosclerosis, which underlies CVD[4].

The high risk of cardiovascular morbidity and mortality in ESRD patients is associated with a high prevalence of classic cardiovascular RF (hypertension,diabetes mellitus, dyslipidemia, smoking, and advancedage). In addition, several uremia-related factors may also play an important role, namely, the presence of multiple comorbid conditions, fluid overload, secondary hiperparatireoidism (SHPT), hyperphosphoremia, high calcium-phosphorous product, anemia, left ventricular hypertrophy (LVH), inflammation, oxidative stress, endothelial dysfunction, insulin resistance, hyperhomocysteinemia, high levels of lipoprotein(a) and increased asymmetrical dimethylarginine[5-8].

Disruption of calcium and phosphate metabolism occurs when the level of glomerular filtration rate (GFR) falls below 60 ml/min. With the decline of GFR is reduced formation of the active metabolite of vitamin D (calcitriol). This results in decreased reabsorption of calcium from the gastrointestinal tract, and an increased secretion of the parathyroid hormone (PTH). Increased phosphate concentration in the serum stimulates the parathyroid gland to produce and secrete increased PTH and this has resulted in the development of SHPT[9,10]. SHPT contributes to the development of vascular and valvular calcification and cardiovascular complications. Calcification of the arteries can affect intimacy and/or medium arterial walls of blood vessels and is associated with an increased deposit of calcium in atherosclerotic plaques,

increase in arterial stiffness, the development of ischemic heart disease and concentric LVH[11]. Elevated phosphate levels is important in triggering artery calcification of media[12,13]. Clinical trial results indicate a correlation between hyperphosphatemia, increased product solubility and left ventricular mass index (LVMi). Patients on HD are at higher risk for sudden cardiac death[14].

The aim of this study was to determine the prevalence of left ventricular hypertrophy, dilatation and systolic disfunction, prevalence of SHPT and the impact of SHPT on left ventricular remodeling and cardiovascular morbidity. Furthermore, we aimed to determine other cardiovascular mortality predictors in patients on regular HD.

METHODS

The study included 53 patients (25 men and 28 women) treated with regular HD three times a week for four hours in Haemodialysis center/Nephrology department od Clinical center of Montenegro. Investigation included hemodynamically stable patients with different primary kidney disease. Patients were followed prospectivelly for two years.

During the examination analyzed parameters were: gender and age structure of patients, PTH and bone-mineral metabolism, homocysteine(Hcy), high-sensitive C-reactive protein (hsCRP), nutritional (albumins) and dialysis parameters (KT/V), serum lipid levels, natriuretic brain peptid(BNP), level of anemia and anthropometric parameters. We analyzed the echocardiographic parameters of the left ventricle: LVMi (g/m²), end-diastolic left ventricular volume index-iEDVLV, posterior wall (PWLVd) and interventricular septum diameter (IVSd) of left ventricule, ejection fraction of left ventricule- LVEF and left ventricular fractional shortening- FSLV. PTH (11-67 pg/ml) was determined from serum on automated system IMMULITE 2000, chemiluminescent immunoassay. Calcium (Ca 2.15-2.55 mmol/l, Schwarzenbach method), phosphate (Phos 0.74-1.52 mmol/l, phosphometric metod), Alkaline phosphatase (AlkP 40-129 U/l men, 35-104 U/l women, colorimetric method), Albumin (Alb 35.6-46.1 g/l, immunoturbidimetric test), cholesterol (CHOL, 3.80-5.17 mmol/l), triglycerides (TRIG, 0.00-1.69 mmol/l), low density lipoproteins (LDL, 0.00-3.90 mmol/l) and high density lipoproteins (HDL, 0.9-1.45 mmol/l) were performed from the serum of the appliance Roche Integra 400. Lipidogram was determined using enzymatic colorimetric test. Blood parameters were performed on the hematology analyzer Cell-Dyn 3700 (Abbott). NTproBNP was performed from serum on automated system IMMULITE 2000, chemiluminescent immunometric assay (ref. values 0.0-53.1 pmol/l).

Echocardiography was performed on the appliance Phillips, the probe of 2.5 MgHz transthoracic approach. LVH was determined by measuring LVMi:

$$\textbf{LVMi = (0.00083x ((+ EDDLK IVSd ZZLKd +) - (EDDLK) 2) +0.6) / TP g/m}^2$$

The volume of left ventricle is calculated by the following formula:

$$\textbf{iEDVLV = ((EDDLK) x0.001047 3)/TP ml/m}^2$$

LVEF is calculated on the basis of the following formula:

$$\textbf{LVEF(\%) = (EDVLV-ESVLV) / EDVLV x 100\%}$$

(ESVLV - end-systolic left ventricular volume, EDVLV - end-dyastolic left ventricular volume, EDVLV- end-dyastolic ventricular volume)
Left ventricular fractional shortening (FSLV) is calculated on the basis of the following formula:

$$\textbf{FSLV = (EDDLK-ESDLK) / EDDLK x 100\%}$$

Normal values of echocardiographic parameters were: LVMi is ≤ 131 g/m² for men and ≤100 g/m² in women, iEDVLV is ≤90 mL/m², LVEF 67 ± 9% and FSLV 42 ± 8%. Systolic dysfunction is defined as a FSLV ≤25% and LVEF ≤50%. LVH is defined as the thickness of IVSd >11 mm, PWLVd >11 mm, LVMi >131 g/m² in men >100 g/m² in women. Left ventricular dilatation is defined as the inner diameter of the LV end-diastolic >57 mm, and LV volume >90 mL/m², with normal systolic function and normal left ventricular mass index. Adequacy of dialysis was evaluated based on Kt/Vsp calculated according to following formula

$$\textbf{Kt / Vsp = -ln (C2 / C1-0.008 x T) + (4-3.5xC2 / C1) x UF / W}$$

where: C1 - predialysis urea value, C2 - postdialisys value of urea(mmol/L), T – duration hemodialysis (h), UF - between dialysis yield (l), W - body weight after hemodialysis (kg).

For the statistical analysis we used Student's t test and Spearman's rank test, using IBM SPSS 20. The threshold of significance was $p < 0.05$.

RESULTS

Our investigation included 53. patients undergoing dialysis. The average age was 56.47±11.79 years and average time on dialysis 5.33±4.48 years. General patients data are shown in Table 1.

According to the monitoring of patients in the two-year period, patients were divided into two groups: alive group (41 patients) and deceased group (12 patients). In our study total biannual mortality was 22.64%.

In group of deceased patients biannual mortality was 30% in patients with CKD and DM, 16.5% in patients with hypertensive nephroangiosclerosis, 37.5% IN CKD caused with polycystic kidney disease and 75% in endemic nephropathy CKD.

The patients with poor outcome had significantly lower hemoglobin(Hgb) levels, lower levels of albumin and higher brain natriuretic peptide($p<0.05$). Furthermore, deceased patients had lower levels of total CHOL and LDL, higher levels of serum Trig and ferritin (Table 2).

Table 1.
General patients data

Patients data(total)	Xsr±SD		
Number (N)	53		
Age (Years)	56.47±11.79		
Time on dialysis (years)	5.33±4.48		
BMI (kg/m²)*	23.53±3.65		
KT/Vsp indeks**	1.12±0.15		
Outcome			
Variables	Alive (41 patients) *Xsr±SD*	Deceased (12 patients) *Xsr±SD*	p
Gender (M/F)	20/21	5/7	0.664
Age (Years)	55.44±11.12	60.00±14.27	0.247
Time on dialysis (years)	5.45±4.81	4.91±3.50	0.716
BMI (kg/m²)*	23.67±4.12	23.04±1.48	0.604
KT/Vsp index	1,13±0.16	1.10±0.10	0.603

*Body mass index

Figure 1.
The distribution of patients according to the LVMi

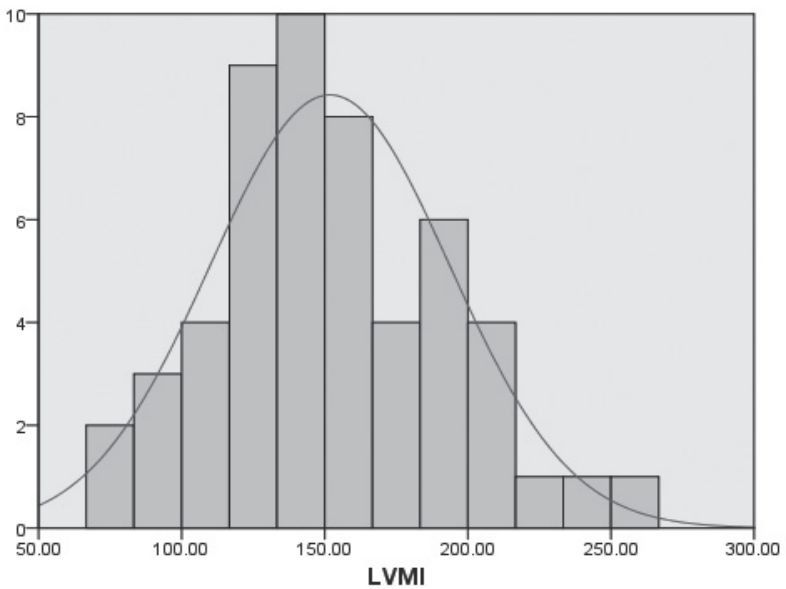

Table 2.

Basic patients parameters based on outcome during the two-year follow-up

Outcome			
Variables	Alive (41 patients) *Xsr±SD*	Deceased (12 patients) *Xsr±SD*	p
Hgb (g/l)	104.50±14.12	94.50±15.46	*0.040*
Hematocrit (%)	0.33±0.04	0.30±0.04	*0.031*
MCV	91.79±6.37	86.9±8.13	*0.035*
Alb (g/l)	38.23±2.79	35.53±3.07	*0.006*
hsCRP (mg/l)	13.39±46.12	13.08±16.68	0.982
Hcy (µmol/l)	30.77±10.90	25.68±12.36	0.173
Total CHOL (mmol/l)	4.28±1.01	3.97±0.92	0.344
Trig (mmol/l)	1.40±0.59	1.51±0.64	0.576
LDL (mmol/l)	2.67±0.83	2.39±0.89	0.313
NT proBNP (pmol/l)	1274.41±1237.71	2200.97±1799.95	*0.046*
Feritin (µG/L)	74.60±69.18	100.85±100.22	0.303

Elevated PTH levels in serum was present in 42 (79.24%) patients. LVH had the 43 (81.13%) patients. Of them 18 (33.96%) patients had concentric LVH and 25 (47.16%) had eccentric LVH. Dilation of the left ventricle had 4 (7.54%) patients, while 6 (11:32%) had normal left ventricle. Disorder of systolic disfunction (FSLK <25%) had 5 (9.43%) patients. Th distribution of patients according to the LVMi values is shown in Fig. 1.

Between the serum concentration of PTH and IVSd, LVPWd exists positive correlation (p <0.01). Between concentrations of serum PTH and LVMi there is a positive correlation (p <0.05). Between PTH levels and other echocardiographic parameters for the assessment of hypertrophy, dilatation and systolic function of the left ventricule there is no correlation (p >0.05).(Figure 2.) (Table 3.)

Figure 2.

The correlation between PTH and LVMi values

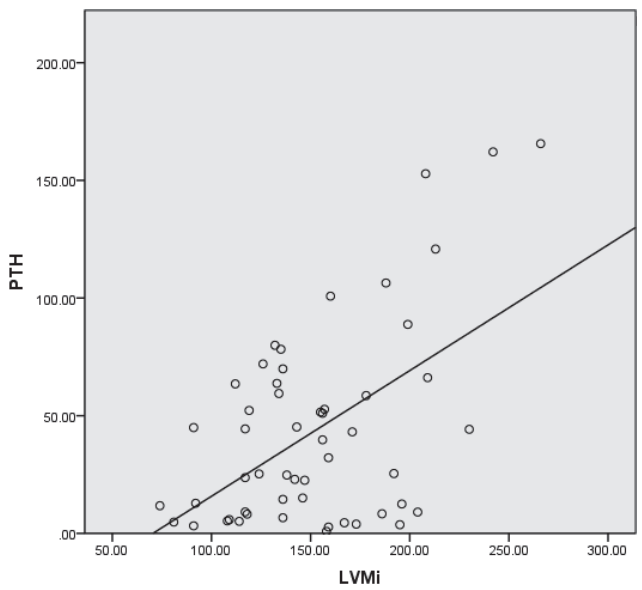

Table 3.

The relationship between PTH and echocardiographic parameters for the assessment of hypertrophy, dilatation and systolic function of the left ventricle

Test parameters	Xsr±Sd	Značajnost - p
LAd (mm)**	41.67±5.67	*ρemp=0.287*
PTH (pmol/l)	43.44±41.86	*p=0.037 < 0.05*
EDDLV (mm)***	55.24±6.47	*ρemp=0.281*
PTH (pmol/l)	43.44±41.86	*p=0.041 < 0.05*
ESDLV (mm)****	37.11±5.86	ρemp=0.164
PTH (pmol/l)	43.44±41.86	p=0.241 > 0.05
IVSd (mm)	11.90±1.62	*ρemp=0.389*
PTH (pmol/l)	43.44±41.86	*p=0.004 < 0.01*
PWLVd (mm)	11.60±1.56	*ρemp=0.378*
PTH (pmol/l)	43.44±41.86	*p=0.005 < 0.01*
RV (d/mm)*****	24.60±3.91	*ρemp=0.430*
PTH (pmol/l)	43.44±41.86	*p=0.001 < 0.01*
LVMi (g/m2)	151.79±41.82	*ρemp=0.315*
PTH (pmol/l)	43.44±41.86	*p=0.022 < 0.05*
iEDVLV (ml/m2)	101.49±32.32	ρemp=0.172
PTH (pmol/l)	43.44±41.86	p=0.218 > 0.05
FSLV (%)	33.03±6.34	ρemp=0.008
PTH (pmol/l)	43.44±41.86	p=0.952 > 0.05
LVEF (%)	64.54±8.20	ρemp=--0.026
PTH (pmol/l)	43.44±41.86	p=0.851 > 0.05

** left atrium diameter, *** left vetricular end-dyastolic diameter,
**** left vetricular end-sistolic diameter, ***** right ventricular diameter

Alive patients had lower PTH and lower values of Phos levels in relation to the deceased. The Phos levels are significantly lower in alive patients against the deceased patients ($p<0.05$). Considering echocardiographic parameters, patients with poor outcome had significantly higher LVMi, lower LVEF and FSLV, less IVSd and PWLVd($p<0.05$) (Table 4).

DISCUSSION

Patients on HD are exposed to many traditional and traditional risk factors for CVD[15,16]. Non-traditional risk factors are consequences of uremic environment and can be connected also with the type of dialysis. These risk factors cause LVH and accelerate atherosclerosis, and that results in increased cardiovascular morbidity and mortality in patients on HD. The monitoring of risk factors for CVD, can significantly improve cardiovascular outcome in patients treated with HD.

Hemodialysis patients are often accompanied by SHPT, which consists of three components: hypocalcemia, hyperphosphatemia and calcitriol deficiency.

Table 4.

Echocardiographic parameters and calcium disorders parameters based on outcome during the two-year follow-up

Outcome			
Variables	Alive (41 patients) *Xsr±SD*	Deceased (12 patients) *Xsr±SD*	p
PTH(pmol/l)	39.56±39.83	56.69±47.62	0.216
Ca(mmol/l)	2.31±0.31	2.33±0.23	0.0887
Phos(mmol/l)	1.72±0.39	2.07±0.49	*0.025*
Alk P(mmol/l)	81.59±68.68	90.58±99.39	0.721
LVMi(g/m2)	145.56±39.06	173.08±45.60	*0.044*
iEDVLV(ml/m2)	99.09±30.52	109.71±38.17	0.322
IVSd(mm)	11.51±1.59	12.58±1.31	*0.039*
PWLVd(mm)	11.36±1.59	12.41±1.64	*0.039*
LVEF(%)	66.05±7.68	60.61±5.72	*0.028*
FSLV(%)	34.30±5.97	29.66±3.84	*0.014*

This association plays an important role in causing cardiovascular disease, arterial calcification, disorders of the immune system, neurobehavioral changes and inadequate erythropoiesis[17]. Arterial calcification lead to an increase in afterload and consecutive result in remodeling of cardiac muscle in the direction of LVH. In patients with CKD phosphate is regarded as a 'uremic toxin'. Statistical association between serum phosphate and all-cause mortality in patients on dialysis has transformed the phosphate molecule from a subject of little interest 10 years ago to the 'dialysis enemy number 1' today[18]. Until recently, PTH and vitamin D were the only recognized regulators of phosphate metabolism. In the last decade, several novel regulators of mineral homeostasis have been discovered: phosphate regulating gene, fibroblast growth factor 23 (FGF23), and the family of stanniocalcins (STC1 and STC2)[19]. Even with the increasing knowledge on phosphate metabolism and its role in renal failure patients, interventional measures are still limited. PTH has a permissive role for fibroblast activation and myocardial fibrosis. Thus, it has been observed that elevated PTH levels in ESRD cause irreversible interstitial fibrosis with collagen deposition[20].

The fact that progression of LVH was strongly linked to subsequent mortality and cardiovascular events independently of baseline LVMi and of a large series of traditional and emerging risk factors is of relevance because it indicates that assessing changes in LVMI is at least as important as estimating LVMI. Like in the study by Foley *et al*[21], we found that LVH worsens with time.
CVD is the most common cause of morbidity and mortality in patients on chronic HD. During the follow-up period, in our study, biannual mortality was 22.64%. Cardiovascular mortality in CKD patients is approximately 9% annually[22,23]. Our results are similar to the results of Sameiro-Faria and associated. In their study, during the follow-up period, 18.5% died[24].

In our study, the prevalence of SHPT was 79.24%, while the prevalence of SHPT in the works of Owda and associates was 79%[17].
The prevalence of LVH in HD is high. In our study LVH had the 43 (81.13%) patients. Of them 18 (33.96%) patients had concentric LVH and 25 (47.16%) had eccentric LVH. Compared to our results, the Canadian Prospective Cohort Study 25, which followed 433 patients with terminal renal disease, 74% of patients had LVH, 35% had left ventricular dilatation, while 15% had systolic dysfunction. In the group of patients LVH, 44% had concentric, while 30% of patients had eccentric hypertrophy of the left chamber. Results of echocardiographic parameters of our patients were consistent with the results of Foley and associates, who followed 227. patients. In their study were given the following values of ultrasonography parameters: LVMi 161 (g/m^2), iEDVLv 88 ml/m^2 and FSLv 34%[21]. In our study, those parameters are equaled LVMi 151.79 (g/m^2), iEDVLv 101.49 mL/m^2 and FSLV 33.03%.

Concentric hypertrophy of left ventricular diastolic function disturbs the heart. As a consequence HD patients can have pulmonary edema and development of hypotension during hemodialysis[26-28]. Diastolic dysfunction occurs in 50-60% of patients treated with regular HD. When you increase the stiffness of the LV and LV load volume, significantly increase the pressure in it. A small increase of volume can be accompanied by the development of pulmonary capillary congestion and the development of pulmonary edema[29]. In HD pa-

tients the risk of de novo development of ischemic heart disease is significantly higher if the LVMi >160 g/m^2, relative to LVMi <150 g/m^2. Concentric LV hypertrophy, LV dilatation and impaired systolic function are independent risk factors for de novo development of ischemic heart disease[30]. Increase LVMi for more than 1 g/m^2 per month increases the risk of developing cardiovascular complications[25]. In patients with normal volume and normal LV systolic function, high index of left ventricle (LVMi >120 g/m^2) and the relationship of weight/volume of left ventricle >2.2 g/ml, are independently associated with late mortality (after 2 years starting hemodialysis). In patients with LV dilatation and normal LV systolic dysfunction, the increased volume of the left LV (iEDVLV >120 mL/min) and LVMi/iEDV <1.8 mL see, are also associated with an increased risk of late mortality[31].

In our work, between total serum PTH and LVMi, IVSd, PWLVd there is a statistically significant correlation. This leads to the conclusion that patients with higher values of PTH have a more pronounced LVH, as compared to those with normal or subnormal levels of PTH. Secondary hyperparathyroidism is associated with LVH and impaired heart function[32,33]. Patients on HD also follows increased concentration of phosphate. Increased serum phosphate levels >2.10 mmol/l, increased solubility equilibrium >5.65 mmol/l and increased PTH >500 pg/ml significantly increase the risk of mortality in patients treated with regular HD[33,34]. Reduced aortic velum opening leads to the development of concentric LV hypertrophy. The mass of the left ventricule may be increased due to a significant increase of myocardial fibrosis of interstitium (fibroblast proliferation, increased production and deposition of extracellular matrix proteins in intersticium infarction). In dialysis patients, increased concentration of PTH leads to the development of myocardial fibrosis of interstitium[16]. The reduction of PTH levels to normal ranges may have beneficial effect to reduce left ventricular hypertrophy and improve heart function. Thus, among hemodialysis population, higher parathyroid hormone concentrations were associated with higher all-cause mortality risk, mostly explained by fatal cardiovascular events[35-39].

Restricted phosphate intake, non-calcium based phosphate binders, new vitamin D metabolites and calcimimetics contribute to better control of secondary hyperparathyroidism, prevent coronary calcification and decrease the morbidity and mortality rate in patients on regular HD[40,41].

CONCLUSION

In conclusion, SHPT, hyperphosphatemia and high Ca×P product are risk factors for adverse outcome in patients on HD. Regular monitoring and maintaining of PTH, serum calcium, phosphorus and Ca×P product within the target range contribute to lowering the cardiovascular morbidity and mortality and improving the quality of life of HD patients. Patients on HD have high risk for cardiovascular morbidity and mortality. Echocardiographic assessment for cardiovascular status in patients on HD identifies those with increased risk of cardiovascular complications, LVH, congestive heart failure, and heart valve calcification. Establishing the most sensitive parameters for identifying patients at risk for cardiovascular complications enables successfull treatment.

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SAŽETAK

UTJECAJ SEKUNDARNOG HIPERPARATIREOIDIZMA NA EHOKARDIOGRAFSKE POKAZATELJE U HEMODIJALIZIRANIH BOLESNIKA

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Srčanožilne (SŽ) bolesti su vodeći uzrok smrtnosti u bolesnika na hemodijalizi. Bolesnici su izloženi brojnim čimbenicima rizika za SŽ komplikacije, koje su u prvom redu posljedica uremije i dijalize. Cilj našeg prospektivnog istraživanja jest ispitati učestalost sekundarnog hiperparatireoidizma i hipertrofije lijeve klijetke, i njihovu međuigru kao predskazatelja smrtnosti u bolesnika na hemodijalizi. Istraživanje je uključilo 53 bolesnika. Svim bolesnicima su mjereni ehokardiografski parametri za procjenu hipertrofije lijeve klijetke i laboratorijski parametri koštanog metabolizma. Pratila se smrtnost bolesnika tijekom dvije godine. Povišena razina PTH u serumu bila je prisutna u 79,24% bolesnika, hipertrofiju lijeve klijetke imalo je 81,13% bolesnika. Preživjeli su imali niže vrijednosti PTH i serumskog fosfora ($p < 0,05$) u odnosu na preminule bolesnike. Analizirajući ehokardiografske parametre, bolesnici s lošim ishodom imali su značajno viši indeks mase lijeve klijetke, niže frakcije izbacivanja i frakcijskog skraćivanja lijeve klijetke, veće promjere interventrikularnog septuma i stražnje stijenke lijeve klijetke ($P < 0,05$). Hipertrofija lijeve klijetke je rani SŽ poremećaj koji se razvija brzo tijekom napredovanja kronične bolesti bubrega i u osnovi je uremijske kardiomiopatije. Hipertrofija lijeve klijetke je jak pokazatelj smrtnosti u bolesnika u završnoj fazi kronične bubrežne bolesti.

Ključne riječi: PTH, ehokardiografski parametri, srčanožilna smrtnost, hemodijaliza

RENAL DENERVATION AND RESISTANT HYPERTENSION: BACK TO THE FUTURE

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Renal sympathetic denervation (RDN) with radiofrequency (RF) is being used to treat resistant hypertension in seven non-responder patients (62±6 years for age, 5F/2M) despite treatment with >4 different antihypertensive drugs in optimal doses. Prior to diagnosing a patient as having resistant hypertension, we document adherence and exclude white-coat hypertension, inaccurate measurement of blood pressure and secondary causes. Office blood pressure (BP) measurements at 1, 3, 6, 12 and 18 months follow-up visits were compared to baseline. We used STATISTICA 10, 2011 software (Stat Soft Inc., Tulsa, OK, USA). Values are mean SD and considered statistically significant if P <0.001. At baseline, values were 184±21 and 106±26 mmHg for systolic (SBP) and diastolic (DBP), 6.7±1 for number of antihypertensive drug classes. One, 3, 6, 12 and 18 months after RDN, office SBP values were significantly lower (144±13 mmHg, 140±17, 141± 15, 139±12 and 135±11 mmHg; P <0.001), with no significant reduction in DBP values at 1, 3, 6, 12 and 18 months after RDN (81±6, 82±9, 79±9, 78±6, and 76±7 mmHg). The number of antihypertensive drug classes before and 6, 12, 18 months after RDN were evaluated. Six months after RDN the number of antihypertensive drug classes required was 6.5±1, after 12 and 18 months was 5.5±1 and 4.5±1. During RDA no complications occurred (the pain during the procedure was well tolerated) and the renal function remained stabile. Renal sympathetic denervation is being a concomitant treatment of drug-resistant hypertension (rHT). The sustained reduction of SBP was observed after the RDN. Patients have benefit the most from procedure after 6-12 months. Further meta-analysis will evaluate the importance of new devices for less pain treatment of RDN.

Key words: resistant hypertension, renal sympathetic denervation

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INTRODUCTION

If pharmacological therapy with at least three antihypertensive drugs in optimal doses, including a diuretic, fails to reduce the office blood pressure to below 140/90mmHg, patients are considered to suffer from drug resistant hypertension (rHT)[(1,2)]. The prevalence of rHT has been estimated between 8 to 13% of all antihypertensive drug treated patients[(2)]. In recent decades, the use of antihypertensive drugs has revolutionised the therapy of hypertension. Despite the available pharmacological inhibition of the sympathetic nervous system, about 50% of patients show suboptimal control and pharmacotherapy does not provide adequate effects in clinical practice[(3-5)]. Although the most common causes of therapeutic failure are undiscovered secondary causes of hypertension and lack of patient/doctors compliance,

in about 10% of cases it can be attributed to resistant hypertension caused by a hyperactivity of the sympathetic nervous system,condition that confers a high cardiovascular risk to the patient[6,7,8]. Renal sympathetic denervation (RDN) produce multilevel inhibition of the sympathetic nervous system, and trigers additional positive metabolic effects[9,10,11].

The reason for the rapid introduction of RDN in the therapy of rHT were the reported high efficiency and safety of the procedure[9]. The effectiveness was demonstrated in the studies Symplicity HTN-1 and HTN-2, and in the EnligHTN-1 Study (by using special RF ablation catheters)[10,11]. According to the results of different trials, including Symplicity HTN-3 (this study did not show differences in SBP reduction between treatment and control groups, but in the context of the study characteristics and the way it was conducted, there are several concerns about inexperienced doctors in the field of RDN, the study population and the medical treatment), RDN seems to be safe and procedure-related complications of catheter-based RDN were rare[11,12].

Based on these findings the objective of this study was to investigate long term effects of RDN on BP control and renal function parameters in our patients.

SUBJECTS, MATERIALS AND METHODS

Study included 7 patients with proven resistant hypertension (rHT) from a cohort of 101 patients referred to ambulance due to suspected rHT. Prior to diagnosing a patient as having rHT, we document adherence and exclude white-coat hypertension, inaccurate measurement of blood pressure and secondary causes. In order to qualify patients as rHT (defined as BP that remains >140/90 mmHg in spite of the use of >4 different antihypertensive agents in optimal dose, including diuretic, and lifestyle changes), patients for RDN had to show a mean systolic BP >150 mmHg in the 24 hr ambulatory blood pressure measurement (ABPM).

Data collection

Basic anthropometric measurements were performed on all subjects. Office Blood pressure was measured twice in the sitting position with a mercury sphygmomanometer after a resting period of 5-10 minutes. Fasting venous blood samples were collected in the morning between 08:00 and 09:30 hours after an overnight fast for the determination of basic blood chemistries. Data on serum creatinine levels, age, sex and race were used to calculate the estimated GFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, which has been shown to be accurate in determining kidney function in rHT[6].

Study procedure

In our Center RDN was performed using standard radiofrequency system with ablation catheter (5F system/ 6F guide catheter; Symplicity TM RDN System) inserted through the femoral artery, engaging the renal artery bilaterally. Five to six nerve ablations of 100 second duration on each side were performed without any complications. During the RDN patients received intravenous narcotic and sedative drugs agains the abdominal pain. Office BP measurements at 1, 3, 6, 12 and 18 months follow-up visits were compared to baseline. At six months after RDN duplex sonography was performed. The number of antihypertensive drug classes before and 6, 12, 18 months after RDN were evaluated.

The study protocol complies with the Declaration of Helsinki as well as with local institutional guidelines, and was approved by the local ethics committees.

Statistical Analysis

Data are expressed as means ± SD for normally distributed values, as median with range for non-normally distributed values, and percentage.
Level of statistical significance was considered statistically significant if P <0.001. Statistical analysis was performed by statistical package STATISTICA 10, 2011 software (Stat Soft Inc., Tulsa, OK, USA).

RESULTS

Purpose of this Study was to evaluate efficacy and safety of renal sympathetic denervation (RDN) with radiofrequency (RF) as additional therapy for rHT pt during the 18-month follow-up. RDN is being used to treat rHT in seven non-drug responder patients (62±6 years for age, two male) with >4 different antihypertensive drugs in optimal doses, with a severe comorbidity (four patients (2F/2M) with well controled diabetes mellitus type 2, one male patient with coronary artery disease, two male patients with chronic kidney disease (defined as eGFR CKD EPI <60 ml/min/1.73m2). At baseline, before RDN, values were 184±21 and 106±26 mmHg for systolic (SBP) and diastolic (DBP), heart rate 67±6 beats/min, 6.7±1 for number of different antihypertensive drug classes. One, 3, 6, 12 and 18 months after RDN, office SBP values were significantly lower (144±13, 140±17, 141±15, 139±12 and 135±11 mmHg; P <0.001), with no significant reduction in DBP values at 1, 3, 6, 12 and 18 months after RDN (81±6, 82±9, 79±9, 78±6, and 76±7 mmHg).
The characteristics of the study subjects are listed in Table 1.

During RDA no complications occurred (the pain during the procedure was well tolerated) and the mean renal function at baseline was eGFR CKD-EPI stage G2 (65±38 ml/min/1.73m^2).

Table 1.
Baseline clinical characteristics and biochemical measures of all patients treated with RDN method (n =7)

Variable	Data
Age (yrs)	62 ± 6
Women	5/7
Type 2 diabetes	4/7
Body mass index (kg/m^2)	32± 2
Antihypertensive drugs (n)	6.7 ± 1
ACEI	2/7
ARB	5/7
ACEI and ARB	0/7
β - blocker	5/7
Calcium-channel blocker	7/7
α - blockers	5/7
Diuretic	7/7
Direct renin inhibitor	0/7
Vasodilator	2/7
Central acting sympatholytic	7/7
Office SBP (mmHg)	184 ± 21
Office DBP (mmHg)	106 ± 26
Heart rate (beats/min)	67 ± 6
eGFR (ml/min per 1.73m^2)	65 ± 38
Serum creatinine (μmol/L)	108± 61

Values are mean SD or number/number of patients
ACEI - angiotensin-converting enzyme inhibitor
ARB - angiotensin II receptor blocker
DBP - diastolic blood pressure
eGFR - estimated glomerular filtration rate (CKD-EPI formula)
SBP - systolic blood pressure

All patients show a small reduction of the mean ABPM but not show a reduction of systolic BP >10 mmHg at 6 months following RDN therapy.

Six months after RDN the number of antihypertensive drug classes required was 6.5±1, after 12 and 18 months was 5.5±1 and 4.5±1. Values of HbA1c were stabile before and (6.5-7.1 and 6.7-7.0%) after RDN on oral hypoglicemic drugs in 50% of patients.

At six months duplex sonography was performed in all patients (to exclude renal artery stenosis after RDN). We did not observe any renal vascular complications during the 18 months of follow up. The renal function remained stabile during 18-month follow up with mean eGFR CKD-EPI stage G2 (61±36 ml/min/1.73m^2).

DISCUSSION

The resistant hypertension treatment is achieved with nonpharmacological and pharmacological approach, treating secondary hypertension causes and invasive procedures such as RDN[1]. Many observational studies and our results have shown that RDN is a safe and effective method of reducing office BP in patients with rHT, with an additional positive effect on blood glucose metabolism, obstructive sleep apnea and signs of hypertensive end organ damage[2-4]. In support of these data, we documented that RDN was associated with good response in SBP regulation and improved stabile kidney function after RDN without complications such as renal stenosis or a pseudoaneurysm of the femoral artery after the procedure.
It is very important to select patients most likely to have benefit from invasive procedures such as RDN, because patients with rHT represent a very mixed group of diagnoses[5]. Chronic kidney disease (CKD) patients have sympathetic nervous system hyperactivation that leads to fluid overload, aggravation of hypertension and further deterioration and loss of renal function, and it has been demonstrated that RDN is associated with stabile kidney function[5]. The most obvious explanation relating effect of stabile kidney function could be that after RDN treatment increase renal blood flow which result in increase in GFR. Studies that have measured kidney function in pt with rHT with gold standard methods (CKD-EPI, MDRD) also found high prevalence of CKD in rHT patients[6-8]. Our results support these observations, we also found mean eGFR CKD-EPI stage G2 (65±38 ml/min/1.73m^2) on beginning, and after 18-month follow up eGFR was stabile.

The present study has a number of potential limitations. First, our study is obviously limited by the small number of patients. Furthermore our analyses were based on measurement of office blood pressure and we did not have performed ABPM in all patients in 12/18-month follow up.

To the best of our knowledge, this is the first report of beneficial RDN treatment for 18-month follow up in rHT patients in Croatia. However, our data show additional effect of treatmen in slowing natural progression of CKD.

In this study RDN with radiofrequency (RF) ablation is being used to treat rHT, with good safety profil and no complications occurred, the pain during the procedure was well tolerated. From other studies as 15-13% of treated patients are non-responders to RDN with radiofrequency, option is to repeat RF or perform RDN with cryoenergy as second line option[9].

CONCLUSIONS

Our results suggest that sustained reduction of SBP after the RDN was observed in 18-month follow-up.
Renal sympathetic denervation is being a concomitant treatment of drug-resistant hypertension (rHT). High risk patients with resistant hypertension have benefit the most from procedure after 6-12 months. Further meta-analysis will evaluate the optimal target population and importance of RDN as rHT treatment.
The future of the RDN systems are noninvasive, delivering externally focused ultrasound energy to the renal nerves using Doppler-based ultrasound image guidance to track and correct for renal artery motion during treatment.

Conflict of Interest: None to declare.

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SAŽETAK

DENERVACIJA BUBREŽNIH ARTERIJA I REZISTENTNA HIPERTENZIJA

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Denervacija bubrežnih arterija (DBA) radiofrekvencijom jedna je od obećavajućih novih metoda liječenja rezistentne hipertenzije refraktorne (RH) na optimalno liječenje kombiniranom antihipertenzivnom terapijom koja uključuje 3 i više lijekova iz različitih antihipertenzivnih skupina od kojih jedan mora biti diuretik. Nakon isključenja sekundarnih uzroka, neadekvatnog mjerenja tlaka te nesuradljivosti prikazujemo učinak DBA u 7 bolesnika (62±6 years for age, 5F/2M) tijekom razdoblja od 18 mjeseci praćenja. Za statističku analizu korišten je program STATISTICA 10, 2011 softwer (Stat Soft Inc., Tulsa, OK, USA), uz razinu značajnosti P <0,001.

Bolesnici su praćeni na redovitim ambulantnim kontrolama 1, 3, 6, 12 i 18 mjeseci nakon DBA uz mjerenje krvnog tlaka i praćenje laboratorijskih parametara. Od početnih izmjerenih vrijednosti tlaka u ambulanti 184±21 za sistolički i 106±26 mm Hg za dijastolički tlak, uz prosječni broj antihipertenzivnih lijekova od 6,7±1 nakon DBA 1, 3, 6, 12 i 18 mjeseci prati se značajno smanjenje sistoličkih vrijednosti tlaka (144±13, 140±17, 141±15, 139±12, 135±11 mm Hg; P <0,001), bez značajnog smanjenja dijastoličkih vrijednosti (81±6, 82±9, 79±9, 78±6, 76±7 mmHg). Nakon 6 mjeseci prosječan broj antihipertenzivnih lijekova ostao je nepromijenjen (važno da se objektivizira učinak DBA) i iznosio je 6.5±1, dok je nakon 12 i 18 mjeseci došlo do smanjenja broja antihipertenzivnih lijekova (5.5±1 i 4.5±1). Tijekom DBA bolest je bila podnošljiva, nije zabilježeno neposrednih ni kasnijih komplikacija DBA, bubrežna funkcija je bila stabilna tijekom praćenja. Dokazana je dugoročna sigurnost DBA i učinkovitost na smanjenje sistoličkog krvnog tlaka u bolesnika s refraktornom RH.

Ključne riječi: denervacija bubrežnih arterija, hipertenzija

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PERITONEAL DIALYSIS CATHETER PLACEMENT USING A REGIONAL ANESTHESIA TECHNIQUE: ULTRASOUND-GUIDED TRANSVERSUS ABDOMINIS PLANE BLOCK

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Peritoneal dialysis (PD) is an established method for renal replacement therapy in patients with end-stage renal disease (ESRD). Transversus abdominis plane (TAP) block is a regional anesthesia technique, since recently used for PD catheter placement. The main aim of this study was to evaluate the efficacy of PD catheter placement using ultrasound-guided TAP block. We studied 43 ESRD patients from our center that underwent PD catheter placement under TAP block between June 2011 and December 2014. TAP block was successful in 38 (91.4%) of 43 patients. The remaining five (8.6%) patients required general anesthesia. All procedures were performed without complications. ESRD patients have a substantially greater number of comorbid conditions compared to general population, many of which are adversely influenced by general anesthesia. Opposite to general anesthesia, regional anesthesia has no systemic effect and using this technique may prove beneficial in this group of patients. In conclusion, TAP block is an effective method for PD catheter placement and should be especially considered in ESRD patients with major comorbidities.

Key words: end-stage renal disease, peritoneal dialysis catheter, regional anesthesia, transversus abdominis plane block

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INTRODUCTION

The number of patients with end-stage renal disease (ESRD) is continuously growing worldwide[(1)]. Peritoneal dialysis (PD) is an efficacious treatment modality in patients with ESRD[(2)]. Patients with ESRD present a challenge to anesthesiologists and surgeons due to the increased number of comorbidities. PD catheter placement can be conducted using different surgical approaches. However, some type of anesthesia is required. Transversus abdominis plane (TAP) block is a form of regional anesthesia[(3-5)]. Using this technique, analgesia of the skin, muscles and parietal peritoneum of the anterolateral abdominal wall is achieved. The aim of this study was to present our experience with PD catheter placement using the ultrasound-guided TAP block.

PATIENTS AND METHODS

Peritoneal dialysis catheter placement using the ultrasound-guided TAP block was performed in a group of ESRD patients without any contraindication for the procedure. All patients were from our center. The patients were followed during the first postoperative month for anesthesia-, surgery- or catheter-related complications. Demographic characteristics, underlying renal diseases, and pre-existent chronic comorbidities were identified based on history and clinical data and previous medical records. ESRD was defined as a permanent, irreversible loss of renal function and glomerular filtration rate less than 15 mL/min/m^2.

All patients were informed about the planned anesthesia

and surgery technique and signed their informed consent. Preoperatively, all patients received low molecular weight heparin and cefazolin 1 gram intravenously. The patient was placed in supine position. The skin was disinfected with antiseptic solution. In all patients, a combined ultrasound-guided subcostal and posterior approach was used, as previously described[6,7]. TAP block was performed using both approaches with a total amount of 30 mL of 0.5% levobupivacaine hydrochloride or 30 mL of 0.75% ropivacaine, depending on the anesthesiologist's preference. Approximately 30 minutes after injecting the anesthetic, the operation commenced. Just before skin incision, all patients received additional drugs such as sufentanil (10 mcg) and/or propofol (0.1-0.2 mg/kg) for better analgesic/sedation effect. Open approach was used as surgical technique in all patients.

Patients were followed for anesthesia-, surgery- or catheter-related complications during the first postoperative month. Continuous ambulatory peritoneal dialysis (CAPD) was started one month after PD catheter placement.

The use of medical records was approved by the Ethics Committee of the Rijeka University Hospital Center. Informed consent was obtained from all patients. The study was in adherence with the Declaration of Helsinki.

RESULTS

Between June 2011 and December 2014, a PD catheter (straight, double-cuff, Tenckhoff type) was placed using TAP block in 43 ESRD patients. The mean age of our patients was 60.81 (range 37-84) years and mean body mass index 27.12 (range 19.6-37.4) kg/m^2. The cause of ESRD was chronic glomerulonephritis in 15 (34.9%), diabetes in seven (16.3%), vascular disease in six (13.9%), polycystic kidney disease in four (9.3%), interstitial nephritis in three (6.9%) and unknown origin in eight (18.7%) patients. All patients had comorbidities: hypertension in 43 (100%), congestive heart failure in 13 (30.2%), diabetes in 12 (27.9%) and peripheral vascular disease in six (13.9%) patients. A catheter was placed in 28 male and 15 female patients. In 40 (93.1%) patients, TAP block was performed using 30 mL of 0.5% levobupivacaine hydrochloride, whereas in three (6.9%) patients, 30 mL of 0.75% ropivacaine was used. The TAP block was successful (no need of general anesthesia) in 38 (91.4%) patients. The remaining five (8.6%) patients had pain at the incision site and general anesthesia had to be used. The mean duration of the operation was 41.63 (range 25-70) minutes. Peristalsis was present continuously in all patients, without any stool disruption. Fourteen (32.5%) patients required postoperative analgesics (tramadol) on the first postoperative day. The mean hospital stay was 5.17 (range 4-7) days. The postoperative course was uneventful in all patients, without any anesthesia-, surgery- or catheter-related complications in the first postoperative month. All patients successfully started CAPD four weeks after PD catheter placement.

DISCUSSION

Dialysis is the best established mode of mechanical organ replacement therapy. Compared to hemodialysis (HD) patients, PD patients seem to be much more satisfied, based on the quality of life during treatment, and preference of PD may be more advantageous in the pre-transplantation period. There is survival advantage for PD patients over the first 1-2 years after the onset of dialysis, with better preservation of residual renal function. Moreover, much lower doses of erythropoietin have been shown to be sufficient in PD patients[8].

Since PD catheter placement is a surgical procedure, some kind of anesthesia is required. Local anesthesia is preferred in patients with significant comorbidities; however, it has some limitations (edema and bleeding at the incision site and need for repeating injections). The most utilized anesthesia technique for PD catheter placement is general anesthesia with all its risks. Using regional anesthesia has just been started for PD catheter placement[6].

The use of TAP block for insertion of PD catheter was firstly described by Varadarajan *et al.*[9]. Their study included 73 patients and the technique was effective in 60 (82%) patients. In contrast to our technique of using TAP block only, they used combined TAP and rectus sheath block.

Chatterjee e*t al.*[10] analyzed 52 patients, of which 41 did not require additional analgesia. Eleven patients complained of pain at the skin incision site and received local anesthetic. Only three patients continued to complain of pain and were administered fentanyl as additional analgesia. There was no need for general anesthesia in any patient.

Complications of TAP block are very rare. As for other peripheral nerve blocks, the complications include nerve injury, injection site bruising, infection and allergic reaction. Other possible complications include spleen, kidney and bowel injury. In our patients, there were no complications related to anesthesia, surgery or PD catheter. Hecquet et al. report its early postoperative complications: hematoma in 11% and hemoperitoneum in 3% of patients[11].

Patients with ESRD have a substantially higher number of comorbid conditions compared with general population, including coronary artery disease, congestive heart failure, hypertension, cerebrovascular disease, peripheral vascular disease, diabetes mellitus, lung disease, and peptic ulcer disease. The aforementioned conditions are associated with a significantly higher mortality rate among HD patients[12,13]. General an-

esthesia can produce significant effects on the cardiac, vascular and pulmonary systems. As direct cardiac and pulmonary effects of regional anesthesia are negligible, this type of anesthesia can be recommended for ESRD patients[14].

In our opinion and in concordance with our experience, TAP block can be used as the main anesthesia technique for PD catheter placement. Because ESRD patients have a high number of comorbidities, avoiding general anesthesia by using TAP block can be recommended.

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SAŽETAK

POSTAVLJANJE KATETERA ZA PERITONEJSKU DIJALIZU PRIMJENOM REGIONALNE ANESTEZIJE: ULTRAZVUČNO VOĐENI TAP BLOK

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Peritonejska dijaliza (PD) je učinkovita metoda nadomjesne terapije bubrežne funkcije u bolesnika koji se nalaze u terminalnom stadiju bubrežnog zatajenja (ESRD). Transversus abdominis plane (TAP) blok spada u regionalnu anesteziju i nedavno se počeo primjenjivati i i kod implantacija katetera za PD. Cilj ove studije bio je procijeniti učinkovitost postavljanja katetera za PD uz pomoć ultrazvučno vođenoga TAP bloka. Analizirali smo 43 bolesnika s ESRD iz našega centra u kojih je postavljen kateter za PD uz pomoć TAP bloka između lipnja 2011. i prosinca 2014. godine. TAP blok bio je uspješan u 38 (91,4%) od 43 bolesnika. U ostalih pet bolesnika bilo je potrebno primijeniti i opću anesteziju. Svi zahvati su prošli bez komplikacija. Bolesnici s ESRD imaju značajan i uvećan broj popratnih bolesti u odnosu na opću populaciju, od kojih se mnoge mogu pogoršati djelovanjem opće anestezije. Za razliku od opće anestezije, regionalna anestezija nema sistemskog učinka te uporaba ove tehnike može biti korisna u ove skupine bolesnika. Zaključno, TAP blok je učinkovita metoda kod postavljanja katetera za PD, pogotovo u bolesnika s ESRD koji imaju brojne popratne bolesti.

Ključne riječi: terminalni stadij bubrežnog zatajivanja, kateter za peritonejsku dijalizu, regionalna anestezija, *transversus abdominis plane* blok

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SPECIFICITY OF DIALYSIS IN THE ELDERLY – DILEMMAS

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The global increase in the proportion of older population contributes to the increasing number of patients with renal insufficiency. This disorder particularly involves the old (age 70-75) and very old (over 80) population groups. The number of comorbidities is increasing and life expectancy reduced with aging. Cross-sectional analysis of ten-year survival showed a rate of 33.9% in patients treated at the Hemodialysis Center, 23.81% in transplanted patients and 19.35% in dialyzed patients. In patients having started hemodialysis (HD) at the age of ≥70, the mean survival was 20.27±18.62 months, in those that died 15.54±17.35 months, and in survivors 30.29±17.85 months. Among HD treated patients, 35% survived for up to one year, 18% for two years and 8% for ≥3 years. Karnofsky index was below 50% in all patients that survived, while the Malnutrition Inflammation Score and Subjective Global Assessment indicated malnutrition. In Croatia, the number of HD patients is constantly increasing as the result of population aging, better, accessible and equal health care that prolongs life span, easier access to substitution methods, more accesses to the vascular system, development of the national transplant network and good immunosuppressive therapy. All this provides biological, economic and normative space for replacement therapy. Old age, comorbidities and poor nutritional status influence high mortality, poor functional status and impaired quality of life. Survival results correspond to reports in the literature.

Key words: elderly patients, dialysis, survival

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INTRODUCTION

There is rapid increase in the number of elderly patients in the world who need dialysis treatment. These reports are consistent from different countries of America, Canada, Europe and Australia. The problems that accompany old age are multiple[(1)]. There are different attitudes to stratify age limits. There are various age group classifications, so that some propose young old age 60-69, middle old age 70-79 and very old age ≥80 years, whereas others set the following limits: young old age 65-74, middle old age 75-84 and oldest old age >85 years. However, life span has extended and the increase in the elderly population with all related comorbidities is inevitable. End-stage renal disease has a much higher incidence in elderly than in young population and is constantly growing worldwide, either as a disease, comorbidity, or as a result of various states. This raises questions of physiology and pathophysiology of aging and changes in the glomerular filtration rate (GFR). Is there a clear stance on normal laboratory values adjusted for age limits? To what degree is GFR a physiological variant for a particular age? Does hemodialysis (HD) extend lifetime of very old people? The answers are not always precise. According to Singh et. al.[(2)], prognosis is often based on subjective assessment and should include the ability to detect patients with end-stage renal disease who will be treated with HD, professional teams for communication with such patients, as well as guidance with solid attitudes[(3)].

Elderly population is often exposed to doctor, family or guardian decisions that are against their wishes, either due to the lack of communication or lack of knowledge about the methods and procedures to be employed. Procedures can leave mental and physical consequences (suffering) in spite of being performed professionally, and these patients say, "if I knew what I had to go through, I would have never agreed to it". Therefore, it is necessary to respect patient decisions, especially when we are aware that they may be close to the end of life and would rather choose palliative care than these procedures. The aforementioned author gives examples of giving up patients having

started dialysis in 25% of cases before their death in the US population. The same source says that in one Canadian study, 60% of patients complained of having started dialysis treatment, and half of them claimed they did so upon doctor persuasion[2]. No matter what, we must not forget individual approach and have to respect the will of the patient when he wants to be subjected to any procedures, including kidney transplantation.

PATIENTS

We performed retrograde analysis of 10-year survival in patients treated in dialysis unit. On cross-sectional analysis of all patients at the time of testing, we determined the types of access for dialysis according to age categories. Then we selected a group of patients aged ≥70 at the time of their starting dialysis treatment. We recorded outcomes at 1, 2, 3, 4 and ≥5 years. In patients that survived 6 months after the end of monitoring the Malnutrition Inflammation Score (MIS) and Karnofsky index were determined[4]. Data were processed using standard statistical analysis. We examined a total of 77 patients from beginning of treatment, 70 66.23% of men and 33.77% of women, 28.57% of them aged 70-75, 45.45% aged 76-80 and 25.97% aged ≥80. (Table 1)

Table 1
Patient distribution according to age and sex

	Age (yrs), n (%)			Total N (%)
	70-75	76-80	≥80	
Male	14 (63.64)	22 (62.86)	15 (75.0)	51 (66.23)
Female	8 (36.36)	13 (37.14)	5 (25.0)	26 (33.77)
Total	22 (28.57)	35 (45.45)	20 (25.98)	77 (100)

RESULTS

Retrograde analysis of ten-year survival of dialysis patients showed that 19.35% of all study patients (age range, 25-87 years) were treated with dialysis for more than 6 months. There was a general trend of elderly patients prevailing on dialysis. The cross-sectional analysis of the test year at the Center showed that there were 31.76% of patients aged ≤60 years and 49.23% of patient older than 71; 57.65% of them had AV fistula, 11.76% temporary catheter and 30.59% permanent catheter. When we selected patients older than 70, there were 77 patients recorded in 5 years. Analysis of five-year survival in elderly patients showed the following mean survival rates: 20.27±18.62 months all, 15.54±17.35 months in those that died, and 30.29±17.85 months in survivors (dialysis).

Table 2 shows outcomes according to age groups. It is interesting to note how death rates changed with age, i.e. younger age was associated with lower mortality rate, whereas the highest death rate was recorded in the 76-80 age group. There were 25 survivors, 14 (56%) male and 11 (44%) female patients, that started HD at age 70. After 6 months, MIS score 7 or more was observed in 10 (40%) patients. The mean MIS was 5.68±2.56, range 1-12. The mean Karnofsky score in patients that survived ≥6 months was 50±12.91, range 30-80.

Table 2
Patient distribution according to outcome and age

Outcome	Age (yrs), n (%)			Total N (%)
	70-75	76-80	≥80	
Died	6 (11.75)	29 (56.86)	16 (31.37)	51 (66.23)
Living (dialysis)	15 (62.5)	6 (25.0)	3 (12.5)	24 (31.17)
Recovered			1	1 (1.3)
Transplanted				0
Other unit or modality change	1			1 (1.3)
Total	22 (28.57)	35 (45.45)	20 (25.98)	77 (100)

Table 3
Patient distribution according to survival and age group

Survival (year)	Age (yrs), n (%)			Total N (%)
	70-75	76-80	≥80	
<1	3 (8.57)	17 (48.57)	15 (42.86)	35 (45.45)
<2	8 (44.45)	6 (33.34)	4 (22.21)	18 (23.38)
<3	4 (50.0)	3 (37.5)	1 (12.5)	8 (10.39)
<4	2 (25.0)	6 (75.0)	0	8 (10.39)
≥5	5 (62.5)	3 (37.5)	0	8 (10.39)
Total	22 (28.57)	35 (45.45)	20 (25.98)	77 (100)

DISCUSSION

Analysis of our data revealed the presence of very old population with a large number of associated comorbidities and a high degree of malnutrition according to MIS and Karnofsky score. In the Center, there were more than 49.23% of elderly patients (older than 70), with a high rate of temporary or permanent central venous catheter (CVC) as access for dialysis (42.35%). Most of the patients that survived 1, 2, and 3 years were in the 76-80 age group, whereas none from the >80 age group survived for 4 or 5 years. Elderly survivors have low ability of independent functioning (the mean Karnofsky score in those surviving ≥6 months was 50%) and poor nutritional status (MIS 5.68). All this favors development of infection, new comorbidities, worsening of the already impaired quality of life, and uncertain prognosis. The question is whether all patients need dialysis treatment, in which context definitive decision should be considered relative to the expected prognosis and especially respecting patient wish. Can we agree that in old age, low clearance without heart failure, hyperhydration, hyperkalemia, acidosis and uremic toxicity with preserved diuresis should be observed because the planned approach may not be used or such intervention could aggravate the patient condition? According to Glassock[2], decreased GFR in the elderly can be explained by anatomical changes in terms nephrosclerosis and decay of individual glomeruli. These morphological changes associated with significant albuminuria or proteinuria are serious warning, regardless of age. Furthermore, GFR declines with age, depending individually on the presence of diabetes, hyperlipidemia, smoking, atherosclerosis, etc., along with primary renal disease which, if present, additionally worsens the condition. Reduction in clearance below 45-59 should not be considered as chronic kidney disease (CKD) without the presence of other signs of the disease[2]. High age negatively affects outcome of patients on HD. In a study in patients aged >75, malnutrition had negative effect on overall survival, regardless of the dose of dialysis[5]. Dialysis accesses are often the source of frustration and failure, especially with AV fistula. It is a pathomorphological substrate for poor outcome. It can be associated with traditional age related factors such as hypertension, dyslipidemia, diabetes, etc. In uremic inflammation, oxidative stress, uremic toxins, damage to the endothelium, calcification of arterial media, vein damage, and eventually intimal hyperplasia cause AV fistula dysfunction.

While on the other side of the CVC, although the only way out, in most cases in very old population it often implies additional risks (infection, thrombosis), this approach is preferred by patients and sometimes by the staff to facilitate manipulation. CVC is much more frequently used in elderly as compared with younger patients on dialysis in Europe, Australia, North America, but rarely in Japan (less than 1%)[1]. Of course, it should be viewed differently in particular groups of the elderly, and AV fistula may be considered the first option; however, if it is not possible, then aretoriovenous graft (AVG) should be applied. Considering survival for the first 18 months, AVG may prove better than AV fistula[2]. Transplantation should not be marginalized in elderly patients because it can prove either beneficial or a risk. Therefore, the choice of treatment modality in these patients should be based on strict and thorough assessment. There is no specific age that would be considered a limit, since the overall condition is essential for transplantation rather than age. In the early postransplant period, there is a high risk of death in this group of patients, but later it progressively diminishes and life expectancy with transplanted organ is longer[6]. We must not forget the frequent postransplant diseases these patients are prone to, i.e. diabetes, osteoporosis, infections, and malignancies. Transplantation is unquestionably beneficial for some patients. There are still problems encountered in practice, related to very old patients with multiple complications and poor prognosis, such as refusing or discontinuing dialysis after starting dialysis treatment, as reported in the literature. These may refer to socioeconomic issues or legally defined procedures and patient rights, or their guardians do not accept this mode of treatment[7].

EHTICAL DILEMMAS

Many nephrologists often meet with the treatment of old people because of the extended life expectancy. Somatic treatment is often very complex, requiring expertise and empathy. In order to make appropriate decisions and provide optimal treatment for the elderly with associated diseases, nephrologists should preferably be familiar with some basic psychological concepts of functioning of every human that are deeply subconscious and serve the patient to pass more easily through traumatic reality. These are also known as defense mechanisms.
When the patient is cooperative, everything is much easier; however, when he is negativistic for any reason, then psychiatric help is needed to eliminate the cause of negativism and if possible proceed with psychiatric treatment in such patients.
When both somatic and psychological or psychiatric resources have been exhausted, ethical dilemmas frequently appear and are very complex. In case of profoundly demented and dying patients, a physician will do everything to support patient survival, at least for some time. Occasionally, it will require patient family consent, and sometimes patient family will refuse it.

In the complex treatment of elderly patients with many associated, complex diseases, it may sometimes be difficult to make the diagnosis, determine prognosis and imminent death. It is even more difficult to make any decisions that affect ethical domain, in addition to those we have been trained, i.e. help the patient until the last moment. In my opinion, it is necessary to work on the issue of our own decisions in a similar situation, and in accordance with current, healthy mental capacity make a decision and thus help their families and doctors, just as in case of organ donation.
Many times, we are faced with the duty of providing bad news to elderly patients, such as news about their disease and its prognosis, which can be rather stressful for both. It is even more difficult to make decisions that are of different ethical perspective than the one that all physicians know, i.e. help every patient until the very last moment. I believe that patients which are psychologically competent should make their own decisions in situations like these, i.e. decide whether they want to keep fighting or give up their battle.

The substitution treatment of elderly CKD patients should have a reasonable individual approach. There are no clear guidelines, as they are mostly vague and neutral. For some patients, replacement procedures can be beneficial, and for the others harmful. Physicians should be trained to provide information about treatment options, taking care of life expectancy, favorable and detrimental effects of the procedures, and the patient wishes. The patient should be allowed to choose the modality of treatment, the type of access and enrolment in the transplant list.

Aging is an integral part of the life cycle that is extended, resulting in accumulation of many factors that directly or indirectly influence GFR decline. Significant GFR reduction in combination with other factors for replacement therapy should be considered individually. The patient must be detected early, properly educated, and should be aware of all treatment modalities. Decisions must be signed by the patient or guardian. The will and dignity of the person should be respected.

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SAŽETAK

POSEBNOST DIJALIZE U STARIH I VRLO STARIH BOLESNIKA – DILEME

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U svijetu je ubrzan porast broja starijih bolesnika koji trebaju liječenje dijalizom. Ti se izvještaji poklapaju iz raznih zemalja. Problemi koje nosi starija dob su višestruki. Različiti su stavovi za stratifikaciju dobnih granica. Bilo kako bilo, dobne granice su produžene i porast starije populacije sa svim pratećim komorbiditetima je neizbježan. Kronična bubrežna bolest ima puno veću incidenciju u među starom negoli među mlađom populacijom i u stalnom je porastu u svijetu bilo kao bolest, komorbiditet ili posljedica raznih stanja. Ova činjenica nameće pitanja fiziologije i patofiziologije starenja i promjena u glomerularnoj filtraciji (GF). Ima li jasnih stavova o normalnim laboratorijskim vrijednostima prilagođenim dobnoj granici? U kojem stupnju je GF fiziološka varijanta za konkretnu dob? Produžava li liječenje hemodijalizom životni vijek vrlo starih osoba? Odgovori nisu uvijek precizni. Stara populacija često je izložena odlukama liječnika, obitelji ili skrbnika mimo svoje želje, bilo zbog nedostatka komunikacije ili zbog nepoznavanja postupaka. Procedure mogu na bolesnika ostaviti psihičke i fizičke posljedice (patnje), bez obzira na to što su sve napravljene profesionalno, oni često kažu “da sam znao što me čeka, ne bih pristao”. Zbog toga je nužno poštivati odluku bolesnika. Analizom vlastitih podataka vidljiva je prisutnost veoma stare populacije s velikim brojem pridruženih komorbiditeta te visokim stupnjem pothranjenosti (MIS) i Karnofskyjeva skora. U Centru je više od 49,23% populacije starije od 70 godina, s velikom zastupljenošću privremenog ili trajnog centralnog venskog katetera kao pristupa za dijalizu (42,35%). Najviše preživjelih do 1, 2 i 3 godine bilo je u skupini od 76-80 godina, a u skupini starijih od 80 godina nitko nije preživio 4 ili 5 godina. Kod preživjelih bolesnika visoke dobi sposobnost za samostalno funkcioniranje je veoma mala. Karnofskyjev zbir za preživjele 6 mjeseci i više bio je u prosjeku 50%.

Ključne riječi: stari bolesnici, dijaliza, preživljenje

MALNUTRITION IN PATIENTS ON DIALYSIS TREATMENT

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Many factors contribute to morbidity and mortality in patients with end-stage renal disease, one of these being malnutrition. Eating disorders are inevitable in patients with uremia. A common associated factor is inflammation with hypoalbuminemia and decrease in serum proteins. In the present study, data on 33 (38.37%) female and 53 (61.63%) male patients were assessed with standard statistical analysis including the R-test for normality. The assessment method used was the Malnutrition Inflammation Score (MIS) composed of 10 components. The mean patient age was 67.28±12, range 32-86 years. The mean duration of hemodialysis (HD) was 48.94±47.57, range 3-224 months. The MIS has three categories: (A) well nourished; (B) mild malnutrition; and (C) severe malnutrition. At the beginning of the study, results were as follows: (A) 6.98%; (B) 51.16%; and (C) 41.86%. The respective figures recorded after 6 months were as follows: (A) 10.47%; (B) 25.58%; and (C) 63.95%. During the study, 53.49% of patients had a MIS of 7 or more, 6.97% of patients passed away, and 3.49% underwent transplantation. The mean MIS was 20.3±1.63 in the deceased, 3±2.6 in the transplanted, and 7.98±5.7 in the rest of patients. Patients having undergone HD for at least 3 months and aged at least 18 years were included in the analysis. The objective of the study was to determine the rate of malnutrition among HD patients and to compare the results recorded in our center with other HD centers around the world. Furthermore, our aim was to compare MIS with mortality rate. We repeated MIS after 6 and 12 months to find out whether there would be a decrease in the rate of malnutrition among patients, since additional nutritional support was introduced after detection of the state. According to our study results, there is strong correlation of malnutrition, hospitalization and mortality.

Key words: malnutrition, dialysis, morbidity, mortality

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INTRODUCTION

It is well known that chronic disease causes loss of appetite and body weight, as well as malnutrition. Uremia is a common state that accompanies malnutrition. In the state of uremia, there is a restriction of protein intake due to the lack of appetite on the one hand and loss of protein through preserved diuresis on the other. Hemodialysis (HD) induces protein catabolism, eliminates nutrients and has a proinflammatory effect. Peritoneal dialysis causes protein leakage through the peritoneal membrane. However, inadequate dose of dialysis contributes to malnutrition considering the proinflammatory and toxic effects of retained uremic metabolites.[1-8] We conducted a cross analysis in our dialysis center among patients having undergone treatment for at least 3 months and aged at least 18 years. Our aim was to assess the rate of malnutrition, compare our results with those of other dialysis centers around the world, and determine the impact of the study score on mortality. We repeated the test after 6 and 12 months to find out whether there would be a decrease in malnutrition among patients, since additional nutritional support was introduced after detection of the state, and patients, their families and personnel realized the importance of nutrition and physical activity.

SUBJECTS AND METHODS

Eighty-six patients (33 female and 53 male) were assessed using standard statistical analysis. The Malnutrition Inflammation Score (MIS) composed of 10 compo-

nents was used as the method of assessment[9]. The MIS is divided into four categories (nutritional history, physical examination, body mass index (BMI) and laboratory parameters). Patients were distributed according to their nutritional status, i.e. MIS, into three categories: (A) well nourished (0, 1, 2); (B) mild malnutrition (3, 4, 5); and (C) severe malnutrition (≥6). The Karnofsky scale was used to evaluate performance status[10].

RESULTS

There were 38.37% of female and 61.63% of male patients, mean age 67.28±12 (range, 32-86) years and mean HD duration 48.94±47.57 (range, 3-224) months. Results are shown in Table 1.

The mean Karnofsky score was 71.16±18.75, range 30-100.

Table 1
Results of Malnutrition Inflammation Score (MIS) in study patients

	MIS (%)		
	A	B	C
Baseline	6.98	51.16	41.86
After 6 months	10.47	25.58	63.95
After 12 months	9.52	30.16	60.38

MIS score: (A) well nourished (0, 1, 2); (B) mild malnutrition (3, 4, 5); (C) severe malnutrition (6 or more)

During the study period, 6.97% of patients died, whilst 3.49% underwent kidney transplantation. The mean MIS was 20.3±1.63 in the deceased, 3±2.6 in the transplanted and 7.98±5.7 in the rest of patients. The mean Karnofsky score was 62.32, range 20-100.

After the 12-month period, 63 out of 86 patients remained in the study, five (5.81%) had been transplanted and 18 (20.93%) passed away. The mean MIS was 6.48±3.78 and the mean Karnofsky score was 71.11±12.96, range 30-90 (Table 2).

Table 2
Correlation between albumin levels and Malnutrition Inflammation Score (MIS)

Start	0.61657465
After 6 months	0.72847086
After 1 year	0.61543457

DISCUSSION

Analysis of data obtained in the study revealed rather poor results in terms of increase in the rate of malnutrition among patients during the first 6 months. However, this increase in malnutrition was primarily due to comorbidities, malignant disease and old age.

Great difference in MIS between the deceased and transplanted patients was expected and confirmed by analysis. The mean MIS was 20.3±1.63 in the deceased, 3±2.6 in the transplanted and 7.98±5.7 in the rest of patients. According to some authors, the prevalence of malnutrition among dialysis patients can be 70% or more[5,6,9].

After 12 months, malnutrition was still a major problem among our patients, even though we detected the state, attempted to correct anemia, and started substitution therapy via parenteral re-feeding with proteins and other nutrients. These results are understandable considering that new patients were not added to the study, while the subjects assessed were aging and acquired new comorbidities during the study. However, it is significant to note that nutrition and performance status did not deteriorate in study patients.

Malnutrition is a common complication of chronic disease, either because of restriction of nutrient intake, or due to other factors such as catabolism or protein leakage via proteinuria, or a combination of these. Uremia is frequently accompanied by anorexia. Anorexia is defined as the lack of appetite and is common among patients with high degree renal disease and patients undergoing HD treatment. There are many causes, being either of physical or psychological nature. The most common causes of poor nutrient intake are changes in the mucous membranes of the mouth and olfactory region causing deterioration of taste and smell, changes of salivary glands causing xerostomia and hypoptyalism that disrupt fragmenting and swallowing of food, gastroparesis (dyspepsia, vomiting) and intestinal motility disorders (constipation, diarrhea)[11, 12].

Hypoalbuminemia frequently accompanies chronic disease, and is a relevant predicting factor of cardiovascular events and poor outcome. Duration of dialysis reduces muscle mass, physical activity, lowers quality of life and is associated with depression. Inadequate dialysis treatment contributes to malnutrition, and dialysis per se contributes to nutrient loss, whatever

the dialysis method. Extracorporeal circulation in HD is proinflammatory due to bioincompatible filters, nonsterile dialysis fluid and plastic dialysis bloodlines. All these lead to higher catabolism and lower anabolism of proteins. The elderly predominate in the dialysis treatment population, involving the process of aging. Serum level of albumin is a strict laboratory predictor of mortality, and hypoalbuminemia is a frequent sign of inflammation and poor nutritional status among individuals[11,12]. C-reactive protein (CRP) levels are determined in our patients on a monthly basis, and more frequently if needed, whereas albumin, ferritin, iron, UIBC and transferrin are assessed every three months. Iron parameters significantly correlate with nutritional status and inflammatory state among end-stage renal disease (ESRD) patients. At the beginning of our study, the mean albumin level was 40.22 g/L and mean CRP 13.31 mg/L. At the end of the study, the mean albumin level was 42.1 g/L. There was a strong correlation between albumin and CRP levels (r=-0.55)[2] and correlation between albumin levels and MIS.

During treatment modalities such as peritoneal dialysis (PD), loss of protein can be 5-15 grams per day, or even more during peritonitis. PD frequently increases body weight due to storage of fat derived from resorbed glucose and water retention due to decreased ultrafiltration, but with loss of muscle mass. A lack of appetite can arise because of glucose and fluid resorption from glucose solutions as well. Depression often accompanies patients with chronic kidney disease (CKD)/ESRD due to a decrease in the quality of life caused by HD treatment. Sometimes, the symptoms of uremia mimic depression (fatigue, slackness, lack of strength, appetite loss, loss of body weight, pruritus, etc.). Sometimes, CKD/ESRD patients acquire depression during their illness. Interestingly enough, recent research has shown a connection between proinflammatory cytokines and depression, which explains the high incidence of depression among ESRD patients due to CKD and impact of treatment methods.

CONCLUSION

The goal of dialysis treatment is to lower inflammation, prevent further loss of serum proteins including albumins and body weight loss, restore nutrients and correct acidosis. Re-feeding with special nutrient preparations after verification of the degree of malnutrition has become standard in our dialysis center. According to tests conducted in our center, we have learned that there is high association of malnutrition, hospitalization and mortality among patients with ESRD. Their physical performance is tightly linked to their nutritional status, and physical therapy should be conducted to preserve remaining muscle mass and slow down additional sarcopenia. It seems that dialysis duration is a powerful and independent morbidity factor, and the longer dialysis treatment lasts, the higher is MIS, as well as physical deterioration.

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SAŽETAK

POTHRANJENOST BOLESNIKA NA DIJALIZI

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Poznato je da teške bolesti uzrokuju gubitak apetita, tjelesne težine i malnutriciju. Uremija je teška bolest i čest pratilac pothranjenosti. Uzroci tome su višestruki: ograničen unos bjelančevina, gubitak bjelančevina uz još očuvanu diurezu. Sama hemodijaliza potiče katabolizam proteina i eliminira neke hranjive tvari te djeluje proupalno. U Centru za kroničnu hemodijalizu svih ispitanika liječenih najmanje 3 mjeseca i starijih od 18 godina napravili smo presječnu analizu. Željeli smo vidjeti kolika je zastupljenost pothranjenosti i u kojoj je korelaciji sa svjetskim podatcima te koliki je utjecaj visine ispitivanog zbira na smrtnost. Ponavljanjem testa nakon 6 i 12 mjeseci očekivali smo smanjenje stupnja pothranjenosti s obzirom na nutricionističku potporu nakon otkrivanja stanja, a na osnovi kojeg se podizala svijest o tom problemu kod bolesnika, obitelji i osoblja, naročito iz područja prehrane i tjelesne aktivnosti. U analiziranim podatcima na prvi pogled došli smo do poražavajućih rezultata u smislu porasta pothranjenosti u prvih 6 mjeseci. Daljnja analiza je pokazala da je pothranjenost bila uglavnom uzrokovana komorbiditetom povezanim s malignitetom te visokom dobi. Logično je da je uočena velika razlika u Malnutrition Inflammation Score (MIS) između umrlih i transplantiranih bolesnika. Kod umrlih bolesnika zbir MIS je bio 20,3±1,63, kod transplantiranih 3±2,6, a kod svih ostalih 7,98±5,7. Ne smijemo zaboraviti da se prema nekim autorima u literaturi navodi učestalost pothranjenosti kod bolesnika na dijalizi od 70% i više.

Ključne riječi: pothranjenost, dijaliza, pobol, smrtnost

NON-MELANOMA SKIN CANCER IN RENAL TRANSPLANT RECIPIENTS: DO WE STILL OVERLOOK IT?

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Non-melanoma skin cancer (NMSC) is the most frequent cancer in renal transplant recipients (RTRs). Clinical and epidemiological studies indicate that long-life immunosuppressive therapy that is essential for preventing graft rejection and obtaining adequate graft function after renal transplantation, combined with older age at transplantation, total sun burden during life, fair skin type and personal history of treated NMSC before transplantation, are the most important risk factors for NMSC development. Since RTRs are more susceptible to developing more aggressive types of skin cancers, especially squamous cell carcinoma (SCC), it is of great importance to develop cancer awareness in these patients, making them sensitive to sun protection and regular dermatologic and skin self-examination. Immunosuppressive therapy as a risk factor of high importance has to be individually tailored and, if necessary, altered in order to decrease cancer formation as much as possible, while preserving graft survival and function. Therefore, interdisciplinary approach, including primarily nephrologists and dermatologists, should be employed in follow up of RTRs, thus enabling prevention, early diagnosing and appropriate treatment of NMSC in these patients.

Key words: renal transplantation, immunosuppression, skin cancer, epidemiologic studies

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INTRODUCTION

Renal transplantation is nowadays established as the best therapeutic approach for end-stage renal failure, enabling patients to abandon chronic dialysis and to get prolonged life span and better quality of life. After transplantation, patients require lifelong immunosuppressive treatment which prevents graft rejection, but also increases the risk of various complications including opportunistic infections and malignancy development[(1)]. Additionally, there is increased mortality for a given stage and grade of malignancy compared with patients not receiving immunosuppressants.

It has been estimated that organ transplant recipients (OTRs) have a three- to six-fold increased risk of developing solid organ cancer or internal malignancy compared to the normal population[2]. Non-melanoma skin cancer (NMSC) is the most common cancer in renal transplant recipients (RTRs). Other malignant skin tumors such as malignant melanoma, Kaposi's sarcoma, Merkel cell cancer, sebaceous carcinoma and cutaneous lymphoma occur less frequently in RTRs, but still at a greater frequency than in the non-immunosuppressed populations[(3)].

EPIDEMIOLOGY

Several studies indicate that up to 40% of OTRs develop precancerous skin growths such as actinic keratosis and Bowen's disease (squamous cell carcinoma in situ), as well as NMSC within the first 5 years after trans-

plantation[4]. NMSC develops most frequently, accounting for 90% of all skin cancers in OTRs[5]. It is well established that immunosuppressed patients develop NMSC more often and much earlier than immunocompetent people[2]. Furthermore, it has been estimated that immunosuppressive therapy carries a 65-fold increased risk of squamous cell carcinoma (SCC) and 10 to 16-fold increased risk of basal cell carcinoma (BCC) development compared to immunocompetent population[6]. These data show that the risk of BCC increases linearly, whereas the risk of SCC increases exponentially.

The incidence of skin cancer among RTRs has been differently estimated, varying from 2% to 30%[3,7-11]. These differences could probably be ascribed to different amount of sun exposure in different populations. Most studies indicate that SCC is predominant to BCC in RTRs, with an SCC/BCC ratio of 3:1, which is reversed compared to the normal[10,12-14]. However, a minor number of studies found BCC to be the most common carcinoma in RTRs[7,15,16], which is consistent with data in the general population[17]. In addition, some authors found similar frequency of both (SCC/BCC ratio 1.1:1)[18].

RISK FACTORS

Remarkable advances in immunosuppressive therapy have led to longer survival of RTRs, which is associated with an increased risk of developing more aggressive skin cancers. Therefore, there is an urgent need to identify patients that are at the greatest risk of aggressive (metastatic) skin cancer.

Several risk factors have been identified to contribute to actuating cutaneous carcinogenesis in RTRs, including age, overall UV exposure, Fitzpatrick skin type, personal history of previous non-melanoma skin cancer and immunosuppressive therapy. The cause of renal insufficiency, HLA mismatch, blood type or RH factor do not seem to influence cancer formation[9,16], nor does the pretransplant dialysis period[9].

AGE

Older age at transplantation has been found as a risk factor for NMSC development in RTRs[12,14]. In the RTRs transplanted after age 55, the risk ratio for NMSC was 12-fold higher than in RTRs that were younger than 34 at the time of transplantation. This increasing prevalence in older age can be explained by the higher cumulative UV dose, an important risk factor for SCC development, in both immunocompetent and immunosuppressed population. Consistent to these data is the finding that OTRs that had been transplanted at the age of approximately 40 years developed skin tumors within a mean of 8 years, whereas ORTs that were older than 60 at the time of transplantation developed skin tumors within a mean of 3 years. This can be explained by the higher incidence of preclinical skin tumors in older age, which are additionally promoted by immunosuppressive therapy.

ULTRAVIOLET RADIATION

In the general population, the major risk factor for BCC development is intensive sun exposure in childhood and adolescence, while for SCC chronic cumulative sun exposure and ultraviolet (UV) cell damage is assumed[17]. Consistently, in RTRs UV exposure is also considered to be an important risk factor for NMSC development. SCC in RTRs is mostly located on sun exposed body areas such as the face, ears and hands, supporting the UV damage being a risk factor[19]. Namely, UV rays together with immunosuppressants alter skin immunity, which leads to the absence of recognition of tumor antigens and tumor initiation.

FITZPATRICK SKIN TYPE

Up to 89% of RTRs with NMSC have been classified by Fitzpatrick into type I, II or III[13]. The risk ratio for cutaneous SCC in OTRs with Fitzpatrick skin type I-II has been estimated to be 65-fold to 250-fold higher when compared with immunocompetent population[20-22].

PERSONAL HISTORY

Immunocompetent patients who develop NMSC have a 10-fold increased incidence of subsequent NMSC development (3-year cumulative risk for development of second NMSC is 18% for SCC and 44% for BCC) comparing to people who do not have personal history of NMSC23. It has been estimated that RTRs with one NMSC have a 49-times higher risk of subsequent cancer formation compared to the matched control group[24]. Usually, SCC arises in so called “field cancerization”, an area of previous great actinic damage and epidermal dysplasia. Therefore, RTRs who developed one SCC will carry a greater risk of subsequent skin cancer formation, already taking into consideration the burden of immunosuppression. Prior use of biologic therapy or a history of leukemia or lymphoma carries an additional risk of NMSC development in RTRs[19].

IMMUNOSUPPRESSIVE THERAPY

The risk rate for NMSC development in OTRs is strongly related not only to the intensity and duration of immunosuppression, but also to the type of immunosuppressive therapy. Induction therapy is introduced before, at the

time of, or immediately after transplantation induction. It includes biologic agents such as lymphocyte-depleting agents or interleukin-2 receptor agonist (IL2-RA). In heart transplant recipients, it has been shown that induction therapy consisting of antithymocyte globulin, OKT3 or monoclonal anti-IL-2 receptor antibodies carries an increased risk of NMSC development[25]. Initial and long term maintenance immunosuppressive therapy is introduced primarily to prevent acute graft rejection and to obtain adequate graft function. Introduction of calcineurin inhibitors Cyclosporin A and tacrolimus to the former double immunosuppressive protocol consisting of prednisone and antiproliferative drug (azathioprine and mycophenolate mofetil) has ameliorated graft survival. However, posttransplant cancer formation is the major problem connected to long and aggressive immunosuppression.

All immunosuppressive drugs may enhance cancer development, but the greatest risk has been attributed to azathioprine and Cyclosporin A. Photosensitivity and actuated photocarcinogenesis induced by azathioprine are caused by the interaction between DNA 6-thioguanine and UVA[26,27]. There are indications that PTCH gene mutations in BCC may also be associated with azathioprine use, particularly with cancers on non-sun-exposed skin areas[28]. Laboratory experiments suggest that Cyclosporin A inhibits mitochondrial permeability transition pore (MPTP) opening and prohibits keratinocyte cell death caused by genotoxic stress, thus promoting skin cancer development. No such effects were observed with the use of mycophenolate mofetil or tacrolimus[29,30]. When comparing azathioprine, cyclosporine and tacrolimus therapy regarding the risk of NMSC development, studies are contradictory. Some authors found a higher incidence of NMSC in patients having received cyclosporine than in those treated with azathioprine or tacrolimus[31-33], whereas others found no significant difference between the patients having received cyclosporine or azathioprine therapy[14,34,35].

Additionally, studies showed that triple immunosuppressive therapy (cyclosporine, prednisone, and azathioprine or sirolimus) posed a greater risk of NMSC than dual therapy (prednisone and azathioprine or sirolimus), and that maintenance monotherapy with calcineurin inhibitor, cyclosporin A or tacrolimus, after stabilization of graft function diminished the risk of cancer development[36].

Based on the above-mentioned studies, it has been proposed that maintenance protocol should be based on mycophenolate mofetil and low-dose calcineurin inhibitor Cyclosporin A or tacrolimus, with or without prednisone. Recent evidence suggests that novel immunosuppressive therapy, mammalian target of rapamycin (mTOR) inhibitors (sirolimus and everolimus) prevents skin cancer formation[37,38]. Even though the use of novel immunosuppressive drugs and their exact impact on skin cancer prevention is not fully established, high risk patients, patients with previous NMSC and patients with potential metastatic spread of a skin cancer may benefit from switch to the new models of immunosuppression.

PROGNOSIS OF NMSC IN RTRS

Generally, BCC grows slowly, but if untreated, it can grow to a great extent, destroying the underlying tissues down through the bone. Opposed to BCC, SCC shows a potential for metastatic dissemination. It has been estimated that 6% of immunocompetent patients with SCC have a metastatic disease, which is connected with poor long-term prognosis.

For dermatologists who deal with skin cancers and for nephrologists who are following RTRs, the ability to recognize patients with a more aggressive type of skin cancer is of great importance. There are several factors in SCC which may point to a more aggressive type of SCC. Location of cancer on the ear and lip, history of previously treated SCC, size of more than 2 cm, depth of more than 4 mm, poor cell differentiation and perineural invasion are considered to mark SCC with greatest chance of recurrence, while all these signs in combination with immunosuppression may serve as a prognostic marker for metastatic cancer spreading[39].

Sometimes, histologic findings alone are not enough. Therefore, there is a comprehensive search for a single biomarker which will be able to recognize more aggressive SCC. It is known that tumor suppressor gene p53 regulates cell response to genotoxic stress, including UV cell damage[40]. Inactivation of both p53 gene alleles promotes surviving of genetically damaged cells and thus promotes cancer formation[41]. Immunohistochemical analysis of the p53 expression pattern is being used as a marker of gene mutation and inactivation[42]. In immunosuppressed patients, a higher intensity of p53 expression pattern has been found[19]. The level of serine protease inhibitor clade A member 1's (SerpinA1 or alpha -1-antitrypsin) expression pattern was elevated in SCC of bullous epidermolysis patients. These patients develop more aggressive skin cancers as a result of mutual action of chronic skin inflammation, skin ulceration, UV exposure and immunosuppression[43]. The role of matrix metalloproteinase 7 (MMP7) in SCC progression has been suggested, as up-regulation of MMP7 has been detected in SCC[44].

THERAPY

As NMSC are most frequent cancers in RTRs, showing a tendency to more rapid progression than in immunocompentent individuals, close monitoring of these

patients, preventive measures and early treatment are mandatory. Patients should be educated, even before transplantation, about the impact of UV radiation and immunosuppression drugs on the skin, as well as about mandatory compliance with sun protection and using both protective clothes and sunscreens. Education on regular skin self-examination is as important as dermatological follow up.

Actinic keratoses and small and superficial SCC should be early and aggressively treated by cryotherapy, topically with 5-fluorouracil cream, imiquimod cream or photodynamic therapy in order to prevent progression to invasive SCC. Lesions suspected of transition to invasive SCC should be biopsied as early as possible and treated. Although electrodesiccation and curettage may achieve acceptable curative rate, surgical excision with clear margins is more advisable. Mohs' micrographic surgery is appropriate for high risk areas. If surgical excision is not curative, adjuvant radiation therapy may be performed. Whether sentinel lymph node biopsy (SLNB) is a mandatory procedure in high risk patients or just close lymph node monitoring is sufficient, is still being debated, especially as there are no clear criteria for SLNB enrolment[24].

High risk patients, including those with metastatic SCC and patients who develop multiple SCCs (5-10 per year) may benefit from adjuvant systemic retinoid therapy. Retinoid use is both chemoprotective and serves as adjuvant therapy, but cannot replace monitoring and surgical treatment. Retinoid therapy is usually life-long, as recurrences have been observed after drug discontinuation[19].

When chemoprotection and sun protection methods are not enough or are contraindicated, switch to a different immunosuppressive regimen is preferred.

CONCLUSION

Renal transplantation promotes longer and prosperous life of patients with chronic renal failure. Chronic immunosuppression needed for graft survival goes along with complications such as infection and cancer development, with skin SCC being the most frequent one. Stronger and longer duration of immunosuppression, combined with older age at transplantation, UV radiation, fair skin color and history of NMSC before transplantation contribute to skin SCC development. Moreover, SCC in RTRs carries a tendency to aggressiveness and higher morbidity and mortality than in immunocompetent patients. RTRs should be educated about the increased risk of cancer development, the importance of skin self-examination and need for early detection, diagnosis and initiation of appropriate treatment. Therefore, interdisciplinary approach to these patients is recommended, bringing together nephrologists and dermatologists, surgeons, pathologists and oncologists. Interdisciplinary cooperation together with further scientific advances in the fields of transplantation and dermato-oncology should help us identify the group of RTRs with a tendency of developing invasive SCC, so that they can be put under more regular and careful supervision.

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SAŽETAK

NEMELANOMSKI KARCINOM KOŽE U PRIMATELJA BUBREŽNOG PRESATKA – PROPUŠTAMO LI TO JOŠ UVIJEK?

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Nemelanomski karcinomi kože najčešći su karcinomi u bolesnika s transplantiranim bubregom. Kliničke i epidemiološke studije ukazuju na to da su najvažniji čimbenici rizika za razvoj nemelanomskih karcinoma kože doživotna imunosupresivna terapija nužna za sprječavanje odbacivanja presatka i održanje njegove funkcije te starija životna dob bolesnika prilikom transplantacije, izloženost UV zrakama tijekom života, svjetliji tipovi kože i osobna anamneza preboljelog karcinoma kože prije transplantacije. Budući da su bolesnici s transplantiranim bubregom skloniji razvoju agresivnijih tipova kožnih karcinoma, osobito planocelularnog karcinoma, izrazito je važno razviti svijest bolesnika s transplantatom o povećanoj sklonosti razvoju karcinoma kože, potrebi za prevencijom te redovitim dermatološkim pregledima i samopregledima kože. Imunosupresivnu terapiju treba prilagoditi svakom pojedinom bolesniku te ju po potrebi modificirati kako bi se smanjio rizik za pojavu karcinoma uz istodobno održanje funkcije presatka. Za praćenje bolesnika s transplantiranim bubregom potreban je interdisciplinarni pristup uključujući primarno nefrologe i dermatologe kako bismo omogućili bolesnicima s transplantatom prevenciju, ranu dijagnozu i odgovarajuće liječenje karcinoma kože

Ključne riječi: transplantacija bubrega, imunosupresija, karcinomi kože, epidemiološke studije

BK VIRUS NEPHROPATHY IN A HEART TRANSPLANT RECIPIENT: THE FIRST DOCUMENTED CASE IN CROATIA

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As outcomes following heart transplantation have improved significantly over the last years, chronic kidney disease has become an increasingly prevalent complication in this population. Polyomavirus-associated nephropathy (PVAN) of native kidneys has also been recognized increasingly as a cause of kidney failure. We report the first case of PVAN occurring in the native kidneys of a solid-organ transplant recipient in Croatia as the eighth case described in the literature worldwide. A 65-year-old female with dilatative cardiomyopathy and good kidney function had a heart transplanted in 2012. Initial immunosuppressive therapy consisted of antithymocyte immunoglobulin with cyclosporine, mycophenolate mofetil and corticosteroids. Soon after transplantation, her kidney function began to fail progressively. Biopsy of the native kidneys revealed PVAN, and everolimus was introduced in immunosuppressive therapy. Nevertheless, her renal dysfunction progressed and she is now being evaluated for cadaveric kidney transplantation. PVAN should be considered in the differential diagnosis of new-onset renal failure following non-kidney solid organ transplantation. Early diagnosis is essential for prevention of irreversible renal damage.

Key words: polyomavirus-associated nephropathy, heart transplantation, kidney failure

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INTRODUCTION

Polyomavirus-associated nephropathy (PVAN) is a well-recognized cause of renal allograft dysfunction and allograft loss in renal transplant recipients, but it is an infrequent cause of nephropathy outside this setting. However, as outcomes following heart transplantation have improved significantly over the last years, chronic kidney disease (CKD) has become an increasingly prevalent complication in this population[(1)] and the number of PVAN of native kidneys reported in the literature is growing. We report the first case of PVAN occurring in the native kidneys of a solid-organ transplant recipient in Croatia as the eighth case described in the literature worldwide.

CASE REPORT

A female Caucasian patient born in 1940 was diagnosed with dilatative cardiomyopathy of unknown origin in 2011. Over a 2-year interval, she developed progressive congestive heart failure and due to deteriorating condition she underwent orthotopic cardiac transplantation on December 14, 2012. She had no concomitant illnesses and a good kidney function at the time of transplantation, with creatinine clearance 75-80 mL/min and proteinuria 0.31g/day. Unfortunately, data on kidney imaging studies done before transplantation were lost during the years. We can only presume that it was satisfactory.

The transplantation and immediate postoperative course were uneventful. Induction therapy included antithymocyte immunoglobulin with cyclosporine, mycophenolate mofetil (MMF) and corticosteroids. Serum creatinine immediately after transplantation was stable around 87-95 μmol/L. Four months after transplantation, the patient's kidney function began to deteriorate progressively without new-onset proteinuria or erythrocyturia. Cardiologist presumed that worsening of kidney function was due to calcineurin nephrotoxicity and in an attempt to reduce it 10 months after transplantation, the patient was switched from cyclosporine to tacrolimus. However, renal function continued to deteriorate further. Two years after transplantation, a nephrologist was consulted for the first time. Imaging studies revealed shrunken, chronically damaged kidneys with creatinine clearance of 35 mL/min and proteinuria 0.15 g/day. Also, BK viremia with 68,500 copies/mL was discovered. Biopsy of the native kidneys showed renal tubular cells with intranuclear inclusions characteristic of PVAN. Immunohistochemical staining for SV40 large T showed strong nuclear positivity in many distal tubular and collecting duct epithelial cells, which confirmed the diagnosis.

The patient had a stable heart function until that time, without any signs of rejection on repeated surveillance heart biopsies. Considering that, we decided to reduce immunosuppressive therapy by switching from tacrolimus to everolimus. Unfortunately, in a few days, the combination of everolimus with MMF and corticosteroids resulted in severe leukopenia that did not recover after reduction of MMF dose. Immunosuppression was changed again to tacrolimus with everolimus and corticosteroids while aiming at low levels (around 4 μg/L both).

After six months, the BK virus blood level fell to 1125 copies/mL, but renal dysfunction progressed further. Her creatinine clearance is now 13-10 mL/min and, as her heart function and overall clinical status is good, she is under evaluation for cadaveric kidney transplantation.

DISCUSSION

Chronic kidney disease and end-stage heart failure (HF) share multiple traditional risk factors such as hypertension, diabetes mellitus, and chronic glomerular ischemia due to poor renal perfusion. No wonder that up to one-third of all patients with New York Heart Association stage 3 or 4 end-stage HF have also evidence of CKD[2]. However, data on the evaluation of kidney function prior to orthotopic heart transplant are less well defined than liver transplant candidates and no formal guidelines exist. The objective of pretransplant evaluation is to establish the likelihood of being left with adequate kidney function after transplantation and the chance of progression to end-stage renal disease (Tablica 1).

Table 1

Proposition for kidney function assessment prior to orthotopic heart transplantation

Evaluation of kidney function prior to orthotopic heart transplantation
Complete patient history
Physical examination
Creatinine clearance
Total urinary protein excretion
Urinalysis
Urine culture
Kidney ultrasound (and color Doppler of renal arteries if necessary)
Kidney biopsy (if necessary)

Yet, kidney function is difficult to assess in patients with HF because they are frequently malnourished with low muscle mass and have edema. A normal or near normal serum creatinine level in this population does not necessarily reflect normal kidney function.

The degree of renal functional impairment posttransplant and the rate of CKD progression greatly depend on the extent of pretransplant kidney functional impairment, but also on the intra- and early postoperative course, the immunosuppressive regimen and individual clinical features that determine susceptibility to renal injury (patient age, presence of pretransplant diabetes and hypertension).

The majority of cardiac transplant recipients will develop CKD within the first year after transplantation. They usually suffer an initial, rapid decline in renal function in the first two years posttransplant, which is followed by a less pronounced decline afterwards[3]. The mechanism underlying this biphasic pattern seems to be different kidney response to early versus late injuries.

Early after transplantation, kidney is exposed to perioperative and postoperative insults (surgical issues and complications, infections, etc.) and effect of calcineurin inhibitor therapy. After that, renal function stabilizes.

It seems that kidney function at the end of the first year posttransplant reflects renal function reserve and also predicts long-term renal outcome and mortality[4].

Late posttransplant kidney injury is a result of ongoing renal insults that accumulate from the traditional CKD risk factors (hypertension, new-onset diabetes after transplantation, and dyslipidemia)[5], and nephrotoxic effects of immunosuppressive drugs such as calcineurin inhibitors (CNI) (cyclosporine and tacrolimus) and mammalian target of rapamycin (mTOR) inhibitors (sirolimus and everolimus)[6]. Chronic CNI injury, clinically manifested by increased serum creatinine, sub-nephrotic range proteinuria, and bland urine sediment, is present in the majority of long-surviving, nonrenal transplant recipients. Kidney biopsy studies demonstrate histologic changes consistent with long-term CNI nephrotoxicity in 60%-70% of heart and liver transplant recipients with posttransplant end-stage renal disease[7]. Apart from direct nephrotoxic and hemodynamic effects that CNI cause through inhibition of nitric oxide and alterations in the RAAS[8], CNI, as also m-TOR inhibitors, cause metabolic changes (diabetes, hyperlipidemia, and hypertension) that contribute to development of kidney injury[9,10]. mTOR-inhibitors also promote development of anemia, potentiate CNI nephrotoxicity, and in some patients cause development of new-onset proteinuria[11].

There are several approaches to reducing CNI nephrotoxicity. The dose of CNI can be reduced with the addition of MMF, resulting in long-term renal functional improvement[12]. If the patient is taking cyclosporine, it can be switched to tacrolimus, as described in our case report. There are single-center case series, registry analyses, and multicenter studies demonstrating the benefit of tacrolimus over cyclosporine in both conversion and *de novo* heart settings[13]. Third strategy involves utilization of regimens that completely eliminate CNI with the introduction of m-TOR inhibitors. In some nonrenal organ recipients, while the elimination or minimization of calcineurin inhibitors has been associated with mild improvement in kidney function, this has often come at the expense of compromised immunosuppressive efficacy and worse patient outcomes[14].

Nephrotoxicity of CNI appears to be the major histologic feature in heart transplant recipients, but such injury may be indistinguishable from other unrelated kidney injuries such as chronic ischemia changes associated with atherosclerotic vascular disease[15] or PVAN[16,17]. PVAN is caused primarily by BK virus (BKV), but JC virus (JCV) and possibly simian virus SV40 may account for some cases. BKV is widely spread among people; however, it is clinically significant only in immunocompromised patients. Primary infection occurs most frequently in childhood and is usually innocent, but the virus stays latent in lymphoid cells and kidney epithelial cells (transitional, tubular and parietal cells of Bowman capsule). The most important risk factor for development of PVAN is the level of immunosuppression and some consider development of BKV replication a clear sign of too high level of immunosuppression. Various combinations of immunosuppressive drugs have been linked with development of PVAN; however, we still lack clear evidence for this connection. PVAN has been proven in patients receiving almost every possible immunosuppressive drugs or their combination. Besides immunosuppressive drugs, risk factors for development of PVAN are older or younger age, male gender, CMV infection, acute rejection treatment, white race and use of corticosteroids.

Polyomavirus-associated nephropathy appears to be a rare cause of renal failure in heart transplant recipients with only eight cases published in the literature, but is it really so? Renal biopsy is the gold standard for diagnosing PVAN[18] and also the only method to distinguish it from CNI nephrotoxicity. However, the high incidence of CNI nephrotoxicity in heart transplant recipients has led to a common assumption that every renal failure in this population can be attributed to CNI toxicity, without renal histopathologic evaluation. This assumption leads to changes in immunosuppression that can further worsen PVAN and cause unnecessary delay in establishing the true cause of renal failure. PVAN should be considered in the differential diagnosis when evaluating worsening kidney function after heart transplantation and a more proactive approach in search for the cause of kidney failure could result in a higher prevalence of PVAN in this patient population.

Treatment of PVAN remains a problem. It is based on the adjustment of immunosuppressive regimens and the empiric use of adjuvant antiviral therapy. Unfortunately, treatment is very often ineffective and preventive screening for BKV replication and empiric reduction of immunosuppression is still the preferred approach[19]. However, BKV replication surveillance studies of non-kidney solid-organ recipients are lacking and the value of regular monitoring of BKV replication in non-kidney transplant recipients is still not clear.

CONCLUSION

Kidney injury in heart transplant recipients is a common problem with serious consequences. Active approach should be taken in establishing the cause of kidney failure and PVAN should be considered in differential diagnosis. We need more studies to determine the value of regular monitoring for BKV replication in heart transplant recipients.

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SAŽETAK

NEFROPATIJA UZROKOVANA BK VIRUSOM U BOLESNIKA S TRANSPLANTIRANIM SRCEM: PRVI DOKUMENTIRANI SLUČAJ U HRVATSKOJ

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Unazad nekoliko godina sa značajnim poboljšanjem preživljenja bolesnika s transplantiranim srcem kronično zatajenje bubrega postalo je sve češća komplikacija u toj populaciji. Nefropatija uzrokovana poliomavirusom (PVAN) nativnih bubrega također se sve češće prepoznaje kao uzrok zatajenja bubrega. Prikazujemo prvi slučaj PVAN nativnih bubrega kod primatelja transplantata solidnog organa u Hrvatskoj i osmi takav slučaj dosad opisan u literaturi. Bolesnici u dobi od 65 godina s dilatativnom kardiomiopatijom i dobrom bubrežnom funkcijom je 2012. godine transplantirano srce. Inicijalna imunosupresivna terapija sastojala se od antitimocitnog imunoglobulina s ciklosporinom, mikofenolat mofetilom i kortikosteroidima. Ubrzo nakon transplantacije dolazi do zatajenja bubrega. Biopsijom nativnih bubrega postavljena je dijagnoza PVAN, a u imunosupresivnu terapiju je uveden everolimus. Usprkos tome dolazi do daljnjeg napredovanja zatajenja bubrega i bolesnica je trenutno u pripremi za kadaveričnu transplantaciju bubrega. PVAN treba razmotriti u diferencijalnoj dijagnozi novonastalog zatajenja bubrega nakon transplantacije solidnih organa. Rana dijagnoza PVAN je bitna u sprječavanju razvoja ireverzibilnog bubrežnog zatajenja.

Ključne riječi: poliomavirusna nefropatija, transplantacija srca, zatajivanje bubrega

KIDNEY TRANSPLANTATION FROM DECEASED DONORS WITH HIGH TERMINAL SERUM CREATININE

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The ever increasing number of possible recipients of kidney transplantation and the relatively unchanged number of organ donors has led to consideration of alternative strategies and expansion of deceased donor criteria in order to expand donor pool. Previously, kidneys from expanded criteria donors were underestimated strongly because of the conventional opinion suggesting these kidneys to have a higher rate of preservation injury, delayed graft function, rejection and non-function. Reducing the difference between graft outcome from patients transplanted with expanded criteria donor (ECD) and standard criteria donor (SCD) is one of the goals of many respectable kidney transplantation centers. This includes strong concern about reduction of cold ischemia time, recipient selection, novel and adapted immunosuppressive regimens, increased nephron mass by dual kidney transplantation, and using histologic criteria for marginal donor graft selection. There are not many reports about the outcome of transplanted kidneys from donors with acute renal failure and high terminal creatinine. In this review, we have tried to show the exact definition of marginal donor, especially donors with acute renal failure. Management of such grafts during preimplantation and implantation period, outcomes and care after transplantation pose a great challenge to transplantation teams. Recipients of such grafts have to be well informed about the possibilities and potential complications, and give their consent accordingly. Some respectable studies have shown that under certain, highly controlled conditions, these kidneys can be used safely, with excellent short- and longterm outcomes.

Key words: renal transplantation, expanded criteria donor, outcome

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INTRODUCTION

Kidney transplantation is the treatment of choice for all patients with end stage renal disease (ESRD) without contraindications for immunosuppressive treatment, while offering better quality of life and survival when compared with dialysis[1,2]. The increasing number of potential renal transplant recipients on waiting lists has not been accompanied by appropriate rise in the number of deceased donors. This discrepancy challenges transplantation centers to consider other opportunites for making more organs available for transplantation. In order to expand donor pool, many centers have started using kidneys from elderly and expanded criteria donors. Until 2002, transplant centers used intuition to discriminate organs that were supposed to have less than optimal function[3]. Based on the "clinical feeling" of transplantation teams, most of the kidneys supposed to have poor graft outcome were discarded. Thus, donors with advanced age, impaired hemodynamics and prolonged ischemia time, as well as donors with elevated serum creatinine level prior to transplantation were refused.

In 2002, Port *et al*. defined expanded criteria donor (ECD) as a deceased donor aged ≥60 or donor aged 50-59 with minimum 2 factors: history of hypertension, serum creatinine level greater than 1.5 mg/dL (132.6 mmol/L) and cerebrovascular cause of death. The risk of

graft failure in these transplantations was much higher than of grafts from standard criteria donors (SCD). Using Cox regression models, Port *et al*. revealed a 70% higher risk of graft failure compared to ideal kidneys (relative risk greater than 1.7). According to their study, grafts from older donors with diabetes, hypertension or renal impairment have a higher risk of failure but are good enough to be transplanted[4]. However, based on the ECD graft definition, first assumption is an increased risk of less favorable outcome compared to SCD graft. In this way, refusals of ECD kidneys are frequent, cold ischemia time is prolonged, leading to organ discarding[5]. Massie *et al*. found that many transplant centers expressed their villingness to accept ECD transplants, but finally refused ograns when they were offered, thus creating delays resulting in organ discarding[6].

As there is no unique definition of adequate kidney graft, transplantation centers differ according to the criteria for refusal or acceptance of grafts considered to be marginal. The most common reason for refusal is hemodynamically unstable donor and high terminal serum creatinine. Nevertheless, the use of ECD has led to an increased number of transplanted patients with better survival compared to patients on dialysis[2]. A new target of modern kidney transplantation is to reduce difference in outcomes between the recipients of allografts from marginal donors and those transplanted from optimal donors.

In the present paper, we discuss the issue of ECD and define strategies to improve outcome of kidneys obtained from these donors.

DONOR WITH ACUTE KIDNEY INJURY

Acute kidney injury (AKI) is rapid deterioration of kidney function that occurs in approximately 5% of all hospitalized patients. It is one of the most common complications in the intensive care units (ICU) affecting 36% of these patients[7]. In more than 50% of AKI in ICU, the cause of kidney injury is septic shock or sepsis.

The causes of AKI in hospitalized patients without previous kidney disease can be prerenal, renal and postrenal. In 60%-70% of cases, the cause is prerenal, which includes dehydration, hypoperfusion, ischemia due to blood loss, sepsis, surgery, severe burn and injury, liver or heart failure. Renal damage is the most complicated cause of AKI which affects filtering function or blood supply within the kidney, or kidney tissue responsible for salt and water balance. Infections cause glomerulonephritis. A common cause of acute interstitial nephritis are nephrotoxic agents, including drug abuse such as heroin and cocaine, crush injuries leading to myoglobinuria, drugs frequently used in ICU in inappropriate doses such as antibiotics, anti-inflammatory drugs and diuretics. Acute interstitial nephritis is usually reversible if kidney damage is not severe. Acute tubular necrosis is usually the final result of other causes of renal damage accounting for 90% of cases of primary renal AKI. Postrenal failure is a rare cause of acute kidney failure in ICU[8,9]. In ICU patients with AKI considered as potential kidney donors, we are searching for correctable causes of AKI in order to optimize kidney function and prepare them for potential grafting. Interpretation of a kidney injury is a problem when evaluating potential donors. In some patients admitted to ICU, AKI is nothing but acutization of chronic renal failure. Some patients admitted with good kidney function experience rapid deterioration of kidney function due to numerous reasons. As mentioned earlier, common reasons of renal failure in ICU are prerenal and renal. Radiocontrast induced kidney injury is usually a reversible form of AKI, defined as an increase in serum creatinine level by more than 25% or its absolute increase of 0.5 mg/dL early after radiographic examination using radiocontrast agent. A frequent question is how to quantify damage in donors to discriminate potential grafts with good outcome. A potential problem is that most studies investigating outcome of kidney transplantation from donors with high terminal creatinine are based on the last serum creatinine level rather than on its change during intensive care management.

Serum creatinine is a widely used parameter for calculating glomerular filtration rate (GFR) in everyday practice, but its sensitivity and specificity in predicting AKI are lacking. As a sole parameter, serum creatinine is a poor predictor of kidney damage because of rapidly changing levels in critically ill patients with AKI and its dependence on muscle mass. In recent studies, there is a question of predicting reversibility of kidney damage and impact of AKI on long-term graft survival, graft function and rejection. Some studies have shown that high serum creatinine solely cannot be a measure to discard kidney for transplantation. Serum creatinine level reduction in donors is not a sign of insult recovery, although high serum creatinine level does not represent irreversible injury[10].

The RIFLE (risk, injury, failure, loss and end stage renal disease) criteria are the internationally accepted classification of kidney damage in AKI in hospitalized patients. In 2010, Rodrigo *et al*. first reported the use of RIFLE criteria to evaluate AKI in deceased donors. The idea of the study was to standardize and quantify renal injury in donors and its possible influence on graft outcome. Risk was defined when creatinine increased x1.5, injury x2, and failure when the last creatinine level increased x3 with respect to its value on the day of admission. The authors concluded that RIFLE criteria were feasible in the diagnosis of AKI in kidney donors but further studies including a larger number of patients need to confirm this hypothesis[11]. However, this classification cannot be used as isolated criteria for discarding donated kidney.

In 2006, Kumar *et al*. reported three-year results of successful kidney transplantation from deceased donor with AKI, but the authors did not use RIFLE criteria to classify AKI. This study reported comparable three-year kidney function between kidneys transplanted from selected deceased donors with acute renal failure without previous positive medical history and chronic histologic lesions, and kidneys from SCD[12].

QUALITY OF KIDNEY GRAFTS – OBJECTIVE MEASURES AND DONOR SELECTION

In 2006, Remuzzi *et al*. assessed outcome of renal transplantation from elderly donors. It was well known from clinical practice that long-term survival of renal grafts obtained from elderly donors was inferior to survival of grafts from younger donors. However, the authors wanted to prove that selection of older kidneys according to histologic characteristics before transplantation could influence graft outcome. The international group of pathologists presented a scoring system for kidneys from donors older than 60, based on biopsy findings. The intention was assessment of kidneys with enough viable nephrons, available for transplantation by thorough analysis of tubuli, vessels, glomeruli and internal changes. Scores ranged from 0 (absence of lesions) to maximum of 12 (marked changes in renal parenchyma). Kidneys with scores 3 or lower were supposed to be used as single transplants. Kidneys with scores 4, 5 or 6 could be used as dual transplants (only if the total number of viable nephrons in two kidneys approached the number in one ideal kidney). Discarded were kidneys with score 7 or higher. Graft survival rate of histologically evaluated marginal kidneys did not differ from kidneys of donors aged <60, but it was better than in recipients whose grafts from donors older than 60 were not evaluated histologically. Remuzzi *et al*. concluded that histologic criteria had a critical role in the evaluation of marginal donors, as they improved graft outcomes and thus may have expanded the pool of donors. Nowadays, many transplantation centers have implemented preimplantation kidney biopsy as a routine procedure in order to identify usable grafts[13].

All kidney grafts, either from old or young, marginal or standard criteria donor, can suffer harm with some events just before donation or previously, even before the donor was admitted to ICU (chronic lesions). Some potential donors may have high serum creatinine at the time of admission to ICU, as they have chronic renal insufficiency. Serum creatinine level may rise a few days before donation because of several reasons related to stay or treatment in ICU. Understandably, only grafts with acute but correctable renal dysfunction are considered for transplantation. Biopsy is necessary to distinguish cases of high entrance serum creatinine due to chronic renal disease and high creatinine due to some acute injury[3]. Specific evaluation and allocation is necessary for marginal grafts with possible chronic lesions before considering for transplantation.

In 2001, a concensus meeting of the American Society of Transplantation and American Society of Transplant Surgeons was held in Crystal City, Virginia. The goal of the meeting was development of guidelines for improving recovery and transplantation of organs from deceased donor. Kidney Work Group discussed how to increase the use of elderly donor kidneys, decrease cold ischemia time and delay graft function. In this way, patient outcome could be improved, as it could decrease the length and cost of hospital stay[14].

In order not to discard kidneys from ECD but improve their allocation and graft survival, Nyberg *et al*. developed a scoring system for these kidneys. Deceased donor score (DDS) includes scores for donor's age, hypertension, creatinine clearance, HLA mismatch and cause of death. If the score is higher than 20, 6-year graft survival is lower than 70%; if DDS is lower than 20, 6-year graft survival is higher than 80%[15].

DUAL KIDNEY TRANSPLANTATION

Transplantation of dual ECD kidneys is one of the possible ways to reduce the number of discarded kidneys and increase nephron mass of 'marginal' kidneys. It may be a good approach in expanding donor pool. Still, there are no determined criteria for single or dual transplantation in a recipient of ECD kidney.

One of the first reports of dual kidney transplantations from elderly donors showed that these recipients had a decreased incidence of delayed graft function, better graft function and survival than recipients of single kidney from similar age donors[16]. Some studies praise the strategy of dual kidney transplantation in expanding donor pool, but found a high incidence of primary non-function[17,18].

In 2003, Bunnapradist *et al*. showed a similar outcome of 403 dual transplantations (mean donor age 60.8 years) with 11033 single kidney transplantations when recipients of single kidney were grafted with donors aged over 55[19].

In 1999, Remuzzi *et al*. compared graft survival of single and dual kidney transplants from ECD (donor age >60, history of diabetes or hypertension, urine protein excretion up to 3 g/24 h) based on clinical or preimplantation histologic evaluation. This study showed that graft evaluated histologically before implantation had similar outcome in dual transplant recipients as single grafted recipients from younger donors. These results strongly suggest that histologic criteria should be considered as an important part on choosing between single and dual kidney transplantation from marginal donor[20].

RECIPIENT SELECTION AND IMMUNOSUPP RESSION

It is important to mention that long-term graft and patient survival after transplantation has improved in the last years as a result of factors such as good patient care, enhanced organ preservation and surgical techniques, effective antimicrobial prophylaxis, and availability of potent immunosuppression regimens[21]. One possible additional factor may be proper selection of recipients for certain graft.

Elderly patients make up an increasing percent of the waitlist, as well as of donated and recovered kidneys. Use of elderly donors for kidney transplantation may create obstacles to long-term survival, as older kidneys are associated with inferior outcomes. However, the major risk for dialysis patients is to stay on dialysis, thus elderly patients should be individually evaluated for renal transplantation. 'Physiological' age is much more important than 'chronological' age in this group of patients[22].

Stratta *et al*. studied 90 recipients of adult donor kidneys transplanted from 2001 to 2003 (37 from ECDs and 53 from SCDs). Recipient selection for marginal kidney was based on their estimated need for nephron mass by using the criteria of age >40 years, low body mass index (<25 kg/m^2) and low immune risk (first transplantation, 0% PRA, HLA matching). They conclude that ECD kidneys should be used for carefully selected patients, employing the "nephron sparing strategy". It means that long-cold ischemia time should be avoided, as well as nephrotoxic immunosuppressive protocols[23]. Severe donor-recipient size mismatching should be avoided.

The Eurotransplant Senior Program (ESP) allocates kidneys from elderly donors to recipients older than 65. This program has significantly increased the number of transplantations performed in elderly patients. Croatia introduced its own Senior Program in 2005, based on the ESP but with HLA matching, which has improved outcomes compared to ET results[24]. Currently, elderly patients wait less than 6 months to receive transplant in Croatia.

As kidneys from ECS have already suffered injury, any further damage should be avoided. Stratta et al. presented a management protocol for ECD kidneys. It was based on a number of nephron sparing maneuvers by minimizing cold ischemia time, pulsatile perfusion preservation, immunosuppression with depletion antibodies to minimize preservation injury and risk of rejection, delayed calcineurin administration, and lower tacrolimus levels to maintain balance between effectiveness and toxicity[23].

Nephrotoxic immunosuppressive protocols should be avoided, which means delayed introduction of calcineurin inhibitors under the umbrella of antibodies (either monoclonal in patients with low immune risk, or polyclonal in patients with high immune risk). Based on our experience, these protocols are safe and are not associated with increased incidence of acute rejections. Mammalian target of rapamycin inhibitors (mTOR) seem promising in this setting. Three preliminary reports suggest that CNI-free protocols with costimulation blockade in recipients from ECDs decrease the incidence of delayed graft function, but further studies have to confirm it. Thus, novel immunosuppressive drugs may contribute to less nephrotoxic protocols[25]. However, current protocols recommend their use at least one month after transplantation to avoid problems with wound healing.

CONCLUSION

Kidney donor pool has evolved over the last few years mainly due to the utilization of ECDs. However, recipients of kidneys from ECD have by definition inferior graft and worse overall survival. Potential recipient has to be well informed about the risks of transplanting grafts from ECD. Such grafts are not for "expanded recipient criteria", but for recipients with low risks and demands. To find the best donor-recipient match, specific allocation policies are required. A challenge is to minimize transplantation outcome differences between the grafts from standard and expanded criteria donors.

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SAŽETAK

TRANSPLANTACIJA BUBREGA OD MOŽDANO MRTVOG DARIVATELJA S VISOKOM KONCENTRACIJOM KREATININA U SERUMU

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Ukupni broj darivatelja organa u posljednje je vrijeme nepromijenjen, a sve veći broj potencijalnih primatelja bubrega na listi čekanja doveo je do razvoja novih strategija i proširenja kriterija kojima se procjenjuje mogući darivatelj organa. Prije se smatralo da su bubrezi darivatelja prema proširenim kriterijima lošiji zbog veće učestalosti oštećenja tijekom prezervacije bubrega, češće odgođene funkcije presatka, odbacivanja i primarne afunkcije organa. Danas je mnogim velikim transplantacijskim centrima cilj smanjenje razlike u ishodu presatka transplantiranog s darivatelja prema proširenim kriterijima i darivatelja prema standardnim kriterijima. Ovaj cilj uključuje strogu kontrolu skraćivanja vremena hladne ishemije, odabira primatelja, prilagođene protokole imunosupresije, povećanja mase nefrona s transplantacijom “dva u jedan” i primjenu histoloških kriterija u odabiru presatka marginalnog darivatelja. Zasad nema mnogo objavljenih radova o ishodu transplantiranog bubrega darivatelja s akutnim zatajenjem bubrega ili visokom zadnjom vrijednosti kreatinina u serumu. Ovim preglednim člankom željeli smo prikazati najnoviju definiciju marginalnog darivatelja i darivatelja s akutnim zatajenjem bubrega. Primatelji bubrega darivatelja prema proširenim kriterijima moraju tijekom prijetransplantacijske obrade biti dobro obaviješteni o svim mogućnostima i komplikacijama takvog postupka te potpisati obaviješteni pristanak. Poznate studije pokazale su da se pod strogo kontroliranim kriterijima bubrezi darivatelja prema proširenim kriterijima mogu sigurno transplantirati odabranim primateljima s dobrim kratkoročnim i dugoročnim ishodom.

Ključne riječi: transplantacija bubrega, darivatelj prema proširenim kriterijima, ishod

WARFARIN-RELATED NEPHROPATHY – A CASE REPORT ON RENAL BIOPSY AND REVIEW OF THE LITERATURE

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Warfarin-related nephropathy (WRN) is a recently recognized condition in patients with chronic kidney disease (CKD). WRN is clinically detected as an episode of unexplained acute kidney injury (AKI). It is defined as a serum creatinine (sCR) increase >0.3 mg/dL (26.5 μmol/L) within one week of an international normalized ratio (INR) measurement >3.0 in a patient treated with warfarin without clinical evidence of hemorrhage. Therefore, warfarin therapy can result in AKI by causing glomerular hemorrhage and renal tubular obstruction by red blood cell casts. WRN appears to accelerate the rate of CKD progression and increase the risk of death in susceptible patients. We report on renal biopsy in a patient on warfarin therapy with unexplained AKI and hematuria associated with increased INR. We would like to stress the necessity of an interdisciplinary approach to patients on warfarin therapy.

Key words: warfarin-related nephropathy, acute kidney injury, chronic kidney disease

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INTRODUCTION

Since its approval in the 1950s, warfarin has become the most commonly prescribed oral anticoagulant which interrupts the synthesis of coagulation factors (II, VII, IX, and X) by inhibiting the C1 subunit of the vitamin K epoxide reductase enzyme complex[1]. Warfarin is metabolized and removed primarily in the liver through the cytochrome P450 pathway, which may be affected by a number of medications and dietary factors. Although it is an effective medication, its use is potentially complicated by supratherapeutic anticoagulation. It is strongly protein bound, mainly to albumin. Warfarin use requires close monitoring and hemorrhage is the main complication of its use[2].

Patients with chronic kidney disease (CKD) are at an increased risk of thromboembolic events. However, the use of anticoagulation in this population of patients remains a clinical challenge to the treating physician. This is mainly due to the fact that CKD patients have an increased risk of over-anticoagulation as they spend less time in the therapeutic range. Therefore, CKD patients require frequent dose adjustments and have a higher bleeding risk[2]. According to a recent study, patients with severe CKD were found to need significantly lower warfarin doses to achieve therapeutic anticoagulation, and they were often over-anticoagulated[3].

A new entity has been recently described by Brodsky et al. in patients with CKD, named warfarin-related nephropathy (WRN). According to them, WRN is clinically detected as an episode of unexplained acute kidney injury (AKI) defined as a serum creatinine (sCR) increase >0.3 mg/dL (26.5 μmol/L) within one week of an international normalized ratio (INR) measurement >3.0 in a patient being treated with warfarin without clinical evidence of hemorrhage. Therefore, warfarin therapy can result in AKI by causing glomerular hemorrhage and renal tubular obstruction by red blood cell (RBC) casts. WRN appears to accelerate the rate of CKD progression and increase the risk of death in susceptible patients. WRN was initially described in CKD patients, but although less frequently, it can develop in non-CKD patients on warfarin therapy as well[1,4].

Hereby, we report on renal biopsy in a patient on warfarin therapy with unexplained AKI and hematuria associated with increased INR. We would like to stress the necessity of an interdisciplinary approach to patients on warfarin therapy, as well as many other conditions (such as celiac disease, hepatopulmonary and hepatorenal syndrome in patients with liver cirrhosis, nonalcoholic fatty liver dis-

ease, scleroderma, etc.) in order to prevent the consequences of this recently described entity.

CASE REPORT

A 46-year-old woman with a 5-year history of diabetes mellitus type 2 presented to our department of nephrology with acute renal failure (ARF) and a 1-year history of gross hematuria. During the past year, urologic and nephrologic diagnostic tests were unfruitful in finding the cause of hematuria. Urologic studies included abdominal ultrasound, cystoscopy and magnetic resonance urography. On admission, the INR was 4.45 IU. Warfarin had been instituted 8 years before because of mechanical heart-valve replacement. Other medications consisted of carvedilol, 6.25 mg twice daily; ramipril, 2.5 mg daily; and aspirin, 100 mg daily. Her history included pulmonary embolism in 1996 and CKD. Her family history was unremarkable.

At presentation, blood pressure was 180/110 mm Hg and pulse 90 beats per minute. She was afebrile and appeared comfortable. Physical examination was uneventful. Serum creatinine (SCR) level was 304 μmol/L. One month before, it was 130 μmol/L. Urinalysis results showed gross hematuria and 24-hour urinary protein level was 800 mg. Serology results including antinuclear antibody (ANA), anti-neutrophil cytoplasmic antibody (ANCA) and paraprotein were negative. Serum complement C3 and C4, as well as immunoglobulin levels were within the normal limits. Blood and urine cultures were negative. Chest x-ray showed no abnormalities, while renal ultrasound scan showed 2 normal-sized kidneys without evidence of obstruction. Symptomatic therapy without dialysis treatment consisted of parenteral hydration (crystalloid solutions) and correction of her coagulopathy (vitamin K and low-molecular weight heparin). After this initial therapy, warfarin therapy was continued and a few days later she experienced gross hematuria again, with an INR of 4.03 I.U. Renal biopsy was performed when the INR was normalized with vitamin K and low-molecular-weight heparin.

Morphologically, light microscopy revealed renal cortex with a maximum of 12 glomeruli, 5 of which were globally sclerosed. The viable glomeruli showed varying degrees of mesangial expansion accompanied by segmental thickening of peripheral capillary loops and segmental sclerosis in 3. In 2 glomeruli, segmental fibrous crescents were seen (Fig. 1). Trichrome-stained sections revealed interstitial fibrosis and tubular atrophy, along with thickening of tubular walls and chronic inflammation in 40%-50% of biopsy specimen. Tubulointerstitial nephritis with infiltration of inflammatory, predominantly mononuclear cells, tubular atrophy, accumulation of foamy histiocytes and widespread interstitial fibrosis was interpreted as a sign of chronic renal injury (Fig. 2). We also could see signs of acute inflammation with focuses of tubulitis accompanied with eosinophils. Numerous occlusive RBC casts predominantly in the distal tubules were seen. Moderate thickening of the walls of the arterioles and of the small and medium-sized arteries with proliferation of elastica was noted. Electron microscopy showed thickened capillary loops and nodular mesangial expansion due to marked increase in mesangial matrix, and sclerosis. We could not confirm immune type dense deposits (Fig. 3). Although we could not confirm immune mediated glomerular injury, the differential diagnosis of possible superimposed postinfectious glomerulonephritis was made.

Figure 1

Glomeruli show excessive mesangial expansion due to matrix multiplication (asterisk), segmental sclerosis (triangle) and segmental fibrocellular crescent (arrow). Between two glomeruli there is fibrosis and tubular atrophy (PAS, X200).

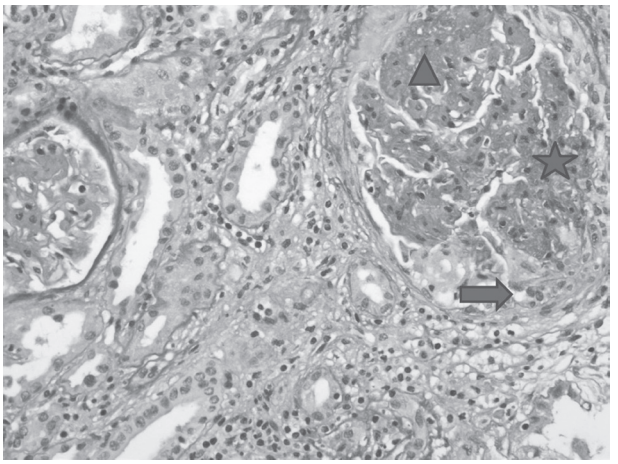


Figure 2

Tubulointerstitial nephritis with heavy infiltration of predominantly mononuclear cells, tubulitis (arrow). Tubular atrophy and fibrosis could be a consequence of underlying diabetic nephropathy (PAS, X100).

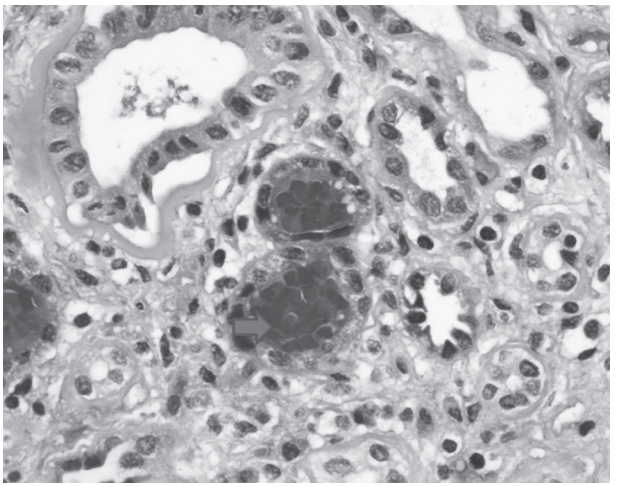
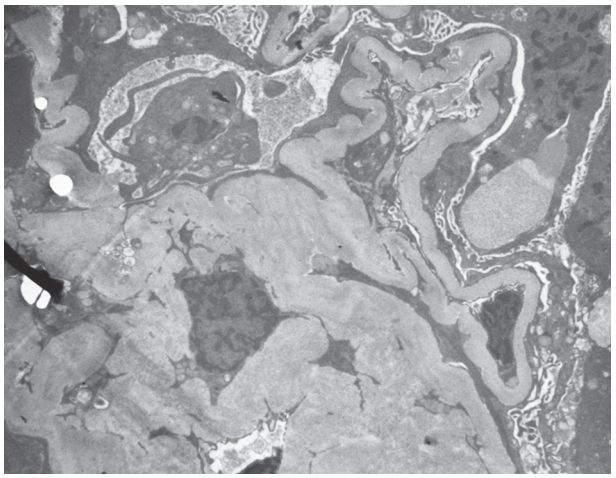


Figure 3

There were no dense immune deposits. Thickened capillary loops and nodular mesangial expansion may be seen in diabetic glomerulosclerosis.



Because of the renal function worsening (sCR 807 μmol/L; BUN 22.1 mmol/L) twenty days after admission to the hospital, a central venous catheter was placed through the right internal jugular vein. Hemodialysis was done by ultrafiltration of 2000 mL. A few hours later, the patient developed chest pain, dyspnea, and hemoptysis. There was no evidence for pulmonary embolism, acute myocardial infarction, or complications of the central venous catheter insertion. She was admitted to the intensive care unit and the next day she died because of cardiorespiratory arrest. Autopsy was not performed upon request of her family. The mean values of serum creatinine and INR during hospital stay are shown in Figure 4.

DISCUSSION

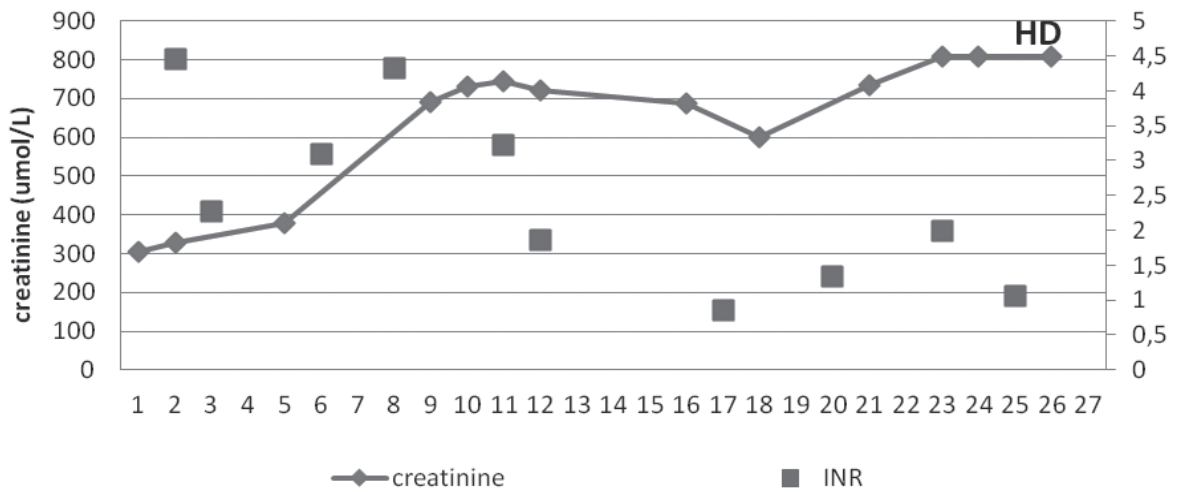
Although the association of hematuria and warfarin use has been reported in the 1960s by Reilly *et al*., WRN is a relatively new entity described in patients receiving warfarin therapy. The question is why such a common complication of a widely administered medication has been unrecognized until just recently? This can partially be explained by the fact that nephrologists might be reluctant to perform kidney biopsy in patients receiving warfarin, due to the increased risk of hemorrhage.

It is possible that previous undetermined causes of hematuria were due to WRN. The patient had a 1-year history of gross hematuria that was undetermined after extensive medical investigations by urologist and nephrologist. The first report noting that warfarin can cause AKI and glomerular hematuria was published by Abt *et al*.[5] in a patient with thin glomerular basement membrane nephropathy. A similar syndrome was reported in 2004 by Kabir *et al*.[6] in a patient with a history of inactive lupus erythematosus (SLE), but abnormally thick glomerular basement membrane. The term WRN was first described by Brodsky *et al*.[7], who performed retrospective analysis of biopsy specimens from 9 patients that presented with unexplained AKI and hematuria while on warfarin therapy. According to Brodsky *et al*., the main features of WRN are AKI, acute derangement of INR, and histological findings of glomerular hemorrhage and large obstructive RBC casts in tubular lumina. The best evidence thus far comes from two animal studies showing an increase in sCR with increasing INR, reversible on vitamin K administration[8,9]. It is important to note that WRN does not require severe warfarin coagulopathy. The mean value of INR in our patient was 4.0, the same as in previous reports by Brodsky *et al*.[4,7].

Figure 4

RB = renal biopsy; HD = hemodialysis

Mean values of serum creatinine and INR during hospital stay.



There are other possible mechanisms by which warfarin could promote kidney injury, such as atheroembolism, interstitial nephritis, and direct effects of warfarin on the glomerulus[4]. Furthermore, a recent study reports that WRN is not an uncommon feature of warfarin use, namely, analysis of more than 15,000 warfarin treated patients has shown that WRN affects approximately 33% of CKD patients and 16% of non-CKD patients that experienced an INR >3.05. As mentioned, the proposed diagnostic criteria for WRN include a 0.3 mg/dL (26.5 μmol/L) increase in sCR in patients that had an INR >3 within the previous week. We wonder if this definition is appropriate for patients that require treatment to reach an INR target of 3.0, such as those with mechanical heart valves, like our patient.

Although previously reported cases occurred in a setting of CKD, recent investigations suggest that WRN may also appear, even less frequently, in the general population, with age, hypertension, diabetes mellitus, and cardiovascular disease being significant risk factors1. The risk factor for WRN is low serum albumin level because approximately 97% of warfarin is bound to plasma protein, primarily albumin, and the other 3% is the unbound fraction that exhibits pharmacological effects. Therefore, it is not surprising that WRN is more frequent in CKD than in non-CKD patients. Namely, due to malnutrition and expansion of plasma volume that results in hypoalbuminemia in CKD patients, they may have a higher incidence of WRN[1,2]. In the setting of impaired renal function as in our patient, it is possible that such dilutional hypoalbuminemia contributed to over-coagulation and consequently to progression of WRN and further kidney damage.

Another important fact that has been described by Brodsky *et al.* is that therapy which tends to increase glomerular hydrostatic pressure is associated with an increased risk of WRN; this is mainly due to concomitant aspirin use4. Our patient took aspirin as part of her chronic therapy.

Furthermore, the question is "does WRN occur early in the course of warfarin therapy, as mentioned by Brodsky *et al*.?" The authors asserted that WRN patients tended to be new to warfarin therapy (warfarin started in the previous 3 months). This definition is doubtful considering that long-term warfarin exposure in animal models results in vascular calcification[1,10]. Furthermore, similar chronic complications have been described in humans, such as tissue necrosis and calciphylaxis[1,10]. Our patient received long-stand warfarin therapy.

Another important complication of WRN was observed by Brodsky et al. Beyond its influence in terms of accelerated progression of kidney disease, they observed that WRN could also be associated with an increased risk of death, with CKD patients having a twofold greater risk found in non-CKD patients. According to Brodsky et al., about one million of three million patients in the USA who receive warfarin therapy may have at least one episode of INR greater than 3.0, and about 200 000 patients can develop WRN with an approximate one-year mortality rate of 30%[4]. Our patient had stable long-standing CKD. The occurrence of WRN probably accelerated the progression of kidney disease, which resulted in death, although the accurate reason of death was not defined because autopsy was not performed.

One of the questions is also whether WRN is unique to vitamin K antagonists and therefore what is the potential impact of anticoagulants other than warfarin? For example, what is the impact of direct thrombin inhibitors such as dabigatran and direct factor Xa inhibitors? Dabigatran has a different mechanism of action and metabolism than warfarin, and it can be used without the need of routine monitoring1. However, it is contraindicated in patients with estimated glomerular filtration rate (eGFR) $\leq$30 mL/min/1.73 m^2, while in patients with eGFR 30-50 mL/min/1.73 m^2 it has to be used with caution. This is due to the fact that it is predominantly metabolized and removed by kidneys, and its use in CKD patients can lead to life-threatening bleeding without the possibility of using a specific antidote for now. A specific antidote, humanized antibody, is in the phase of animal model investigation. Future studies possibly will investigate if this medication can cause similar complications as WRN or we can safely administer it to CKD patients, especially considering dosage in earlier stages of CKD. According to our experience in a small cohort of patients (unpublished data), dabigatran also causes deterioration of renal function in CKD patients.

In conclusion, WFR appears to be a common clinical problem, although it was unrecognized until recently. Warfarin therapy is a special problem in the population of CKD patients, considering that they have an increased risk of over-anticoagulation and are less in the therapeutic range. Therefore, these patients require frequent dose adjustments. According to current investigations, the pathogenesis of WRN has not yet been properly determined, considering that warfarin is a widely used medication. However, without understanding the pathogenic pathways of the disease, it will be difficult to develop strategies for its prevention and treatment. Further prospective, multicenter studies are needed to define clinical features and the exact prevalence of WRN, and also to investigate and define the features of susceptible patients.

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SAŽETAK

NEFROPATIJA POVEZANA S VARFARINOM – PRIKAZ BOLESNIKA NA TEMELJU BIOPSIJE BUBREGA I PREGLED LITERATURE

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Nefropatija povezana s varfarinom (WRN) je odnedavno prepoznato stanje u bolesnika s kroničnom bolešću bubrega (KBB). WRN je klinički prepoznata kao epizoda neobjašnjivog akutnog oštećenja bubrega (AOB). Definira se kao povećanje kreatinina u serumu (sCR) >0,3 mg/dL (26,5 micromol/L) unutar tjedna INR mjerenja >3,0 u bolesnika liječenog varfarinom bez klinički utvrđenog krvarenja. Zbog toga terapija varfarinom može dovesti do AOB uzrokujući glomerularno krvarenje i opstrukciju bubrežnih tubula odljevnim cilindrima eritrocita. Čini se da WRN ubrzava napredovanje KBB i u osjetljivih bolesnika povećava rizik od smrtnog ishoda. Izvješćujemo o biopsiji bubrega u bolesnika na terapiji varfarinom s neobjašnjivim AOB i hematurijom povezanom s povećanim INR. Namjera nam je naglasiti potrebu interdisciplinarnog pristupa bolesnicima na terapiji varfarinom.

Ključne riječi: nefropatija povezana s varfarinom, akutno oštećenje bubrega, kronična bolest bubrega

CT PERITONEOGRAPHY – DIAGNOSTIC METHOD OF DETECTING SWEET HYDROTHORAX IN PATIENTS ON PERITONEAL DIALYSIS

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Peritoneal dialysis (PD) can be considered as the first method to start dialysis treatment because it improves the patient quality of life and survival compared to hemodialysis (in the first two years). Hydrothorax is a rare complication of PD. We present a 66-year-old female patient diagnosed with end-stage renal disease caused by chronic tubulointerstitial nephritis. One month after peritoneal catheter had been inserted, the patient started continuous ambulatory PD. Several weeks after PD had been introduced, the patient complained of cough and weight gain. Chest x-ray revealed pleural effusion on the right side and pleural puncture proved a high concentration of glucose in the aspirate, and the diagnosis of 'sweet hydrothorax' was made. Additionally, computerized tomography (CT) peritoneography clearly showed contrast leak from peritoneal cavity to thoracic cavity. PD was stopped and the catheter for PD removed. Now, the patient is on the waiting list for kidney transplantation. 'Sweet hydrothorax' is a rare complication of PD and CT peritoneography is the most sensitive noninvasive diagnostic tool. In most patients, PD is replaced by hemodialysis, although surgical treatment is also possible.

Key words: end stage renal disease, computerized tomography peritoneography, peritoneal dialysis

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INTRODUCTION

Hydrothorax is a rare complication of peritoneal dialysis (PD), with the incidence ranging from 1.6% to 6%[(1-3)]. Clinical presentation may vary from incidental findings in asymptomatic patients to respiratory compromise, so its incidence cannot be determined with certainty. The time to developing complication ranges from several hours to up to 8 years[(1,2)]. Hydrothorax developing in PD patients is a consequence of communication created between pleural and peritoneal space3. These communications can be primary (congenital) or secondary (acquired). Primary communications, i.e. congenital diaphragmatic hernia, are produced by failure of the diaphragm to fuse properly during fetal development[(3)]. Secondary communications develop due to high pressure within the abdominal cavity during dialysate exchange, which leads to separation of the diaphragmatic collagen fibers and results in opening of the pleuroperitoneal communication. This consequently leads to the passage of the PD solution in the pleural space[(3)].
In this report, we present a patient who developed hydrothorax after starting PD.

CASE REPORT

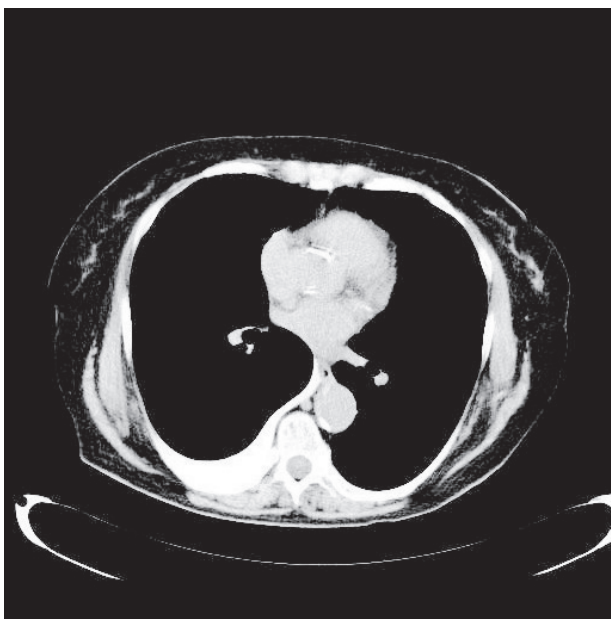
A 66-year-old female patient was diagnosed with end-stage renal disease. Kidney biopsy confirmed that the cause of chronic kidney disease was chronic tubulointerstitial nephritis due to seronegative spondyloarthritis B27 positive (Reiter's syndrome) treated with low dose prednisolone. The patient also suffers from type 2 diabetes mellitus, which is treated with oral hypoglycemics.

The patient was hospitalized because permanent deterioration of kidney function was observed. Serum urea

was 21.5 mmol/L and creatinine 452 μmol/L, while the estimated glomerular filtration rate (eGFR) was 8.5 mL/min/1.73 m^2. After predialysis education, the patient opted for PD and peritoneal catheter was inserted. A month and a half after starting PD, the patient noticed weight gain of 6 kg. She also complained of dry cough and leg swelling around the ankle, while denying pain and shortness of breath. Physical examination showed that there was no respiration on the right side and chest x-ray was ordered to show right-sided pleural effusion. The patient underwent thoracocentesis and 1200 mL of fluid was evacuated. Biochemical analysis showed 'sweet' hydrothorax. Pleural "leak" and pleural-peritoneal space communication was suspected. In order to prove pleural "leak", computerized tomography (CT) peritoneography was performed.

Before performing CT peritoneography, the peritoneal cavity was completely drained of dialysate. Next, 100 mL of nonionic contrast material containing iodine 300 mg/mL (Omnipaque 300, Amersham, Princeton, New Jersey, USA) was mixed with about 2 L of dialysate and infused into the peritoneal cavity. Dialysate was administered one hour before scanning and the patient was encouraged to walk and strain for appropriate fluid distribution to delineate any leak. Scanning was performed with the patient in supine position, one hour after contrast administration. The contrast material dialysate mixture was drained at the end of the procedure. CT peritoneography showed that the contrast from abdominal cavity leaked in the right pleural space (Figs. 1 and 2).

Figure 1
Computerized tomography peritoneography demonstrated leakage of dialysate from the peritoneum to the right pleural space.



Consequently, it was decided to suspend PD and the catheter for PD was removed. After 15 days, a forearm arteriovenous fistula was constructed. The patient is currently on the waiting list for kidney transplantation.

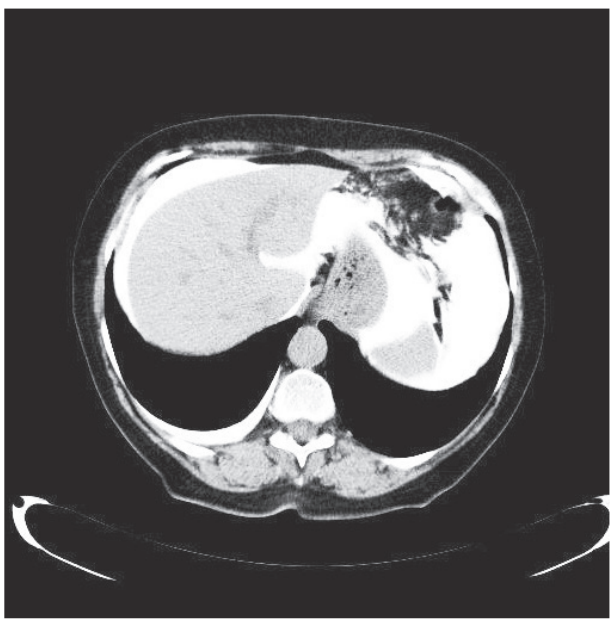
DISCUSSION

Although there are many causes of hydrothorax, it can also occur as a complication of some diagnostic and therapeutic procedures[1,4]. Pleural effusion is rarely caused by PD. Right-sided predominance in PD patients occurs because the heart and pericardium prevent the passage of fluid through the left hemidiaphragm. An increased intra-abdominal pressure in the right subphrenic space, enhanced with breathing and physical activity, contributes to this phenomenon[5].

"Sweet" hydrothorax is more common in women, and the phenomenon can be explained by dilatation of the diaphragm during previous pregnancy and the possible damage to the diaphragm during that time[5,6].

Diagnosis is mostly based on the history of shortness of breath (sudden or gradual) and chest pain[7]. However, in our 66-year-old female patient, the symptoms were nonspecific, including dry cough and weight gain with negative ultrafiltration that had started two weeks before. After physical examination, chest x-ray is the initial diagnostic method, followed by pleural puncture of the effusion. Thoracocentesis with pleural fluid analysis is an important step in the process.

Figure 2
Computerized tomography peritoneography showed good contrast distribution in the abdominal cavity but also in the right pleural space.



High concentration of glucose in pleural effusion ('sweet hydrothorax') is an important finding, since no other type of hydrothorax has elevated glucose level[7]. A glucose gradient (pleural-fluid glucose level minus simultaneous serum glucose level) of more than 50 mg/dL (2.7 mmol/L) has a 100% sensitivity and specificity to detect 'sweet hydrothorax'. However, some patients have a lower glucose gradient, probably secondary to glucose reabsorption by pleural mesothelium[6,8].

Computerized tomography peritoneography involves CT of the abdomen and pelvis after administration of a mixture of contrast material in dialysate[4, 7]. Scanning is performed with the patient in supine position, one hour after contrast instillation. Delayed 4-hour scanning may be repeated if 1-hour scan is negative. Lateral decubitus or prone position may be performed for questionable findings[7]. CT peritoneography can demonstrate a variety of complications of PD such as peritoneal leaks, hernias and abscesses. Disadvantages of the method are exposure to ionizing radiation and iodinated contrast media[7].

Peritoneal scintigraphy with technetium-99m is a diagnostic method that can also be used to detect this condition[9].

Different therapeutic approaches are proposed. The first-line treatment is temporary intermission of PD procedures for 1-4 months with redirection to hemodialysis. This conservative approach can be effective in half of the cases[4,7]. Other treatment options include chemical and surgical pleurodesis (obliteration of the pleural space) with talc, tetracycline, autologous blood and other agents[7].

Greater diaphragmatic defects can be closed during thoratocomy by suturing and at the same time, pleurodesis by pleurectomy or pleural abrasion can be performed. Pleural abrasion and/or endoscopic closure of the diaphragmatic defects can also be performed by video-assisted thoracoscopy[10].

In conclusion, 'sweet' hydrothorax is a rare complication of PD. It is important to include this condition in the differential diagnosis of PD patients with respiratory problems. Whereas clinical manifestations can be diverse, from asymptomatic patients to respiratory failure in significant hydrothorax, it is necessary, even in the slightest doubt, to refer suspected patients to additional diagnostic tests, of which the most sensitive and noninvasive is CT peritoneography. The treatment can be conservative or surgical.

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SAŽETAK

CT PERITONEOGRAFIJA – DIJAGNOSTIČKA METODA U OTKRIVANJU "SLATKOG HIDROTORAKSA" U BOLESNIKA NA PERITONEJSKOJ DIJALIZI

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Peritonejska dijaliza (PD) se može smatrati metodom dijalitičkog izbora, jer u odnosu na hemodijalizu poboljšava kvalitetu života i preživljenje bolesnika u prve dvije godine. Hidrotoraks je rijetka komplikacija PD. Prikazujemo 66-godišnju bolesnicu kojoj je dijagnosticiran završni stadij kronične bubrežne bolesti uzrokovan kroničnim tubulointersticijskim nefritisom. Jedan mjesec od postavljanja katetera za PD bolesnica je započela s dijalitičkim liječenjem. Nekoliko tjedana od početka dijalitičkog liječenja bolesnica se počela žaliti na kašalj i porast težine. RTG snimka prsnih organa pokazala je desnostrani pleuralni izljev. Njegovom punkcijom dokazana je visoka koncentracija glukoze u aspiratu te je postavljena dijagnoza "slatkog hidrotoraksa". CT peritoneografija je nedvojbeno pokazala da kontrast iz abdominalne šupljine ide u pleuralnu. PD je zaustavljena, a kateter za PD izvađen. Sad se bolesnica nalazi na listi čekanja za transplantaciju bubrega. "Slatki hidrotoraks" je rijetka komplikacija bolesnika na PD, a CT peritoneografija je najosjetljiviji neinvazivni dijagnostički test. U većine bolesnika PD se zamijeni hemodijalizom, ali je moguće i kirurško liječenje.

Ključne riječi: završni stadij kronične bubrežne bolesti, CT peritoneografija, peritonejska dijaliza

NOTES FOR CONTRIBUTORS

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Original papers s should contain: Introduction, Objective(s), Methods, Results, Discussion and Conclusions. In the Introduction section, the issue should be clearly and concisely presented. In Objective(s), the aim of the study is briefly described. In the Methods section, the methodology, apparatus and procedures used in the study should be identified in sufficient detail to allow other workers to reproduce the results. Widely known methods need not be described but original references should be used. For drugs, generic names should be used (trade names can be mentioned in parentheses). Results should be clearly and logically presented, and their significance should be demonstrated by appropriate statistical methods. In Discussion the results obtained are discussed against the existing state of the art. Conclusions should correspond with the aim(s) set in the Objective(s).

The title, first and last name(s) of the author(s), institution(s) and address of the corresponding author should be submitted on a separate sheet of paper. Synopsis written in Croatian should contain maximum 200 words on a separate sheet of paper.

Typescript should contain extended structured [Objective(s), Methods, Results, Discussion, Conclusion(s)] abstract (500-600 words) with title of the manuscript, initials of authors' first name(s), full last name(s) and institution(s) in English.

Below the Abstract, key words that will assist indexers in cross indexing the article should be provided.

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References are submitted on separate pages in the numbered sequence following their mention in the text. References are cited according to the «Vancouver style» proposed by the International Committee of Medical Journals Editors (N Engl J Med 1991; 324: 421-8 and BMJ 1991; 302: 338-41). The titles of journals should be abbreviated according to Index Medicus.

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Supplement

Djelmiš J, Ivanišević M, Mrzljak A. Sadržaj lipida u placenti trudnica oboljelih od dijabetesa. Acta Med Croatica 2001; 55 (Supl. 1): 47-9.

Books and monographs

Mould RF. Introductory medical statistics. Turnbridge Wells: Pitman Medical, 1976.

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

Chapter (of a book)

Weinstein I, Swartz MN. Pathogenic properties of invading microorganisms. U: Sodeman WA, ur. Pathologic physiology: mechanism of disease. Philadelphia: WB Saunders, 1974, 457-72.

Disertation or MA Thesis

Cigula M. Aktivnosti nekih enzima u humanom serumu kao pokazatelji apsorpcije žive (disertacija). Zagreb: Medicinski fakultet, 1987, str. 127.

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Examples done in Notes for Contributors in Croatian (preceding page).

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The Oxford English dictionary [knjiga na CD-ROMu]. II. izdanje. New York, N. Y: Oxford University Press, 1992.
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