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Review article

Kidney Transplant and Pregnancy

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Abstract

The prevalence of chronic kidney disease (CKD) worldwide is increasing. According to a simulation study published in the American Journal of Kidney Disease in the following 20 years the number of people with chronic kidney disease (CKD) will notably increase, and more than half of the people affected will be from 30 to 64 years of age. The number of pregnant women with various degrees of kidney dysfunction is expected to grow. Even mild kidney dysfunction can increase considerably the risk of adverse maternal and fetal outcomes. There is a bidirectional relationship between CKD and pregnancy. The pregnancy can have a deleterious impact on various aspects of CKD and renal dysfunction negatively affects pregnancy outcomes.

Key words: chronic kidney disease, transplantation, pregnancy

Introduction

Chronic kidney disease (CKD) affects almost every organ and tissue leaving consequences on structure and function, moreover it significantly affects quality of life [1]. Loss of fertility is considered to be one of the features of CKD [1,2]. It is estimated that approximately 4% of women of childbearing age have certain degree of CKD [2]. Female patients with CKD have elevated levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH) and prolactin. Uremia is known to promote premature aging in humans, so female patients may also be affected with premature menopause [3]. Besides the CKD itself, there are other causes of the disturbance, such as vasomotor dysfunction, medications used in treatment and prevention of complications of CKD and psychological changes [4]. Dialysis worsens the fertility issue due to chronic inflammation and protein malnutrition. Pregnancies in women on maintenance dialysis are rare.

Chronic kidney disease

Female patients with end stage renal disease (stage 5) that undergo dialysis have decreased rate of fertility with an annual possibility of pregnancy from 0.3% to 12.5% [5]. Confirming the pregnancy can be challenging due to false positive results of beta-Human Chorionic Gonadotropin testing in women that undergo dialysis. If the patient that undergoes dialysis gets pregnant then more intensive dialysis schedule with blood urea nitrogen below 17 mmol/L is needed what may be achieved by increasing the frequency of hemodialysis sessions or switching to prolonged nightly hemodialysis. In petients on peritoneal dialysis lowering the volume of dwells to 800 mL and raising their frequency is recommended [1].

Renal transplantation

Renal transplantation is an optimal replacement of kidney function. Renal transplantation increases the possibility of pregnancy in women with end stage renal disease, however adverse effects regarding mother and fetus are more often. It is of utmost importance to control and observe the pregnancy from a multidisciplinary point of view. First successful pregnancy after kidney transplantation was documented in 1958 [6]. Since then there are data for hundreds of successful pregnancies. Davison and Baylis gathered information in 2001 for 14 000 pregnancies after kidney transplantation [7]. Until today the number of successful pregnancies has drastically increased, however it is hard to determine exactly how much regarding the fact that there are many centers around the world that deal with this kind of patients. Hormonal changes amend after successful kidney transplantation as well as ovulation and menstrual cycle, patients have stronger sexual desire and higher fertility rates [8]. Due to everything mentioned above every patient of childbearing age should be warned about the changes in order to start contraception to avoid unwanted pregnancies.

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The effects of immunosuppressive therapy on fertility

Little is known about the effects of some immunosuppressants on fertility after kidney transplantation [9-11]. Detailed review of literature suggests just that immunosuppressive therapy with mTOR inhibitors (sirolimus, everolimus) can affect menstrual cycles during the first year after the transplantation and can cause forming of ovarian cysts that are reversible. It is considered that other immunosuppressants used after transplantation do not affect the hypothalamic-pituitary-gonadal axis or gametogenesis. In pregnant women after kidney transplantation (including other organs) or in women with autoimmune diseases (such as SLE and lupus nephritis) immunosuppressive therapy is continued during the pregnancy [12,13]. Pregnancy planning and drug choices for prevention of complications in mother and fetus are very important [12]. Until recently, pregnancy was not recommended in first two years after transplantation. Nowadays number of clinicians consider pregnancy safe for mother and fetus already at six months after the transplantation [10]. Every patients, not only in transplantation medicine, has to be carefully accessed for potential risks. Sexuality is very important for the quality of life. Patients should be well educated about every method of contraception due to necessity of pregnancy planning [14]. The use of intrauterine device is increasing the possibility of infections. Hormonal contraceptives can interfere with the metabolism of immunosuppressive therapy. Protection (male condoms) are recommended contraceptive options because they are efficient birth control and they protect from sexually transmitted diseases [14]. Barrier methods and intrauterine devices are not optimal birth control methods because they are not safe enough [14]. Intrauterine devices require healthy immune system to work properly, so the recommendations are to use hormonal contraceptives along with good regulation of hypertension.

When to recommend pregnancy after the transplantation?

Pregnancy can be recommended in patients with good graft function (serum creatinine levels below 132 umol/l, steady doses and concentrations of immunosuppressive therapy, proteinuria less than 500 mg/day, and without recent transplant rejection or infections [8]. Blood pressure has to be below 140/90 mmHg with antihypertensive drugs. Patients have to have normal ultrasound findings of transplanted kidney, moreover treatment with mycophenolate mofetil and mTOR inhibitors should be ceased at least six weeks before pregnancy due to known teratogenic effects [9]. It is clear that the first couple of months after transplantation are not good for pregnancy planning because of the intense immunosuppressive therapy and high risk of acute transplant rejection. Pre-existing kidney disease is a risk factor for preeclampsia, whereas proteinuria above 500 mg/day increases the risk of chronic dysfunction of transplantted organ [15]. Hypertension is very common (up to 75% patients during pregnancy) and results from existing disorder or can develop during pregnancy.

Mother and fetal complications

According to the data from literature around 12% of women of childbearing age that underwent kidney transplantation can get pregnant. Miscarriage happens in about 11% to 26% of patients. Successful pregnancies happen above 90% after the first trimester [10,15]. Average duration of pregnancy in transplanted patients is around 34 weeks. Most common complications that affect the mother are preeclampsia, arterial hypertension, reversible dysfunction, transplant rejection and infections [10,16]. Low birth weight happens in around 50% of newborns. Newborn survival rate is very high, while the rates of miscarriages and malformations are low [10]. Although cesarean section is more common there are no medical barriers for natural birth since transplanted kidney is located in pelvic region. Illness that caused the transplantation affects the pregnancy and complications during the period.

Discussion

In the years 2020 and 2030 the number of people with CKD will increase from 13.2% in the present to 14.4% and 16.7%, respectively [17]. It is considered that around 4% of women of childbearing age have a certain degree of CKD [1]. The risk for the development of CKD is higher in women than in men (14% to 12%) [18]. Low birth weight happens in around 50% of newborns, premature children is common condition in pregnancy of transplant woman. Minor reductions in nephron numbers that are seen in low-birth weight and small for gestational age newborns are emerging as important predisposing factors to CKD in adult age [19]. It is very important that in humans, all of the branches of the ureteric bud (UB) and the nephrons have been formed by the 32nd to 36th week of gestation. The capacity of generating new nephrons is lost at the time of birth so that human kidneys have an estimated number of nephrons of one million per kidney or more [20]. It is an important issue for all nephrologists as the number of premature children continues to grow [20]. During pregnancy issues of women with transplant kidney as patients particularly stand out and require a multidisciplinary approach.

Conclusion

Around 50% of pregnancies after kidney transplant end with pre-term birth. Younger patients with good

transplant function and good regulation of arterial hypertension have better pregnancy outcomes. Longer period of time between pregnancy and transplantation has better outcomes. Comprehension of the necessity of continuous healthcare for women from pregnancy to kidney disease is improving.

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Review article

Long-Term Outcome In Children With Kidney Transplant: A Review

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Abstract

Kidney transplantation is a preferred treatment for end-stage renal disease in children. The purpose of this article is to review the factors affecting the long- term outcome of renal allograft and patient survival. We also would like to emphasize the impact of kidney transplantation in childhood on long-term psycho-social and economic outcome in these patients.

Keywords: long-term outcome, kidney transplantation, children

Introduction

End-stage renal disease (ESRD) is a rare condition in children. In comparison with the adult population where, according to the ERA-EDTA Registry, the average incidence of ESRD is 117-121 per million population, the incidence of ESRD in children is 7-9 per million age-related population [1]. There is also an important difference between the adult and children populations regarding the etiology of ESRD. The most common cause of ESRD in adults is diabetes mellitus type 2, whereas in children congenital anomalies of the kidneys and urinary tract are the most common cause of ESRD [1]. The preferred renal replacement therapy in children with ESRD is kidney transplantation, because it improves growth, increases life expectancy, and provides for a better quality of life [2-4]. Despite all the advantages of kidney transplantation in children, there are also multiple factors which affect patient and renal allograft survival. Kidney transplantation also has an important effect on long-term psycho-social and economic status in pediatric patients [5].

Patient survival

Compared with adults, the patient survival rate in pediatric transplant recipients is longer [6,7]. The life span of children who received a renal allograft is also longer in comparison with those who underwent dialysis [8] or were placed on a waiting list for renal transplantation [9]. However, the relative risk of death after transplantation is still assessed as 12.7 times higher compared to the age-related general population [10]. The patient survival rate varies between 89% and 98% at 3 years, 84% and 97% at 5 years, 68% and 94% at 10 years, and 54% and 86% at 20 years [10-17]. In one study the patient survival rate was 81% after 25 years [18]. There were no differences in patient survival by donor source (living versus deceased donor) [19].

The major causes of death after transplantation are cardiovascular disease (CVD), infection, and malignancy [13,20,21]. The main causes of cardiovascular deaths are heart failure and arrhythmias [22]. With the purpose to at least partially prevent CVD, a healthy lifestyle and weight control should be encouraged among patients with renal transplants and their families. Additionally, anemia correction, arterial hypertension and hyperlipidemia treatment are also recommended. As a consequence of immunosuppressive therapy, sepsis due to bacterial infections and CMV infections are most common [20]. Compared with the general population, the risk of malignancy is 10 times more common than expected for age. Non-Hodgkin lymphoma represents the majority of cases and is a cause of death in children with kidney transplants [20]. EBV-driven PTLD is also an important cause of morbidity and mortality in pediatric renal transplant recipients. Reduction of the dose of immunosuppressive drugs is a common first-line practice [23,24].

Non-adherence to therapy or treatment withdrawal and obesity are also indicated as contributing to death in children with kidney transplants [10,25].

Renal allograft survival

In recent decades, kidney transplant survival has markedly improved particularly in the immediate post-operative period as the result of refinements in surgical techniques, optimization of immunosuppressive protocols, introduction of new immunosuppressive drugs, and improvements in patient care [26]. The overall renal graft survival rates varies between 82% and 84% at 3 years, 74% and 87% at 5 years, 56 % and 68 % at 10 years, 45% in 53% at 15 years, 25% and 54% at 20 years, and 31% at 25 years [10,11,13,14,18,27,28]. Despite impro-

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vements in graft survival, there are many factors affecting long-term renal allograft survival.

Effect of donor type-According to literature, living donor transplantation offers an advantage in renal allograft survival as compared to deceased donor transplantation [29-32]. Despite the advantages of living donation, there are settings where a deceased donor is preferred, such as in patients with focal segmental glomerulosclerosis, hemolytic uremic syndrome, or primary hyperoxaluria [33].

Age of donor and recipient-Grafts from pediatric donors show a superior long-term kidney function compared with grafts from adult donors, most likely due to their ability to adapt to a growing child. There is, however, a higher risk of graft loss in the recipients of very young donors, most likely due to surgical complications, graft thrombosis, and early rejection. Recipient age also has an important effect on graft survival because there is a higher rate of graft failure in the youngest and adolescent recipients. In recipients younger than 5 years, graft failure in the first 3 months post-transplant is mostly due to surgical difficulties. In adolescents, poor graft survival is usually the result of inadequate adherence to immunosuppression regimens. Additionally, the highest rate of graft failure occurred in the recipients of young donor grafts [34].

Infections-have an important role in the morbidity of children with renal allografts, and can also lead to renal graft failure. Viruses are among the most common causes of opportunistic infections after transplantation. CMV infection is among the most common infections during that period, and is associated with increased morbidity and mortality. Antiviral prophylaxis may improve patient and allograft survival [35]. Infections with polyomavirus BK can also cause chronic renal allograft dysfunction with secondary rejection and have a poor prognosis [36].

Acute rejection episodes-are one of the most important negative predictors of renal allograft survival and among the most frequent complications of renal transplantation [27,37,38]. Acute rejection episodes may also increase the risk of chronic rejection and enhance the possibility of graft loss over time [39]. In order to prevent acute rejection episodes, it is important to have optimal HLA matching and to optimize immunosuppression regimens.

Human leukocyte antigen (HLA) matching-HLA plays an important role in the cellular and humoral responses that determine the outcome of a kidney transplant. It is one of the most important modifiable factors for reducing the risk of renal allograft loss. Superior HLA matching improves renal allograft outcome [40]. Sensitized patients with panel reactive antibodies (PRA) above 40% have a poorer outcome [8]. Additionally, an association between positive post-transplant, donor-specific HLA antibodies (DSA) and subsequent rejection was found [41].

Arterial hypertension-Hypertension after renal transplantation is common and its estimated prevalence in children ranges from 58% to 89% [42,43]. It is a predictor of poor long-term renal allograft function, regardless of the number of rejection episodes or transplant function at 1 year [44]. It is a significant and modifiable risk factor for CVD.

Kidney and urinary tract anomalies with bladder dysfunction-Children with congenital anomalies of the kidneys and urinary tract with bladder dysfunction are even more prone to repeated urinary tract infections when on immunosuppressive therapy after kidney transplantation. Despite this, several studies have found no significant effect on renal allograft outcome [45,46]. Due to numerous urological complications, careful surveillance of lower urinary tract function is needed before renal transplantation. There is no need to correct vesicoureteral reflux before renal transplantation, unless it is causing symptoms or infections [47].

Immunosuppressive therapy-is imperative in the reduction of immune-related injury to an immunological, non-identical renal allograft, and in the prevention of allograft rejection and functional failure. The conventional regimens nowadays include corticosteroid, calcineurin inhibitors, antimetabolite purine antagonists, and less routinely used mammalian target rapamycin inhibitors (mTORIs). According to NAPRTCS [12], the use of cyclosporine has significantly decreased, while the use of tacrolimus has increased over the same period. Also, the use of mycophenolate mophetil (MMF) exceeded the azathioprine prescription. The use of steroid sparing regimens is becoming increasingly more common [48].

MMF-based protocols improved long-term graft survival without any increase in side effects. Cumulative rejection-free survival was better in the MMF group compared to the azathioprine group [49]. It was also evidenced that tacrolimus was significantly more effective than cyclosporine in preventing acute rejection in pediatric renal recipients. Renal function and graft survival were also superior with tacrolimus [50].

Delayed graft function (DGF)-is defined as the requirement for dialysis within the first seven days following renal transplantation. Several clinical factors related to donor, recipient and organ transplantation procedures could increase the risk of DGF. The factors that may increase the risk of DGF include long cold ischemia, drug nephrotoxicity, and surgical problems. DGF may decrease long-term graft function. The strategies to minimize DGF are: reduction of individual risk factors for DGF and specific pharmacologic strategies designed to prevent or treat ischemia and reperfusion injury [51].

Underlying primary disease and recurrence-The risk of disease recurrence becomes relatively high, with greater prevalence in children than adults. It increases patient morbidity and graft loss. The diseases that most commonly lead to recurrence are: focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, hemolytic uremic syndrome, and hyperoxaluria type

1 [52], where oxalate will continue to be deposited in the transplanted kidney, unless a liver transplant was performed at the same time. Congenital nephrotic syndrome (Finish type) and Alport syndrome can recur due to the development of antibodies to the "missing" proteins.

Adherence (compliance)-This is a difficult problem in all ages, particularly in adolescence. It is associated with increased episodes of acute and chronic rejection and graft loss of up to 71% [53]. The reasons for non-adherence in the adolescent period are mostly transition to adulthood, health care system, difficulties in patient-parent relationships, lack of parental supervision, cosmetic effects of medication, and poor knowledge. Not only failing to take medication, but also incorrect timing of medication intake and inappropriate drug dosage are signs of poor adherence. Multiple methods of assessing adherence are used, such as drug level assays, pill counting, and patient self-reporting [54]. Patients with kidney transplants are also exposed to a high drug and pill burden, which further increases the risk of non-adherence and adverse treatment effects, both of which influence graft survival. According to a Slovenian study, fifty percent of children have been receiving more than 10 different drugs daily, resulting in over 23 pills per day [55]. The daily drug and pill burden is high and can trigger non-adherence, which is why strategies to reduce drug and pill burden should be developed.

Long-term psycho-social and economic outcome

The main goals of kidney transplantation in children are not only to increase life expectancy, but also to improve the social and professional components of life that importantly affect its quality. In pediatric transplant recipients, quality of life also depends on the primary diagnosis and on graft function.

Educational level-In a Slovenian study, 24% of patients with kidney transplants in childhood completed elementary school or have no education, and 76% of pediatric patients achieved a certain education level that can increase their chances of employment [27]. In a French study, the distribution of education levels was similar, but lower compared to the national averages [56]. It was found that renal transplant children have significantly worse scores on intelligence quotient tests compared to healthy individuals (86 vs 107). Lower maternal education level was also significantly associated with lower cognitive test scores. Additionally, children with renal allograft and comorbid conditions also had a significantly lower verbal ability and IQ score [57].
Employment-Some studies have shown a satisfactory level of employment. Between 54% and 86% patients were employed, which is similar to the general population [19,56,58]. In a Slovenian study, only 36% of patients were employed, which can partially be explained by the relatively high percentage of students (16%) who will apply for a job only after completing their education. According to different studies, the rate of unemployed patients was between 6.5% and 12.1% [18,27,58]. Additionally, the number of retired patients receiving a government pension and classified as non-employees was between 18.7 and 36% [27,56]. It has been confirmed that patients with childhood onset ESRD are unemployed more frequently than the age-matched population [59].
Relationships-According to different studies, 23% to 50% of patients were involved in a steady relationship or are married. It was also reported that between 12% and 27% of patients had children [27,56,58,59]. A significant correlation between education level, paid activity, marital life and independent housing was found [56].
Quality of life-Many studies confirm that the quality of life is reduced with chronic renal failure and dialysis, but is improved after renal transplantation. Transplant patients tend to score their quality of life higher than the controls, but parents rate their affected children more pessimistically, usually with regard to physical complaints, social functioning, and negative emotions [60]. The findings of a Slovenian study showed that a substantial number of patients (76%) meet with friends regularly, and 40% of them are regularly involved in sport activities. These data were in agreement with the fact than 60% of those patients expressed no particular worries regarding their health, and three quarters of them rated the quality of their life as excellent or good [27]. However, quality of life is also strongly correlated with illness associated variables and family relationships [60].

Conclusion

Kidney transplantation is the preferred renal replacement treatment modality in children because it improves growth, prolongs life expectancy, and improves the quality of life. Nevertheless, there are multiple factors affecting the long-term outcome of renal allograft and patient survival in the pediatric population, among which acute rejection episodes and non-adherence are among the most important. Additionally, kidney transplantation in childhood has a significant impact on long-term psycho-social and economic outcome in adulthood.

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Original article

Febrile Proteinuria in Children: an Evaluation of Causes and Finding

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Abstract

Introduction. Transient proteinuria can be caused by high fever. It does not involve underlying kidney disease. Present study was designed to evaluate the prevalence of transient proteinuria in pediatrics with febrile diseases.

Method. One hundred eighty six febrile children were studied in one year according to enumeration method between August 2017 and 2018. Patients with renal diseases were excluded. The urine analysis was taken at the time of admission and after the fever improvement. A blood sample was taken and CRP, ESR and WBC were evaluated.

Results. Proteinuria was detected in 21 patients (11.4%). Among them 8 patients (38%) were male and 13 patients (62%) were female with the average age of 1.87±1.94 years. There was no difference between sex and age in patients with or without proteinuria ($p>0.05$). The intensity of proteinuria at the time of admission in 4 patients (19%) was trace, in 12 patients (57%) was one plus (+), in 4 patients (19%) was two plus (++) and in 1 patient (5%) was three plus (+++). Proteinuria disappeared after fever improvement in all patients. Febrile convulsion and gastroenteritis were the common diagnosis. The mean of fever, SG, ESR and WBC in children with proteinuria were 38.78±0.56 ^{0}C, 1017.58±8.58, 45.05±10.92 and 13247.05±6501.06 cell/mm^3 respectively. CRP was positive in 16 patients (76%) and 73 patients (44.24%) with and without proteinuria. Difference was significant ($p=0.01$).

Conclusion. Prevalence of proteinuria in febrile children was 11.4%. Gastroenteritis and febrile convulsion were the most common diseases in febrile children with proteinuria.

Key words: child, fever, proteinuria

Introduction

The excretion of protein in urine is a usual laboratory finding in pediatrics [1]. In spite of proteinuria is generally benign, but it can be a sign for a major systemic disease or renal disorder [2,3]. Proteinuria is defined as urinary protein excretion more than 150 mg/day [4]. It may result from non-pathological (stress, fever, exercise) or pathological (kidney diseases) conditions. Asymptomatic proteinuria may be transient or persistent [5]. While transient proteinuria is a benign state and almost requires no intervention, persistent proteinuria can be the first marker of kidney disease [1].

The relationship between proteinuria and fever was first described many years ago. In spite of its importance the pathogenesis are not fully understood, it is usually considered to be a benign and transient occurrence [6]. Despite transient proteinuria being often benign, persistent proteinuria can be a marker of progressive kidney disease and is related with increased cardiovascular morbidity [7]. So, proteinuria presents a challenge to the primary care physician in regards to distinguishing benign proteinuria and proteinuria that requires referral to the nephrologists [8]. The glomerular basement membrane provides the barrier between the urinary space and blood. This barrier is negatively charged because the existence of glycosaminoglycans and glycocalyx [9]. Therefore, the nature of the crossable particles is dependent to the molecular size and the charge of the particle. The major of the proteins that are filtered through the barrier are reabsorbed by the proximal tubule, and the residuals are degraded and so excreted as low-molecular weight proteins. Albumin, transferrin and macroglobulin constitute 30% of proteins. The remaining (70%) is the Tamm-Horsfall protein which are secreted by the Henle loop. Increased urinary protein excretion can result from increased filtration across the glomerular barrier (glomerular proteinuria), decreased reabsorption from the proximal tubule (tubular proteinuria) or increased secretion of protein from the tubules (secretory proteinuria) [9].

Present study was carried out to determine the prevalence, causes, clinical and laboratory symptoms of proteinuria in febrile children referred to emergency room of Dr. Sheikh hospital, Mashhad University of Medical Sciences, Mashhad, Iran from August 2017 to 2018.

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Materials and methods

A cross sectional study was performed in emergency room of Dr. Sheikh hospital, Mashhad University of Medical Sciences, Mashhad, Iran from August 2017 to 2018. This study was approved by Mashhad University Medical Ethics Committee (code: IR.MUMS.fm.REC. 1396.803). The study participants included were 186 admitted febrile children, aged less than 18 years. Fever was defined as a temperature rise above 38^0C axillary. Parental informed consent was obtained prior to the study. Since renal diseases in general are associated with abnormal urinalysis, patients with renal disease diagnosis were excluded on the basis of the physical examination and normal urinalysis, either at the time of the fever or after. Therefore 5 patients with febrile UTI were excluded in spite of positive proteinuria. Temperature, duration of fever and pulse rate was checked for all patients. Also a blood sample was taken and parameters including WBC (using Sysmex kx-21N, automated hematology analyzer), ESR (through infrared technique using Sed rate device (Lena)) and CRP (qualitative assessment by agglutination latex) were measured for each patient at the time of admission. A midstream, clean-catch specimen was collected in toilet trained patients and in non toilet trained subjects, the sample was collected using urine bag or urethral catheterization. All urine samples were sent to the laboratory within an hour. Urinalysis was done at the time of admission and after fever improvement. The urine protein was assessed according to dipstick method. False positive samples were excluded using sulfosalicylic acid 3%. The WBC more than 15000 cell/mm^3 was considered abnormal.

Sample size

The sample size study population was 186 patients in one year according to enumeration method between August 2017 and 2018.

Analysis

Statistical analysis was performed using SPSS windows program version 16 (SPSS Institute, Inc., Chicago, IL, USA). All experimental values are presented as Means ± standard deviation (SD). Two groups were compared using independent student t test or nonparametric equivalent. Relationship between qualitative variables was evaluated by chi-square test. P values less than 0.05 was considered statistically significant.

Table 1. Demographic characteristics of febrile patients

Variable	Positive proteinuria (n=21) Frequency/mean±SD	Negative proteinuria (n=165) Frequency/mean±SD	P value
Sex			
Male	8	93	0.12*
Female	13	72	
Age (year)	1.87±1.94	1.99±1.84	0.83#

*Chi square, # Independent t test

Table 2. Characteristics of patients with febrile proteinuria

Case number	Age	Gender	Temperature (^{0}C)	Urine protein	Diagnosis
1	8 M	F	38.5	1+	Kawasaki
2	8 M	F	38.5	1+	Febrile convulsion
3	6 M	M	39	1+	Others
4	7 M	M	38.5	1+	Gastroenteritis
5	2 M	M	38.9	1+	Gastroenteritis
6	5.5 Y	F	38.2	1+	Febrile convulsion
7	1.2 Y	F	38.5	1+	Febrile convulsion
8	1 Y	F	40.5	1+	Febrile convulsion
9	6 Y	F	38.5	1+	Gastroenteritis
10	3 Y	F	39.5	1+	Pneumonia
11	7 M	F	38.5	1+	Febrile convulsion
12	1.5 Y	F	38.8	1+	Gastroenteritis
13	2.5 Y	M	38.5	2+	Gastroenteritis
14	9 M	F	38.5	2+	Febrile convulsion
15	7 M	M	38.5	2+	Gastroenteritis
16	3 M	F	39.4	2+	Gastroenteritis
17	8 M	M	38.5	3+	Febrile convulsion
18	4 Y	F	38.7	trace	Pneumonia
19	8 M	M	38.5	trace	Gastroenteritis
20	7 M	F	39.5	trace	Viral infection
21	3.5 Y	M	38.5	trace	Febrile convulsion

M= month, Y= year, F= female, M= male

Results

Of the 186 included children, 85 cases (45.7%) were female and 98 cases (54.3%) were male. The average age of patients was 1.98±1.84 years. The minimum age was 40 days and the maximum was 9 years. The mean fever temperature and pulse rate were 38.66±0.56ºC and 125.49±19.9 pulse/minute respectively. Duration of fever in 112 patients (63%) was 48 hours or less.
Proteinuria was detected in 21 cases (11.4%). Among the 21 patients with proteinuria 8 patients (38%) were male and 13 patients (62%) were female with the average age of 1.87±1.94 years. There was no significant difference between sex and age in patients with or without proteinuria (p=0.12 and p=0.83 respectively). Demographic characteristics were presented in table 1. The intensity of proteinuria at the time of admission in 4 patients (19%) was trace, in 12 patients (57%) was one plus (+), in 4 patients (19%) was two plus (++) and in 1 patient (5%) was three plus (+++). Characteristics of patients with febrile proteinuria were presented in table 2. A second UA was obtained from 19 cases with proteinuria a week after fever improvement (Two patients did not return for follow up). Proteinuria disappeared after fever improvement in all patients.
Final diagnosis in febrile patients with or without proteiuria was present in table 3. Febrile convulsion and gastroenteritis were the most common diagnosis in the patients. There was not significant relationship between proteinuria and final diagnosis (p=0.21).

Table 3. Final diagnosis of febrile patients

Final diagnosis	Positive proteinuria (n=21)	Negative proteinuria (n=165)	P value*
Gastroenteritis	7 (20%)	32 (80%)	0.21
Febrile convulsion	8(8.4%)	87 (91.6%)	
Pneumonia	2 (14.3%)	12 (85.7%)	
Kawasaki	1 (33.3%)	2 (66.7%)	
Viral infection	1 (5.3%)	18 (94.7%)	
Other diseases	1 (7.1%)	13 (92.9%)	

*Chi square test

Table 4. Comparison of laboratory variables between patients with and without proteinuria

Laboratory variables	Positive proteinuria (n=21)	Negative proteinuria (n=165)	P value
Fever	38.78±0.56^{0}C	38.65±0.56^{0}C	0.37*
SG	1017.58±8.58	1012.01±7.87	0.15*
ESR	45.05±10.92	27.47±28.65	0.02*
WBC (cell/mm3)	13247.05±6501.06	11500±5961.11	0.25*
Positive CRP (%)	76%	44.24%	0.001#

SG: specific gravity, ESR: erythrocyte sedimentation rate, WBC: white blood cell, CRP: C reactive protein, *Independent t test, # Chi square test

The mean±SD of fever, SG, ESR and WBC in children with proteinuria were 38.78±0.56^{0}C, 1017.58±8.58, 45.05±10.92 and 13247.05±6501.06 cell/mm^3 respectively. The mean±SD of fever, SG, ESR and WBC in children without proteinuria were 38.65±0.56^{0}C, 1012.01 ±7.87, 27.47±28.65 and 11500±5961.11 cell/mm^3 respectively. Difference was not significant in fever and WBC (p= 0.37 and p=0.25 respectively) (Table 4).
Among studied children CRP was positive in 16 patients (76%) and 73 patients (44.24%) with and without proteinuria respectively. Difference was significant (p=0.01).
Among the 186 febrile children, microhematuria was detected in 11 patients (5.9%) in the first urine sample. Among these, 5 patients (45.45%) were diagnosed with positive proteinuria. Also microhematuria was detected in 1 patient (5.3%) with positive proteinuria in the second urine sample.

Discussion

One hundred eighty six patients were studied for the evaluation of proteinuria in their febrile conditions. Proteinuria was detected in 21 cases (11.4%) in range of trace to three plus (3+). Proteinuria disappeared after fever improvement in all patients. Gastroenteritis and febrile convulsion were the most common diagnosis in febrile children with proteinuria.
The normally excretion of protein in urine is variable. The average of urinary protein in children is about 75-100 mg/24 hours [4]. The mechanism of normal proteinuria is not fully understood. But probably it is influenced by the relative rates of protein filtration at the capillary basement membrane and the rate of proximal tubular re-absorption [10]. Proteinuria could be considered benign if it disapears when fever abates. As seen in present study, the proteinuria has been resolved after treatment in all patients indicating the importance of febrile conditions in benign proteinuria. Usually, only repeat urinalysis is necessary to confirm transient nature of this phenomenon in majority of cases.
Proteinuria has been seen in a number of conditions in which there is no identified kidney disease including

fever, exercise, stress, or cold exposure [11]. It may also be caused by hemodynamic alterations in glomerular blood flow.

Numerous hypotheses have been suggested to describe the proteinuria which may be seen with fever [1]. One theory suggests that proteinuria is occurred in response to an infectious agent that triggers an inflammatory response in the kidney [12,13]. However, Welty [14] showed that fever could lead to an increased protein excretion even in the absence of demonstrable infection. King and Baldwin [15] showed that fever induced stress caused the release of Adrenal hormones**.**

Similarly, Melvin *et al*. in a study on 198 febrile patients reported that 11 cases (5.6%) have proteinuria with variable causes including pneumonia, septicemia, otitis media and others [6]. The results of Melvin are in agreement with our study.

Valavi *et al*. in a study on children with febrile UTI reported that the prevalence of proteinuria was 41% [16]. In another study on children with kavasaki, it was reported that the prevalence of proteinuria was 53.9% [17].

In present study among 168 febrile patients, 21 cases have transient proteinuria in grade of trace to 3+. These patients did not had any proteinuric renal disorder. According to present study the febrile convulsion and gastroenteritis were the most common causes responsible for transient proteinuria. Proteinuria is a common finding in pediatric practice, often detected incidentally.

A CRP test may be used to find or monitor conditions that cause inflammation including bacterial infections, fungal infection and inflammatory bowel disease. In our study there was significant relationship between proteinuria and positive CRP which may be due to bacterial infection. Also in present study ESR was significantly higher in children with proteinuria compared with children without proteinuria which confirmed the probability of infection presence in children with proteinuria.

Conclusion

Prevalence of proteinuria in febrile children in absence of renal diseases was 11.4%. Gastroenteritis and febrile convulsion were the most common diseases in febrile children with proteinuria. More studies with larger sample size were suggested to confirm the result of present study.

Limitations

There is no quantification assessment of proteinuria. Also there are no data if the proteinuria is tubular or glomerular.

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Conflict of interest statement. None declared.

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Original article

Short-Term Sole Treatment with Sevelamer Carbonate in Patients on Hemodialysis with High and Low Bone Turnover – Is it Essential for Both Extremes?

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Apstract

Introduction. Chronic kidney disease (CKD) patients on hemodialysis (HD) are burdened with higher co-morbidity and mortality compared to the general population due to the loss of various kidney functions. The maintenance of serum phosphate and calcium homeostasis in end-stage renal disease (ESRD) is severely disrupted. Subsequently, the disordered mineral metabolism stimulates parathyroid glands to secrete higher levels of parathyroid hormone (PTH) in order to maintain normal phosphate and calcium levels. Phosphate binding agents are administered to control hypephosphatemia and to prevent development of hyper parathyroid bone disease (HPTH). Among them non-calcium based one-sevelamer carbonat is preferred for many various benefits.
We aimed to explore the short-term effect of the treatment with sevelamer carbonate in groups of patients with high and low bone turnover assessing the mineral and bone (PTH) parameters.
Methods. We conducted a prospective, postmarketing, two-arm, single center study in maintenance HD patients aged >18 years, with either PTH<150 pg/ml or >600 pg/ml, without previous sevelamer treatment. Based on the PTH level we stratified patients in arm A-PTH <150 pg/ml as presumably adynamic bone disease group (ABD), and arm B-PTH >600 pg/ml, presumed with HPTH. The primary objective was to investigate the efficacy of sevelamer carbonate in HD patients by improving the PTH levels (increase in ABD, and reduction in HPTH patients). The secondary objective was to observe normalization of Ca and P levels and Ca x P product.
Results. The study enrolled in total 23 patients with CKD-MBD, 15 males (65.22%). The average age was 57.03±13.03 years. Older participants developed ABD compared to HPTH (p=0.04). There was no difference found regarding the patients gender (p=0.18). Dialysis vintage showed development of HPTH in patients with longer HD vintage (p=0.04). A significant improvement was observed in the Ca level over the study course, while the phosphate (P) level worsened from 1.96 to 2.15 (p=0.03) in the first month and returned to 1.96 (p=0.95) at the study end (3 months). The Ca x P product level did not change during the study in the whole cohort. The PTH significantly increased (p=0.00) but remained in the reference range for HD patients.
There was a significantly lower level of calcium at the end of the study (p=0.01) in the ABD group, the phosphate levels tend to further increase, while PTH levels significantly improved towards the reference range.
In the HPTH group, there was an improvement in the calcium level compared to baseline and trend for an increase in the phosphate levels that leveled off at the end of the study. In contrast, the level of alkaline phosphatase and PTH significantly increased over time.
Conclusion. The study met the primary objective by increasing the PTH level in ABD patients. Additionally, normalization of Ca and P levels and Ca x P product was achieved only for the Ca level in the ABD arm. Relatively small sample size and short time period might have been the reasons for not reaching all secondary objectives.
The level of PTH and alkaline phosphatase could not have been controlled over the course of the study in patients with HPTH. Hence, a higher dose of sevelamer carbonate in combination with vitamin D is required in order to adequately suppress PTH levels in patients with already established HPTH.

Key words: sevelamer carbonate, phosphate, calcium, parathyroid hormone

Introduction

Chronic kidney disease (CKD) patients on maintenance hemodialysis (HD) treatment are burdened with higher comorbidity and mortality compared to the general

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population due to the loss of various kidney functions with the maintenance of serum phosphate and calcium homeostasis as crucial one. Along with the CKD progression to end-stage renal disease (ESRD) the excretion of phosphate is impaired, and there is a reduction in the synthesis of 1 α-hydroxylase and vitamin D leading towards hyperphosphatemia and hypocalcemia. Thus, if appropriate measures are not taken, the parathyroid glands begin secreting higher levels of parathyroid hormone (PTH) in order to maintain normal levels of phosphate and calcium by stimulating the synthesis of 1 α-hydroxylase and inhibiting phosphate resorption. Ultimately, these compensatory mechanisms are overcome due to renal function loss and ensuing secondary hyperparathyroidism [1].

The result from these metabolic disturbances are all named chronic kidney disease-mineral and bone disorders (CKD-MBD) [2,3]. Clinically it comprises of several bone conditions known as renal osteodystrophy (ROD) that range from high bone turn-over i.e. hyperparthyroid bone disease (HPTH) to low bone turn-over state or adynamic bone disease (ABD). In between are conditions named as osteomalacia and mixed lesions, possibly combined with osteoporosis [4,5].

All ROD patterns share almost similar symptoms with bone and joint pain, muscle weakness, increased fracture rate, and also extra osseous bone depositions of phosphate and calcium in soft tissues and in the vascular bed [6]. Such vessels are stiffer and fail to react to change in the blood flow because of the lower elasticity. There are increasing epidemiological findings that there is a positive correlation in cardio-vascular and all-cause morbidity and mortality in these patients associated with vascular calcification [7,8].

Primary focus in the management of CKD-MBD is to treat hyperphosphatemia. Main sites responsible for maintenance of normal level of phosphate are the gastrointestinal tract and kidneys. The main source of phosphate in ESRD patients is through the dietary intake of protein rich food. Dietary restriction is seldom a choice of phosphate lowering treatment option due to the risk of protein malnutrition. Standard 4-hours high flux HD treatment removes around 800 mg of phosphate per treatment and is not sufficient enough to remove all of the daily phosphate intake and thus CKD-MBD cannot be effectively controlled.

Considering the fact that the kidneys in ESRD are incapable to regulate the phosphate excretion, an option to control the phosphate level is to reduce the amount of phosphate resorption in the small intestines by phosphate binders. Several phosphate binders can be used in patients who are on chronic HD regimen: aluminium and calcium-based salts, and non-aluminum, non-calcium-based phosphate binders like sevelamer hydrochloride and from recently sevelamer carbonate with an improved safety profile [9]. Calcium-based salts could achieve a good control of phosphate level but this is usually followed with hypercalcemia as adverse effect, in around one-third of patients with ESRD. In addition, the hypercalcemia *per se* is associated with an increased risk of vascular calcification [10].

Thus, the most widespread non-calcium-based phosphate binder alternative today is sevelamer hydrochloride, and even better with carbonate composite. Structurally it is a cationic hydrogel, a polimer containing polyallylamine chloride cross-linked with epichlorohydrin, which makes it being hydrophilic but insoluble in water. It is not absorbed from the gastro-intestinal tract and binds phosphate in exchange for chloride ideally at pH 7 [11,12]. In addition, there are a couple of pleiotropic effects concerning the lipid lowering ability and amelioration of acidosis in CKD patients [13].

Material and methods

We conducted a prospective, postmarketing, comparative, two-arm study from 12th December 2018 till 13th March 2019 in a single dialysis center. Inclusion criteria were: ESRD patients older than 18 years undergoing hemodialysis trice weekly, with abnormal level of PTH (below 150 pg/ml and above 600 pg/ml) and have not used sevelamer as phosphate binder in the previous six months.

Study participants were stratified into two arms regarding the level of PTH; Arm A enrolled participants with PTH level < 150 pg/ml (ABD group), and Arm B participants with PTH level >600 pg/ml (HPTH group). The dosing of sevelamer carbonate was dose dependent based on the phosphate blood level (P=1.7-2.1-3 x 0.8 g/daily; P=>2.1-2.6-4 x 0.8 g/daily; P>2.6-5 x 0.8 g/daily). There were no study participants who were discontinued from the study for any reason. Local Ethics Committee approved the study protocol and each study participant signed an Informed Consent prior their enrollment into the study.

The primary objective of the study was to investigate the efficacy of sevelamer carbonate in improving the PTH levels (an increase in ABD patients, and reduction in patients with HPTH). The secondary objective was to observe normalization of the level of Ca, P and calcium x phosphate product.

Demographic characteristics of participants were noted at the study entry. Clinical and laboratory variables were recorded at baseline and with subsequent measurements in the following three months.

The variables that were collected and analyzed were serum levels of calcium, phosphate, PTH, alkaline phosphatase, C-reactive protein, hemoglobin, ferritin. Clinical parameters that were examined were blood pressure and mean arterial pressure from three separate measurements during HD prior to study entry, and in the following three months. Each of the study laboratory variables estimated as an average value of the previous six months was also noted as an average before the study entry baseline value, and monthly values were

recorded in the following three months. The average number of calcium carbonate tablets and average dosage of calcitriol were also noted in the same period. The descriptive statistics of the patients is shown as frequency (percentage). The continuous variables were shown as mean and standard deviation (SD). Intra-patient comparison of clinical and laboratory variables was computed using T-test for normally distributed samples. Relationship between qualitative variables was evaluated by chi-square test. P values less than 0.05 was considered statistically significant. All statistical analysis were performed using IBM Statistical Package for the Social Sciences® (SPSS) software platform, issue 15.0 Command Syntax Reference. Chicago, Illinois: SPSS Inc. 2006.

Results

This study enrolled in total 23 patients with CKD-MBD, 15 males (65.22%). The average age of the study population was 57.03±13.03 years, for patients with HPTH 51.78±16.63, and for those with ABD 61.07±8.98 years that were predominantly older age males (78.6%). Demographic characteristics of the participants at study entry are shown in Table 1.

Patients' age was shown to be associated with various CKD-MBD state, whereas older study participants developed ABD compared (p=0.04). No significant difference was found regarding the gender (p=0.18). Comparison between primary cause of ESRD showed no impact of DM type II presence on bone metabolism (p=0.18). Dialysis vintage showed development of

Table 1. Demographic characteristics of participants at study entry

	Study population N = 23	**Arm A Adynamic bone disease** N=14	**Arm B Hyperparathyroidism** N=9	**P value**
Gender				0.18
Female	8(34.78%)	3(21.43%)	5(55.56%)	
Male	15(65.22%)	11(78.57%)	4(44.44%)	
Age	57.43±13.03	61.07±8.98	51.78±16.63	**0.04***
Female	55±19.99	68±7.55	47.2±21.63	0.08
Male	58.73±7.86	59.18±8.67	57.5±5.92	0.36
Primary cause of ESRD				0.18
GN	6(26.09%)	3(13.04%)	3(13.04%)	
DM II	6(26.09%)	1(4.35%)	5(21.74%)	
HTA	5(21.73%)	4(17.39%)	1(4.35%)	
ADPKD	2(8.7%)	1(4.35%)	1(4.35%)	
Others	4(17.39%)	1(4.35%)	3(13.04%)	
HD vintage (y)	7.13±5.22	5.57±5.4	9.56±4.07	**0.04***

Abbreviations: Data expressed as mean ±SD-Standard deviation; ESRD-End Stage Renal Disease; HD-Hemodialysis; GN=glomerulonephritis; DM diabetes mellitus; HTA- hypertension; ADPKD-adult dominant polycystic kidney disease; Others-nephrocalcinosis, Wegener granulomatosis, systemic lupus erythematosus. *P value significant between the groups

Table 2. Laboratory variables in all study participants

	Average	**Baseline***	**1st measurement**	**2nd measurement**	**3rd measurement**
Ca	2.28±0.2	2.39±0.23	2.22±0.19 (**p=0.00**)	2.21±0.18 (**p=0.00**)	2.25±0.20 (**p=0.00**)
P	1.98±0.23	1.96±0.33	2.16±0.39 (**p=0.04**)	2.15±0.37 (**p=0.03**)	1.96±0.36 (p=0.95)
Ca x P	4.54±0.73	4.67±0.95	4.79±0.86 (p=0.53)	4.73±0.88 (p=0.67)	4.43±1.03 (p=0.36)
AF	198.87±363.00	188.78±351.90	175.84±288.34 (p=0.38)	197.78±374.29 (p=0.25)	222.00±374.12 (**p=0.00**)
PTH	412.77±553.29	421.39±542.74	486.13±529.70 (p=0.1)	422.27±394.44 (**p=0.02**)	*600.25±599.79 (**p=0.00**)
CRP	9.26±10.09	12.69±25.93	15.49±25.48 (p=0.65)	9.23±20.87 (p=0.47)	11.00±19.04 (p=0.75)
Hb	115.13±6.69	113.65±10.29	116.00±9.18 (p=0.15)	115.03±10.06 (p=0.47)	117.22±9.97 (p=0.75)
Ferritin	170.18±117.22	196.22±142.27	210.83±129.46 (p=0.52)	183.47±100.62 (p=0.61)	322.51±238.47 (**p=0.01**)

Abbreviations: Ca, calcium (mmol/L); P, phosphate (mmol/L); Ca x P, calcium x phosphate product; AF, alkaline phosphatase (U/L); PTH, intact parathyroid hormone; CRP, C Reactive Protein; Hb, hemoglobin (g/L). *P value statistics versus baseline values

HPTH in patients with longer HD vintage (p=0.04).
From the clinical variables, the mean arterial pressure of the whole cohort did not change over time. The average value prior the study entry was 102.35 mmHg±12.94, followed by 101.3 mmHg ±12.02 in the first month, and 104.65 mmHg ±9.18 (p=0.48) and 103.91 mmHg ±12.32 (p=0.34) in the second and third month, respectively. In addition, there was no significant change in the body weight (BW) after dialysis treatment over the course of the study period.
Comparison of the laboratory variables of the whole study population is shown in table 2. A significant change was observed in the level of calcium over the study period, the level of phosphate was worsened from 1.96 to 2.15 (p=0.03) in first month and returning to 1.96 (p=0.95) at the end of the study. The level of calcium x phosphate product did not change during the study in the whole cohort. The PTH significantly increased (p =0.00) but remained in the reference range for patients on HD. There was also change in the markers of inflammation (ferritin increase, p= 0.01).
The average dose of calcium-containing phosphate binders in all of the participants prior to entry of the study was 3.97g±1.17 and of calcitriol was 0.8 mcg±1.71. The dosage of sevelamer carbonate was titrated in relation to the level of phosphate, average values were 2.68 g± 0.57, 2.68 g±0.57 and 2.61 g±0.5 at the subsequent measurements (Table 3). Slightly higher doses of sevelamer were prescribed in HPTH patients but it didn't reach statistical difference.

Table 3. Sevelamer dosage and significance in all study participants and between groups

	Baseline*	**1st measurement**	**2nd measurement**	**3rd measurement**
Sevelamer (all study participants)	2.68±0.46	2.68±0.57 (p=1.00)	2.68±0.57 (p=1.00)	2.61±0.50 (p=0.16)
Sevelamer (arm ABD)	2.63±0.49	2.57±0.56 (p=0.34)	2.57±0.56 (p=0.34)	2.57±0.56 (p=0.34)
Sevelamer (arm HPTH)	2.76±0.42	2.84±0.58 (p=0.68)	2.84±0.58 (p=0.68)	2.67±0.40 (p=0.35)

Abbreviations: ABD-Adynamic Bone Disease; HPTH-Hyperparathyroid bone disease; *P value statistics versus baseline values

In addition, the analysis was performed for each of the groups in the study, separately. Given the differences in the development, symptoms, treatment and outcome in the ABD and HPTH the results was expectedly different.
Vitamin D was not administered at the beginning of the study in order to omit any confounding effect on the sevelamer treatment, but after the second measurement in a single patient of ABD group (significantly increased PTH) and in the majority of patients in HPTH group (0.11±0.40 vs 4.06 ± 2.58, p<0.001, respectively).
The results from the study Arm ABD are shown in Table 4. There was a significantly lower level of calcium at the end of the study (p=0.01), the phosphate levels tend to further increase, while PTH levels significantly improved towards the reference range. There was no change in the level of markers of inflammation.
The results from the study Arm HPTH are shown in Table 5.
In the HPTH group, it can be observed that there is an improvement in the calcium level compared to baseline

Table 4. Laboratory variables in Arm ABD

	Average	**Baseline***	**1st measurement**	**2nd measurement**	**3rd measurement**
Ca	2.23±0.17	2.35±0.22	2.12±0.10 **(p=0.01)**	2.12±0.09 **(p=0.01)**	2.17±0.16 **(p=0.01)**
P	1.99±0.27	1.89±0.37	2.17±0.47 (p=0.08)	2.17±0.45 **(p=0.03)**	2.01±0.36 (p=0.32)
Ca x P	4.46±0.81	4.44±1.01	4.59±0.93 (p=0.62)	4.61±0.97 (p=0.5)	4.38±0.94 (p=0.86)
AF	77.06±19.29	80.93±36.86	77.46±18.99 (p=0.61)	197.78±374.29 (p=0.92)	222.00±374.12 (p=0.15)
PTH	86.25±50.54	88.93±63.64	77.46±72.98 **(p=0.01)**	150.93±93.15 **(p=0.00)**	198.32±119.88 **(p=0.00)**
CRP	11.40±11.87	19.06±32.02	14.25±23.50 (p=0.52)	12.94±26.33 (p=0.44)	15.45±23.41 (p=0.68)
Hb	113.09±6.94	109.21±10.58	113.29±10.10 (p=0.07)	112.93±12.06 (p=0.21)	115.36±10.56 (p=0.12)
Feritin	162.07±128.46	187.79±154.13	182.36±114.81 (p=0.87)	155.99±88.32 (p=0.39)	278.02±244.24 (p=0.15)

Abbreviations: Ca, calcium (mmol/L); P, phosphate (mmol/L); Ca x P, calcium x phosphate product; AF, alkaline phosphatase (U/L); PTH, intact parathyroid hormone; CRP, C Reactive Protein; Hb, hemoglobin (g/L). *P value significance versus baseline values

Table 5. Laboratory variables in Arm HPTH

	Average	Baseline*	1st measurement	2nd measurement	3rd measurement
Ca	2.36±0.22	2.45±0.23	2.38±0.19 **(p<0.05)**	2.34±0.20 **(p<0.05)**	2.37±0.19 **(p<0.05)**
P	1.98±0.16	2.06±0.23	2.15±0.24 (p=0.29)	2.10±0.23 (p=0.47)	1.89±0.35 (p=0.26)
Ca x P	4.67±0.60	5.02±0.77	5.11±0.65 (p=0.70)	4.93±0.74 (p=0.58)	4.52±1.22 (p=0.25)
AF	365.35±552.13	356.56±535.09	328.89±429.84 (p=0.47)	380.78±568.11 (p=0.14)	418.89±558.64 **(p=0.00)**
PTH	984.18±572.06	938.56±556.03	1032.00±460.68 (p=0.36)	898.25±209.17 (p=0.19)	1303.64±404.99 **(p=0.01)**
CRP	5.95±5.55	2.78±1.03	14.25±23.50 (p=0.52)	12.94±26.33 (p=0.44)	15.45±23.41 (p=0.68)
Hb	118.29±5.15	120.56±4.61	113.29±10.10 (p=0.07)	112.93±12.06 (p=0.21)	115.36±10.56 (p=0.12)
Feritin	182.80±103.31	2097.33±129.38	182.36±114.81 (p=0.87)	155.99±88.32 (p=0.39)	278.02±244.24 (p=0.15)

Abbreviations: Ca, calcium (mmol/L); P, phosphate (mmol/L); Ca x P, calcium x phosphate product; AF, alkaline phosphatase (U/L); PTH, intact parathyroid hormone; CRP, C Reactive Protein; Hb, hemoglobin (g/L). * P value significance versus baseline values

and trend for an increase in the phosphate levels that leveled off at the end of the study. Almost the same pattern was observed for the CaxP product. In contrast, the level of alkaline phosphatase and PTH significantly increased over time. Again in this study arm, there was no change in the level of markers of inflammation.

Discussion

Bone and mineral abnormalities have a major impact on morbidity and mortality in patients with CKD treated with dialysis. Additionally, hyperphosphatemia as an integral component of the CKD-MBD syndrome has been associated with increased mortality and with the development of cardiovascular calcification, an independent predictor on mortality [14]. Several treatment strategies were investigated in clinical trials and routine practice for management of CKD-MBD in dialysis patients. Almost all of them used calcium-containing phosphate binders with consecutive risks of soft tissue calcifications. Discovery of sevelamer, as non-calcium based phosphate-binding agent, brought some light in reducing those treatment related complications, reducing the morbidity and mortality rates. The effect of sevelamer had been investigated in several clinical studies. Reasonably, it has been shown that it causes smaller increase in calcium levels compared to calcium-containing phosphate binders [15,16]. The Treat-to-Goal study, randomized study which enrolled 200 hemodialysis patients to take either sevelamer or calcium-based phosphate binders demonstrated a decrease in phosphate of approximately 2.5 mg/dL and Ca×P of approximately 20 mg/dL in both groups (P=0.33 and P=0.12, respectively), but with an 0.4 mg/dL increase in serum calcium in the calcium-treated group, compared to 0.1 mg/dL in the sevelamer group (P=0.002) [17]. Another study showed serum levels of phosphate, calcium, and intact parathyroid hormone were well controlled within both study groups, calcium-containing phosphate binders and sevelamer group with consistently lower calcium and higher iPTH [18].

In our study significantly decreased levels of calcium in ABD patients (p=0.01), may reduce the risk of soft tissue calcification, indirectly lowering the impact on the level of PTH and thus possibly improving the effect on bone metabolism. This also may go in line with the well reduced risk of calcification in patients receiving sevelamer. Regarding the level of calcium x phosphate product, unlike the other studies, it did not change significantly (p=0.77). The phosphate level in ABD group started to increase significantly over the course of the study, although did not reach statistical significance at the study end (p=0.26). However, the upper normal level of phosphate directly stimulates the secretion of PTH and the bone metabolism slowly returns to its' normal state of daily bone mineral turnover, possibly continuing with the beneficial impact stated previously. In this regard, the level of PTH increased significantly (p=0.01), followed by the increasing trend of alkaline phosphatase (p=0.15) compared to baseline value, and one may speculate this state may be viewed as a sign of a gradual bone recovery.

Several studies had shown the beneficial effect of the sevelamer use in lowering blood phosphate levels. In the prospective randomized Renagel in New Dialysis Patients (RIND) trial, there was relatively less progression of coronary artery calcification in 127 incident hemodialysis patients randomly assigned to sevelamer versus calcium-based phosphate binders [19]. An another two-year study has supported the findings that calcium carbonate use is continuously associated with progressive arterial calcification in haemodialysis patients [20]. In addition, while it may be associated with a decreased trabecular bone density, the beneficial effect of sevelamer on bone has been shown in several other studies [21,22]. Anibal *et al.* found that phosphate control with

sevelamer resulted in no statistically significant changes in bone turnover or bone mineralization compared with calcium-based binders, but bone formation was significantly increased with sevelamer, being also associated with improved trabecular architecture.[13]

In the HPTH arm of our study, the phosphate control remained stable over the study course, with significantly reduced calcium levels compared to baseline (p=0.02). Expectedly, almost the same pattern was observed for the CaxP product while, the level of PTH and alkaline phosphatase significantly increased over time. It could be partially explained by both known PTH stimulus, i.e. lower calcium and a higher phosphate levels, and somewhat late vitamin D administration in the third month of the study. Importantly, even higher vitamin D doses could have been administered in order to adequately suppress PTH in the absence of potential high calcium absorption from calcium based binders. Hence, higher doses of vitamin D could be safely used knowing that sevelamer limits the risk of hypercalcemia, in order to control PTH and HPTH.

In both study arms there was no change in the level of markers of inflammation, something that was observed as pleiotropic effect in other studies.[23,24] The effect by which sevelamer reduces inflammation is not quite understood, there is one study that states that it binds endotoxins in the intestinal lumen, but no clinical trials have been performed to investigate this hypothesis [25]. In addition, improving the acidosis may slow the rate of kidney function decline and potentially reduce the risk of ESRD in patients with CKD and metabolic acidosis [26].

Finally, about some study limitations. It's surely the relatively small sample size, but all patients were enrolled from a single center that met the inclusion criteria. Second, the time period of the study was relatively short that might have been one of the reasons for partial achievement of the study objectives.

Conclusion

The short-term treatment with sevelamer increased PTH in ABD patients, which in turn may possibly improve the bone turnover and symptoms of CKD-MBD. There was also normalization of the level of Ca and slight increase in phosphate towards upper level of normal that in turn was in fact a potent stimulus for PTH increase.

The level of PTH and alkaline phosphatase could not have been controlled over the course of the study in patients with HPTH, along with no significant change in the levels of Ca and P. Hence, a higher dose of sevelamer carbonate in combination with vitamin D should be administered in order to adequately suppress PTH levels in patients with already established HPTH.

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Original article

Serum Vitamin D Levels in Kidney Transplant Recipients

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Abstract

Introduction. Vitamin D deficiency is very common, and in kidney transplant recipients (KTRs) it has a high prevalence of up to 80%. The classical and non-classical effects of vitamin D deficiency are complicated by the use of steroids and calcineurin inhibitors (CNIs) in the KTRs.
Methods. This cross-sectional study has been performed at Clinic of Nephrology, Clinical Center University of Sarajevo. The total of 106 KTRs has participated in the study. Based on serum vitamin D values they were divided into 3 groups: deficiency, insufficiency and sufficiency of vitamin D.
Results. Vitamin D deficiency was diagnosed in 32.2% of patients, vitamin D insufficiency in 60% of patients, while only 7.7% had sufficient serum vitamin D values. The Vitamin D deficiency was associated with CNIs and mycophenolate treatment, while no association was seen with oral or pulse steroid treatment. Other variables included in analysis: proteinuria, eGFR, the time elapsed after transplantation, and kidney transplantation diseased or living donors were significantly associated neither with vitamin D insufficiency, nor vitamin D deficiency.
Conclusion. Our study showed a high prevalence of hypovitaminosis D in kidney transplant recipients. The vitamin D status of the patients in our transplant center was influenced by a broad spectrum of factors. In addition to the well-known determinants of vitamin D, a significant influence of calcineurin inhibitor and mycophenolate treatment on vitamin D was observed. Further studies still need to investigate and explicitly clarify the possible link between immunosuppressive therapy and vitamin D in kidney transplant recipients.

Keywords: kidney transplant recipients, vitamin D, insufficiency, deficiency

Introduction

Vitamin D deficiency results in increased risk for osteoporosis in adults. Also, the deficiency is associated with myopathies, autoimmune and cardiovascular diseases, and an increased prevalence of various cancers. Vitamin D is produced de novo following sun exposure, and 10-20% of the recommended daily intake is typically obtained from dietary sources. Vitamin D deficiency is prevalent worldwide, particularly among patients with chronic kidney disease [CKD] [1]. It is difficult to predict vitamin D levels in the kidney recipient population. Deficiency can be expected for several reasons. Hypovitaminosis D appears in kidney transplant patients as a result of immunosupression therapy and low sun exposure, as well as prefiguring kidney disease. Some degree of CKD exists in most of the recipients, and patients are advised to avoid sun exposure because of an increased skin cancer risk. Also, corticosteroids commonly used against rejection, increase vitamin D catabolism. However, compared to CKD patients, transplant recipients can maintain an active lifestyle with possibly more sun exposure and can consume a more diverse diet that could be richer in vitamin D [2]. Several studies examined vitamin D deficiency prevalence in kidney transplant recipients, mostly finding it to be common. Inadequately low levels were found in 80–97% of kidney recipients [KTRs] examined in various countries in Europe [3-6]. In our country, the exact prevalence of nutritional vitamin D deficiency in this population is unknown. The aim of the present study was, therefore, to explore, in a cross-sectional design, the prevalence of vitamin D deficiency in kidney recipients in Clinical Center University [CCU] of Sarajevo, Bosnia and Herzegovina, and to identify possible associated factors.

Material and methods

This cross-sectional study has been performed at Clinic of Nephrology, CCU Sarajevo, Bosnia and Herzegovina. The total of 106 kidney transplant patients participated into the study. Based on serum vitamin D values they were divided into 3 groups: deficiency, insufficiency,

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and sufficiency of vitamin D. The only exclusion criterion was the refusal or inability of the patient to sign the informed consent.

Each patient was asked to complete a questionnaire on demographic details, the cause of end-stage kidney disease, transplant type, or time when dialysis begun. The questionnaire also included questions of patients' consumption of vitamin supplements, food additives, and "natural" supplements.

Patients' records were used to complete the reported data and prescribed treatment. The immunosuppressive regimen, vitamin supplements, and cholecalciferol were recorded for dosage, whereas other medications were documented as taken or not. Serum vitamin D levels were tested using an electrochemiluminescence immunoassay on Elecsys [Roche Diagnostics, Mannheim, Germany]. Vitamin D status was defined according to the K/DOQI guidelines for kidney disease patients, considering serum concentrations ≥30 ng/ml as adequacy, 16-30 ng/ml as insufficiency, and ≤15 as a deficiency. Blood urea nitrogen, serum creatinine, and urine for 24 hours protein and creatinine secretion were measured using a Cobas system (Roche Diagnostics). Serum calcineurin [CNIs] trough levels were measured: tacrolimus, cyclosporine using CMIA assays on an Architect i1000SR system (Abbott Diagnostics, Abbott Park, IL, USA).

Statistical analysis was performed using the three above mentioned categories of vitamin D sufficiency state as well as a two-category set contrasting patients with a proper deficiency from patients with insufficiency or adequacy pooled together. Statistical analyses were performed using SPSS 21 Windows (version 21.0, SPSS Inc, Chicago, Illinois, USA). Analyses of variance or Student's t-test were performed for normally distributed variables, and Mann-Whitney tests for variables that were not. Categorical variables were analyzed using Pearson's chi-square test, as appropriate. Correlations between continuous variables were assessed using Pearson's correlation or Spearman's rho. Multiple regression analysis was applied to examine the relationship between vitamin D levels and a set of immunosuppressive regimen and laboratory parameters. All tests were two-sided, and P values <0.05 or at a confidence level of 95% were considered significant.

Results

We enrolled 106 patients who met our inclusion criteria. Table 1 shows characteristics of the patients, including their vitamin D and proteinuria results (provided as means ± standard deviation). Majority of patients were treated with triple immunosuppressive regimen (CNIs, mycophenolate, and steroids).

Table 1. Characteristics of the kidney transplant recipients

	All patients	Vitamin D deficiency	Vitamin D insufficiency	Vitamin D adequacy
No. of patients (%)	106 (100)	31 (32.3)	67 (60)	8 (7.7)
Gender (M/F)	76/30	24/7	47/20	5/3
Age (years)	48.03±13.19	49.22±9.18	47.12±12.21	48.84±12.22
Creatinine (μmol/L)	114.5(93-164)	122.0 (97-157)	115.0 (98-150)	133 (125.5-189)
eGFR (ml/min/1,73m^2)	64.6 (44.7-86.3)	59.8 (49.1-86.3)	76.5 (55.7-106.7)	62,8 (53.15-76,4)
Parathyreoid hormone (pg/ml)	117 (78.2-227)	132 (107-228)	127.5 (98-216)	113.5 (70.5-239)
Proteinuria (g/l)	0.125 (0.05-0.34)	0.13 (0.05-0.22)	0.15 (0.07-0.36)	0.45 (0.35-0.85)
Time after Tx (years)	5.3 (2.7-9.96)	4.75 (2.7-6.25)	5.5 (3.8-6.65)	5.92 (4.23-10.16)
Tx Live related (No.)	59 (55.7%)	18	37	4
Tx Live unrelated (No.)	27 (25.5%)	8	18	1
Tx deceased donor (No.)	20 (18.9%)	5	12	3
Tacrolimus QD (No.)	67 (63.2%)	8	41	18
Tacrolimus BID (No.)	30 (28.3%)	16	11	3
Cyclosporin A (No.)	9 (8.5%)	5	4	
Mycophenolate mofetil (No.)	17 (16.04%)	10	5	2
Mycophenolate sodium (No.)	86 (81.1%)	9	67	10
Glucocorticoids (No.)	49 (46.2%)	21	20	8
Sirolimus (No.)	1 (0.9%)	1	0	
Everolimus (No.)	2 (1.9%)		2	
Vitamin D(ng/ml)	19.45±8,5	12.15±4.5	19.35±10.5	30.5±9.5
Supplement vit.D (Yes/ No)	47 (44.3%)	24	13	10

The mean value of vitamin D in patients after kidney transplantation was 19.45+8.5 ng/ml. Out of the total number of patients, 32.3% were in the vitamin D deficiency group, 60% belonged to the group with the insufficiency of vitamin D, and 7.7% of patients had sufficient values of vitamin D (Figure 1).

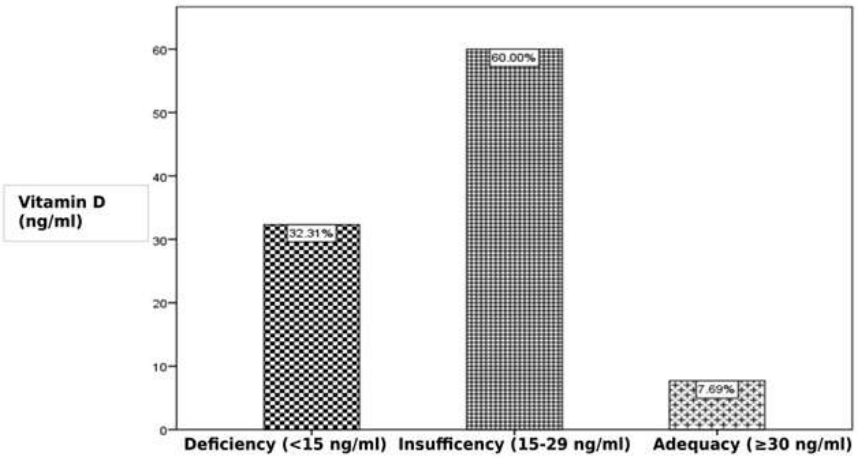

Fig. 1. Distribution of Vitamin D in kidney transplant patients

Of the total number of patients, 47 patients used therapy with vitamin D substituents. No significant statistical differences between the values of vitamin D were observed in the group of patients treated with supplement vitamin D in comparison to the group od patients without vitamin D substituent treatment [19,95 (14,78-25,53) vs. 15,55 (9,42-24,33)] ng/ml (Figure 2).

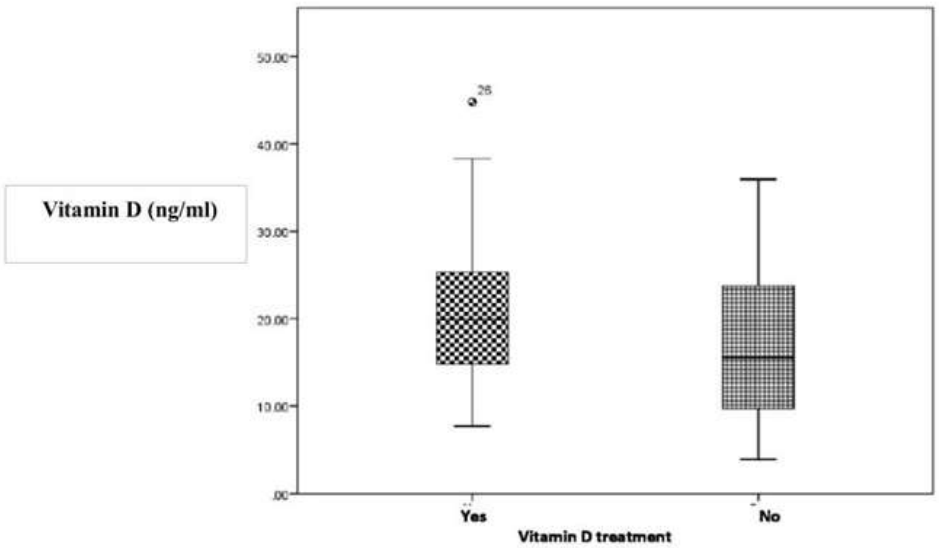

Fig. 2. The difference between the values of vitamin D depending on vitamin D treatment

Also, we tested whether the time elapsed from the transplantation was associated with vitamin D deficiency (Table 2). Vitamin D deficiency was not associated with the type of transplantation, history of previous kidney transplantations, or cause of the kidney failure. Interestingly, the deficiency was significantly associated with a shorter time from transplantation. Most of the kidney recipients at our clinic are treated with a combination of a corticosteroid, an antimetabolite, and a CNIs. We explored the effect of prescribed doses of these medications on the vitamin D levels (Table 2). Increased prednisone doses were associated with lower vitamin D levels, both by correlation to measured levels [P=0.04, correlation coefficient -0.201] and by the association to deficiency state categories [P=0.004]. Treatment with mycophenolate mofetil irrespective of dosing was significantly associated with vitamin D deficiency (P= 0.04). Interestingly, no correlation was found between the dosing of mycophenolate sodium and vitamin D levels. When considered irrespective of preparation (as sodium or mofetil), mycophenolate dose was signifycantly inversely correlated with vitamin D levels (P= 0.054, correlation coefficient -0.130), but was not associated with deficiency. Treatment with tacrolimus irrespective of dosing was also associated with vitamin D deficiency (P=0.02) (Table 2). Also, we found a significant association of higher vitamin D level with tacrolimus QD treatment in comparison to tacrolimus BID and cyclosporine treatment (P=0.015) (Figure 3).

Table 2. Transplantation characteristics, cholecalciferol and immunosuppression regimen in kidney transplant patients according to the status of vitamin D

	All patients (106)	Vitamin D Deficiency (%)	Vitamin D Insufficiency (%)	Vitamin D Adequacy (%)	P †*
Time elapsed from transplantation (yr)	5.3(2.7-9.96)	3.8 (3.1-5.4)	5.5(2.7-8,8)	7.1(3.3-9.9)	0.03
Prednisone daily dose (mg)	6.1 ± 5.8	8.0 ± 9.3	6.0 ± 4.8	4.6 ± 1.8	0.004
Treatment with prednisone (%)	89(98)	23(22.8)	54(53.5)	24(23.8)	NS
Treatment with mycophenolate mofetil (%)	17(16.04)	4(23.52)	13(17.47)	1(5.8)	0.042
Treatment with mycophenolate sodium(%)	86(81.1)	16(18.6)	63(73.3)	7(8.1)	NS
Treatment with tacrolimus (%)	92(86.8)	26(28.3)	61(66.3)	5(5.4)	0.022
Treatment with cyclosporine (%)	9(8.5)	2(22.2)	6(66.7)	1(11.1)	0.197
Treatment with everolimus (%)	3(2.83)	1	1	1	-
Treatment with sirolimus (%)	2(1.9)	-	2	-	-
Tacrolimus trough level (ng/ml)	5.53 ± 3.9	5.2 ± 2.2	5.7 ± 2.7	6.7 ± 3.0	NS
Cyclospoirne trough level(ng/ml)	66.3 ± 19	60 ± 16	69 ± 19	70 ± 21	NS
Everolimus trough level (ng/ml)	4.5 ± 1.4	-	5.4 ± 1.1	3.5 ± 0.8	NS
Sirolimus trough level (ng/ml)	12.4 ± 5.1	-	12.4 ± 5.1	-	-
Cholecalciferol (daily dose (IU))	407 ± 646	248 ± 443	454 ± 625	600 ± 865	0.056

Legend: †Two-sided P values for comparisons between the three categories of vitamin D sufficiency state; *P values < 0.05 were considered significant; NS not significant

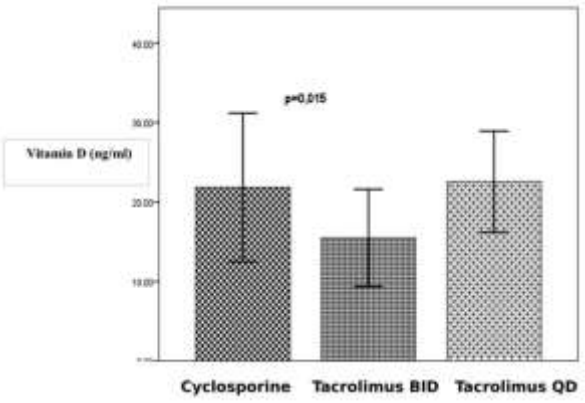

Fig. 3. Vitamin D values depending on the type of calcineurin inhibitor treatment

Due to the large number of possible factors influencing vitamin D status in KTRs, linear regression analysis was performed. The model was statistically significant and could explain between 52% (R2 Cox and Snell) and 77% (R2 Nagelkerkea) variance results and correctly classified 60% of cases (Table 3). Variables included in this statistical method were proteinuria, eGFR, time after kidney transplantation, kidney transplantation diseased or living donors, and treatment with CNIs, mycophenolates treatment, as well as oral and pulse steroid treatment. We evaluated which factors were independent predictors of vitamin D deficiency and insufficiency in KTRs during the monitoring period. Among all factors tested, several statistically significant predictors were identified, with a negative or positive influence on vitamin D values. Treatment with CNIs, mycophenolates treatment, and pulse steroid treatment were significantly associated with vitamin D insufficiency, while oral steroids intake was not. Furthermore, CNIs treatment and mycophenolates treatment were significantly associated with vitamin D deficiency, while oral steroid treatment and pulse steroid treatment were not. Other variables included in linear regression analysis: proteinuria, eGFR, the time elapsed after transplantation, and kidney transplantation diseased or living donors were significantly associated neither with vitamin D insufficiency, nor vitamin D deficiency. A logistic regression model for vitamin D deficiency as a dependent variable, taking as independent variables the va-

Table 3. Effect of immunosuppressive regimen on vitamin D levels in KTRs

Model	B	SE	p-value	Exp(B)	95% CI
Vitamin D insufficiency					
CNIs	-0.173	0.080	0.038	0.033	0.002-0.898
Oral steroids	0.019	0.076	0.642	0.877	0.795-0.967
Pulse steroids	-1.402	0.652	0.032	4.063	1.131-14.591
Mycophenolates	0.171	0.078	0.029	1.186	1.018-1.383
Vitamin D deficiency					
CNI	-0.434	0.204	0.033	1.544	1.035-2.304
Oral steroids	-0.096	0.066	0.264	0.658	0.485-0.893
Pulse steroids	-0.159	0.086	0.821	0.733	0.611-0.880
Mycophenolates	-3.137	1.546	0.042	0.043	0.002-0.898
Dependent variable: Vitamin D level					

Legend: SE- Standard error; CI- Confidence Interval; CNIs- calcineurin inhibitors

riables found associated independently with deficiency, revealed that the use of tacrolimus or mycophenolate were both associated with vitamin D deficiency, quasi-R^2 being 58%.

Discussion

This study was undertaken to explore the prevalence of vitamin D deficiency in KTRs in CCU of Sarajevo and to assess possible factors affecting the vitamin D status of these patients.

Adequate vitamin D levels were found in only 7.7% of the kidney recipients, 60% had insufficient levels and 32.3% showed a definite deficiency. This distribution is substantially better than demonstrated in most previous studies of kidney transplant patients [7,8].

Stavroulopoulos *et al*. [6] found 90% of hypovitaminosis D in renal transplant recipients in England, Unger *et al*. observed 77.4% rate of hypovitaminosis in healthy individuals [9], and Jean *et al*. [10] has reported it in approximatively 90% of CKD and dialysis patients.

In this study, the prevalence of hypovitaminosis D in renal transplant recipients was similar to those found in other geographic regions of the world [7]. The factors responsible for this high prevalence of hypovitaminosis D after the kidney transplant, even in high sun exposure areas, are unclear.

Although hypovitaminosis D was the aim of many studies, still there is not a consensus about the cholecalciferol dosage, especially in renal transplant recipienta. The Kidney Disease Outcome Quality Initiative gave recommendations concerning the treatment of vitamin D deficiency in both CKD and renal transplant recipients, suggesting treatment strategies applied to the general population [11].

Serum levels of vitamin D were directly correlated with vitamin D supplementation, though only weakly, and vitamin D deficiency was associated with lower vitamin D supplementation doses. Vitamin D supplementation at doses of 400 IU/day led to no significant change in vitamin D levels of kidney recipients, while supplementation doses in the order of 7000 IU/day produced a dramatic increase [12]. Supplementation doses in our study were low, which might account for the partially observed effect of supplementation. We found no association between vitamin D and kidney function or proteinuria, being in line with previous reports [13]. Our findings confirmed the data from previous studies that have shown low doses of vitamin D supplements did not improve vitamin D deficiency [14]. There were not more treated patients in the group with normal vitamin D levels, and there were no differences in vitamin D concentrations between treated and untreated patients.

Prevalence rates of vitamin D deficiency and insufficiency found in our study were similar to those of the general population [15]. This might be explained by the intensity of medical follow-up of the transplant patients, counteracting their multifactorial stronger predisposition toward hypovitaminosis D. Schreiber *et al.* [16] found the lack of difference in hypovitaminosis D between kidney and liver transplant patients, despite limitations of the comparison. Those results suggest that the type of organ transplanted is not of paramount importance to the risk of vitamin D deficiency. The lack of difference in vitamin D deficiency prevalence between KTRs with organs from different donors in our study implies that kidney function is not a major risk factor for deficiency in this population, concurring with our finding of no association between eGFR and vitamin D deficiency within the kidney transplant group (data not shown).

Vitamin D deficiency was associated with several aspects of the immunosuppressive treatment, partially contrasting with the results of previous studies of these agents in autoimmune diseases [17]. Higher prednisone doses were associated with lower vitamin D concentrations and a greater tendency towards deficiency. This might be explained by the stimulatory effect of glucocorticoids on vitamin D catabolism [14], or related to the reason necessitating the higher steroid dose. Tretment with mycophenolate sodium, irrespective of dose, was found to be associated with vitamin D insufficiency. Crucial for the study, in our institution the choice between mycophenolate preparations is arbitrary; hence, a confounding factor related to the choice of preparation seems less plausible.

The relationship between calcineurin inhibitors [CNIs] and vitamin D metabolism has been studied with conflicting reports. Grenet *et al.* [18] reported increased 1,25-(OH)2D levels, decreased calbindin-D28k, decreased vitamin D receptor and 24-hydroxylase expression in Wistar rats treated with cyclosporine A. Our results indicate that CNIs intake is associated with lower 25 (OH)D concentrations, while treatment with mTORI and their affection on vitamin D status after kidney transplantation could not be estimated because of the very small number of patients on that treatment. Eyal *et al*. [19] found a negative influence of tacrolimus and other immunosuppressive medications on 25(OH)D in KTRs. A possible explanation for these findings may be the fact that liver CYP3A4 has 25-hydroxylase activity which is suppressed by CNIs resulting in lower 25(OH)D [18].

Our study demonstrated that tacrolimus QD and cyclosporine treatment is superior to the tacrolimus BID treatment in maintaining better vitamin D levels in KTRs.

The fact that CNIs and mycophenolate intake, but not steroids dosage, showed a significant association with vitamin D deficiency, suggests that the association reported here might result from a factor associated with both vitamin D levels and the need for greater tacrolimus doses to reach goal concentrations, such as metabolism rates or intestinal lipid absorption [20]. Due to the results of our study, we have concluded that CNIs and

mycophenolate intake are an independent predictor of vitamin D deficiency in KTRs.

Our study is a cross-sectional retrospective one, which is its major disadvantage. However, most reports on vitamin D after kidney transplant share this limitation. Further prospectively designed research would be needed for more accurate assessment of the link between CNIs and vitamin D status.

Conclusion

Our study revealed high prevalence of hypovitaminosis D in kidney transplant recipients. The vitamin D status of the patients in our transplant center was influenced by a broad spectrum of factors. In addition to the well-known determinants of vitamin D, a significant influence of calcineurin inhibitor and mycophenolate treatment on vitamin D was observed. As calcineurin inhibitors are currently the backbone of immunosuppressive treatment after renal transplantation, further studies still need to investigate to explicitly clarify the possible link between immunosuppressive therapy and vitamin D in kidney transplant recipients.

Conflict of interest statement: None declared

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Original article

Tacrolimus Variability In Transplantation

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Abstract

Introduction. Current immunosuppressive drug treatment in renal transplantation includes tacrolimus (TAC). Individual variability of TAC blood level burdens the efforts of clinicians to achieve its optimal dose and to reduce the chance of either rejection or toxicity. The purpose of our study was to determine the intra-patient variability and metabolism type of tacrolimus.

Methods. Weekly tacrolimus trough levels were obtained in 40 stable kidney transplant recipients 6 months after transplantation, receiving TAC twice daily. As inclusion criteria, at least three consecutive TAC values were needed. Demographic (age, gender, body weight), laboratory (albumin, creatinine, TAC) and TAC prescription data was obtained from medical charts. Renal function was estimated by Cockroft-Gault Equation. TAC variability was quantified as the coefficient of variation (CV). TAC metabolism rate was estimated as TAC blood trough concentration (C) divided by the daily dose (D). Fast TAC metabolism was defined by C/D rate below 1.05 Predictors of intra-patient TAC variability were estimated with regression analysis on the demographic, laboratory data and renal function.

Results. The mean age of study participants was 43± 13.37 years, 29(72%) were men. TAC values ranged from 2.46-12.48, with mean value of 6.42±1.86 ng/ml. The median CV for the entire population was 22.49% (range 7.95%-48.12%). The regression analysis did not identify any demographic, laboratory characteristics, or graft function associated with CV. Twenty percentage of patients had CV > 30% and 12.5% were identified as fast metabolizers.

Conclusions. In our study tacrolimus did display a moderate intra-patient variability. High tacrolimus variability may identify a subset of patients who warrant increased surveillance and patient education regarding dietary and medication compliance.

Keywords: tacrolimus, intra-patient variability, fast metabolizers, predictors, transplantation

Introduction

Current immunosuppressive drug treatment in renal transplantation includes tacrolimus (TAC). Individual variability of TAC blood level burdens the efforts of clinicians to achieve its optimal dose and to reduce the chance of either rejection or toxicity [1,2]. The importance of trough level as a practical indicator is widely used from introducing the drug [3] and still being investigated [4,5]. After rapid absorption and peak achieved within the first 3 hrs following the dose TAC shows marked intra-and inter-patient variability in its absorption [6]. It depends on gastrointestinal transit time and may be affected by interaction with food, especially lipids [7]. The daily dosage requirements also depend on age, gender, body mass index, serum albumin, hematocrit, and liver disease [8,9]. The industry is still seeking for different and new formulations with better pharmacokinetic and tolerability profiles [10], even including genotype investigations [11,12]. The purpose of our study was to determine the intra-patient variability and metabolism type of tacrolimus in stable kidney transplant patients.

Material and methods

A retrospective analysis on a cohort of kidney transplant patients at our Department in the period between 2014 until 2018 was conducted. As inclusion criteria, at least three consecutive TAC values were required during the outpatient follow up. Weekly tacrolimus trough levels were obtained in 40 stable kidney transplant recipients 6 months after transplantation, receiving TAC twice daily. All patients were blood sampled in the morning at 9 o'clock, 12 hours after the last tacrolimus dose was taken. Demographic (age, gender, body weight), laboratory (albumin, creatinine, TAC) and TAC prescription data was obtained from medical charts. Renal function was estimated by Cockroft-Gault Equation calculation. TAC variability was quantified as the coefficient of variation (CV), when the standard deviation was divided with the mean and multiplied by 100. Patients with CV >30% were considered with high va-

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riability. TAC metabolism rate was estimated as the TAC blood trough concentration (C) divided by the daily dose (D). Fast TAC metabolism was defined by C/D rate below 1.05 Predictors of intra-patient TAC variability were estimated with regression analysis on the demographic, laboratory data and graft function.

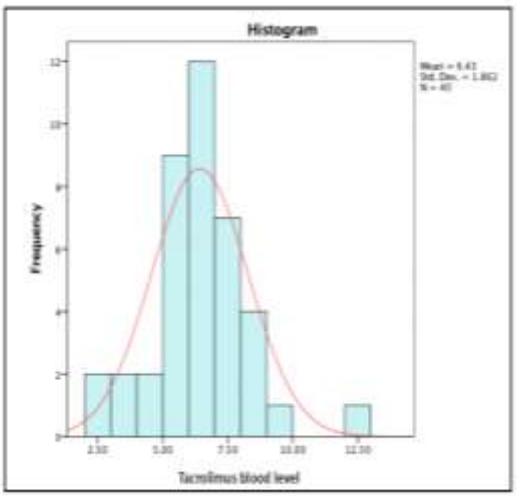
Results

Out of 40 transplanted patients, in 33 of them first living kidney transplantation was performed. The remaining 7 were transplanted from cadavers, and in one patient this was second transplantation. Clinical, demographic and laboratory parameters of study group are shown in Table 1. The mean age of study participants was 43±13.37 years, 29 (72%) were men. TAC values ranged from 2.46-12.48, with mean value of 6.42±1.86 ng/ml. The median CV for the entire population was 22.49% (range 7.95% - 48.12%). The mean daily dose of TAC ranged from 1-7.2 mg. Twenty percentage of patients had CV > 30% and 12.5% were identified as fast metabolizers.

Table 1. Clinical, demographic and laboratory parameters of the study cohort

N=40	Mean SD	min-max
Men (%)	29(72%)	
Age (years)	43.0± 13.37	19-75
Body weight (Kg)	69.47±12.88	35-96
Albumin (g/l)	41.82±3.39	32-49
Creatinine (mol/l)	148.45±80.42	61.67-431.51
eGFR (ml/min)	65.28±24.99	22-128
$C_{(Mean\ TAC\ in\ blood)}$ (ng/ml)	6.43±1.86	2.46-12.48
$D_{(Mean\ TAC\ daily\ dose\ )}$(mg)	2.96±1.31	1-7.2
$SD_{(Mean\ TAC\ in\ blood)}$	1.43±0.71	0.45-3.26
Mean CV_{TAC} (%)	22.41± 9.10	7.95-48.12
Mean C/D	2.69±1,57	0.34-8.90
CV > 30%	(20%)	
C/D <1.05	(30%)	

Out of 238 TAC measurements, 169 (71%) were within the target range of 5-10 ng/ml, 57(24%) were below and 12 (5%) were above it. The bell-shaped curves of both parameters for TAC blood level and CV showed the normal distribution (Figure 1 and 2). In only one patient the mean level of TAC was above 10 and in three it was below 5 ng/ml.The regression analysis did not identify any demographic, laboratory characteristics, or graft function associated with CV (Table 2). There was no significant correlation between CV and C/D ratio (r=0.073, p=0.654).



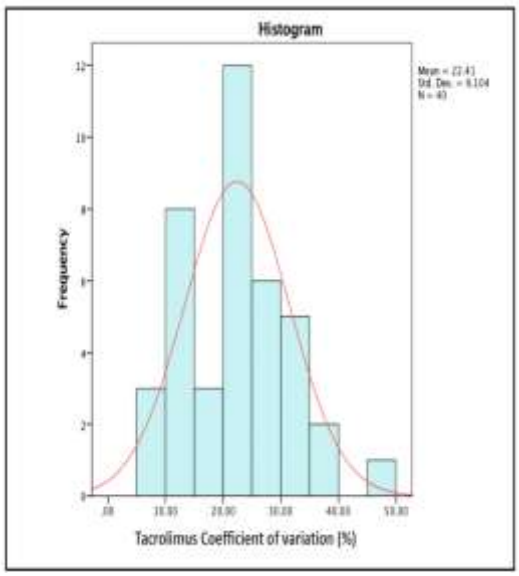


Fig. 1 and 2. Bell shape curves of Tacrolimus blood level and Coefficient of variation

Table 2. Regression analysis on tacrolimus variability

Factor		p
Gender	- 0.121	0.897
Age (years)	- 0.115	0.485
Body weight (Kg)	- 0.120	0.467
Albumin (g/l)	0.047	0.366
eGFR (ml/min)	0.115	0.487

Discussion

Our results on TAC blood though levels suggest appropriate drug management in the vast majority of patients. Even though, 20% of patients had tacrolimus variability over 30%, the value that was found in other study was as significant predictor of worsened graft survival [2]. Also the standard deviation of tacrolimus level in our patients was rather low, when compared to other studies where the values above were found as significant predictor of worse graft outcomes. In the Sapir-Pichhadzes study, among 356 patients, there was a significant 27% increase in the adjusted hazard of the composite end point for every 1-unit increase in TAC

$_{SD}$ [1]. Considering suboptimal dosing of tacrolimus as risk for graft loss [13], we found 24% of all 238 tacrolimus measurements to be under 5mg/ml. No significant factor of tacrolimus variability emerged from the regression analysis. As a limitation of our study, we did not have any data on food patterns or gene expressions, which are currently being explored [7,11]. Also, the number of patients was only forty, with potential influence on statistical significance considering gender. Partly, the variability could be explained by fast metabolism, and 30% of our patients were identified in this group. In this retrospective analysis based on patients' charts, we did not found prescribed medications that could interact with tacrolimus, apart from diltiazem in few of them. The medication compliance is also potent factor on tacrolimus variability that we did not take into consideration [14]. Since no other influencing factor on variability of tacrolimus levels we found modifiable, we considered exploring it and providing education for patients at risk for the graft lost.

Conclusion

In our study tacrolimus did display a moderate intra-patient variability. High tacrolimus variability may identify a subset of patients who warrant increased surveillance and patient education regarding dietary and medication compliance.

Conflict of interest statement. None declared.

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Letter to the editor

Acute Renal Allograft Rejection after Ingestion of Royal Jelly

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Dear Editor,

Royal jelly (RJ) is a secretion produced by the hypopharyngeal and mandible glands of worker honey bees. It has numerous compounds with diverse biological activity, including proteins, fatty acids, free amino acids, sugars, minerals and vitamins [1]. Beneficial effect has been observed on numerous conditions while RG was found to have antitumor, anti-inflammatory and antioxidant properties, decreases blood pressure and serum cholesterol. Additionally, an immunomodulatory effects have been demonstrated [2,3]. Herein, we describe a case of renal transplant recipient who developed acute humoral rejection after ingestion of RJ.

A 36-year-old female with lupus nephritis, who received a renal allograft from a deceased donor in February 2007 after two years of peritoneal dialysis, was admitted to hospital for evaluation of sudden increase in serum creatinine from the baseline 140 µmol/l to 370 µmol/l. She had an episode of acute cellular rejection in 2011 (Banff 1A) without signs of humoral rejection. She did not tolerate mycophenolate because of the diarrhea, so her immunosuppressive protocol included tacrolimus, azathioprine and steroids. Basiliximab was used for induction. On admission she was afebrile, with normal blood pressure, in good overall condition. Graft was not sensitive to palpation but was enlarged and tender. Patient reported that she used royal jelly for a month "for improvement of the immunological status", and it should be emphasized that she worked as a pharmacist. Biopsy revealed acute cellular rejection Ib with C4d positive in 75% of peritubular capillaries and positive donor specific antibodies, DQ2 (MFI 19800). Immunological results revealed that lupus was not active. She received steroid pulses (2 g of metilprednisolone in 5 doses) and 7 plasma exchanges. Her serum creatinine fell to 230 µmol/l and remained stable after 6 months of follow up.

Renal transplantation requires finely tuned balance between over- and under-immunosuppression to achieve optimal result. Use of different immunosuppressive drugs is a major tool in these efforts. However, availability of different over-the-counter drugs and remedies provides a permanent challenge. Our patient, a pharmacist by profession, used RJ for one month when she experienced significant increase in serum creatinine and developed biopsy proven acute humoral rejection. Royal jelly is efficient for numerous pathological conditions. Its bioactive properties include antibacterial, antiviral, wound-healing, antioxidant, anti-inflammatory, nephroprotective, and also immunomodulatory activities. In animal models of systemic lupus erythematosus, RJ induced decrease in the serum level of IL-10 and in different autoantibodies as well as a reduction in the number of splenic autoreactive B cells [4]. Royal jelly had inhibitory effects on the release of the nitric oxide and interleukin-10, and production of the TNF-α [5]. After RJ therapy the percentages of $CD4^+$ regulatory T cells and $CD8^+$ regulatory T cells were significantly increased, while apoptotic CD4 T lymphocytes were significantly decreased when compared with the baseline values [6]. In the rat model, it was also found to modulate the immune responses by affecting their dendritic cells through modification of the fatty acid content [7]. A hydroxyl-2-decenoic acid which was found in RJ has recently been found to promote the growth of T lymphocyte subsets and IL-2 production [1]. In clinical studies, RJ was found to have an immunomodulatory role in autoimmune thyreoiditis [8] and in systemic lupus erythematosus [9].

In conclusion, the knowledge about the immunological effects of RJ is scarce. However, it is clear that profound changes in immunological system may be associated with its use. To the best of our knowledge, this is the first reported case of acute renal allograft rejection after the use of RJ. Thus, royal jelly should be avoided in renal transplant recipients. Our case clearly emphasizes a need for permanent patient education and need for maintenance of compliance even in the most educated patients.

Conflict of interest statement. None declared.

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The 6th Congress Of The Macedonian Society Of Nephrology, Dialysis, Transplantation And Artificial Organs (MSNDTAO)

Abstract Book

26 - 29 September, 2019, Skopje, N. Macedonia

Invited lectures

IL-01 What do we know about renal functional reserve in adult living kidney donors?

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Introduction. Living kidney donors are an important source of kidneys given the shortage of organs required for transplantation. Good short-term outcomes in living kidney donation has led to more recent acceptance of "borderline" donors (with hypertension, obesity, older age), although recent studies have pointed to increased long term risk in some donor subgroups. The long-term impact of donation on hemodynamics and function of the remaining kidney is less well understood. The capacity of a kidney to increase its glomerular filtration rate (GFR) in response to a higher functional requirement is known as the renal functional reserve (RFR). The change and relevance of RFR after donation in living donors is insufficiently clarified.

Methods. A systematic literature review was performed of studies that assessed RFR in donors pre- and/or post-donation. Web of science, PubMed and EBSCO were searched using the following terms: kidney function, glomerular filtration rate, renal functional reserve capacity, renal blood flow and kidney donor.

Results. 3250 studies published between 1956 and 2019 were identified. Sixteen studies met final inclusion criteria. RFR measurements are not standardized. A trend towards loss of some RFR was observed after donation, although RFR in young donors with no risk factors is largely preserved. Donors with hypertension, obesity or older age had a lower RFR after kidney donation.

Conclusion. RFR testing is rarely done in clinical evaluation of potential living kidney donors. Given the increasing acceptance of borderline donors, better understanding of the relevance of RFR may complement donor assessment and inform long-term risk estimation.

IL-02 UP-TO-date in diagnosis and treatment of membranous glomerulonephritis

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Membranous glomerulonephritis (MGN) is the most common cause of non-diabetic nephrotic syndrome in adults. It may be associated with a secondary cause in 25-30% of the cases. Although the majority of patients present with signs and symptoms of nephrotic syndrome, microscopic hematuria and hypertension and, asymptomatic proteinuria may be seen at presentation. Urinary sediment generally appears benign.

The definitive diagnosis is made by renal biopsy. The main histopathological findings are thickening of the glomerular basement membrane on light microscopy, which should be distinguished from that seen in diabetic nephropathy and renal amyloidosis. The deposition of IgG and C3 across the entire basement membrane on immunofluorescence staining and subepithelial electron-dense immune deposition on electron microscopy are other histopathological features. It is not possible to distinguish between primary and secondary MGN by histopathology.

In the clinical course of MGN spontaneous remission occurs in approximately one-third of patients with nephrotic syndrome. Some clinical, laboratory and histopathological findings are considered as indicators of poor prognosis. Thrombotic complications are most commonly reported in MGN among glomerulonephritis. Therefore, prophylactic anticoagulation is frequently recommended in nephrotic MGN patients.

Recently, 50-80% of idiopathic MGNs were found to have antibodies against M-type phospholipase A2 receptor (PLA2R) in the serum, and in later publications, it was found that this antibody might be present in secondary MGN. This antibody is not detected in any disease other than MGN; hence it is very specific to MGN. Moreover, PLA2R antibody can be found on biopsy tissue at a higher rate (85%). For these reasons, there is strong evidence that MGN can be diagnosed in the presence of PLA2R antibody in patients who cannot undergo renal biopsy (e.g. due to use of anticoagulants, solitary kidney, etc.).

Conservative treatment is recommended to all patients in MGN treatment. The patients can be followed clinically with conservative treatment as there is the possibility of spontaneous remission for 3-6 months. Immunosuppressive therapy should be commenced in patients whose proteinuria do not regress at the end of this period, or earlier in patients who develop complications of nephrotic syndrome or patients who develop rapid renal dysfunction.

The main immunosuppressive therapies used as initial therapy in MGN treatment are; cyclic corticosteroid-alkylating agent (Cyclophosphamide or Chlorambucil), calcineurin inhibitor (cyclosporin-A or Tacrolimus) or Rituximab treatments. Patients can be switched from one treatment to another in case of contraindication, non-response or relapse. GFR and proteinuria are used

in the follow-up. Changes in serum anti-PLA2R levels may also be used in PLA2R positive patients.
In addition to diagnostic utility, anti-PLA2R can also be used as a predictor of response or relapse. Recent studies have highlighted the role of Rituximab in treatment of MGN.

IL-03 Challenges in diagnosis and management of aa amyloidosis

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Amyloidosis constitutes a group of disorders that are characterized by extracellular deposition of amyloid fibrils which are composed of misfolded protein precursors. Amyloidosis is classified according to the protein precursors that form amyloid fibrils. Diagnosis and typing depends on histopathological evaluation. New methods like electron microscopy, mass spectrometry are identified for typing. One of the most common forms of systemic amyloidosis is AA amyloidosis in which amyloid fibrils are derived from serum amyloid A (SAA) protein. AA amyloidosis is a complication of chronic inflammatory diseases. Inflammatory arthritides are the most common underlying diseases, however in some countries, Familial Mediterranean Fever is the most common cause. Renal involvement is a major cause of morbidity and mortality. Identification of genetic factors that regulate susceptibility to deposition of SAA is important for detection of high risk patients. Surrogate biomarkers predicting effectiveness of treatment have been investigated. Management primarily depends on reduction of serum amyloid A production by treating underlying inflammatory condition. Biologic agents may reduce the risk of development of AA amyloidosis as well as treating existing amyloidosis. Drugs that inhibit AA fibrillogenesis and destabilize AA fibrils have recently been employed. It was shown that eprodisate reduced the progression of renal disease by inhibiting polymerization and deposition of fibrils. A novel bis (proline) compound (CPHPC) binds to serum amyloid P component of amyloid fibrils, resulting in rapid clearance.
Significant improvements have been made in understanding pathogenesis, diagnosis and clinical treatment of chronic inflammatory diseases. But AA amyloidosis is still a significant complication that is difficult to prevent and treat. Identification of patients with poor prognosis and detection of effectiveness of treatment modalities by the help of biomarkers are important challenges in prevention and treatment of systemic AA amyloidosis. In recent years, new drugs that control inflammation improved the management of chronic inflammatory conditions and also systemic AA amyloidosis. Novel treatment modalities that inhibit new fibril formation and target deposited fibrils are expected to be further treatment options for patients with AA amyloidosis.

IL-04 Factors influencing the progression in autosomal dominant polycystic kidney disease

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Autosomal-dominant polycystic kidney disease is the most common hereditary kidney disease and it is the fourth leading cause for end stage renal disease in adults. PKD1 and PKD2 are expressed in most organs and tissues of the human body. The proteins that are encoded by PKD1 and PKD2, polycystin1 and polycystin2, seem to function together to regulate the morphologic configuration of epithelial cells. Many factors contribute for progression of the disease. In order to evaluate the factors influencing the progression in adult polycystic kidney disease, we have analyzed the results of several clinical studies of other Nephrology departments, comparing with the results in our department. It is well known that renal cysts contribute to morbidity and can impair the quality of life early in the course of the disease. The size of the cysts formations and the number of the cysts, influence the progression of the disease, but in our study there is not statistical significance for the progression of the renal failure. Younger age at diagnosis and male gender are important in the course of the disease, with earlier progression to renal failure. Arterial hypertension is the most important factor for progression of the kidney diseases which is conformed in our results, especially together with proteinuria in these patients. Urinary tract infections, also infections of the cysts, are important for the progression of the disease. In conclusion we can say that among the other factors influencing the progression, most important are the PKDI gene, gender, age of the patients, hypertension, gross hematuria, urinary tract infections and renal size expressed as renal volume.

Free Communication

FC-01 Urinary fetuin-a peptides correlate with glomerular filtration rate

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Introduction. The hepatokine fetuin-A, which is released by fatty liver, promotes the proinflammatory effects of perivascular fat. The involvement of inflammation in type-2 diabetes can affect the kidney and cause diabetic nephropathy. Therefore, we examined the association of urinary fetuin-A protein fragments with renal damage in diabetes type-2 patients.

Methods. The urinary proteome of 1494 diabetes type-2 patients was analysed by capillary-electrophoresis coupled to mass-spectrometry, to investigate the correlation of fetuin-A peptides with the estimated glomerular filtration rate (eGFR) to assess the severity of kidney damage. The correlation coefficient was estimated with non-parametric Spearman's rank correlation analysis.

Results. We identified 11 different protein fragments, which belong to 2 different motifs of the total fetuin-A protein [motif A: amino acid (AA) 302-319; motif B: AA 322-340]. The corresponding peptides of each motif were combined (sum of amplitudes) and correlated to eGFR. Both fetuin-A motifs displayed significant correlations with eGFR (A: rho=-0.207, p=0.0037; B: rho=-0.243, p<0.0001). To investigate that urinary fetuin-A does not reflect proteinuria, we also used multiple regression analysis with adjustment for urinary albumin. This regression, as well as the adjustment for age and gender resulted in significant correlation of the fetuin-A peptides with eGFR.

Conclusion. The urinary proteome analysis demonstrated the association of fetuin-A peptides with kidney damage in diabetes type-2 patients. Therefore, fetuin-A peptides could be markers for early inflammatory processes in the kidney as a result of diabetes type-2 and therefore a possible new marker for kidney dysfunction.

FC-02 Comorbidity and age as prognostic factors for the short and long-term outcome in elderly with acute kidney injury

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Introduction. Acute kidney injury (AKI) is a complex syndrome characterized by abnormal loss of renal function that leads to the increase of nitrogen compounds, dysregulation of extracellular volume and electrolyte homeostasis. The structural and functional changes that occur during the aging process, also and coexisting diseases, are disposing factors that increase the risk of AKI in elderly population.

Methods. We prospectively studied 101 patients with an AKI age of 65 years. Patients were divided into 2 groups by age, group <75 and group> 75 years old. In terms of outcome they were divided in group with short and 90-day survival. The burden of the simultaneous presence of comorbid conditions was estimated through the Charles Comorbid Index. (CHI)

Results. The intra-hospital mortality rate in adult patients with AKI was 22.8%. The mortality rate for the 90-day follow-up period after the AKI event was 45.5%. Age was not confirmed as a risk factor for intra-hospital and 3-month outcome in patients with AKI in our study. The presence of comorbid conditions estimated through the Charles Comorbid Index (CHI), differed insignificantly between surviving and deceased patients with AKI (p=0.39, p=0.28 consecutive). But Cox regression analysis confirmed the CCI score as a significant factor in survival in patients with ABO (p=0.036). The risk of fatal outcome increases by 16.3% with each increase in this unit score. Cox regression analysis confirmed heart diseases as a significant prognostic factor for survival, increasing the risk of fatal outcome by about 2 times higher than patients without heart disease. Statistical analysis showed a significant difference in survival time, depending on the presence of heart disease as a comorbidity (p=0.037). Cox regression analysis also showed that HR for heart disease, as a comorbidity is 1.837 (95% CI: 1.020-3.306) and p=0.043. The death rate for patients with heart disease is about 2 times higher than patients without heart disease. Cumulative survival was higher in the group of patients without cardiomyopathy-64.2% (0.07) compared to the group of patients with cardiomyopathy-43.8% (0.07).

Conclusion. CCI score is significant independent high-risk prognostic factors for poor outcome in elderly patients with AKI. AKI survivors with high burden of comorbidities are at high risk for post-discharge death. Cardiomyopathy, as a risk factor, for two times increases the risk of death. Recommendation for individual clinical approach, assessment and selection for treatment application still remains, taking into account the overall condition in adult patients with acute renal injury.

FC-03 Connection between biomarkers of inflammation and oxidative stress and cardiovascular diseases in patients with chronic kidney disease

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Introduction. An increasing number of biomarkers are being tested for evaluation of cardiovascular (CV) risk in patients with chronic kidney disease (CKD).
The aim of this study was to investigate the association between biomarkers of inflammation (Interleukin 18-IL-18; Ischemia modified albumin-IMA) and oxidative stress (Superoxide dismutase-SOD) with newly occurred cardiovascular events (CVE) in patients with CKD stages 3-5HD.
Methods. Our prospective study included 87 patients, who were grouped into four groups: CKD stage 3a, 3b, 4 and 5HD. During 18 months of follow-up, the following events were reported: myocardial infarction, worsening of the existing and newly occurred angina pectoris, cerebrovascular insult, peripheral arterial disease and cardiac death. The values of SOD, IMA and IL-18 were measured in the patients' serum.
Results. The highest number of CVE were registered in group of dialysis patients (45.9%). In patients with registered CVE, significantly lower values of hemoglobin (p=0.005) and albumin (p=0.011), as well as higher values of troponin (p=0.018) were observed compering with patients without CVE. For each unit of the increase in albumin, the likelihood of CVE declines by 15.2%. Connection of the tested biomarkers with newly occurred CVE was not observed.
Conclusion. The association of examined biomarkers with the occurrence of CVE events in CKD patients has not been established, but this should be confirmed on a larger number of patients and during a longer follow-up period.

FC-04 The role of vitamin D supplementation on iFGF-23 and PTH in hemodialysis patients-interactions between vitamin D, iFGF23 and PTH

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Introduction. Fibroblast growth factor-23 (FGF-23) is a major regulator of calcium and phosphate homeostasis. Together with calcitriol and parathyroid hormone (PTH), it is part of a complex multi-tissue feedback system. Both 1, 25 $(OH)_2 D_3$ and PTH induce skeletal FGF-23 production. This interaction becomes more complicated in hemodialysis patients.
Aim. We studied the effects of vitamin D supplementation on serum iFGF-23 and PTH in dialysis patients.
Methods. This was an interventional clinical trial on 51 ESRD patients (36 males, mean age 60.9±15.2 years) who received HD for a mean period of 48.08±40.7 months. 1,25 $(OH)_2 D_3$ serum levels were recorded for all patients before and after a six-month period of alfacalcidol supplementation. Monthly data, including intact PTH, were collected. The levels of intact-FGF-23 were measured before and after vitamin D administration with Diasorrin Liaison assay. Patients with acute inflammation, malignancies, hemorrhage diathesis and uncontrolled hyperparathyroidism were excluded. The management of serum calcium and phosphate, became accordingly with the official guidelines. The patients didn't receive any calcimimetic drugs.
Results. Mean baseline 1,25 $(OH)_2D_3$ serum levels was 12.5±5.2 ng/ml and increased to 20.32±27.8 ng/ml ($p<0.01$) after alfacalcidol supplementation. The levels of PTH were reduced significantly (353.9±236 to 262.6±169pg/ml, p=0.03). iFGF23 levels increased significantly after six months vitamin D administration from: 1840,8±1981,6 to 4684,8±3123,7pg/ml, p<0,0001. Regardless of vitamin D administration, iFGF-23 had a negative correlation with PTH (r1=-0,10 and r2=-0,069) and 1,25$(OH)_2 D_3$ (r1=-0,043 and r2=-0,10) before and after vitamin D supplementation, but not significantly.
Conclusion. Vitamin D supplementation in ESRD dialysis patients, induced significant increased levels of intact FGF-23 and decreased levels of PTH. iFGF-23 has been shown to have a negative correlation with PTH and 1,25$(OH)_2 D_3$.

FC-05 Renal biopsy in the elderly: data from 15 years of experience

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Introduction. The incidence of renal disease increases with age. However, data on histological evidence of renal injury in elderly patients are limited.
Aim: To examine renal biopsy indications and histological diagnoses in elderly patients over 70 years of age.
Methods. This is a retrospective study of native kidney biopsies performed between 2000 and 2015 in patients over 70 years old. Patient demographics, co-morbidity factors, clinical indications and histological diagnosis of biopsies were recorded.
Results. From 2000 to 2015, 1137 natural kidney biopsies were performed in our center. Of these, 98 biop-

sies (8.62%) corresponded to 96 patients with an average age of 76 years. Fifty-seven were men and 39 women. A history of arterial hypertension was recorded in 65 patients (67.70%) and diabetes mellitus in 16 (16.67%). The main indications were acute kidney injury (AKI) (56.12%), isolated proteinuria (17.34%), nephrotic syndrome (6.122%), AKI and nephrotic syndrome (4.08%). At the time of the biopsy, the median serum creatinine was 2.5 mg/dl (IR1.3-5.1) and the median proteinuria value was 2.7g/24h (IR1.5-6.525). Pauci-immune vasculitis was the most common histological diagnosis (18.36%), followed by membranous glomerulopathy (17.34%) and focal segmental glomerulosclerosis (10.20%). The number of glomeruli was insufficient in three biopsies, two of which were repeated. Macroscopic hematuria after the biopsy was recorded in 4 patients (4.16%).

Conclusion. Older age should not be considered as a contraindication for renal biopsy upon indications. It is a valuable diagnostic and prognostic tool that can guide treatment decision for patients over 70 years of age.

FC-06 A report of 12 cases with fibrillary glomerulonephritis from a single center

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Introduction. Fibrillary glomerulonephritis (FGN) is a rare glomerular disease found in less than 1% of native kidney biopsies. FGN is characterized by glomerular presence of randomly arranged fibrils measuring 12 to 25 nm by electron microscopy. FGN is usually idiopathic (primary), however, it has been associated with underlying infective, malignant or systemic autoimmune disease in some patients as well. Therapeutic strategies in primary FGN, particularly the use of immunosuppressive drugs, are not clearly defined. We aimed to investigate clinical characteristics and outcomes of patients diagnosed with FGN in our center.

Methods. We identified patients with FGN by retrospective review of all renal biopsies in the Department of Pathology, University Hospital Dubrava, from 2009 until 2018. Clinical and histologic features of patients and kidney disease outcomes were analyzed. For the purpose of outcome analysis, following definitions were used: complete remission (CR) was defined as reduction of proteinuria to <0.5 g/d with normal kidney function, partial remission (PR) was defined as reduction in proteinuria by >50% and to <2 g/d with stable kidney function (no more than a 20% increase in serum creatinine), end-stage renal disease (ESRD) was defined as decrease in eGFR (based on MDRD formula) under 15 ml/min/1.73m² or beginning of renal replacement therapy and persistent renal dysfunction (PRD) was defined as failure to meet criteria for CR and PR but not reaching ESRD.

Results. There were 12 patients with FGN, whose mean age at biopsy was 60.6 years and 10 of them were females. Presentation at the time of biopsy included proteinuria (in 10 patients), hematuria (9), reduced eGFR <60 ml/min/1.73m² (8), hypertension (10), pretibial oedema (4) and anemia (4). Primary FGN was found in 7 patients, 2 had autoimmune diseases (SLE and primary antiphospholipid syndrome) and 3 had monoclonal gamapathy of renal significance. Four patients were treated with renin-angiotensin-aldosterone system (RAAS) blockade alone, six (including 2 with autoimmune diseases) with combination of steroids and RAAS blockade and one patient was treated only with supportive therapy without progression of disease. In patients treated with combination of RAAS blockade and steroids, cyclophosphamide was added in three, cyclosporine in one and rituximab in two cases with favorable effect. One patient with secondary FGN was lost to follow-up. Of the remaining patients with primary FGN two reached ESRD, two entered sustained remission (one had CR and one had PR) and three patients had PRD. Of the patients with secondary FGN one entered CR and three had PRD.

Conclusion. According to clinical presentation and outcomes, FGN is a very heterogeneous glomerular disease. The therapeutic approach in FGN remains challenging. The use of immunosuppressive therapy needs to be assessed in larger prospective studies.

FC-07 Frailty and depression in hemodialysis patients

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Introduction. Frailty is a state of increased vulnerability to physical stressors, such as illness or trauma. Depression is the most widely prevalent psychological complication of hemodialysis (HD) patients. Depression and frailty symptoms partly overlap and both contribute to lower quality of life (QoL) of these patients.

The aim of the study was to evaluate the prevalence and relation between frailty and depression among our patients and its association with socio-demographical data.

Methods. We studied 281 patients, on HD more than 3 months. For examination of frailty, we applied The Fried Phenotype model of frailty tool that defines the frailty phenotype as meeting three or more of the five criteria: weight loss, exhaustion, weakness, slow walking speed and decreased physical activity. We classify patients as non-frail, pre-frail and frail. Depression symptoms were screened by Beck Depression Inventory (BDI).

Results. 44.8 % of participants were categorized as frail and 20.6% as pre-frail. 42.2% of our patients suffer

from some degree of depression, the most of them from mild depression. 88.9% of our depressed patients were frail. The correlation between depression and frailty was highly significant ($p<0.05$). Even correlations between BDI items and frailty were highly significant ($p<0.05$), except between BDI-9-suicidal thoughts and desire and frailty ($p>0.05$), that is related to religious beliefs of patients, where the suicidal thoughts are considered to be the greatest sin. As expected, the prevalence of frailty significantly increased with age and HD duration ($p<0.05$). Older adults are usually at higher risk for depression and dementia. Less educated and unemployed patients have shown significantly higher level of frailty in relation to highly educated and employed patients ($p<001$), who had better QoL in general.

Conclusion. Frailty and depression are obviously overlapping syndromes, both highly prevalent in our HD patients, particularly the older ones. A better understanding of these syndromes could result in a better efficiency of treating HD patients.

FC-08 Evaluation of hydration and nutritional status in patients receiving maintenance hemodialysis

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Introduction. Fluid overload and malnutrition are risk factors of morbidity and mortality in dialysis patients.

Aim: To compare the hydration and nutritional status of young and elderly patients under hemodialysis (HD) using bioimpedance (BIA) and anthropometric parameters.

Methods. This is an observational study involving clinically stable patients undergoing HD for more than three months. Clinical and laboratory data (hemoglobin, albumin, ferritin, C-reactive protein-CRP) were evaluated, anthropometric data (body mass index-BMI, arm circumference-MAC, mid-upper arm circumference-MUAC, triceps skin-fold-TSF, and hand grip strength-HGS) and the frailty status of patients using the Clinical Frailty Score. Three BIA readings were performed over a 9-week period and the degree of fluid overload (FO), intracellular and extracellular water (ICW and ECW respectively), total body water (TBW) and ECW/TBW ratio were recorded. BIA measurements were performed before the dialysis session in the middle of the week. Patients were divided into 2 groups according to their age: younger patients <65 years (n: 19) and elderly ≥65 (n: 15).

Results. The median time on HD in younger and elderly patients was 3.5 [IQR: 0.7-10.3] and 4 [IQR: 1.6-8] years, respectively. The mean systolic and diastolic blood pressure before the session was 117±21/73±16mmHg in the younger group and 122±29/67±13mmHg in the elderly. Hemoglobin, albumin and ferritin values did not differ significantly between the two patient groups. Elderly patients had a higher median CRP (6.7 [IQR: 3.1-11.2] vs. 4.9 [IQR: 3-11.1], p: NS). The mean HGS was lower in elderly patients than in the younger ones (13.7±10.3 versus 18.4±11.2 kg, p: NS). There was no difference between the two groups with respect to other anthropometric parameters. In the group of elderly and young patients, severely impaired were 33.3% (n: 5) and 10.5% (n: 2) of the patients respectively. The degree of FO did not differ significantly between the two groups. The median ECW/TBW in younger patients was 0.46 (0.44-0.49) versus 0.49 (0.46-0.50) in the elderly. The median FO deviation from patients' dry weight was -1.2 (-2.9/-1) versus -1.6 (-2.9/0.7).

Conclusion. There was no difference in the degree of fluid overload and nutrition between older and younger HD patients. The evaluation of body fluid status using bioimpedance seems to be a useful method complementary of the clinical assessment in dry weight determination.

FC-09 Impact of renal replacement theraphy on renal outcome in critically ill patients in the icu setting

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Aim. To study the impact of the two methods of renal replacement therapy (RRT), continuous and intermittent, on the renal outcome of acute renal failure (AKI).

Methods. This is a single-center retrospective, observational study of critically ill patients admitted in the ICU who developed AKI and were treated with RRT. APACHE II score, urine output, creatinine levels, potassium levels, presence of multiorgan failure and shock, severity of AKI, type of RRT and renal outcome were recorded (Table 1).

From January 1st until December 31st 2016, 263 patients were admitted to the ICU. Thirty- three patients (13%), 9 female and 24 male, with a mean age of 69±12 years, developed AKI and were treated with RRT.

Results. Patients were divided into three groups: 11 out of 33 patients (33%) were treated with intermittent dialysis (ID), 15 (45%) with continuous methods and 7 patients (22%) received both intermittent and continuous RRT. The mean APACHE II score at the time of admission to the ICU was 32±5. APACHE II score and potassium levels were similar between the groups. At the time of RRT initiation more patients in groups 2 and 3 were hemodynamically unstable, while the distribution of critically ill patients with multiorgan failure was similar between all three groups. According to the severity of AKI, failure was present in 4 out of 11 patients

in group 1(36%) versus 10 out of 15(66%) and 3 out of 7(42%) in groups 2 and 3 respectively. Renal recovery occurred in 9 out of 11 patients (82%) from group 1, in 2 out of 15 in group 2(13%) and 2 out of 7(22%) in group 3 (Table 2).

Conclusion. In the ICU setting ID is associated with higher rates of renal recovery, possibly verifying the better hemodynamic status of patients selected for this method.

Table 1. Patients characteristics on admission

On Admission	**Group 1-ID**	**Group 2-CVVHDF**	**Group 3-ID + CVVHDF**
Number of Patients	11	15	7
APACHE II score	33±5	32±5	29±5
Creatinine (mg/dl)	4±2	1.7±0.97	2.6±1.2
Shock	4/11	14/15	5/7
Multiorgan failure	10/11	13/15	4/7

Table 2. Patients characteristics at initiation of treatment *(Risk: R, Injury: I, Failure: F)*

Treatment Initiation	**Group 1-ID**	**Group 2-CVVHDF**	**Group 3-ID + CVVHDF**
Shock	4/11	15/15	6/7
Creatinine (mg/dl)	5.9±2	2.5±1.1	4.7±2.2
Potassium (mmol/L)	4.6±0.9	5.3±0.8	4.5±0.8
AKI - Risk	1/11	1/15	1/7
AKI - Injury	6/11	4/15	3/7
AKI - Failure	4/11	10/15	3/7
Renal recovery	9/11	2/15	2/7

FC 10 One year experience with etelcalcetide in hemodialysis patients

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Introduction. Secondary hyperparathyroidism (SHPT) is one of the most common complications in patients with chronic kidney disease. Prevention and treatment of SHPT is a great challenge for nephrologists. Etelcalcetide, new calcimimetic, is a very promising drug in the treatment of SHPT. In our first report etelcalcetide was effective without serious side effects in short term, i.e. up to 4 months.

Methods. We present results of long-term treatments with etecalcetide in three hemodialysis patients.

Results. In all three patients' initial dose of etelcalcetide was 5 mg i.v. after dialysis and dose was adjusted according to Ca level. All patients were taking stable doses of vitamin D analogs and phosphate binders; dialysate Ca concentration was 1.5 mmol/L. Parathormone (PTH) concentrations in the beginning were 98.2; 197 and 104.1 pmol/L. After 12 months, PTH concentrations were 31.9, 41 and 45.3 pmol/L. Apart from mild hypocalcaemia (Ca concentration 1.8 mmol/L), no serious side effects were observed.

Conclusion. Based on our first small experience, etelcalcetide is effective and safe in treatment of SHPT.

FC-11 Hemodiafiltration or hemodialysis-which is better? (intra-patient comparison)

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Introduction. For decades, end-stage renal disease (ESRD) patients had the chance only to undergo chronic intermittent hemodialysis (HD). But recently, successful efforts were made to improve the clearance of uremic toxins and decrease the high risk of morbidity and mortality. The development of online hemodiafiltration (OL-HDF) has resulted in markedly enhanced clearance of middle to large toxin's molecules better than high-flux HD. Few clinical studies pointed out the benefits of OL-HDF in patient's overall survival. Primary objective of our study was to show the superiority of OL-HDF compared to high-flux HD in ESRD patients on routine renal replacement treatment. Secondary objective was to identify which variables are showing improvements in OL-HDF compared to high-flux HD.

Methods. In this retrospective, single arm, comparative study, 31 HD patients were studied during 2 years' dialysis treatment as follows: 12 months on high-flux HD, then 12 months on OL-HDF. Study cohort's demographic, clinical and laboratory variables were collected for both treatment regimens. Further statistical analysis and intra-patient comparisons were made.

Results. Our study showed that switching from high-flux HD to OL-HDF treatment regimen improved several hemodialysis outcomes. In 74.2% of patients eKT/V was significantly improved (p=0.006); which was in line with the significant increase of blood flow. The levels of phosphorus were in reference values in 64.5% of the patients and decreased in 54.5% out of 35.5% significantly changed (p=0.009). The usage of anti-coagu-

lants was significantly decreased in 42% of patients (p=0.006), in 9.7% significantly increased and in the rest of the cohort there were not significant changes. Overall consumption of EPO in the study cohort was decreased, in 32.3% was significant (p=0.017), in 45.2% remained similar in the two regimens and in only 22.5% of patient its need was significantly increased.

Conclusion. This study showed that online hemodiafiltration is superior treatment regimen compared to high-flux HD in patients on chronic hemodialysis. Significant improvements were noticed in the most important HD treatment outcomes who will potentially result in improvement of quality of life. Further long-term analysis is needed to show the benefits in decreasing the risk of morbidity and mortality in OL-HDF patients.

FC-12 Bloodstream catheter related infection caused by staphylococcus aureus meticilin resistant (mrsa) in patients on chronic hemodialysis program

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Introduction. The incidence of invasive MRSA infection among patients (pts) undergoing chronic dialysis is >100 times higher than in the general population. Increased risk of MRSA infections in dialysis patients is related to repeated vascular access for hemodialysis patients through central venous catheters (CVCs).

Methods. Epidemiological and laboratory data were collected from all cases of MRSA bacteremia in pts on hemodialysis with CVC, from December 31st 2010 till December 31st 2017. Demographic data, comorbidities (diabetes), duration of CVC, duration of hospitalization and antibiotic therapy, function and complications were recorded.

Results. We identified 52 episodes of MRSA bacteremia from 46 patients (24 males, 22 females, aged 57 years). Thirty nine pts had temporary CVC, and 7 permanent CVC. More than a half of the patients had diabetes, and one third of the pts were on chronic hemodialysis program more than 3 years. There were no differences in age, gender or severity of bacteremia and comorbidities. Logistic regression analysis showed that the following variables; duration time of CVC, type of previous venous access, previous use of antimicrobials, and previous hospitalization related to BCRI. Previous hospitalization increased the chance of developing CRB, 6.6-fold (CI 95%: 1.9-23.09) All CVC were removed and new ones were inserted. Only one patient died, and two had complications (spondylodiscitis), all others were successfully cured. Vancomycin was most frequently administered antibiotic.

Conclusion. All MRSA catheter-related bacteremia were successfully resolved by changing CVC and appropriate antibiotic therapy. Therefore, prevention activities should focus on improving CVC maintenance. Infection prevention measures for bloodstream infections related to central venous catheter use should be intensified. Adherence to current infection prevention guidelines should be encouraged and reinforced to help sustain the decreasing trend of invasive MRSA infections.

FC–13 Disturbances of b lymphocyte subsets in pre-dialysis end stage renal disease patients

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Introduction. End-stage renal disease (ESRD) is associated with immunodeficiency, which makes a significant contribution to morbidity and mortality. The present study aimed at analysis of B lymphocyte subpopulations in a cohort of pre-dialysis ESRD patients.

Methods. B cells (CD19+) and their subsets innate B1a (SD19+ CD5+), naïve (CD19+ CD27-). Memory (CD19+ CD27+), CD19+ BAFF+ and CD19+ IgM+, as well as the expression of CD45, a regulator of T- and B-cell antigen receptor signaling on lymphocytes were quantified using flow cytometry in the peripheral blood of 21 pre-dialysis patients, and results were compared to age-matched healthy control group. Exclusion criteria were age <18 or >75 years, active autoimmune or chronic inflammatory disease, medical history of malignancy, corticosteroids or immunosuppressive treatment for the last 12 months. Furthermore, CRP, C3, C4, IgG, IgA, and IgM levels were also evaluated.

Results. Mean age of the patients (n=21, M/F 12/9) was 62.4±12.5 years. ESRD patients had reduced lymphocyte count (1579±711μ/L vs. 2276±482μ/L, p=0.005) compared to controls. Likewise, whereas the percentages of B cell subsets were not particularly affected, the absolute number of almost all subsets was significantly smaller in ESRD patients (CD19+: 81.3±60.4μ/L vs. 162.1±64.5μ/L, p=0.005; Naive:55.3±50.9μ/L vs. 97.3±46.3μ/L, p=0.043; Memory: 25.8±16.7μ/L vs. 64.8±40.2μ/L, p=0.001; CD19+BAFF+: 67.9±51.1μ/L vs. 136.8±80.1μ/L, p=0.007; CD19+IgM+: 59.1±47.6μ/L vs. 117.1±70.4μ/L, p=0.013; CD45+: 361.8±278μ/L vs. 812.1±361.1μ/L, p=0.002). The only exception was innate B1a cells which were increased in the ESRD group (percentile: 4.7±4% vs. 0.6±1%, p=0.006; count: 4.1±5.5μ/L vs. 1.1±1.5, p=0.027). Furthermore, IgG was elevated in this group (1259±406mg/dL vs. 842±350mg/dL, p=0.026), as well as CRP (7.86±12.96mg/dL vs. 0.28± 0.1mg/dL, p=0.02), while there was no statistically significant difference between C3, C4, IgA and IgM between the two groups.

Conclusion. Significant alterations were noticed in innate and adaptive immunity in patients with ESRD

on pre-dialysis stage, with a significant reduction of almost all subsets of B cells, and these changes may be implicated in clinical manifestations, such as increased incidence and severity of microbial infections, impaired response to vaccination and increased risk of virus associated cancers.

FC-14 Long-term impact of chronic therapy with sucroferric oxyhydroxide on iron and anemia markers in dialysis patients

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Introduction. Interventions to reduce hyperphosphatemia in chronic kidney disease involve medications with different ways of action. Sucroferric oxyhydroxide is a recently approved, iron-based phosphate binder, for which is not clarified yet whether it affects iron markers in dialysis patients. Purpose of this observational study was to evaluate the long-term effects of sucroferric oxyhydroxide to the above-mentioned markers.

Methods. A total of 110 patients from three dialysis units were included in the study; 49 were under chronic treatment with sucroferric oxyhydroxide in combination or not with other binders, while 61 were either receiving other phosphate binders or no treatment for hyperphosphatemia. Phosphorus, calcium, parathormone, ferritin and transferrin saturation were recorded, as well as hematologic parameters, both at the moment of recording and six months earlier. Moreover, dose of erythropoietin and intravenous iron were also recorded. In the first phase of the study, these parameters were compared between the two cohorts, while in the second phase the changes of the same parameters were evaluated in the cohort of sucroferric oxyhydroxide over a period of six months.

Results. Patients under treatment with sucroferric oxyhydroxide had similar levels of serum phosphate (4.57± 1.05 vs. 4.3±0.96mg/dl, p=NS) and parathormone (286±313 vs. 239±296pg/ml, p=NS) with the control group patients. Marginally higher but significant calcium levels and calcium-phosphate product were also found in the sucroferric oxyhydroxide group (9.18±0.58 vs. 8.9±0.51 mg/dl, p=0.008). No statistically significant differences were observed between the two groups, neither in iron markers, nor hematologic parameters. Additionally, no important changes were observed during a six-month treatment with sucroferric oxyhydroxide.

Conclusion. Treatment with sucroferric oxyhydroxide does not seem to result in iron accumulation in dialysis patients.

Poster presentations

PP-01 Parathyroid hormone hypersecretion-unusual cause and manifestation

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Introduction. Secondary hyperparathyroidism (SHPT) can manifest in 0.1% as a brown tumor. It is a giant cell granuloma which usually presents as osteolytic lesions on radiographic imaging. SHPT is treated with medications or parathyroidectomy (PTx). Ectopic parathyroid adenomas are frequent cause of failed initial surgery. Neck ultrasound and sestamibi scan are first-line imaging modalities, followed with SPECT or SPECT/CT, fine needle-aspiration cytology of a lesion and measurement of parathyroid hormone (PTH) in the aspired material.

Case report. We present the case of a 44-year-old female patient with ESRD who underwent hemodialysis due to untreated vesicoureteral reflux (VUR). She had an advanced hyperparathyroidism with multiple osteolytic bone lesions and prominent mass in mandible, which was extirpated and histological finding confirmed the diagnosis of brown tumor. Subtotal PTx was done and histological finding confirmed hyperplastic parathyroid tissue. During the later pre-transplantation workup, chest x-ray showed nodular lung changes which were confirmed with MSCT. Ultrasound guided biopsy of the lesions showed no clear signs of malignancy. Sestamibi scan excluded hyper functional parathyroid tissue as well as ectopic parathyroid glands on the neck. Also, complete MSCT scan found no primary site of potential neoplastic process. Thoracotomy was performed and two nodular lesions were extirpated with histologic diagnosis of carcinoid. Nonetheless, a second opinion on histological finding showed that these changes match to parathyroid gland adenoma, and these was also confirmed by immunohistology-tumor cells were positive for PTH.

Conclusion. Parathyroid gland disorders in CKD can have various clinical manifestations. Brown tumor is a rare complication of unregulated SHPT that may resemble metastatic bone disease. Moreover, in cases of treatment failure of SHPT, especially after PTx has been done, we must always search for possible ectopic parathyroid activity.

PP-02 Therapeutic plasma exchange-our experience in last 4 years

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Introduction. Therapeutic plasma exchange (TPE) is extracorporeal procedure in which patients' plasma is removed by centrifugation or by filtration through semi-permeable membrane and replaced with appropriate replacement fluid.

Methods. We analyzed 56 patients that underwent TPE in our department from 2015 till 2018. Data were retrospectively analyzed from our Department of dialysis database.

Results. During period of 4 years total of 394 procedures were done on 56 patients, with average of 7 procedures per patient (minimum one TPE and maximum of 128 procedures in one patient). Among them 54 % were women (N 30/56), and 46 % were men (N 26/56) with median age 58 years. Therapeutic indications for the procedure included neurological (N 25/56), nephrological (N 23/56), hematological disorders (N 7/58) and one was performed due to paraneoplastic syndrome. The most common neurological indications were Guillain-Barre syndrome and myasthenia gravis, while the predominant nephrological indication was pauci-immune glomerulonephritis. Among hematological indications, we did most of TPE in patients with TTP. 80% of indications were in ASFA I category, 16% in ASFA II category and in remaining percentage of patients TPE was done in neurologic disease of unknown etiology or in nephrological disease from ASFA III category. There were no major complications and no fatal outcomes during the procedures. Most common complication was allergic reaction to fresh frozen plasma.

Conclusion. TPE used in variety of approved indications from ASFA category I and II, is safe and effective method for treating many conditions.

PP-03 Evaluation of arteriovenous fistulas for hemodialysis, duration and complications in 12-18 months follow-up

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Introduction. In 1966, Brescia and Cimino created the first arteriovenous fistula between the radial artery and the most suitable forearm vein, mostly often cephalic vein. These fistulas remain functional with adequate blood flow after one year of theirs creation, in more than 65% of patients. The aim of the study was to show functionality of primary fistulas for hemodialysis in a period of 12 to 18 months of theirs creation.

Methods. A total of 40 patients in a terminal stage of renal disease were taken in consideration, who were operated in the period from 1st of July 2002 till 31st of December 2002. The fistulas in all patients were with

direct latero-terminal anastomosis between radial artery and cephalic vein. Afterwards they were followed for 12-18 months.
Results. The average age of the patients was 63 years old. 42% of the patients were female and 58% were male. As for the complications after creating the AV fistula, we had 6 patients with thrombosis (in two cases new vascular access was created), 2 patients had late occlusions (new vascular access was done) and 1 patient with wound infection (resolved with antibiotics). We had functional A-V fistula with no complications afterwards in a total of 30 patients.
Conclusion. Arteriovenous fistulas are superior with longevity and lesser complications as a mode for hemodialysis access.

PP-04 Survival of patients in one dialysis unit
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Introduction. Dialysis treatment as one mode of renal replacement therapy for end stage renal disease, from one side prolongs patients' lives and improves their quality of life, but from another side it may impact negatively on their survival. The aim of this analysis was to study survival parameters of patients on dialysis treatment.
Methods. Data from 45 patients (M: 27; F:18) was used for this purpose. Medium age at the beginning of renal replacement therapy was 52.2±16.2 years and they were followed for 64±36.5 months.
Results. Kaplan-Meier analysis was done for survival as a whole as well as regarding the cause for kidney disease, age at beginning with dialysis, presence of diabetes and/or hypertension and serum antibodies against hepatitis C virus. Cumulative median (50th percentile) survival was 67 months, while the lower quartile (25th percentile) and the upper quartile (75th percentile) were 36 and 92 months, respectively. The cause for kidney disease influenced patient survival (p <0,001): interstitial nephritis 39.4±46.5; obstructive nephropathy 39.2±49.3; polycystic kidney disease 65±9.8; diabetic nephropathy 35.1±36.0; glomerulonephritis 58.7± 28.7. Survival also showed significance (p <0.001) after stratification based on age of starting hemodialysis treatment: 20-29 years: 73±74.9 months; 30-39 years: 37.1±26.9; 40-49 years: 83.1±41.4; 50-59 years: 63.0±29.9; 60-69 years: 40.4±21.4; 70-79 years: 25.8±33.5; > 80 years: 41.0±26.9. Survival with regard anti-HCV antibodies test was not different (p=0.77); positive 55.4±44.6; negative 48.2±34.5.
Conclusion. The type of kidney disease, age at the beginning of replacement therapy and presence of diabetes, mainly affect survival of patients on maintenance hemodialysis treatment.

PP-05 Infection of central venous catheters in the Institute of nephrology - Struga
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Introduction. Beside all efforts in using arterio-venous fistulas as a permanent vascular access for hemodialysis, the number of central venous catheters (CVC) is still increasing. Furthermore, infection of CVCs remains an important factor in morbidity and mortality in our patients with end stage of renal disease.
Methods. In the Institute of Nephrology and Dialysis in Struga, in the period from 2000 till 2013, 3399 CVC were inserted: 2702 femoral catheters, 603 subclavian catheters, 23 jugular catheters, and 51 Hickman catheters. The primary objective was to estimate proportions of specific infectious causes by blood culture.
Results. Catheter-associated infections with Staphylococcus appeared in 72% of the patients, infections with Pseudomonas was in 5.9%, and Acinetobacter-infections in 2.6%. Proteus mirabilis as a cause for catheter-associated infection appeared in 3.2%, Enterococcus in 4.1%, and other rarely-frequent bacteria appeared in 12.3%.
Conclusion. The primary and most-frequent cause for CVC-infections is Staphylococcus aureus. Vancomycin is still the optimal choice for treatment of Staphylococcus aureus infections.

PP-06 A rare case of idiopathic hypocomplementemic interstitial nephritis, differential diagnosis and follow up
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Introduction. Idiopathic hypocomplementemic interstitial nephritis is a rare but severe form of tubulointerstitial disease characterized by massive tubulointerstitial immune deposits and low levels of complement's proteins. Differential diagnosis includes other causes of TIN with associated hypocomplementemia such as SLE, Sjogren's disease and especially IgG4-related TIN.
We describe a rare case of a patient who developed idiopathic hypocomplementemic interstitial nephritis and was treated with steroids.
Case report. A 72 year-old male patient with medical history of diabetes mellitus, arterial hypertension and coronary artery disease was admitted to our hospital due to progressive aggravation of renal function. Creatinine levels gradually raised from 1.23 mg/dl to 3 mg/dl during the last six months. The patient mentioned an episode of acute bronchitis a month previously to his admission. Laboratory work up showed renal failure (urea 153 mg/dl, creatinine 4 mg/dl), mild proteinuria (0.5 gr/d), low levels of C3 and C4 and increased serum IgG levels.
Renal biopsy demonstrated massive inflammatory infiltration of tubulointerstitial tissue and diffuse tubular fibrosis. The number of IgG4-1` plasma cells was minimal. Immunofluorescence showed granular tubular basement membrane deposits of IgG and C1q. Other causes

of TIN were excluded and the patient was administered oral methylprednisolone for 4 months resulting in improvement of renal function (urea 89 mg/dl, creatinine 2.2 mg/dl) and normalization of complement levels as well as serum IgG levels. Six months later creatinine rose to 3.35 mg/dl and steroid treatment was re-administered.
Conclusion. Idiopathic hypocomplementemic interstitial nephritis is a rare but severe disease with rapid progression. Prompt diagnosis and immunosuppression treatment may contribute to better prognosis.

PP-07 Kidney biopsy in patients with hemorrhagic fever with renal syndrome-cases from a single centre

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Introduction. Hemorrhagic fever with renal syndrome is caused by one of the Hantaviruses. Most prevalent in Croatia are serovars Dobrava, often with more serious clinical picture, and Puumala, often with milder one. The disease is spread by certain rodents excretions which particles are most commonly inhaled. Classical clinical picture contains 5 phases, but often isolated symptoms and signs are found. The most prevalent are fever, headache, lumbar backache, thrombocytopenia and acute renal failure. The latter is the reason why in some cases a kidney biopsy is performed while waiting for the serology results.
Methods. We investigated clinical and histopathological data from four patients from our Centre who presented with acute renal failure and in whom a kidney biopsy was performed and serology for Hantaviruses was made.
Results. Our four patients were all young males, with mean age at the time of illness being 27.5 years, presenting from March till July. They were all previously healthy. All of them presented with fever and fatigue, two of them had headache and two of them had lumbar backache. All of them presented with acute kidney failure (creatinine 244-629 μmol/l) and with thrombocytopenia (50-77 $x10^9$/l, with one missing complete data here). At last, minor proteinuria was also found. After the kidney biopsy, on the light microscope two of them had similar findings, with acute tubular injury and hemorrhage in the medulla, which are typically found in the later discovered disease. One of the previous patients also had acute interstitial nephritis which was also a finding in the third patient - with many eosinophils, so he was initially prescribed with corticosteroids. The last patient had a biopsy done one month after the illness because of persistent proteinuria (24-hour proteinuria was max. 4.69g/dU, and later 0.10g/dU) and the biopsy findings were without pathological changes. The immunofluorescence and electron microscopy did not provide specific data. Ultimately all patients had positive IgM and IgG for Puumala virus which explained all the findings. They all had biopsy done in the same year, which was one of those years known as 'mice year', when a lot more cases of the disease were found due to increased number of rodents. Serology for leptospirosis, which can have similar clinical presentation, was done in two cases and was negative. A complete resolution of acute kidney failure and recovery of thrombocyte number as well as general condition ensued.
Conclusion. Hemorrhagic fever with renal syndrome is a disease that can affect multiple organs but most prominently it attacks kidneys. That is the reason why sometimes patients with more prominent acute kidney failure end up having kidney biopsy, although it's actually not necessary. Still, until the serology is done the exact cause of the failure is often unknown.

PP-08 Rivaroxaban induced nephropathy-case report

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Introduction. Non-vitamin K antagonist oral anticoagulants (NOACs) are since their registration gaining in popularity as the anticoagulant therapy of choice for atrial fibrillation (AF), deep vein thrombosis and pulmonary embolism. Compared to Warfarin the dosing is much simpler and the studies show less acute kidney injury (AKI) overall however there are some case reports describing AKI due to NOACs and there are isolated reports describing AKI due to rivaroxaban treatment. At least two of them were like ours associated with IgA nephropathy.
Methods. An 82-year-old-women was referred to our department for evaluation of gross hematuria and AKI. Due to recurring paroxysmal AF she was prescribed apixaban, which was changed to rivaroxaban after a month because of a vesicular and hemorrhagic rush appearing on the shin.
Results. She first noticed macroscopic hematuria one week after having started rivaroxaban. She had been on rivaroxaban for 15 days before she sought medical attention in our hospital. She was admitted with already poor kidney function and during hospitalization continued to decline. The kidney biopsy showed drug induced kidney injury which was superimposed on her probably preexistent IgA nephropathy. She was started on high dose prednisolone therapy.
Conclusion. Her current therapy consists of prednisolone in gradually decreasing doses, low molecular weight heparin for anticoagulation as well as her other treatment. She has stage 4 chronic kidney disease.

PP-09 Predictors of peritonitis in patients on peritoneal dialysis

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Introduction. Peritonitis is the most common complication of peritoneal dialysis (PD). PD associated peritonitis could lead to the technique failure and infection-related mortality.

The aim of the study was to determinate the predictors of peritonitis in patients on peritoneal dialysis.

Methods. Medical records of 88 patients undergoing peritoneal dialysis from January 1999 to December 2015 were retrospectively studied. Most of the patients were on continuous ambulatory PD, only four patients were on automated PD. Demographic variables (gender and age), dialysis-related variables (PD vintage, peritoneal membrane transport function, residual diuresis and body weight) and laboratory variables (serum level of hemoglobin, albumin and urea) were included in the simple regression analysis for determination of the predictors of episodes of peritonitis in the study population. All variables with a p level lower than 0.05 in the simple regression analysis were included in the multiple regression analysis.

Results. The peritonitis rate was 1 episode of peritonitis per 23.9 patient-months. The primary cure from peritonitis only with antibiotic treatment was present in 89.1% of episodes of peritonitis. The predictors associated with the episodes of peritonitis identified by simple regression analysis were longer PD vintage (p= 0.004), lower residual diuresis (p=0.036) and slower peritoneal membrane transport function (p=0.043). The multiple regression analysis determined that the independent predictor of the episodes of peritonitis was longer PD vintage (OR=1.45, 95%CI: 1.18-1.80, p=0.001).

Conclusion. Longer PD vintage is associated with the episodes of peritonitis because as long as the patient is on peritoneal dialysis there is higher risk for development of peritonitis.

PP-10 IL28B single nucleotide polymorphisms are associated with the response to treatment with pegylated interferon in hemodialysis patients with chronic hepatitis C

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Introduction. Hemodialysis patients among many comorbidities are burdened by the risk of hepatatis C infections. The efect of the antiviral drugs that are used may vary compared to the general population.

Aim. The aim of the study was to determine the predictors of sustained viral response in hemodialysis patients with chronic hepatitis C treated with pegylated interferon alpha-2a.

Methods. Twenty eight hemodialysis (HD) patients with chronic hepatitis C virus infection (HCV) were treated with 135 μg of pegylated interferon alfa-2a (PEGIFN α-2a). The primary end point was sustained viral response (SVR), defined as an absence of detectable HCV RNA in the serum, 6 months after termination of the antiviral treatment. Gender, age, renal disease, HBV co-infection, HCV genotype, early viral response, end-treatment viral response, and single nucleotide polymorphisms (SNPs) near IL28B gene were evaluated as possible predictors of SVR in treated HD patients. The IL28B SNPs (rs12979860, rs8099917, rs12980275) were determined using SNP Genotyping Assays. The association between the possible predictors and SVR was determined with the univariate logistic regression. The independent predictors of SVR were determined with the multiple logistic regression analysis.

Results. The mean age of the treated patients was 47.2± 11.0 years. Early viral response and end-treatment viral response were presented in 75% (21/28) and 71.4% (20/28) of patients, respectively. The overall SVR rate was 42.8% (12/28). The IL28B SNPs genotype presented with CC genotype of rs12979860, TT genotype of rs8099917, and AA genotype of rs12980275 was significantly more frequent in patients with SVR than SNPs genotype presented with non CC genotype of rs12979860, non TT genotype of rs8099917, and non AA genotype of rs12980275, (75% vs. 25%, p=0.027). The predictors associated with SVR identified by univariate logistic regression were early viral response (OR= 1.77, 95%CI: 1.21-2.59, p=0.006), end-treatment viral response (OR=1.82, 95%CI: 1.28-2.59, p=0.002) and IL28B SNPs genotype (OR=1.53, 95%CI: 1.08-2.16, p=0.021). Multiple logistic regression analysis determined that the independent predictor of SVR was IL28B SNPs genotype (OR 1.43, 95%CI: 1.06-1.92, p=0.046).

Conclusions. The single nucleotide polymorphisms (SNPs) near IL28B gene are associated with the response to treatment with pegylated interferon alpha-2a in hemodialysis patients with chronic hepatitis C.

PP-11 Collapsing glomerulopathy-case report

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Introduction. Focal segmental glomerulosclerosis (FSGS) is classified into five variants, with the collapsing variant being the most rare. However, the number of idiopathic cases is increasing and the presentation becoming more routine.

Case report. 77 years old female patient was admitted with nephrotic syndrome and histopathologic features of glomerular capillary collapse. She presented chronic renal failure with serum creatinine 174 μmol/L. Nephrotic syndrome with lower extremities edema, progressively extended, resistant to treatment with diuretics. The value of total serum protein was 54 g/l, albumin 28g/L. Urinalysis demonstrated proteinuria 7.8 g/L and 12.3 g/D. Presence of 25-30 erythrocytes and 2-3 leukocytes in urine sediment was also noticed. Renal biopsy, was performed to determinate the glomerular disease. The histopathologic analysis showed fibrously thickened Bowman membrane, with discreetly thickened glomerular basal membrane and collapsed vascular lumen on TEM analysis. The treatment of the patient included corticosteroids, angiotensin converting enzyme inhibitor and lipid lowering agents, successfully with lowering the proteinuria, followed by withdrawal of the edema.
Conclusion. The nephrologist and nephropathologist have a main role for early diagnosis and better treatment procedure, in collapsing glomerulopathy.

PP-12 Treatment strategy of humerus fracture in patient with arteriovenous fistula for hemodyalisis: case report

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Introduction. The arterio-venous fistula (AVF) is the first and the best vascular access for hemodialysis (HD), that providing adequate treatment, multi-decade survival and better quality of patients' lives.
Case report. 81 years old Caucasian male patient on HD with a functional AVF and humeral fracture was admitted in our hospital for treatment. He was with chronic kidney disease stage 5 on HD almost 8 years and had AVF as vascular access. From comorbidities he had high blood pressure (HBP), chronic cardiomyopathy (CMP), anemia, chronic obstructive pulmonary disease (COPD). The patient was presented with fracture of the left humeral bone due to the fall at home. At clinical presentation patient his left arm was immobilized, he had limited movements, mild pain in the whole body and sarcopenia. According the whole patient's condition we decided to use AVF for HD because all extra manipulation could had caused additional complication. The HD was performed through AVF without complication. After 1 mount his immobilization was removed and control radiogram on left arm showed good position of the fractured fragments of the humeral bone and calluses formation.
Conclusion. The treatment and maintenance of these patients is a challenge for all nephrologist, that requiring assessment of whole health condition with apply the most suitable treatment.

PP-13 Mesangioproliferative glomerulonephritis associated with polycythemia vera and ulcerative colitis: a case report

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Introduction. Membranoproliferative glomerulonephritis (MPGN) is a kidney disorder that involves inflammation and changes to kidney cells. It may lead to kidney failure.
Case report. A case of MPGN associated with polycythemia vera (PV), inflammatory bowel disease (ulcerative colitis) and seropositive rheumatoid arthritis (RA) in 60 years old man is described. The patient had a high blood pressure, granulated parenchyma on ultrasound, normal serum creatinine and glomerular filtration rate. The 24 hour proteinuria was 5.3 g/diuresis (g/Du) at the time of renal biopsy. Deposition of C3 complement was +3 on immunofluorescence examination. Pathological observation under a light microscope showed mesangiocapillary and endocapillary proliferation. PV was treated only with phlebotomy. Ulcerative colitis was under control with sulfasalazine. After treatment with intravenous corticosteroid therapy and oral corticosteroid therapy the patient's proteinuria decreased. On the following check-up after 6 months, proteinuria appeared high again. He was given a methylprednisolone pulse therapy followed up with oral therapy. On the last check up the result was 2.9 g/Du.
Conclusion. MPGN is usually a secondary disease and found in patients with autoimmune diseases, cancer, or infection. This is a rare case of MPGN associated with PV, ulcerative colitis and seropositive RA due to mix etiology.

PP-14 Catheter associated urinary tract infections (cauti) in patients hospitalized in intensive care unit at University Clinic of Nephrology-Skopje

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Introduction. Urinary tract infection (UTI) is common in hospitalized patients as a part of a Healthcare-associated infections (HAIs). It has been estimated that more than 80% of UTIs are associated with an indwelling catheter and notably, catheter-associated UTI (CAUTI) has been related with such complications that prolonged hospital stay, and increased cost, morbidity and mortality.
The aim of our study was to determine the related risk factors and to identify the causative agents contributing to the CAUTI and their resistance to antibiotics.

Methods. A retrospective study was conducted at Intensive care unit at University Clinic of Nephrology-Skopje on 100 patients with placed urinary catheter before or during the hospitalization. We checked up the results of urine culture, antibiogram and sensitivity/resistance to antibiotics, inflammatory markers in blood, leukocytes in urinary sediment, and the patients' comorbidity.
Results. The mean age of study was 70.3 years. Among them 53 male and 47 female, with placed urinary catheter (95% foley and 5% permanent urinary catheter) and different types of AKI and CKD [AKI=30 (30%), CKD= 70 patients (70%)]. Positive urine culture was found in 65% of the patients (58.84% female and 47.69% male) in whom 26.15% with obstructive nephropathy, 49.23% with diabetes mellitus type 2, 9.23% with malignant illness of the urinary tract. Regarding the duration of catheterization, positive urine culture was found of 43.75% of the patients with urinary catheter present <5 days, 62.96% present >5 days, at 65.21% present >15 days and 90.90% in patients present >20 days. Confirmed or suspected urosepsis was found in 10%. The most common agent that cause CAUTI was Enterococcus in 30.76%, Escherichia coli (21.4%), E. coli ESBL+(11.5%), Klebsiella pneumoniae (7.7%), Klebsiella pneumonie ESBL + (5.3%), followed by Pseudomonas aeruginosa (10.0%), and Enterobacter spp. (4.1%). A smaller proportion of CAUTI was caused by other gram-negative bacteria or by Staphylococcus spp. Microorganisms were often multidrug resistant probably following the increased use of broad-spectrum antibiotics in hospitals which is a considerable problem in ICU units.
Conclusion: An understanding of the risk factors in development of CAUTI, helps in reducing the patient complications. Shortening the duration of catheterization and sterile precautions in insertion can help in prevention on CAUTI.

PP-15 Tacrolimus intra-patient variability and metabolism type in stable kidney transplant recipients

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Introduction. Tacrolimus (TAC) is a most widely used immunosuppressive drug in transplantation. It is a challenging task for clinicians to achieve an optimal dose of TAC to reduce the chance of rejection and toxicity due to individual variability. The purpose of this study was to determine the intra-patient variability and metabolism type of tacrolimus.
Methods. Weekly tacrolimus trough levels were obtained in 40 stable kidney transplant recipients 6 months after transplantation, receiving TAC twice daily. As inclusive criteria, at least three consecutive TAC values were needed. Demographic (age, gender, body weight), laboratory (albumin, creatinine, TAC) and TAC prescription data was obtained from medical charts. Graft function was calculated by Cockroft-Gault Equation. TAC variability was quantified as the coefficient of variation (CV). TAC metabolism rate was estimated as the TAC blood trough concentration (C) divided by the daily dose (D). Fast TAC metabolism was defined by C/D rate below 1.05. Predictors of intra-patient TAC variability were estimated with regression analysis on the demographic, laboratory data and graft function.
Results. The mean age of study participants was 43±13.37 years, 29(72%) were men. TAC values ranged from 2.46-12.48, with mean value of 6.42±1.86 ng/ml. The median CV for the entire population was 22.49% (range 7.95%-48.12%). The regression analysis did not identify any demographic, laboratory characteristics, or graft function associated with CV. Twenty percentage of patients had CV > 30% and 12.5% were identified as fast metabolizers.
Conclusion. In our study tacrolimus did display a moderate intra-patient variability. High tacrolimus variability may identify a subset of patients who warrant increased surveillance and patient education regarding dietary and medication compliance.

PP-16 Relationship between stroke and mortality in hemodialysis patients

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Introduction. Stroke incidence in hemodialysis (HD) patients is up to 10 times greater than in the general population, but the implications for mortality after stroke in these patients are not fully understood. The aim of this study was to examine predictive value for stroke death of various clinical variables after long-term HD.
Methods. We performed retrospective single-center study to determine the risks for stroke among 261 prevalent HD patients (mean age at beginning of HD 49.69±15.59 years, diabetes 17.2%) during 10-years. Cerebrovascular disease death was defined as fatal-stroke death with evidence of compatible neuroimaging.
Results. During the 10-year follow-up, 171 out of 261 patients (65.54%) had died, 40(23%) patients from fatal-stroke, 64(37%) patients from cardiac disease (CD) and 67(39 %) patients from non-cardiovascular disease (non-CVD). Patients deceased from fatal-stroke are significantly different from patients who died from CD and non-CVD with higher systolic blood pressure (mmHg) (157.28±23.16; 135.25±21.35; 130.31±24,71, p=0.000), higher diastolic blood pressure (mmHg) (91.68±16.68; 76.62±13.97; 76.56±17.12, p=0.000), higher pulse pressure (mmHg) (65.60±14.33; 58.63±17.29; 53.75±13.82, p=0.001), higher ultrafiltration (L) (3.06±0.84; 2.74±0.65; 3.03±0.81L; p=0.045), and higher phosphate levels (mmol/L) (1.61±0.38; 1.41±0.36; 1.47±0.35, p=0.024). Kaplan-Meier analysis showed that patients

with systolic blood pressure >150mmHg (log rank, p=0.000), pulse pressure >65mmHg (log rank, p= 0.000) and ultrafiltration>3.0l (log rank, p=0.002) had a higher morality from fatal-stroke than patients with systolic blood pressure <150mmHg, pulse pressure <65 mmHg and ultrafiltration <3.0l.

Conclusion. Hemodialysis patients have high mortality after fatal stroke which has multifactorial reasons. Our findings confirmed the association of systolic blood pressure >150mmHg, pulse pressure >65mmHg and ultrafiltration >3l with higher mortality from fatal stroke among maintenance HD patients. Strict management of volume overload in HD patients are urgently required to direct prevention and treatment of this significant disease.

PP-17 Are renal patients with o blood type frailer and neglected on the transplant waiting list?

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Introduction. Development of the program for cadaveric transplantation requires additional information on potential risks of organ shortage. The export of blood group O donor kidneys to other blood groups leads to longer waiting times. If a certain population is characterized with less frequent O type, this problem can be emphasized. Also patients with O blood type are in higher risk of mortality.

Aim: In this study we aimed to assess the difference between renal patients and healthy subjects in respect of blood groups distribution. We hypothesize that O blood group patients are more frequent among critically ill patients.

Methods. We tested the blood groups in 1737 hospitalized renal patients in tertiary University clinic of Skopje, N. Macedonia during 6 years period. The distribution of blood groups was compared to 1547 healthy blood donors. Also the critically ill patients hospitalized in the Intensive Care Unit (ICU) were compared to the other renal patients.

Results. The healthy and renal group were not different in respect of ethnicity. We found blood group A in 757 patients (43.6%), blood group B in 281 patients (16.1%), blood group O in 588 patients (33.9%), blood group AB in 111 patients (6.4%) and these results were comparable to the blood types in the general population: 42.2%, 16.3%, 32.6%, and 8.7%, respectively. Amon patients hospitalized in the ICU, there were significantly more patients with O blood type than in others 221/606 (36.4%) vs 367/1132 (32%), p<0.05, respectively.

Conclusion. The frailty of O blood type renal patients should imply review and further research in order to improve the balance of the transplant health care towards all blood types.

PP-18 Glucose levels during dialysis with glucose-free versus glucose-rich dialysate fluid

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Introduction. Asymptomatic hypoglycemia has been reported in both diabetic and non-diabetic patients on hemodialysis. Uremic symptoms as inadequate appetite, nausea and vomiting worsen the risk of hypoglycemia at starting dialysis. In our dialysis unit, as a standard therapeutic approach for decreasing this risk, continuous venous 5% glucose solution is applied during the glucose-free dialysate (GFD) dialysis. In this interventional study we sought to assess the glycemic control during standard starting dialysis protocol versus novel approach with glucose rich dialysis fluid (GRD).

Methods. Twenty-one dialysis patients with chronic renal failure were subsequently dialyzed using GRD (5.6 mmol/l) and GFD fluid. They did not take hypoglycemic medication prior or food during dialysis. Blood was sampled at regular intervals during dialysis. The dialysis prescription consisted of ultrafiltration (UF) up to 1l, membrane surface (MS) up to 1.4 m^2 and time of 2-2.5 hours. Intra-patient glycemic variability was defined by Coefficient of variation (CV). Paired t-test was used to determine the difference in glucose variability for both therapeutic approaches.

Results. The mean age of study participants was 62.9511.73 years, 7(33%) had diabetes. The two dialysis approaches did not differ in respect of starting blood pressure, UF and MS. Only two episodes of hypoglycemia occurred in both types of dialysis. The mean glucose level was higher during GRD (8.151.89 vs.6.291.33, p=0.001), respectively. The glucose CV was lower in GRD dialysis, but the difference was insignificant (16.97 8.86 vs. 21.0511.99, p=0.151). When only diabetic patients were analyzed, also the glucose CV difference was not significant (p=0.151).

Conclusion. The GRD approach for starting dialysis is non - inferior to standard GFD care.

PP-19 Prostatic specific antigen level and ultrasound - calculated prostate gland volume in prostatic cancer and benign prostatic hyperplasia

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Introduction. Although the levels of prostate-specific Antigen (PSA) in serum above 4 ng/ml suggest the presence of prostatic cancer, benign prostatic hyperplasia (BPH) is also frequently accompanied by levels

above this normal value. Furthermore, enlarged ultrasound-calculated prostate gland volume can also be found either in prostatic cancer or BPH.
Aim. To compare PSA levels and volume of the prostatic gland in patients with BPH and prostatic cancer.
Methods. We did retrospective analysis on all prostatic biopsies performed between April 2018 and April 2019, in our University Clinic. Patients with prostatitis were excluded. Two groups were formed based on the histopathological finding-either prostatic cancer or BPH. Both groups were subdivided by cut-off serum values for PSA-10 ng/ml, and also by the ultrasound measured prostatic gland of volume 60ccm^3. The groups were compared with X squared test.
Results. Out of total 128 patients, 76 patients were diagnosed with prostatic cancer (59.37%), and 52 patients with BPH (40.63%). Patients with prostatic cancer had more often smaller sized prostatic volume 65ccm^2 (86%) vs 14ccm^3 (18%), p=0.018, and higher values for PSA 38ng/ml (73%) vs 20ng/ml (39%), p=0.048, than patients with BPH, respectively. The correlation between PSA and prostatic volume in patients with prostatic cancer was positive and significant, but not in patients with BPH.
Conclusion. Prostate size was inversely associated with the risk of prostatic cancer at final pathology.

PP-20 Active smoking is associated with lower dialysis adequacy in prevalent dialysis patients
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Introduction. Dialysis adequacy measured by spKt/V and lower than 1.2 or URR lower than 60% is associated with a significant increase in the patient mortality rate. Patients' adherence to the medical treatment is crucial to achieve recommended targets for spKt/V. Smoking is recognized factor of non-adherence. In this study we sought to assess the association of active smoking and dialysis adequacy in dialysis patients.
Methods. 134 prevalent dialysis patients were included in 6 months observational study. Number of missed or on purpose interrupted dialysis sessions was obtained. Dialysis adequacy was calculated as spKt/V and URR. Patients were questioned about current active smoking status. T-Test and Chi-Square test were used for performing comparative analysis.
Results. The majority of patients declared as non-smokers 100(75%) and 34(25%) were active smokers. Men, younger age and shorter dialysis vintage were significantly more often in active smokers, 9 (26%) vs 25(73%), p=0.028; 57.26 12.59 vs 50.15 14.10, p=0.012; 118.59 76.25 vs 88.82 57.63, p=0.030, respectively. spKt/V and URR were significantly lower and Kt/V target was less achieved in smokers,1.46 0.19 vs 1.30 0.021, p= 0.019; 67.14 5.86 vs 63.64 8.30, p=0.002; 14(14%) vs 11(32%), p=0.023, respectively. Shorter dialysis sessions, larger ultrafiltration and higher percentage of missed/ interrupted dialysis session on patients demand were observed in smokers, 4.15 0.30 vs 4.05 0.17, p=0.019; 3.10 0.78 vs 3.54 0.92, p=0.017; 25(0.3%) vs 48(1.9%), p=0.031, respectively.
Conclusion. Active smokers, especially younger men, achieve less recommended levels for dialysis adequacy. Non-adherence to treatment duration in smokers is a problem to be solved.

PP-21 Morphometric analysis of glomeruli, clinical features and outcome in obese and non-obese focal segmental glomerulosclerosis patients
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Introduction. In the past three decades focal segmental glomerulosclerosis (FSGS) was commonly regarded as a part of obesity related glomerulopathy (ORG) a distinct entity featuring proteinuria, glomerulomegalia, progressive glomerulosclerosis and renal functional decline. The aims of the study were to evaluate the glomerular morphometry, clinical features and two years outcome in obese and non-obese FSGS patients.
Methods. The study included 35 FSGS patients (23 males, mean age 46.5±15.2 years) divided in two groups: obese (BMI ≥27 kg/m2- 18 patients, mean age 47.2±15.5 years) and non-obese (BMI <27 kg/m2-17 patients, mean age 45.7±15.2 years). The serum concentrations of proteins, albumin, cholesterol, triglyceride and creatinine were determined at the time the kidney biopsy, 6, 12 and 24 months after the kidney biopsy. Formula Cockcroft-Gault; Cockcroft- Gault (BMI < 27 kg/m2) and Cockcroft-Gault LBW (BMI ≥27 kg/m2) was calculated. Glomerular radius (GR), glomerular volume (GV) and glomerular density (GD) were compared morphometrically between two groups.
Results. At the time of kidney biopsy and 6 months later the obese had significantly lower GFR compared to non-obese. After 24months follow-up there was not any difference between groups. Obese had significantly higher GR (109.44±6,03 μm vs 98.53±14,38 μm) and GV (3.13±0.49 x106 μm^3 vs 2.26±0.83 x106 μm^3), only mildly lower GD (1.91±0.39/mm^2 vs 1.95±0.61/mm^2) compared to non-obese. Significant positive association

between GV and BMI (r=0.439) was found. After 12 months follow-up significantly higher percentage of non-obese patients reached complete remission (71.4% vs 37.5%) compared to obese ($\chi 2$=0.041), but after 24 months there were no significant difference.

Conclusion. Obese patients at the time of kidney biopsy and 6 months later had already the significant lower kidney function compared to non-obese. However, after 12 and 24 months, this difference was still lower and without significance as well as after 24 months percentage of patients with complete remission between two groups.

PP-22 Clinical impact of cardiorenal anemia syndrome in heart failure

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Introduction. Cardio-renal syndrome is a very complex disease, in which both kidneys and heart are involved and create a feed-back cycle with worsening the progression and carries a bad prognosis. Based on pathophysiology, if the organ that was primary damaged subsequently leads to the damage of the other organ, and if the organ damage is acute or chronic, cardio-renal syndrome is divided in five subtypes. The prevalence of cardio-renal syndrome is highly increased by aging, on the other hand, anemia is often present in both CKD and CSV, and it is an independent risk factor, on outcome and survival of this patients. The triad of CVD, CKD, and anemia has been named cardio-renal-anemia syndrome.

The aim of the study is to evaluate the epidemiology and the classification of CRS in heart failure patients, the presence and the role of anemia in this group of patients.

Cardio-renal treatment remains a huge challenge for both cardiologist and nephrologist and cardio-renal anemia syndrome is an entity that should be identified. The early identification of anemia and cardio-renal subtypes, especially in the initial stages, plays an important role in assessment of high risk patients. Also, early identification has been proven to reduce complications over the long term.

Conclusion. Appropriate intervention are important to modify reversible factors, which leads to better outcome. Tailor therapy is the best way to manage this patients.

PP-23 Connection of troponin with the onset of cardiovascular diseases in patients with chronic kidney disease

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Introduction. Despite the use of numerous biomarkers for the prediction of cardiovascular events (CVE), there is still a problem of estimating CV morbidity and mortality in patients with chronic kidney disease (CKD).

The aim of our study was to investigate the association of troponin with newly occurred CVE in patients with CKD stages 3-5HD.

Methods. The prospective study included 87 patients, who were divided into four groups: CKD stages 3a, 3b, 4 and 5HD. During 18 months of follow-up, the following events were reported: myocardial infarction, worsening of the existing or newly occurred angina pectoris, cerebrovascular insult, peripheral arterial disease and cardiac death.

Results. The highest number of CVE was registered in hemodialysis patients (45.9%). Patients with CKD stage 3a had normal troponin levels, but with further progression of CKD, troponin value increased so that the highest value was found in the group of hemodialysis patients (p=0.003). In patients with registered CVE, significantly lower hemoglobin (p=0.005) and albumin values (p=0.011), as well as higher troponin values (p =0.018) were observed compered to patients without CVE. The correlation between troponin and the occurrence of CVE has not been confirmed by the Cox regression analysis.

Conclusion. Analysis of patients with CKD stages 3-5HD did not confirm that elevated troponin was a risk factor for the CVE. The finding should be analyzed in a larger study during longer follow-up time.

PP-24 Adherence to the mediterranean diet and metabolic parameters in patients with chronic kidney disease stage 5

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Introduction. Mediterranean diet has been associated with lower risk of cardiovascular disease and cancer. Dietary restrictions often imposed to patients with Chronic Kidney Disease (CKD) stage 5 leads to lower adherence to this dietary pattern, due to the limited allowance in the consumption of foods of plant origin. The aim of this study was to evaluate the level of ad-

herence to the Mediterranean diet in a sample of patients with CKD stage 5.
Methods. Fifty patients (33 men), 24 undergoing hemodialysis (HD) and 26 under peritoneal dialysis (PD) were consecutively enrolled in the study. Body mass Index (BMI) based on dry body weight was calculated and a semi quantitative food frequency questionnaire was completed in order to evaluate the adherence to the Mediterranean diet by the MediterraneanDietScore (MedDietScore). Data from the medical history of the patients were also recorded, namely the years on dialysis, medications and biochemical analyses.
Results. According to our analysis our patients (Mean age 54.4±17.7 years, BMI 25.5± 3.87 kg/m^2, average duration of dialysis 6.6±7.1 yrs) had medium level of adherence to the Mediterranean diet (MedDietScore 30±3.27). No statistical significant differences were detected between sexes and between HD and PD patients. MedDietScore was negatively associated with age (-0.354, p=0.016) but it was not significantly associated with the levels of phosphate, potassium and albumin.
Conclusion. The patients in our study had similar level of adherence to the Mediterranean Diet with the general population. Adhering to this dietary pattern did not have a significant impact on the metabolic profile of these patients.

PP-25 Hyperuricemia and CKD-new insights into novel treatments

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Introduction. Hyperuricemia is a common finding in CKD. There is no doubt about the strong relationship between CKD and hyperuricemia. It is still to be proven and open for discussion if high serum acid levels can be a result of CKD or indicate a path that leads to kidney disease. Uric acid-lowering therapy has been reported to delay the progression of kidney disease and/or reduce cardiovascular risk in patients with CKD. As we know, CKD patients are often accompanied by other comorbidities: hypertension, diabetes, ischemic heart disease, etc. These comorbidities impact therapeutic decision making, since available uric acid-lowering agents have precautions and/or contraindications in these settings, so the effective choice of urate-lowering therapy, still remains a challenge. The current urate-lowering strategies include reducing the urate production with xanthine oxidase (XO) inhibitors and accelerating the urinary excretion of uric acid (UA) with uricosuric-agents which have limited effectiveness in patients with reduced renal function. Allopurinol is widely recommended for the treatment of hyperuricemia, but requires dose adjustment in subjects with renal impairment, which may lead to a reduced benefit. Febuxostat is an alternative option for the treatment of hyperuricemia in patients with chronic kidney disease (CKD) because it undergoes hepatic metabolism and may require less dose adjustment in association with the renal impairment.
The aim of our study was to evaluate the effectiveness of febuxostat in lowering acid uric levels in patients with mild to moderate CKD.
Methods. The follow up was six months. Levels of uric acid decreased significantly after six months of treatment with febuxostat. More than 85% of study subjects reached the target of uric acid levels less than 6mg/dL and no serious adverse events were noted. Administering febuxostat over a 6 months period appears to normalize uric acid levels and preserve or even improve kidney function in hyperuricemic patients with mild to moderate kidney disease.
Conclusion. Febuxostat is highly effective and well-tolerated uric acid lowering drug, but more studies with larger population size are needed to fully explore the clinical benefits of this novel agent.

PP-26 Vancomycin induced linear IgA bullous dermatosis in a patient on peritoneal dialysis

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Introduction. Linear IgA bullous dermatosis (LABD) is a rare autoimmune sub-epidermal bullous dermatosis, characterized by linear IgA deposition along the basement membrane. It can be induced by drugs, where half of the cases is associated with the use of vancomycin. LABD manifests as tense bullae with erythematous skin changes accompanied with pruritus, leading to creation of numerous papules covered with crusts. Histologically, there is sub-epidermal formation of bullae with variable lymphocytic and neutrophilic infiltrate, and the direct immunofluorescence (DIF) detects autoantibodies as linear IgA deposition.
Case report. A 70-year-old man undergoing CAPD program due to ESRD, with prior implanted mechanical aortic valve, was hospitalized due to fever and suspicion on endocarditis. Empirically, he was treated with vancomycin. TEE has been made, but showed no vegetations. Urinalysis and chest x-ray were also unremarkable. There has been a regression of inflammatory parameters along with good clinical response on applied therapy so he was discharged. Two days later, he noted bullous skin changes on trunk and intertriginous area, and was hospitalized again. Skin biopsy was performed and the light microscope found clusters of inflammatory cells, predominantly neutrophils, inside of tense blisters. DIF demonstrated linear IgA deposition in basement membrane and confirmed that it was LABD probably caused by vancomycin. Vancomycin is immediately discontinued and combination of topical antibiotics and corticosteroids was administrated with regression of skin changes.

Conclusion. LABD usually occurs one day to two weeks after drug administration, therefore we must always think of that entity in patients that have recently taken vancomycin. Cutaneous biopsy and DIF are the basis for establishing diagnosis. Discontinuation of drug with supportive measures leads to resolution of changes.

PP-27 N-Terminal PRO-B-type natriuretic peptide and cardiac dysfunction in hemodyalisis patients

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Introduction. In hemodialysis (HD) patients plasma levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) are almost always markedly raised for reasons largely unknown. This study examined the effect of baseline NT-proBNP as a prognostic factor for determination of patients at high risk of cardiac dysfunction.

Methods. We measured NT-proBNP in 57 prevalent HD patients (mean age 50.49±12.64 years, mean HD vintage 108.70±64.46 months, diabetes 10.5%, CV disease 50.9%) to examine the relationship of this marker with cardiac dysfunction. Echocardiography was performed in all patients and left ventricular mass index was estimated using the Devereux formula.

Results. The mean pre-HD NT-proBNP value was 10229.61±10027.87pg/ml (345-35000). Patients with CV disease have significantly higher levels of NT-pro BNP compared to patients without CV disease (14614.31 ±11302.21 vs. 5688.30±5415.47; p=0.005). There was an inverse correlation between NT-pro BNP and left ventricular (LV) ejection fraction (r=-0.322, p=0.027) and a positive correlation with systolic blood pressure (r= 0.379, p=0.003), pulse pressure (r=0.446, p=0.000) and LV hypertrophy (r=0.438, p=0.002). Patients with NT-proBNP >10.000pg/ml had significantly higher systolic blood pressure (151.58±25.24 vs 130.05±18.80mmHg, p=0.000), diastolic blood pressure (87.37±16.99 vs 78.21 ±13.89mmHg, p=0.040), pulse pressure (64.21±15.35 vs 51.84±11.23mmHg, p=0.001), LV hypertrophy (157.56 ±42.58 vs 121.49±37.83g/m^2, p=0.001) and significantly lower hemoglobin (102.51±7.63 vs 109.09±11.30 g/l, p=0.036), length of HD (3.94±0.16 vs 4.02±0.12/ hours, p=0.045) and ejection fraction (63.36±8.30 vs 68.86±6.68%, p=0.028), than those with NT-proBNP <10.000pg/ml.

Conclusion. Our results suggest that basal NT-proBNP concentration are associated with volume overload and left ventricular dysfunction in HD patients. Furthermore, identifying HD patients with NT-proBNP >10.000 pg/ml suggests that monitoring NT-proBNP may be useful for assessing cardiovascular risk in HD patients.

PP- 28 Hepatitis E virus and chronic kidney disease

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Introduction. Hepatitis E virus infection in immune compromised patients, including end stage chronic kidney disease (CKD) and kidney transplant patients, is not always a benign, self-healing disease. It can be invasive and chronic with life-threatening consequences. Transplanted patients have a high risk of developing persistent hepatitis E virus (HEV) infections and progressive liver fibrosis. Incidence and prevalence are also increasing in more developed countries. Disease is transmitted fecal-orally. The most frequent sources of HEV infection in developed countries are pigs, wild animals and insufficiently thermally processed meat products. Seroprevalence of HEV is more prevalent in patients on dialysis and kidney transplant patients.

Methods. The goal of our work is to establish HEV seroprevalence in a subgroup of 115 patients at Polyclinic B. Braun Avitum in Zagreb, which is an integral part of the national study involving more than 1,600 participants.

Results. At this point we have the results of the HEV IgG antibody assay and are still processing IgM antibodies and HCV RNA. IgG antibodies are present in 33% of subjects. More frequent in male subjects, not found in subjects younger than 40 years and more frequent in older age groups. They are more frequent in the rural population and the participants who have been in contact with wild animals and pigs. Significantly elevated in subjects receiving blood transfusions.

Conclusion. Further clinical studies are needed to clarify incidence and prevalence of HEV and clinical consequences. It is essential to educate nephrologists in prevention, diagnosis and treatment of these potentially serious hepatic disease.

PP-29 Long-term hemodialysis survivor: 33 years of mantenance hemodialysis in a diabetic female with non-cuffed catheter during last 18 years

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Introduction. In cases of frequent fistula thrombosis or when the possibility for constructing a new native AVF or arteriovenous graft (AVG) is exhausted, one or two "temporary", precurved, non-tunneled, non-cuffed, single-lumen jugular catheters can serve as long-term vascular access, with a complication rate comparable to that in "permanent", tunneled catheters.

Case report. Patient described is 63-year-old female patient with diabetes mellitus type 1 with 33-year history of end-stage renal disease and hemodialysis treatment with different vascular accesses. During her lifetime on hemodialysis she had two native AVF, five Gore-tex AVG on the both arms and thigh and tunneled Ash-split catheter inserted into the right jugular vein

which was later adherent to the right atrium wall. Because of exhausted vasculature she has been performing double-needle hemodialysis with single pre-curved, non-tunneled, single-lumen jugular catheters (for blood take) and the peripheral vein (for blood return) for last 18 years. Our case report demonstrates that it was possible to use such jugular catheter as the long-term vascular access, providing double-needle hemodialysis by using peripheral vein for blood return, for 18 years. During this time, she had one bacteremia, one Staphylococcus aureus sepsis and, for the second time, the adherence of the catheter tip to the right atrium wall. The peripheral veins of the legs and arms 'matured' like fistula vein, both in vein diameter (about 4.2 mm) and thickness of the wall (1mm).

Conclusion. New evidence revealed that tunneled and pre-curved non-tunneled catheters may be comparable in terms of reaching the combined endpoint of catheter-related infections and malfunction. Furthermore, our dialysis center's experience, including the case we presented on, also suggests that such jugular hemodialysis catheters locked with 30% trisodium citrate can be an efficient long-term access for hemodialysis in selected patients not eligible for an AVF or AVG creation.

PP-30 Nutritional assesment in peritoneal dialysis patients show to low protein and energy intake

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Introduction. Protein malnutrition is common in peritoneal dialysis patients and depends on many factors.
The aim of the study was to analyze dietary intake of dialysis patients and to determine if it meets their nutritional needs.

Methods. A clinical study was carried out on 25 dialysis patients in the Peritoneal Dialysis Unit of University Clinical Center of Ljubljana. Nutritional interview was conducted unannounced three times over a period of one month with the 24 hour recall method. Results were analyzed with the Prodi 6.7 Expert software. Body composition has been measured with bio impedance spectroscopy.

Results. Average caloric intake of 25 patients is 22.74 ±6.54 kcal/kg body weight per day, average protein intake is 0.86±0.30 g/kg body weight per day. Average values of body weights were 73.33±13.76 kg, BMI (body mass index) was 24.26±2.53 kg/m^2, average lean tissue index 13.67±3.21 kg/m^2 and values of Phase angle were 5.08±1.17. It was monitored in 24 hours also intake of fat (0.82±0.35g/kg bw/day), carbohydrate (2.68±1.08 g/kg bw/day), sodium (3.39±6.66 g/day), potassium (2.01±0.55g/day) and phosphorus (0.87±0.29) Caloric and protein intake values were lower than recommended for dialysis patients.

Conclusion. Successful collaboration between patient and dietitian is crucial for objective results of nutritional assessment and malnutrition therapy. Protein and energy intake were found to be lower in peritoneal dialysis patients than recommended.

PP-31 Serum vitamin D levels in kidney transplant recipients

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Introduction. Hypovitaminosis D may be present in kidney transplant patients as a result of immunosuppression therapy and low sun exposure, as well as prefiguring kidney disease.

Methods. This cross-sectional study has been performed on Nephrology Clinic, University Clinical Center Sarajevo. The total of 106 kidney transplant patients had participated in the study. Based on serum vitamin D values they were divided into 3 groups: deficiency, insufficiency and sufficiency of vitamin D.

Results. Vitamin D deficiency was diagnosed in 32.2% of patients, vitamin D insufficiency was diagnosed in 60% of patients, while 7.7% had sufficient serum vitamin D values. Deficiency was associated with higher prednisone doses, use of mycophenolate sodium, tacrolimus, and lower doses of vitamin D supplementation. Furthermore, there was no significant difference in glomerular filtration rate (GFR) values between the groups. Significant medium negative correlation between vitamin D and parathormone (PTH) values was found (rho=-0.370; $p<0.01$). There was also no significant difference in vitamin D levels between groups of patients made based on time after kidney transplant.

Conclusion. More than 90% of patients had hypovitaminosis D. Despite potential ultraviolet B exposure, inadequate vitamin D levels were prevalent in our study group. Importantly, some immunosuppressive medications were associated with vitamin D deficiency and high doses of vitamin D were associated with less deficiency. The study showed no link between time after kidney transplant and vitamin D values as well as the no impact of vitamin D on graft function.

PP-32 Incorect course of central venous hemodialysis catheters in patients with end stage renal disease requiring hemodialysis

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Introduction. Venous catheters are commonly used for acute angioaccess. The optimal insertion site is the internal jugular vein. The subclavian site should generally be avoided because it is associated with a higher incidence of insertion-related complications. Catheteri-

zation of the femoral vein is a good choice when there is a need for short term hemodialysis (<1-2weeks).
Methods. We present six patients in which we placed central venous hemodialysis catheters. In two patients the central section of the subclavian venous catheter was shown into the internal jugular vein and then into the right atrium (No1 and No2). In one patient the subclavian venous catheter, instead of the right atrium, continued his course into the internal jugular vein (No3). In one patient the initial part of the subclavian venous catheter had curved course (No4), while in another patient the subclavian venous catheter was refolding in the right atrium (No5) and, finally, in the last patient the internal jugular vein continued its course into the azygos vein (No6).
Results. In patients No1, No2, No3 and No6 the central venous catheters were removed. In patient No5 we moved the catheter towards out. Patient No4 was treated for some time with hemodialysis using this catheter, but the catheter did not have adequate supply.
Conclusion. Hemodialysis central venous catheters sometimes during insertion follow incorrect course and may need to be moved or removed and reinserted in other site. Catheter insertion, especially in internal jugular and subclavian vein, should always be followed by a chest x-ray examination.

PP-33 Psychological evaluation of living kidney donors: why and how
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Introduction. The psychological evaluation is an important part of the preoperative evaluation of kidney donors. According to the literature data transplant centers in Europe vary in the content and methods used for psychological assessment of potential donors. The Psychological Care for Living Donors and Recipients working group of ELPAT (European platform on ethical, legal and psychosocial aspects of organ transplantation), developed an evidence-based instrument to standardize the psychosocial screening process of potential donors.
Methods. The psychological evaluation of potential donors is performed as a standard procedure at the Clinic of Nephrology in Skopje. It is implemented through semi-structured interview, Personality test and a Red Flag Checklist developed by ELPAT.
The semi-structured interview consists of 40 questions about the following topics: a) informed consent (ambivalence, determination regarding the decision of donation), b) motivation for donation and decision making process (how the decision to donate was made), c) expectations about the process (health expectations for the recipient, expectations regarding the effect of the donation on the relationship with the recipient), d) comprehension/knowledge/awareness/ understanding of the process including potential risks, benefits, health outcomes, recovery process, e) cognitive status, f) current stressors (relationships, home, work, financial), g) adequacy of social support and donor-recipient relationship, h) socio-demographic characteristics and lifestyle.
In order to understand and describe the psychological profile (personality and psychopathology) that characterizes kidney donor, we use personality test MMPI (Minnesota Multiphasic Personality Inventory). In situation where the donor is perceived as potentially "high risk" additional psychiatric evaluation is required.
Conclusion. The purpose of the psychological evaluation is not to exclude every potential donor who has psychopathology or behavior problems, but to anticipate the risks and to provide timely psychological support and counseling.

PP-34 Increase of diabetic patients on hemodialysis and multidisciplinary challenges for nephrologists
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Introduction. Diabetes was nearly assent in our hemodialytic population before the 2000. Changing of lifestyle, westernization of food and stress have brought the increase of this morbid condition.
Methods and results. In 2005 there were 30 000 diabetics in Albania and in 2018 there are 80 000. Diabetic nephropathy is increasing too and now is our everyday clinical practice challenge. Diabetics on hemodialysis are now more and more present with their problems and difficulties that need not only nephrological but a multidisciplinary approach. Diabetic nephropathy in 2011 had only 11.3% of hemodialytic pie and now is reaching 17.2% of primary cause of ESRD in our hemodialytic population. We are below the European and North American data but in incident patients it is becoming the second predominant cause of renal failure, after the hypertensive nephrosclerosis, reaching the 25%-27%. Increasing number is translated into increased problems especially in vascular access, cardiovascular problems, diabetic foot problems, glycemic control, etc.
Conclusion. Caring about the glycemic levels, type of hypoglycemic drugs, time and dosage, eating or not during the hemodialysis session, are every session challenges. Cardiovascular problems with frequent hypotensions, coronary heart disease and cardiac heart failure are another difficult field to manage. But the most important and continuous care is that of vascular access, the "Achille's Heel" of our patients. Results from our studies reveal diabetes like the second cause of arteriovenous fistulas failure, after the age of patients, so we are reinforcing the whole medical chain for referring patients in the fourth stage of CKD for the creation of permanent vascular access, especially diabetics.

PP-35 Bacterial infections after kidney transplant

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Introduction. Kidney transplantation is the best choice for patient treatment with advanced chronic renal disease. Successful renal transplantation is depended on a good compromise between sufficient immunosuppression and adequate level of immune competence which avoid acute rejection and maintaining immunity to prevent infection occurrence, respectively. Infections remain a frequent complication.

The aim of study was to evaluate the incidence of bacterial infections in renal transplant recipients during the first year after transplantation according to different characteristics of patients and therapies aiming to recommend interventions in periods and groups with higher risk.

Methods. This is a longitudinal retrospective study, conducted in UHC "Mother Thersea", Tirana, Albania. 100 patients that had undergone renal transplantation during January 2015-December 2018, were included in the study. Patients were selected in Transplant Register. The necessary information was collected from patient individual medical files. The data was analyzed using SPSS 22 program.

Results. Mean age resulted 35.3±12.8 and male/female ratio was 1.8. In only 40 % of patients were observed at least one infectious episode. Most common were urinary tract infections 35%, predominately in male gender. E. coli was the most common causative organism (19%), followed by Proteus (10%) and Enterococcus (6%). 21% of infectious episodes occurred between 2 to 6 months after transplantation.

Conclusion. Based on the results of this study, men had higher risk of developing bacterial infections, especially UTI. The period 2-6 months after transplantation showed to have greater incidence of bacterial infections. The age group 15-31years had the greater incidence, respectively. Studies with greater samples are recommended in order to improve the quality of life in these patients.

PP-36 The challenges of bone mineral disorder mangement in a transplanted pediatric patient

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Introduction. The authors present a case report of the first total parathyroidectomy performed in our clinic in an adolescent with G 4T stage CKD associated hyperparathyroidism, secondary anemia and hypokalemia. The difficult management of postoperative complications, electrolytic balance, anemia and infections are presented in this case report.

Case report. After the surgical procedure the intact PTH values dropped significantly during the first 72 hours (from an initial of 3974pg/ml to 4,3pg/ml) manifested by severe hypocalcaemia and hungry bone syndrome. Hypocalcaemia was treated with intravenous calcium gluconate and high dose oral vitamin D. Severe hypocalcaemia manifested with multiple episodes of tetany and stridor was difficult to reduce with oral calcium carbonate treatment, requiring a longer intravenous treatment (up to 3 months). Another challenge was the control of hypomagnesemia which required long term treatment. Blood transfusions were necessary to control the anemia. Multiple infections (pneumonia, acute pyelonephritis, and catheter associated infection) were treated with broad spectrum antibiotics.

Conclusion. Parathyroidectomy is an option in patients with severe hyperparathyroidism associated to chronic kidney disease after renal transplantation. The management of mineral-bone disorder in the pediatric patients is difficult due to the lack of studies. In this case, the control of calcium and magnesium balance required up to 6 months of aggressive treatment.

PP-37 Catheter related complications in incident hemodialysis patients - ten years study

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Introduction. Vascular access is one of the most important factors that affects survival of hemodialysis patients. Native arteriovenous (AV) fistula is still considered the gold standard for vascular access. However, use of central venous catheters for hemodialysis is constantly increasing. This is largely because of the older population starting renal replacement therapy and whose blood vessels are often inappropriate for AV fistula construction. Catheter related complications include early complications, occurring during catheter placement and delayed complications, such as infection and thrombosis.

Aim: To investigate the incidence rates and risk factors for catheter-related complications in incident patients at Hemodialysis Clinic, Clinical Centre University of Sarajevo, during ten (10) year period, from 1st of January 2006 till 31st of December 2015.

Methods. Our retrospective study included 391 incident patients on hemodialysis, from whom 159 patients had catheter inserted (temporal or tunneled cuffed) and were included in further examination. Patients' demographic data, line placement and post-procedure complications were collected.

Results. Catheters were placed in 159 patients (40.6%), out of 391 incident patients. Temporary catheters (TC) had 119(74.8%) patients and tunneled cuffed catheters had (TCC) 40(25.2%) patients. Incidence rate of TC placement related complications was 2.6%, with the insufficient blood flow as the most common complica-

tion. TCC placement related complication occurred in one case (2.5%) as bleeding. Delayed catheter related complications occurred in 62(52.1%) patients with TC and in 14(35.0%) patients with TCC. Thrombosis was the most common TC complication (18.5%) while infection was the most common in patients with TCC (15.0%). Time spent on TCC represented high risk factor for the development of delayed complications. Higher number of catheter insertions was associated with catheter placement related complications and delayed complications, in both TC and TCC.

Conclusion. Incidence rate of complications was significantly higher in patients with TC, rather than in patients with TCC. Low incidence rate of placement related complications indicates that radiological-guided placement was performed safely with excellent technical success. Incidence rate of delayed catheter related complications, for both TC and TCC, was favorable in comparison with other studies reported in the literature.

PP-38 Proteinuria and anti-HLA antibody in renal alogfrat function

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Introduction. Proteinuria is a marker of kidney tissue injuries, regularly used in assessment of renal allograft function. The presence of de novo anti HLA antibody (Ab) can cause ABMR or "silence rejection".

The aim of our investigation was to explore their occurrence and clinical importance after transplantation.

Methods. We follow up 51 kidney transplant recipient, non-sensitized, on the quadruple immunosuppressive protocol 1, 12 and 24 month after transplantation. Anti HLA Ab were detected with Luminex technic and MFI >800 was taken as a significant. 24 our proteinuria was measured in g/L and value >0.07 was taken as a significant. Kidney biopsy was performed on the month 12 and for tissue analysis Banff classification was used.

Results. From all, 17 pts developed de novo anti HLA ab. More of them had proteinuria >0.07 on the month 12 after transplantation (3 v.s. 14, p=0.026). Also high number of pts with anti HLA ab from class I had significant proteinuria (2 v.s 11, p=0.041). Findings of C3 >2 deposition on IF was accompanied with higher proteinuria (0.51±0.5 v.s. 1.24±1.3, p=0.044). Higher percentage of pts with significant proteinuria had mix tissue injuries including ABMR and other different categories of Banff classification (42% v.s. 70%, p= 0.037). Univariate linear regression analysis found donor age, presence of cat. 2 (ABMR) according to Banff classification, DSA and MFI as statistical significant prognostic values for appearing of proteinuria in kidney allografts.

Conclusion. Our study showed significant proteinuria in presence of de novo anti HLA ab and mix tissue injuries including ABMR and confirmed them as an importance factors in follow up kidney allograft function.

PP-39 Paratireoidectomy in therapy of secondary hypeparathyreoidism in UHC Rijeka

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Introduction. Parathyroid glands in the earliest stages of chronic renal failure (CRF) undergo multi glandular generalized hyperplasia in response to hyperphosphatemia, hypocalcemia, and decreased active vitamin D levels. Majority of the patients on dialysis treatment, ultimately develop refractory secondary hyperparathyroidism, a true neoplastic disorder of the parathyroid glands. Observed enhancement of parathyroid tissue apoptosis or reduced proliferation using various medications could cause significant regression of hyperplasia. However, surgical correction still remains the final therapy primarily reserved for symptomatic patients despite optimal drug therapy. As regard, the prevalence of parathyroidectomy has been lowered in the first decade of the 21st century most likely due to the introduction of active vitamin D analogs and cinacalcet.

Aim: To correlate trends in rates of parathyroidectomy in periods before and after 2003.

Results. The period from 1977 to 2003, 54 patients on dialysis underwent parathyroid surgery. The average length of dialysis treatment prior to surgery was 8.5 years. Patients were normocalcemic (2.4±0.4 mmol/l) with pronounced hyperphosphatemia (1.83±0.8 mmol/l and markedly elevated values of PTH (37.96±57.25 pmol/l) and AF (389.05±363.82 U/ml). During the period from 2003-2018 parathyroidectomy was performed in 23 patients with a slightly shorter period on dialysis and with much higher mean values of PTH (173.2 pmol/l) and AP (228.5U/ml) which were impossible to control by drugs.

Conclusion. The study showed a sustained reduction in parathyroidectomy rates during the years, probably due to better therapeutic possibilities of secondary hyperparathyroidism controlling in early stages of CRF.

PP-40 Arteriovenous fistula stenosis and the association with other vascular access complications

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Introduction. Among the most important complication of hemodialysis (HD) arteriovenous fistulas (AVF) is stenosis. This may precipitate either AVF premature failure, AVF complete occlusion or dialysis inadequacy. Peak systolic velocities over 400 m/s and lumen reduction >50% are considered criteria for AVF stenosis.

The current cross-sectional study aims to assess the prevalence of AVF stenosis among chronic HD patients and their association with other vascular access complications.
Methods. Our study included 174 chronic HD patients, mean age of 58±12 years, 35% female, with 35.9% radio-cephalic AVF, 12.1% brachio-basilic AVF, 52% brachio-cephalic AVF, average dialysis vintage 44 months. The same nephrologist experienced in vascular access performed Doppler and B-mode AVF US scans. We also recorded the average kT/V in the week of the ultrasound assessment. The aim of the study was to analyze how many AVF stenoses were incidentally found in our patient group, as well as to see whether AVF stenosis associates with other vascular access complications.
Results. In our group of 174 HD patients, we found that 26 patients (15%) had significant AVF stenosis. There was no significant distribution difference in the type of AVF (radio-cephalic, brachio-cephalic, brachio-basilic) in the groups with/without stenosis. The AVFs that presented stenosis also seemed to develop more calcifications (68%) than the group with no AVF stenosis (34%, p=0.04). Moreover, stenotic AVFs tended to develop more aneurysms than the non-stenotic group-38% VS 28% (p=0.04). There was no significant difference in the association with dialysis efficiency, cardiac calcifications, AVF flux or inflow arterial diameters and the presence of significant collaterals (p>0.05).
Conclusion. Stenotic AVFs tend to develop more wall calcifications and aneurysms than non-stenotic AVFs, which may contribute to their lower survival, which is why prompt intervention should be undertaken.

PP-41 The cardiac ultrasound prognostic value in HD patients-a three years multicenter follow-up study
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Introduction. The aim this study was to assess the cardiac ultrasound role in predicting mortality in HD patients.
Methods. 1104 with CKD 5 on HD therapy in 9 HD centers have been included (average age 58.8 years, 669 males, 23% with DM). 1090 patients underwent 1/year post therapy cardiac ultrasound. Left ventricular hypertrophy (LVH), valve calcifications (VCa) and ejection fraction (EF) have been assessed.
Results. At inclusion, the prevalence of VCa was 66.2% (61.6%-single valve, 4.4% 2 valve). From the patients without VCa at inclusion, 17% died during the follow-up and 51% developed one or two VCa. In the patients with VCa, the mortality during the follow-up was higher 24.7% (p=0.001). At inclusion, 67.7% of the patients presented LVH. From the patients without LVH 20.2% died and 20% developed LVH. In the patients with LVH at inclusion the mortality was 24.1%. EF was found <50% at inclusion in 15% of the patients Mortality during follow-up was significantly higher in these patients (34.9% vs 24.5% p=0.001). EF varied during the follow-up time. According to this variation, we divided the cohort into 3 groups: Group 1 with EF varying -5 to +5% (30.2% of the cases), Group 2 with increasing EF >5% (34.8% of the cases) and Group 3 with EF decreasing >5% (34.8%). During the follow-up, mortality was higher in Group 2 (33.4%) and significantly lower in Group 3 (23.7%).
Conclusion. Yearly monitoring of some echocardiographic parameters in HD patients may contribute to a better assessment of mortality risk in HD patients.

PP-42 "Renaissance" of kidney biopsy in Albania and adequate treatment of glomerulonephritis
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Introduction. Glomerulonephritidis are still an open, beautiful and disputable field of nephrology. But treating them without a kidney biopsy leads to more open, disputable, unsatisfactory and sometimes dangerous results. Our University Clinic of Nephrology has really a successful background and history in this field with a lot of kidney biopsies during the 1985- 1990, published also in foreign reviews. Than with the political system transition to democracy accompanied with forms of depression in several fields of medicine and not only, the biopsy slowly, gradually was left aside. It was a holster of about 2 decades without this crucial examination in the field of glomerulonephritis. The "renaissance" was very welcomed also not in a public hospital. Now is about ten years that we treat glomerulonephritis after having the kidney biopsy results.
Material and results. The first data and results are satisfactory: Our diagnosis changed in about 30-35% of cases and our treatment too. The strategy and management of our patients changed in about 23% of cases this especially in grave proteinuria and unresolved acute kidney injuries with active urinary sediment. Forms of glomerulonephritis diagnosed were as follows: IgA nephropathy 19%; Focal segmental glomerulosclerosis 17%; Membranous GN 16%; Membrano-proliferative glomerulonephritis15%; Minimal change Disease 12%; Lupus nephritis 8%; ESRD 4%; Rapid progressive glomerulonephritis 2%; Pauci imun glomerulonephritis 2%; Amyloidosis 1%; Diabetic nephropathy 1%; IGM glomerulonephritis 1%; C3 glomerulopathy 1%; Post preeclampsia nephropathy 1%. There were few complications including hematoma, hematuria. The regimens implemented for these glomerulonephritis treatments were: Ponticelli regimen, Pozzi regimen, oral prednisone, methylprednisolone pulse, cyclosporine, mycofenolate mofetil.
Conclusion. Following the international guidelines, Italian experiences and studies, Anglo-Saxons directives or mixing together to have a tailored therapy for each patient's clinical presentation and its' specifics is very

important but the most important thing is to have clear form of glomerulonephritis to cure for whom the kidney biopsy is a crucial and unsubstitutable tool.

PP-43 The use of ultrasound in determining the position of central venous catheter for hemodialysis - flow signal

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Introduction. Central venous catheters (CVC) are common vascular access for hemodialysis. The introduction of a catheter into a blood vessel is associated with many risks due to the proximity of vital organs and previously damaged blood vessels. The use of ultrasound is of great help in orientation, introduction and positioning of CVC.

Methods. Before inserting the CVC patients undergo ultrasound examination of the neck blood vessels. Ultrasound guided internal jugular vein catheterization is performed. After catheterization, position of the catheter tip can be determined by ultrasound. After visualization of the right atrium a jet stream of 20 ml saline is injected through the venous line of catheter. If the catheter is in the correct position jet stream is ultrasonically visualized in the right atrium ("a flow signal"). Absence of "flow signal" tells us about the abnormal position of CVC. Orientation with the ultrasound examination is very important in cases of emergency dialysis or revision of CVC position.

Results. In our center all catheterization are made under ultrasound guidance. Percentage of the blood vessel puncture with the first puncture is 83%, and the number of complications such as puncturing the carotid artery, hematoma, pneumo/hemothorax is negligible. The position of the catheter is routinely confirmed by chest X-ray, patients who must be urgently dialyzed undergo echocardiography, and after the hemodialysis chest X-ray is performed.

Conclusion. Ultrasound is not only an immense help, it also has a major role to determine position of the catheter tip. In urgent cases it shortens the time from catheterization to the initiation of hemodialysis. The X-ray identified anomalies of position and attempting to revise the same reduces the number of x-rays.

PP-44 Vascular approach as a predisposing factor for infections in hemodialysis patients

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Introduction. Frequent infections in patients treated with dialysis are one of the most common causes of mortality and morbidity in that population. In these patients, infections are most often associated with dialysis access.

Aim of this study is to point to high risk of infections in patients with central venous catheter (CVC) and the need for creation of preventive AV fistula.

Methods. We examined hemodialysis patients at the Clinic for nephrology, Clinical Center of Montenegro, and their medical documentation. The research was carried out retrospectively for a period of 3 years (January 2016.-January 2019). Obtained results were processed with descriptive statistics.

Results. Study showed that 22 patients had some form of infection and they were on a chronic hemodialysis program in the observed period, independently of the vascular approach. In that period, 80 to 85 patients were treated monthly with hemodialysis. Of 22 patients 16(72.7%) had CVC and 6(27.3%) were on immunosuppressive therapy. All 22 had comorbidities. Four patients had positive hemocultures. Staphylococcus aureus was isolated in three patients, Citrobacter and Enterococcus were isolated in one patient. Three had a positive urine cultures and one was positive for hepatitis B. Febrile state was clinically dominant in 15(68.2%) patients without any other manifestations. Sepsis was diagnosed in 4 patients. One respiratory, urinary and infection of soft tissue each were also verified. Three patients (13.6%) died and 19(86.4%) were cured.

Conclusion. Of infected patients, 72.7% had CVC which has the highest risk for the development of infection from all vascular approaches, but there is still a large number of patients who start treatment with hemodialysis via CVC.

PP-45 Intradialytic blood pressure in hemodialysis patients

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Introduction. Hypertension is a major risk factor for renal disease. Conversely, chronic kidney disease (CKD) is the most common form of secondary hypertension with mutual influence. In patients treated with hemodialysis, hypertension is common and often poorly controlled. The aim of the study was to investigate the rate of intradialytic hypertension (IDH) and its associated factors among patients with chronic kidney disease.

Methods. In a cross-sectional study one hundred-forty five patients with chronic renal disease treated with hemodialysis (HD) for at least 3 months in the Fieri regional hospital in Albania during the year 2018 were enrolled in the study. Demographic and clinical characteristics and ultrasound findings were evaluated. A multivariable linear regression model was used to find factors associated with pulmonary artery pressure.

Results. The mean age of participants was 59.9+13.2 years. 65(44.8%) of the sample were females and 80 (55.2%) males. The mean duration of HD was 36±29 months. The mean uricemia value in females was

5.68+1.40 mg/dl, while in males was 6.45+1.66 mg/dl, (p=0.01). There was no significant difference in systolic and diastolic blood pressure according to the stages of dialysis (p=0.6). The prevalence of IDH was 21.3%. Males had a significantly higher prevalence than females (p<0.01). In multivariate analyses, predictors of the IDH were volume excess (p=0.02), serum albumin levels (p<0.01) and intradialytic hypotension (p<0.01).
Conclusion. Clinicians assess the prognostic significance of intradialytic BP profiles and its change over time to prevent cardiovascular events and mortality.

PP-46 Mortality analysis in patients on maintenance hemodialysis-single center experience
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Introduction. Despite the development and advancement in medicine, mortality rate amongst hemodialysis patients is still high. According to literature data it is around 8-10% in Japan, 15-20% in Europe, and the highest in the USA, around 30%.
Methods. We performed a retrospective observational single center study in patients on maintenance hemodialysis (HD) within February 2014 to June 2019. We assessed crude mortality rate in correlation to primary cause of end-stage kidney disease (ESKD), dialysis vintage, comorbidities and causes of deaths.
Results. The number of patients who died within February 2014-June 2019 was 72. In 2014 out of 72 patients on maintenance hemodialysis there were 8 deaths. In 2015, 80 patients were treated and 14 died. In 2016 fifteen out of 87 patients died. The mortality rate in 2017 was 13.68% and in 2018 15.79%. In the first six months in 2019 out of 92 patients treated in the center there were 7 deaths. Regarding the primary cause for ESKD, arterial hypertension (HTA) was predominant (37.5%), followed by DM type II (27.8%), obstructive nephropathy (13.9%), chronic glomerulonephritis (11.1%), adult dominant polycystic kidney disease (5.5%) and other (4.2%). The youngest patient had 31 years of age, and the oldest was 85. There was slight female predominance in the mortality rate, males were 32 (44.5%) and females were 40 (55.5%). The mortality rate according to dialysis vintage was: < 90 days on HD 31.9%, 3-6 moths 2.8%, 6-12 months 9.7%, 1-5 years 40.3%, 5-10 years 9.7%, and >10 years 5.6% deaths. The causes of death were as follows: cerebrovascular event 29.2%, sudden cardiac death 27.8%, and terminal malignant disease 25%, complication regarding vascular access 8.3%, and other 9.7%.
Conclusion. It can be concluded that the overall mortality rate in a single center is 15-17% which is close to the average in Europe. The primary cause for ESKD in the patients who died was HTA and DM type II. Mortality rate was higher in female than in male. Cardiovascular comorbidities were amongst the most frequent, but in the recent years also malignancies are becoming significant. Regarding the dialysis vintage, the highest mortality rate is in patients who are <90 days on HD and between 1-5 years.

PP-47 Hematological disorders after kidney transplant
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Introduction. Renal transplantation is the best choice for treating patients with advanced stages of chronic renal disease. A successful renal transplant relies on a good combination of immunosuppressive therapy and the maintenance of an appropriate level of immune defense of the body, avoiding acute bone turnover and the occurrence of possible infections.
Aim: The purpose of this study is to determine the incidence of hematological disorders in transplant patients, categorized according to 3 main periods in the first year after the transplant, in order to intervene rationally in the most frequent periods and groups up.
Methods. This is a longitudinal retrospective study conducted in Albania at the University Hospital Center, QSU "Mother Teresa", Tirana. This study included 97 patients who performed renal transplantation between January 2015 and December 2018. Patients were selected from the Basic Transplant Record. Based on the individual patient records, information was available about the hematological disorders that these patients had during the first year after the transplant. Statistical data packets SPSS 22 were used in data processing.
Results. The average age of the patients in the study was 35.3±12.8 and the male/female ratio was 1.80. Predominate patients who have had a hematological disorder during the first year after the renal transplant. The worst hematologic disorders were post-transplant anemia 38%, cytopenia after transplantation of 12% of which thrombocytopenia was most frequent and no high mortality. The most frequent episode of disorders was the second post-transplant period, from the 2nd to the 6th month. The most common etiologic causes were viral infections and immunosuppression.
Conclusion. Based on the data analysis of this study, the most endangered by hematological disorders are male patients and the highest risk period is the second post-transplant period. Patients under treatment with high doses of immunosuppressive treatment were most affected by hematological disorders. The most affected age group was 15-31 years old. Larger studies in the population of transplanted patients are recommended to interfere with improving the quality of life in these patients.

PP-48 Erysipelas in dialysis patient
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Introduction. Cellulitis/erysipelas is a clinical diagnosis based on erythema, swelling and local tenderness of the skin and subcutaneous tissues accompanied by fever and malaise. Cellulitis of the lower limb shares several clinical characteristics with deep venous thrombosis (DVT) and both have variability of clinical signs. These factors may lead to diagnostic uncertainty, which is particularly important in pts with clinically diagnosed cellulitis who are slow to respond to antimicrobials. Erysipelas is an infrequent infection of the skin and soft tissues. Streptococcal etiology is more common in rural areas and females, and the average age is approximately 60 years. Pts often have comorbidities such as DM 2, venous insufficiency in the leg and chronic lymphedema, leg ulcers and chronic renal failure. All these conditions favor local infections or are capable of compromising the immune system.

Case report. 65 years old female patient with primary diagnosis APKD; with edema, pain and redness of left lower limb. Blood count was insignificant, only CRP was elevated at the beginning (74.4) and slowly declined to normal values with treatment (2). Blood test for hemostasis showed elevated d-dimers with secondary activated fibrinolysis. Patient was firstly treated with quinolone group of antibiotics, clarithromycin 500mg, and LMWH in the days of hemodialysis. There was slight improvement of the condition. The edema, redness and pain of the leg remained, so hospitalization was indicated. She was switched to double therapy with ciprofloxacine and clindamycin, LMWH 4000I.E. remained. After two weeks, she was dismissed from the hospital. Doppler ultrasonography of lower extremities found masses in the right VFC and VF. After three weeks of therapy there was normalization of values of d-dimers and INR, OAK was stopped. Her condition improved after one month from the first appearance of the disease. Edema and redness of the lower limb disappeared; only brown pigmentation remained. Therapy with sol. boric acid locally, tabl.ACE selen 1x1caps Serapeptase 1x1 for 20 days remains. Because of the difficulty of obtaining bacterial cultures from patients with cellulitis/ erysipelas the microbiology of these common infections remains incomplete. Positive blood cultures in the most cases showed streptococcocus pyogenes (46%) after that staphylococcus aureus (14%), and on the third place gram negative microorganisms 11%. Blood cultures are unlikely to change the management of simple located SST in otherwise healthy. Immunocompromised pts however, because of the potential for deep tissue involvement cultures are useful in pts with severe infections or sings of systemic involvement in older or immunocompromised pts. Imaging studies are not indicated for simple SSTs .Plain RTG<US, CT, or magnetic resonance may show soft tissue edema or fascial thickening, fluid collections or soft tissue air. Immunocompromised pts are more prone to SST and may not demonstrate classical clinical features and less findings because of their attenuated immune response. Diagnostic testing should be performed early to identify the causative organism and evaluate the extend of involvement and antibiotic therapy should be commenced to cover possible pathogens, including atypical organisms that can cause serious infections (resistant gram-negative bacteria, anaerobs, fungi). Pts admitted with lower limb cellulitis prospectively underwent a likelihood assessment for DVT using the Wells criteria followed by investigations with d-dimers and ultrasound.

Conclusion. Severe venous congestion produces a clinical appearance that can be indistinguishable from the appearance of cellulitis. Pts with warm, swollen, tender leg should be evaluated for both cellulitis and DVT, because pts with primary DVT often develop a secondary cellulitis while pts with primary cellulitis often develop a secondary DVT. Superficial thrombophlebitis, likewise is often associated with a clinically inapparent underlying DVT.

PP-49 Significant differences in mortality between diabetic versus non-diabetic hemodialysis patients: the 5 year follow-up analysis

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Introduction. The study objective was to determine the differences between diabetic and non-diabetic hemodialysis (HD) patients, at initiation and during the 5year follow-up analysis.

Methods. A total of 261 HD patients (mean age 49.69± 15.59 years, diabetes mellitus 17.2%), were prospectively followed up for 60 months. We examined several risk factors at initiation of HD and uremia and dialysis related risk factors during 5 year HD treatment.

Results. At initiation of HD, diabetic vs non-diabetic patients were significantly older (55.64±11.89 vs 48.44±15.38 year, p=0.00), had higher systolic blood pressure (175.64± 26.11 vs 165.81±28.08 mmHg, p=0.04), pulse pressure (81.79±22.61 vs 68.41±20.64mmHg, p=0.00), left ventricular mass index (176.46±50.46 vs 156.01±47.59 g/m², p=0.04), but lower creatinine (755.50±301.37 vs 1024.86± 373.91 µmol/l, p=0.00) and albumin (34.32±5.29. vs 37.81±5.86 g/l, p=0.001). An estimated glomerular filtration rate (eGFR) was significantly higher in diabetic vs non-diabetic patients (8.31±4.01 vs 6.01±3.26 ml/min, p=0.04). During the HD treatment diabetic vs non-diabetic patients have lower hemoglobin (100.26±16.13 vs 105.53±13.37, p=0.02), albumin (36.53±3.96 vs 38.54±3.21, p=0.00), but higher CRP (26.00±39.04 vs 15.92±20.53, p=0.001) and left ventricular mass index (169.38±41.75 vs 138.13±51.28, g/m², p=0.006). Kaplan-

Meier analysis showed that all cause (log rank, p=0.012) and CV mortality (log rank, p=0.008) were significantly higher in diabetic vs non-diabetic patients. When compared with non-diabetic patients, HR for all-cause (1.8; CI95%1.16-2.75, p=0.008) and CV mortality (2.1; CI95%1.24-3.52, p=0.006) was significantly higher for diabetic patient.

Conclusion. We concluded that diabetic patients, despite the higher eGFR at initiation of HD, have higher all-cause and CV mortality which has multifactorial reasons.

PP-50 The predictors of parathormone variability in hemodialysis patients

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Introduction. KDIGO Clinical Practice Guidelines recommended that in hemodialysis (HD) patients serum parathormone (PTH) levels should be maintained in the range of approximately 2-9 times the upper normal limit for the assay.

The aim of the study was to evaluate the predictors of PTH variability in HD patients over a 12 months period.

Methods. The study encompassed 398 patients (256 M and 142 F) with the average age 59.64±13.29 years and the average HD vintage 78.63±64.26 months. Over a 12 months period serum calcium, phosphorus, alkaline phosphatase (APh), oral calcium carbonate daily dose, oral calcitriol weekly dose, and dialysis fluid calcium concentration were monitored monthly, and PTH at 6 months. According to PTH assay reference level (18.4-80.1 pg/ml) 3 groups of patients were categorized: patients with low PTH <160, with target range PTH= 160-721, and with high PTH >721. For statistical analysis chi-square test, combined analysis of variance with repeated measures and logistic regression analysis were performed by softer SPSS.

Results. Over a 12 months period the number of patients with low PTH significantly decreased, but the number of patients with target range PTH and high PTH increased. In 35 patients consistently hemodialyzed with dialysis fluid Ca=1.25mmol/L the highest Ca and Pi and the significant increase of PTH and APh were observed. In 24 patients consistently hemodialyzed with dialysis fluid Ca=1.75mmol/L, the lowest Ca and Pi and the significant decrease of PTH were observed. In 195 patients consistently hemodialyzed with dialysis fluid Ca=1.5mmol/L, no significant changes in Ca, Pi, PTH and APh were observed. The dialysis fluid Ca=1.75 (OR=8.33), increased Ca (OR=7.7), and presence of diabetes mellitus (OR=2.44) were the most significant predictors of low PTH <160, but the increased Ca (OR= 6.88), dialysis fluid Ca=1.25 (OR=5.08), and increased Pi (OR=2.72) were the most significant predictors of high PTH >721 by model of logistic regression analysis.

Conclusion. The prolonged use of dialysis fluid with high calcium concentration and oral calcitriol high dose in patients with low level of calcium led to PTH decrease, but prolonged use of dialysis fluid with low Ca concentration and oral calcitriol low dose in patients with high level of calcium led to PTH increase.

PP-51 Urinary tract infection in adults living in the community

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Introduction. Urinary tract infection (UTI) is one of the most commonly diagnosed infections in adults. Consensus guidelines have been published to assist clinicians with diagnosis and treatment of urinary tract infection, however, diagnosis, management, and prevention of urinary tract infection in the general population is still challenging.

Aim of our study was to evaluate incidence of UTI in a general population of age >18 years, and to find factors associated with UTI.

Methods. Patients of age >18 years followed by the general practitioner (GP) during January-June 2017 were included and screened for the presence of genitourinary symptoms and/or a significant bacteriuria with a quantitative count of ≥105 colony forming units of bacteria per milliliter (CFU/ml) in one urine specimen.

Results. 2820 patients needed the GP consultation during the study time. 74(2.6%) patients completed criteria for the diagnosis of UTI. The ratio female (69%)/male (31%) was 2.2/1, and the mean age was 56±12 years. Patients >65 years were (37%). Comorbidity was present as prostatic hypertrophy and urinary retention (12%); Diabetes Mellitus (19%); dementia and bladder incontinence in 6%. Patients with recurrent UTI were 35%. No one had a urinary catheter. Comorbidity was independent predictor of recurrent UTI: odd ratio 31; confidence interval 2.4-417.4; p=0.008. The frequency of localized genitourinary symptoms were: dysuria (40%), frequency and urgency (2.5%), lower abdominal pain (22.9%), back pain (25.7%), hematuria (15.4%), fever or chills (15.4%). Escherichia coli was found in all of urine cultures performed.

Conclusions. The diagnosis and treatment of UTI remains a significant challenge for clinicians caring for adults. Older adult patients with comorbidity should have frequent examination and longer follow up.

PP-52 Treating secondary glomerulonephritis right by treating primary disease

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Introduction. Happiness is when we diagnose a hidden, treatable secondary cause of glomerulonephritis - this very nice statement that I have seen last month brought me to report a successful case of remission of glomerulonephritis due to hepatitis C treatment.

Case report. A 34 year-old female was admitted in Nephrology Unit for malaise, hypertension, purpuric cutaneous lesions in both legs and face, arthralgia, acute renal failure. She revealed Hepatitis C positivity. After full immunologic screening resulted a low complement (C4) titer, positive type II (IgM) cryoglobulins, increased rheumatoid factor, positive anti HCV and very high levels of HCV-RNA(over 4 million copies). After the kidney biopsy that resulted Type 2 cryoglobulinemic membranoproliferative glomerulonephritis she was treated with rituximab and for a period of one year she was on remission. The hepatitis continued to be untreated, active and after rituximab it aggravated with higher titers of HCV RNA. Finally she initiated interferon and ribavirin combination for the treatment of Hepatitis C with a lot of hematological and infectious side effects. At the end of treatment, the HCV RNA decreased but did not became negative, the hepatitis was not eradicated, not fully recovered. Six months later she presented with proteinuria, microscopic hematuria, hypertension, high cryoglobulin levels and purpuric lesions especially in legs and face. The evident hepatic fibrosis in elastography and the high HCV RNA titer were imperative for an aggressive, modern, costly treatment like HARVONI (ledipasvir 90 mg and sofosbuvir 400 mg) 1 tablet per day for three months. After three months of therapy she was HCV RNA negative. Two months later her glomerulonephritis was on remission. She presented in our ambulatory last month, one year after the treatment with HARVONI and she is still in remission without proteinuria, hematuria, and hypertension.

Conclusion. When diagnosing a secondary glomerulonephritis we better need to treat the primary cause for having the satisfaction of kidney recovery.

PP-53 Urinary tract infections (uti) caused by intra-hospital strains of bacteria at the University Clinic of Nephrology in Skopje

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Introduction. Urinary tract infections (UTI) are among the most common infections caused by intra-hospital strains of bacteria. Many studies show that they account for 23-49% of intra-hospital infections. The most common triggers are Gram negative bacteria and they contribute significantly to the increase in morbidity, mortality and costs of treatment. The risk factors for UTI include female sex, urological interventions, other present infections, diabetes mellitus, chronic kidney disease/ hemodialysis, antimicrobial therapy, etc.

Methods. At the University Clinic of Nephrology in Skopje, a retrospective study was conducted where positive urine cultures for intra-hospital bacteria strains were analyzed in patients who were hospitalized at the Clinic for various reasons over a period of 2 years. The study analyzed a total of 84 pts (45 women and 39 men, average age 55g). Analyzed data: primary disease (especially DM and carcinomas) and comorbidities, gender, age, clinical and laboratory signs of infection, urine cultures, urological interventions, administered antibiotics and antimicrobial resistance in some of them.

Results. In most of the patients there was only one bacteria as a cause of the infection (90.7%), while in 9.3% of the patients there were two bacteria as causes of UTI. Raised values of Le and CRP, as well as febricity, were registered in the majority of patients (80%). Urosepsis was reported in 7 patients. Diabetes mellitus had 16 patients (19%); patients with transplanted kidney (15 pts-17.8%) in whom there was no positive urinary culture, still antibiotics were given because of immunological suppression; obstructive nephropathy and suspected/confirmed malignant process (part of patients with JJ stents) had 12 pts (16.6%). The most common triggers: Escherichia coli (39.1%, mostly ESBL+), Klebsiella spp (18.7%, part of them ESL+), Pseudomonas aeruginosa (12.5%) and much less Proteus mirabilis, Enterococcus faecalis and etc. Most of the infections were treated with imipenem/meropenem, tazobactam or colistin (according to an antibiogram). Several results were obtained where only one antibiotic was susceptible. Vancomycin resistant Enterococcus was registered in 2 cases and was treated with Linezolid.

Conclusion. The examined patients were in large part at risk factors that could not be affected (underlying disease, comorbidities, etc.) but there are factors that can be affected. First of all, it is implementation of all measures for prevention of intra-hospital infections - rational setting of urinary catheter, urological interventions and rational administration of antibiotic therapy.

PP-54 Short-term postpartum follow-up of patients with chronic hypertension and preeclampsia by the nephrologist

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Introduction. Hypertensive disorders in pregnancy cause significant maternal and fetal morbidity and mortality and may cause future renal complications.

The aim of our study was to define management of hypertension short-term postpartum as well as the renal outcomes and the need of further check-ups of these patients by the nephrologist.

Methods. Patients with chronic hypertension and preeclampsia were referred to the University clinic of nephrology for a checkup after delivery. The check-up included blood pressure measurement, kidney ultrasound, 24-hour proteinuria, serum creatinine, estimated GFR according to Cockroft-Gault and determination of risk factors.
Results. A total of 80 patients with chronic hypertension or preeclampsia were referred postpartum to the University clinic of Nephrology in the period 2016-2019 for a regular checkup. Sixty patients had chronic hypertension and twenty had preeclampsia. At a mean time of follow up 90 days after delivery, mean blood pressure (BP) was 135/90 mm Hg and the mean glomerular filtration rate was 112 ml/min. Thirty percent of patients had a blood pressure of 140/90 mmHg or higher and received antihypertensive medications (95% of patients received Methyldopa and 5% received other antihypertensive drugs). Proteinuria was present in 10% (8 patients) and proteinuria and hypertension was present in 5% (4 patients). Kidney ultrasound revealed normal findings in 74 patients, unilateral kidney hypoplasia in 5 patients and suprarenal adenoma in 1 patient. Glomerulonephritis was proven by renal biopsy in 4 patients. Risk factors for uncontrolled hypertension (BP >140/90 mmHg) were age, preeclampsia and persistent proteinuria.
Conclusion. Regular checkups by the nephrologist for women with chronic hypertension and preeclampsia postpartum are recommended.

PP-55 Some psychological specifics in patients on hemodialysis

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Introduction. Chronic Renal Disease is a public health problem that tends to take dimensions of epidemic. Statistical data confirm that CKD affects 10-15% of the adult population worldwide and is associated with poor quality of life, increased risk for cardiovascular disease, and reduced life expectancy. Frequent hospitalizations and dependency on technology and providers place individuals with CKD at high risk for multiple safety events. Threats to their safety may be physical, emotional, or psychological. Additionally, protein-bound uremic toxins (PBUTs) play a role in the multisystem disease with a serious threat for the function of nervous system and psyche. In this context, the level of anxiety and depression are confirmed to be high, as well as some personality characteristics.
The aim of our study was to evaluate the level of depression and personality characteristics in a group of randomly selected patients treated with hemodialysis.
Methods. The evaluated sample comprised 230 patients, mean age 55.5±13.5 years, with duration of dialysis about 6.5 years, and both genders. Used psychometric tools were Beck Depression Inventory, Taylor Alexithymia Scale, as well as MMPI-201.
Results. Obtained results confirmed variable level of depression (minimal in 21-43%, mild in 35-71%, moderate in 17-85% and severe in 14-28%) significantly positively correlated with age and educational level. Scores for TAS-20 showed that 50% of patients were indicative for alexithymia construct, 18% had possible alexithymia and the rest of 32% were non-alexithymic. MMPI-201 showed hypersensitivity, depressive mood, and withdrawal from friends and relatives. More specific emotional traits were accentuated anxiety, low level of hostility but very high positive aggression which destroys their social communications.
Conclusion. Study confirmed psychological specifics in patients treated with hemodialysis and need for some psychological interventions (support, cognitive-behavior therapy, biofeedback, and in some patients medications). However, the team which is responsible for this group of chronic patients' needs the collaboration with psychologist/psychiatrist for preventing serious problems with suicide as a threatening possibility.

PP-56 Be aware of bilateral renal artery thrombosis in akute kidney injury and atrial fibrilation patient

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Introduction. Renal infarction is an underdiagnosed and underreported event which needs to be diagnosed rapidly to prevent permanent loss of renal function. It is often mistaken for more benign pathology and is worthwhile reviewing and reporting.
Case report. 77-year-old female patient was admitted with symptoms of weakness, dyspnea, diarrhea and anuria starting week before admission. One month prior to hospital admission she had abdominal pain in the right upper quadrant, similar to cholecystitic pain, which she had suffered many years ago (Gilbert syndrome) which was resolved by cholecystectomy. She had a history of chronic atrial fibrillation and was off anticoagulant drugs. Her relevant past medical history included hypertension and dyslipidemia. Physical examination revealed no obvious abdominal pain, flank tenderness, a blood pressure of 130/80 mmHg and an irregular rhythm with a heart rate of 110 beats per minute. She was afebrile, with normal saturation, had peripheral edema and bilateral pleural effusion.
Laboratory studies on admission, showed white blood count $10.8\times10^3/mm^3$, absolute neutrophil count $7.8\times10^3/mm^3$, red blood cells count $4.06\times10^6/mm^3$, hemoglobin level 11.3g/dl, thrombocytes count $425\times10^3/mm^3$, normal liver functions tests, a tendency for hyperkalemia, normal INR and prothrombin level and high urea and creatinine level (152 mg/dl, 10.2mg/dl, respectively).

On hospitalization, the first most important step was solving the rapid decline in renal function and anuria so we started treatment with hemodialysis. The second step was a more accurate diagnosis of this unexplained AKI and for this, it was immediately performed a total body contrast-enhanced computed tomography (CT). No signs of pancreatitis or kidney stones were found, but multiple micro areas of infarction in the left kidney, as well as a superior hemi renal infarction in the right kidney, were reported.

Conclusion. Renal infarction is an easily missed diagnosis due to its nonspecific presentation. Sudden onset of abdominal pain with nausea and vomiting, and high aspartate transaminase and lactate dehydrogenase in a patient with atrial fibrillation should raise high suspicion for renal infarction. Early diagnosis, early anticoagulation, and early thrombectomy is the key to rapid recovery.

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