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Editorial

Challenges Facing the Improvement of Kidney Transplantation - Issues in a Developing Country, Republic of Macedonia

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Abstract

Chronic kidney disease (CKD) is a global health problem presented in between 8-10% of the adult population, and about 2 million people need renal replacement therapy (RRT) or have a kidney transplant. The renal transplantation provides quality of life and long-lasting survival superior to the other types of RRT. The treatment and maintenance of quality life of these patients is a challenge for whole community that requires multidisciplinary collaboration between medicine, political, law and sociology field.

Economic deprivation in our and other developing countries and also the meager expenditure on health care, translates into a poor transplantation activity. Although living donors provide the majority of organs in the developing world, social issues and cultural beliefs presents also a barrier to donation. Having poorly-developed renal transplantation is maybe primarily based on the fact that cadaver renal transplantation is not yet developed in our country. In addition, due to the lack of well - organized cadaver transplantation and the problematic events of the resent history in this region, the people of the Balkan countries are prone to go abroad to buy a kidney wherever it is available. Furthermore, the shortage of donor organs is not only a result of a lack of suitable donors, but rather a result of failure to identify donors and obtain consent. Finally, public media coverage has significant effect on people's awareness about transplanting organs by putting positive spirit on the matter.

The resolution of challenges in kidney transplantation in a developing country such as Republic of Macedonia is greatly influenced by the health care authority's willingness and capacity to develop a successful national kidney transplant program. Improving the public awareness of the benefits of organ donation through continuous media coverage and close collaboration with influential figures in the society, shifting from deceased to donation in close collaboration with the health professionals should be a strategy to follow.

Keywords: kidney transplantation, developing country, organ donation

Introduction

Chronic kidney disease (CKD) is a global health problem presented in between 8-10% of the adult population, and about 2 million people in need of renal replacement therapy (RRT) [1,2]. CKD is unique in sense of the choice of treatment modalities (hemodialysis, peritoneal dialysis and transplantation). As in other European countries, Republic of Macedonia has a continuous increase in the number of patients requiring RRT. The number of patients with RRT in Macedonia for 2015 is 1598 (929 males), 1353 on hemodialysis (HD), 32 on peritoneal dialysis (PD) and 213 with transplanted kidney [3], while for 2016 the number is 1665 (989 males), 1433 on hemodialysis, 25 on peritoneal dialysis and 207 with transplantation [4], as presented in Figure 1 and 2. CKD is associated with the risk of ESRD, cardiovascular disease and premature mortality. In addition to the implications for morbidity and mortality, the growing prevalence of CKD has significant implication for health and social care systems, because of the high cost of RRT, and its greatest burden experienced in developing countries. The World Health Organization (WHO) estimates that 10% of patients are in need for kidney transplantation annually [5]. The organ transplantation is world widely accepted procedure as successful method for treatment of patients with end-stage organ function damage, such as the liver, kidneys, the heart, lungs etc., improving the quality of life of these patents.

What kind of feelings people may face once they find out their illness, especially those suffering from a chronic irreversible disease? The treatment and maintenance of the quality life of these patients is a challenge for the whole community, which requires multidisciplinary collaboration between medicine, political issues, law and sociology fields.

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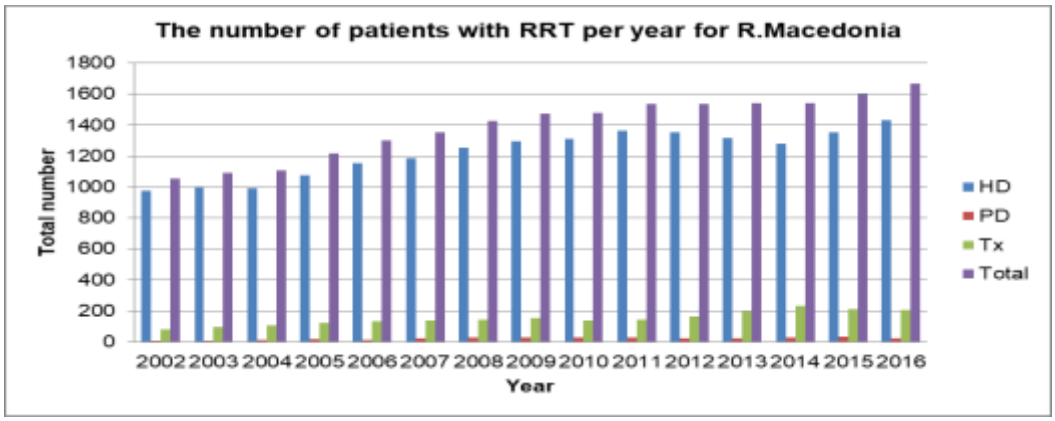

Fig. 1. RRT patients over the years expressed in absolute numbers
*data from ERA-EDTA registry (annual reports), *HD (hemodialysis), *PD (peritoneal dialysis), *Tx (transplantation), *Total

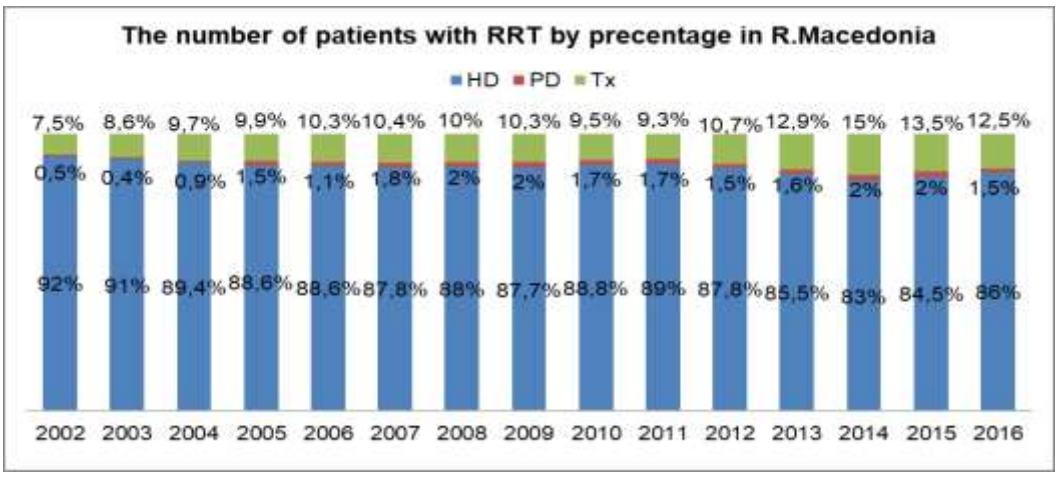

Fig. 2. RRT patients over the years expressed as percentage
*data from ERA-EDTA registry (annual reports), *HD (hemodialysis), *PD (peritoneal dialysis), *Tx (transplantation), *Total

Analysis

A living donor kidney transplant program has been developed in Republic of Macedonia since 1977 but without real improvement and progress in the following years. There was a great success with 15 cadaver kidneys transplanted (1987-1989) followed by an average of 13.5 living donor kidney transplantation per year in the period 1996-2011 [6]. In order to increase the number of organs, living donor (LD) transplantation from unrelated and ABO-incompatible (ABOi) donors have been introduced over the last few decades**.** Facing all the infrastructural, organizational and economical problems in a developing country in transition, the effective organ shortage was slightly overcome by introducing the expanded criteria for living donation, including elderly and marginal donors [7]. Economic deprivation in our and other developing countries and also the meager expenditure on health care, translates into poor transplantation activity with a rate of less than 10 per million populations in contrast to the developed world [8]. Although living donors provide the majority of organs in the developing world, social issues and cultural beliefs are also a barrier to donation.

Having poorly-developed renal transplantation maybe primarily based on the fact that cadaver renal transplantation is not well developed and frequent in our country. In addition, due to the lack of well-organized cadaver transplantation and the problematic events of the resent history in this region, the people of the Balkan countries were prone to go abroad to buy a kidney wherever it is available. The "Promised Land" in the past was India, and also Pakistan [9]. This organ commercialism apart for being unethical is also live threatening, and additionally burdens the health system in a developing country treating the complications that follow solid organ transplantation. Initially, the lack of suitable legislation and infrastructure has prevented growth of deceased donor programs. To address the growing problems of organ commercialism and exploitation of poor vulnerable populations, the Declaration from the Istanbul Summit (DOI) aimed to reinforce the resolution of governments and international organizations developing laws and guidelines to bring an end to the wrongful practices and to preserve the

nobility of organ donation [10]. Furthermore, the shortage of donor organs was not only the result of a lack of suitable donors, but rather the result of failure to identify donors and obtain consent. The low level of awareness in the population, without suitable medium support increased the barrier of the potential donors for transplantation. FInally, the media-coverage has a significant effect on people's awareness about transplanting organs by putting positive spirit on this matter. For example, the Spanish experience in the past is solid and highly relevant. The number of organ donors increased progressively, which is currently twice the rate in 1989 when the Organization Nacional de Trasplantes (ONT) was created. The explanation was improved by the fact that there was a creation of an efficient network of motivated and well-trained transplant coordinators that have been devoted to the effort to inform the media on issues relating to organ donation correctly and in a positive spirit. Thus, the ONT takes responsibility not only for coordination and guidance with regard to the medical profession, but also attempting to optimally use the important mass media impact on the public opinion improving the level of information of the Spanish population on these topics [11]. A 24-hrs transplantation phone-line has also been established. One single telephone number for the entire country with instant access to the ONT at any time was successfully used in this regard. The line was served by trained professionals. This has proved to be a simple and useful tool, and as well an example for our and other developing countries to follow that path towards improving renal transplantation. Maybe the solution of the problem should be sought in multidisciplinary social collaboration, which will increase the public awareness for transplantation and emphasize the importance of organ harvesting.

In our developing region in 2009 a memorandum was signed by the Ministers of Health of the South-Eastern Europe Health Network (SEEHN) [12,13]. This network is a multi-governmental collaboration on health systems from Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Macedonia, Moldova, Montenegro, Romania and Serbia. Its aim was to transform regional projects into programs of cooperation in between these countries and thus further improving solid organ transplantation. This joined collaboration helped identified national focal points and include health care professionals in implementing action plans specific for each country. It raised number of meetings, workshops, trainings and educational activities that helped health professionals in addressing country-specific needs and development of collaboration with the health care authorities to meet the target objectives for successful solid organ donation [14,15]. These activities were supported by the European Commission and became a model of success for kidney transplantation in this region.

However further and continuous action is needed in order to improve the number of transplants (from living and deceased donors), standardization of clinical practice and possibility for paired kidney donation that will decrease the number of patients treated with hemodialysis or those waitlisted. In other words developing a concept of national self-sufficiency where each country or region obtains its resources within itself or by regulated and ethical regional collaboration [16]. This must include efforts to decrease the incidence and prevalence of CKD and efforts to increase the number of kidney grafts.

Conclusions

Resolving the challenges in kidney transplantation in a developing country such as republic of Macedonia is greatly influenced by the health care authority's capacity and effort to develop a successful national kidney transplantation program in close collaboration with health professionals. This program must include the resolutions of DOI as a framework to achieve self-sufficiency in every aspect of kidney transplantation, improving public awareness of the benefits of organ donation for the ones mostly in need through continuous media coverage and close collaboration with influential figures in the society, shifting from a deceased to donation successful process. This is demandable but achievable, all for the wellbeing and better quality of life for our patients.

Conflict of interest statement. None declared.

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Original article

Improvement of Renal Failure Using Wharton's Jelly Derived Mesenchymal Stem Cells

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Abstract

Introduction. Renal failure is one of the major health problems worldwide, dialysis and kidney transplantation are the only available therapies used in clinic. However, high cost and increasing demand with limited organ donor still provide challenges. An alternative therapeutic approach to the present treatment is the utilization of stem cells to treat kidney diseases owing to its high proliferation rate and multipotency. Additionally, stem cells possess anti-inflammatory and antioxidant effects, which in turn help in tissue repair by decreasing cell damage resulting from injury. The current study aims to evaluate the role of mesenchymal stem cells derived from Wharton's jelly tissue (WJMSCs), and hyaluronic acid (HA) in the restoration of kidney functions in acute renal failure model.

Methods. MSCs were enzymatically isolated from Wharton's jelly tissue and expanded *in vitro.* The isolated cells were then characterized to confirm their MSCs criteria. The therapeutic potential of WJMSCs both treated and untreated with HA was evaluated by injecting the isolated cells into the renal cortical region of ischemic renal failure model. Blood, urine, and tissue samples were collected for biochemical and histological measurement to assess the improvement of renal functions in all experimental groups.

Results. The results revealed that Wharton's jelly derived MSCs exhibit the general characteristic features of MSCs isolated from other sources. better renal function amelioration was observed in the treated groups compared to the positive control group. The utilization of hyaluronic acid along with WJMSCs enhance the ability of WJMSCs to repair the injured kidney tissue

Conclusions. In conclusion WJMSCs were able to restore the renal functions and prevent tissue damage after ischemia reperfusion injury. Furthermore, the utilization of HA increased the regenerative capability of WJMSCs.

Keywords: Regenerative Medicine, Renal Failure, Wharton' Jelly, MSCs, Hyaluronic Acid

Introduction

Kidney failure is a major health trouble facing several patients worldwide, with the only accessible treatments being dialysis and kidney transplantation. The current available medical therapies include kidney dialysis, which is non-curative and costly, and kidney transplantation, which is curative, however, risks organ rejection and there exists an organ shortage. An alternative treatment approach to kidney diseases is to utilize stem cells therapy. It has been speculated that stem cells are able to boost tissue repair in several experimental models via transdifferentiation, cell fusion, or paracrine effect through release of cytokines and growth factor, consequently stem cell therapies hold a promising option for regeneration of several organs, including kidneys [1-11].

Renal IR injury is a complex inflammatory process that may happen during kidney transplantation, partial nephrectomy, or renal vascular surgery and may result in rejection and/or delayed graft function. IR injury causes impairment of kidney function, which may be attributed to glomerular endothelial cell injury or tubular obstruction [12].

Stem cells are undifferentiated cells capable of give rise to more specialized cells, they are commonly derived from embryonic and adult sources. MSCs are the most major type of adult stem cells, they are located in several tissues and prominent in the bone marrow and umbilical cord [13]. The isolation of bone marrow derived MSCs requires invasive procedures and yields low quantity [14]. Thus, this study utilized MSCs isolated from Wharton's jelly tissue of the umbilical cord (WJMSCs) to treat renal ischemia reperfusion (IR) injury, due to WJMSCs properties, such as self-renewal,

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high proliferation rate, multipotency, and their anti-inflammatory and antioxidant effects. Furthermore, they possess immunomodulatory properties, meaning they are able to reduce immunogenicity to avoid the risk of allogenic cell rejection by host tissue [15]. All these features allow these cells type to be used in clinical therapy. Hyaluronic acid (HA) is non-sulfated glycosaminoglycan and has a high molecular weight up to 20 MDa. HA is natural polysaccharide composed of repeating disaccharide units of N-acetyl glucosamine and glucuronic acid. HA is located in several tissues, including epithelial, neural, and connective tissues. HA also enhances cell proliferation, migration and homing. Furthermore, HA increases healing rate and decreases fibrosis, as well as regulates cell-cell and cell-matrix adhesion [16,17].

We hypothesize that WJMSCs help in restoring the kidney function after IR injury. Treatment of WJMSCs with HA enhances cell proliferation and homing in injured tissues, thus increasing its reno-protective function. First, we aimed to isolate MSCs from tissue and evaluated their features and their ability to restore the kidney function in a renal failure model. Second, we investigated the effect of HA treatment on the maturation and differentiation of WJMSCs. We evaluated the improvement of renal function of rats with kidney disease through blood chemistry for creatinine, BUN, and creatinine clearance analysis and histological examination.

- **Experimental Design**
- **Isolation and characterization of Wharton' Jelly Mesenchymal stem cells**
- **Umbilical cord collection and Cell isolation**

Umbilical cords were collected from healthy, full-term deliveries rapidly after prior consent of the volunteers according to a policy approved by the IRB and Ethical Committee. The umbilical cord was rinsed with sterile phosphate buffered saline (PBS; PH 7.4) under aseptic technique to remove blood and other debris. The umbilical vein and arteries were dissected from Wharton's jelly tissue, then the tissue was chopped into small pieces ~2-3 mm^3 in size and collected into 50 ml sterile centrifuge tube. MSCs were enzymatically isolated from Wharton's jelly tissue using collagenase type I (Sigma Aldrich, SCR103) at a concentration of 1mg/ml for 1 hour at 37ºC under continuous shaking. The cells were obtained by centrifugation of the previous mixture for 10 min at 1500 rpm, after which the supernatant was discarded and the cell pellet was resuspended in complete growth medium composed of [DMEM high glucose, 10% fetal bovine serum FBS and 1% Penicillin/ Streptomycin] and cultured into 75 cm^2 flasks then incubated in CO2 incubator in humidified atmosphere at 37°C with 5% CO2. The media was changed twice per week. The cells were passaged when confluency reached 70-90 % by incubating with trypsin EDTA 0.25% for 3-5 min at 37 ^oC. The reaction was stopped by adding 5 ml of growth medium and the suspension was centrifuged at 1500 rpm for 5 minutes. The cell pellet was resuspended in complete growth medium and reseeded at ratio 1:3 [18].

Cell Growth and population doubling time (PDT)

A short-term cell growth assay was performed by seeding WJMSCs into 6 well plates at a concentration of 1×10^4 cells/well and incubating with growth media in CO_2 incubator. The cells detached at days 2, 4 and 7 and the cell numbers were counted to create a growth curve. Additionally, cell viability was assessed using Trypan blue exclusion test. To determine the population doubling times (PDT), MSCs were plated into 6 well plates at a concentration of 1×10^4 cells/well. When the cells reach 80-90% confluence, the cells were harvested, counted and reseeded at the initial density. This procedure was repeated every passage. PDT value was analyzed according to the following equation: where Tc is the culture time (hours), whereas N0 is the number of seeded cells and Nt represent the number of harvested cells [14].

Colony forming unit-fibroblast (CFU-F) assays

A CFU-F assay was used to evaluate the proliferation and colonogenic capacity of the MSCs expanded in culture. WJMSCs were seeded in triplicate at 5×10^3 concentration into 60 mm cell culture plate then incubated for 7-10 days at 37°C in 5% humidified CO_2 incubator, the cell monolayer was washed with PBS, fixed in ice cold methanol, and stained with 0.1% crystal violet solution for 10 min. Clones of more than 50 cells were scored as a colony forming unit-fibroblast [19].

Immunofluorescence staining

WJMSCs were characterized by immunofluorescent staining of cell surface marker Vimentin. WJMSCs at Passage 3 were seeded on a chamber slide (BD Falcon, USA) with growth medium and incubated overnight in CO_2 incubator. The cells were fixed with 4% para formaldehyde and permeabilized with 0.1% TritonX-100. Non-specific sites were blocked using Dako protein blocking solution, the cells were incubated with primary antibodies mouse anti-Vimentin (ab20346) using 1:100 dilution at 4^oC overnight, then incubated with secondary antibody goat anti-mouse IgG labelled with Alexa Fluor® 488 (ab150117) at 1:400 dilution for 1 hour at room temperature. Nuclear DNA was labelled in blue with DAPI stain. The images were taken using fluorescence microscope (Leica, Germany) [20].

Osteogenic Differentiation

WJMSCs were harvested at Passage 3 using Trypsin EDTA as previously described, then seeded in triplicate

into 6 well plate at a concentration of 5×10^4 cells per well, then divided into two groups; the first group was cultured in osteogenic differentiation media composed of [DMEM supplemented with 10% FBS, 0.1μM dexamethasone, 10mM β-glycerol phosphate and 50μM Ascorbic acid]. The second group was cultured with normal growth media and used as a control. The media was changed twice per week for 2 weeks. The differentiation potential of WJMSCs was assessed by Alizarin red stain and alkaline phosphatase (ALP) activity. For Alizarin red stain, the cells were fixed using 10% neutral buffered formalin and stain with Alizarin red dye. During this reaction, the dye reacts with the Ca^{2+} ion and gives a red color, after which the images were taken using inverted light microscope (Zeiss Axiovert, Germany). Additionally, the stain was quantitively analyzed spectrophotometrically by extracting the dye by incubation with 4M guanidine-HCl (Sigma-Aldrich) overnight at room temperature. The extracted dye solution was diluted 10-fold and absorbance was measured at 490 nm Using spectrophotometer (SpectraMax M5, USA). Cellular ALP activity was evaluated using a QuantiChrom™ Alkaline Phosphatase Assay Kit (BioAssay system #DALP-250) according to the manufacturer's instructions [21].

Adipogenic Differentiation

WJMSCs at Passage 3 were harvested, counted, and seeded at a concentration of 10×10^4 per well into 6 well plate. The cells were divided into two groups, the first group cultured in adipogenic differentiation media composed of [DMEM supplemented with 10% FBS, 1μM dexamethasone, 500 μM isobutylmethylxanthine (IBMX), 5μg/ml insulin and 200μM Indomethacin]. The second group was cultured in normal growth media and used as a control, with the media being changed twice per week for 2 weeks. The adipogenic differentiation capability was tested by Oil-red-O stain. The images were taken using an inverted light microscope. The staining was assessed quantitively by extracting the dye using isopropanol incubation for 15 minutes at room temperature, and absorbance of a two-fold dilution of the extracted dye was measured at 550 nm [21].

***In vivo* study**

The cells used for treatment were divided into two groups. For the first group, WJMSCs were treated with HA (Sigma Aldrich catalog number 53747) at a concentration of 1 mg/ml for 14 days and in the second group, the cells were maintained in normal growth media. The animal study was carried out using 72 male Sprague-Dawley rats weighing ~250-300 g and in accordance with the Guide for the Care and Use of Laboratory Animals approved by the ethical committee (ECSR), Zagazig University. The rats were divided randomly into 4 groups: (1) **Sham group** (n=18) involved rats undergoing an identical surgical procedure, but without renal pedicle occlusion **(2) Control group (IR injury) (n= 18)** involved the renal pedicles (artery and vein) being obstructed for a period of 45 minute to induce the ischemia reperfusion injury to create acute renal failure model **(3) WJMSCs group (n=18) was** the same as in IR injury group with administration of 1×10^6 MSCs and **(4) WJMSCs/HA groups (n=18)** was the same as the IR injury group with administration of 1×10^6 MSCs pretreated with HA. The treatment groups included MSCs and MSCs/HA group, in which the cells were injected directly into the cortical region of the left kidney using 24-gauge syringe in 2-3 injections of 0.03-0.05 ml each at different locations along the lateral aspect of the kidney. Animals were sacrificed at 1,4 and 7 days after surgery and blood, urine, and tissue samples were collected to assess the efficiency of the treatment.

Kidney Function assessment

Blood and urine samples were collected at the sacrifice time of all animal groups, the blood was centrifuged and serum was collected. Urine samples were collected using metabolic cage biochemical parameters, including creatinine, blood urea nitrogen (BUN) and creatinine clearance were measured by standard laboratory methods. The anti-inflammatory marker monocyte chemoattractant protein 1 (MCP-1) was measured in the serum of all groups at day 7 post-surgery using MCP-1 Rat ELISA Kit (Abcam, ab100778) according to the manufacturer's protocol. Anti-oxidant superoxide dismutase (SOD) activity was evaluated in all groups at day 7 post-surgery using Superoxide Dismutase Colorimetric Activity Kit (Invitrogen, EIASODC) according to the manufacturer's protocol. The degree of fibrosis was evaluated in the tissue sample of all experimental animals 7 days post-surgery through measuring the total collagen content using Total Collagen Assay Kit (Biovision, K218).

Gene Expression

Total RNA was extracted from kidney tissue of sham, MSCs and MSCs/HA groups using RNeasy Mini Kit (Qiagen,74104). Isolated RNA was purified using RNeasy MinElute Cleanup Kit (Qiagen,74204). For cDNA synthesis, 1 μg RNA was transcribed using QuantiTect Reverse Transcription Kit (Qiagen, 205310) according to the manufacturer's protocol. Kidney-specific metanephric differentiation marker Cadherin 11 and CD 24 mRNA expression was analyzed using 2 μl of the obtained cDNA using Real-Time PCR system (Applied Biosystems, USA). Primer sequence used for Cadherin11 and CD24 are summarized below in table 1.

Table 1. Primer sequence used for Cadherin11 and

Gene	Sense	Primer sequence
Cadherin 11	Forward	5′-ATCGTCATTCTCCTGGGTTG-3′
	Reverse	5′-GCCACCACATAGAGGAAAGG-3′
CD 24	Forward	5′-GCCAGTCTCTTCGTGGTCTC-3′
	Reverse	5′-TGTTTTTCCTTGCCACATTG-3′
GAPDH	Forward	5′-CCTGCACCACCAACTGCTTA-3′
	Reverse	5′-GGCCATCCACAGTCTTCTGAG-3′

The reactions were initially heated for 10 min at 95^{o}C, followed by 40 cycles of 15 seconds at 95^{o}C and 60 seconds at 60^{o}C were performed. After a final denaturation (melt curve stage) step of 1 min at 95^{o}C, the amplification curve was recorded. Cadherin 11 and CD 24 mRNA was quantified in proportion to GAPDH as endogenous gene. The expression levels were scaled relative to the sample with the lowest expression level (Sham group).

Histological analysis

The kidney tissues were collected at day 7 post-surgery then cut into two equal halves, one half was fixed in 10% neutral buffered formalin and processed for paraffin blocks and the other half was kept in liquid nitrogen for RT–PCR analysis. Paraffin tissue blocks were cut into 5μm thickness sections and stained with hematoxylins & eosin stain (H&E), images were taken using a light microscope (Zeiss Axiovert, Germany). 10 fields were examined for cortex and medulla region by high power field. Degeneration and regeneration score were examined as described by Kinomura *et al*. [22]. In brief, the degree of tubular injury was quantified as a score between 0 and 5 as the following: score (0) for normal tissue; score (1) indicate that less than 20% of the tubules exhibiting tubular basement membrane injury, swelling, vacuolar degeneration and necrosis; score (2) involve 20-40% tubules injury, score (3) for 40-60%, score (4) 60-80% and score (5) for more than 80% of injured tubules.

Statistical analysis

Data were analyzed with student's *t*-test or one-way ANOVA using GraphPad Prism software version 7.04 (GraphPad Software, Inc., La Jolla, CA). $P < 0.05$ was considered statistically significant.

3. Results

3.1 Isolation and Characterization of WJMSCs

3.1.1. Cell Growth and expansion

Mesenchymal stem cells were isolated enzymatically from Wharton's jelly tissue of umbilical cord and

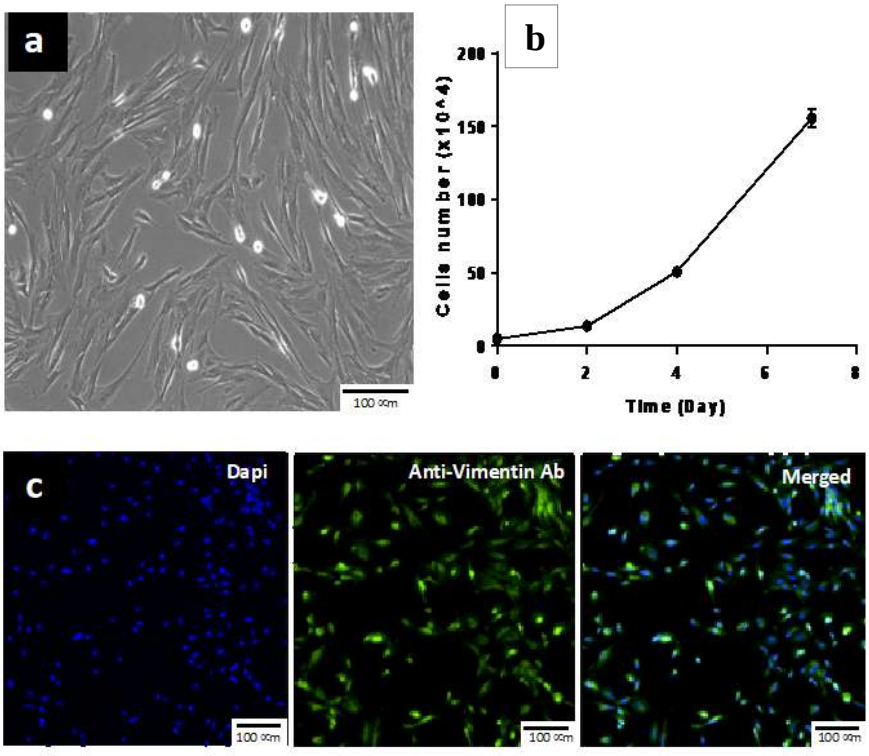

Fig. 1. Isolation and characterization of MSCs from Wharton's jelly tissue. (a) Morphology of WJMSCs at passage 3, (b) growth curve of WJMSCs during *in vitro* cultures (c) immunofluorescent staining for mesenchymal marker vimentin

demonstrated spindle-shaped morphology after 7 days of culture. The cells displayed a more fibroblast-like shape with increasing passage number, and at passage 3 the cells were able to form homogenously fibroblastic cell monolayers (Figure 1a). WJMSCs also possess high proliferation rate and cell growth kinetic (Figure 1b). WJMSCs showed short PDT value of 30±0.34 hours. The colony forming unit fibroblast (CFU-F) used to evaluate the ability of WJMSCs to proliferate and form colonies revealed the presence of cologenic cell population with a value of 14±0.58.

Immunofluorescence staining

Immunocytochemical detection of mesenchymal marker vimentin on WJMSCs showed positive cytoplasmic staining for MSCs markers indicating that WJMSCs possess MSCs features. The cytoplasmic marker vimentin stained with green, nuclei were counterstained with DAPI (blue) (Figure 1c).

Differentiation potential of WJMSCs

The differentiation potential of WJMSCs toward the osteogenic and adipogenic lineages was confirmed by incubating the cells with osteogenic and adipogenic differentiation medium respectively. The cells cultured in osteogenic differentiation medium showed calcium formation, which was detected by Alizarin red staining (Figure 2a). The optical density of the extracted dye showed a value of 0.39±0.03 compared to 0.04 for the control, while no calcium was detected in the control groups (Figure 2d). Additionally, alkaline phosphatase activity in osteogenic differentiated cells was significantly higher compared to the control group, (Figure 2c). Meanwhile, the cells cultured in adipogenic differentiation medium showed accumulation of lipid droplets which was detected by Oil red O stain (Figure 2b), and the spectrophotometric analysis of the extracted dye revealed that the differentiated cells have a value of 0.12±0.01compared to 0.02±0.01for the control groups, in which no lipid vacuoles were observed.

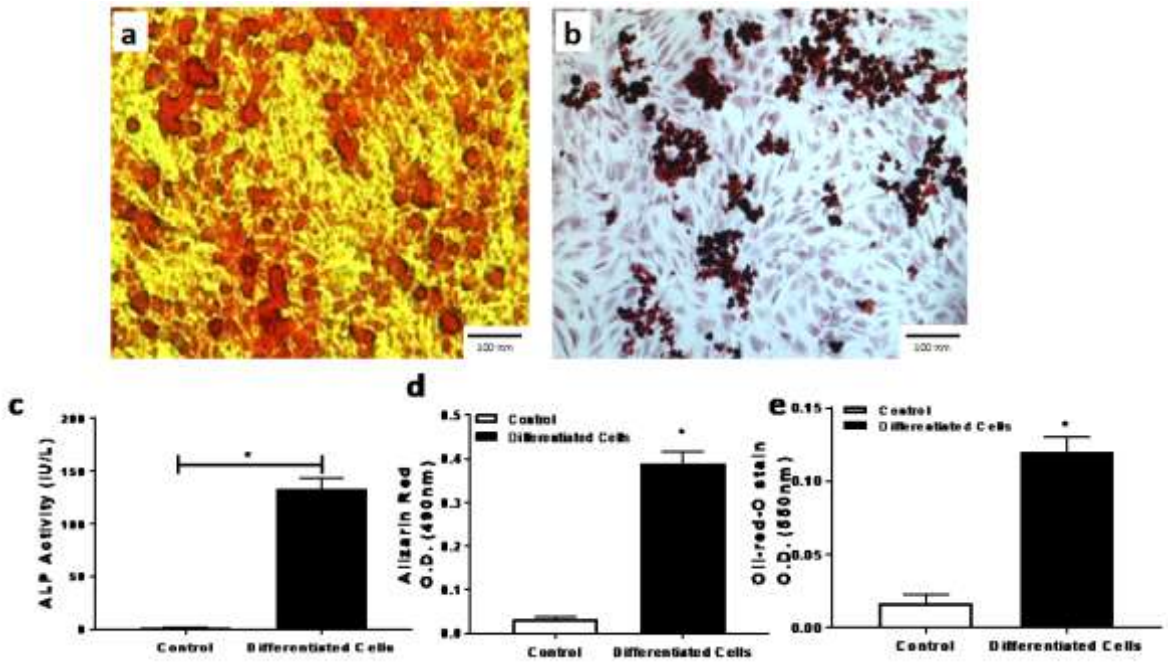

Fig. 2. Differentiation Capability of WJMSCs, (a, c and d) osteogenic differentiation capability of WJMSCs, (b,e) Adipogenic differentiation (n=3, *P<0.05)

***In vivo* study**

Analysis of biochemical marker to evaluate Kidney function

Renal function was assessed in all experimental groups by measuring the biochemical parameter BUN, Serum creatinine and creatinine clearance at days 1, 4 and 7 post-surgery. The obtained data revealed that the renal function returned to its normal level at day 7 post-surgery in all groups, even though rapid recovery happened in both treatment groups (MSCs and MSCs/HA) compared to the positive control (IR) group. MSCs preconditioned with HA help in shortening the recovery time compared to MSCs group only.

Serum creatinine and BUN level (mg/dl) at day 1 decreased in both treatment groups compared to IR group, while MSCs/HA showed significantly lower value compared to IR group ($p<0.05$). At day 4 both treatment groups showed that BUN and creatine level were decreased compared to IR group, meanwhile, the treatment groups showed that creatinine and BUN level at day 4 were significantly decreased compared to the same

groups at day 1 ($p<0.05$). At day 7 BUN and creatinine level returned to their normal values in all groups (Figure 3A-B).

Creatinine clearance value (ml/min) of the treatment groups was statistically significantly higher than that of IR group at all time points. Meanwhile, MSCs/HA showed significant higher values compared to IR group ($p<0.05$) (Figure 3C).

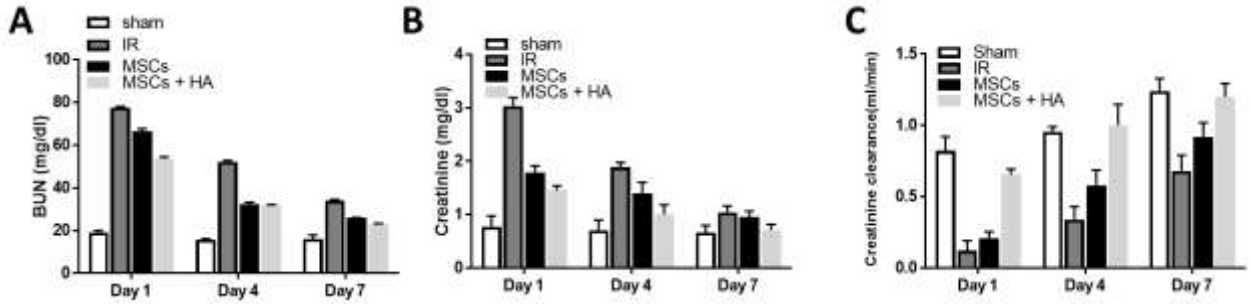

Fig. 3. Biochemical evaluation of kidney function at 1, 4 and 7 days in all experimental groups. (A) Blood Urea Nitrogen level (mg/dl), (B) Serum Creatinine level (c) Creatinine Clearance (ml/min.) (n=6, *P<0.05)

The antioxidant and anti-inflammatory effects of MSCs were evaluated at day 7 post-surgery in all experimental groups by measuring the activity of Super oxide dismutase (SOD) and monocyte chemoattractant protein 1 (MCP-1) concentration respectively. The anti-inflammatory marker MCP-1 values (pg/ml) for both treatment groups was decreased compared to IR group, moreover the MCP-1 level of MSCs/HA group significantly decreased compared to IR group ($p< 0.05$) (Figure 3A). The antioxidant activity of SOD was higher in the treatment groups compared to IR group. Meanwhile, the SOD activity increased significantly in MSCs/HA group increased compared to IR group ($p<0.05$) (Figure 3B).

Total collagen deposition in renal tissue was assessed among all experimental groups at 7 days post-surgery. The collagen content decreased significantly in the treatment groups compared to IR group, while the decrease was significant in MSCs/HA group in comparison to IR group ($p<0.05$). (Figure 3C).

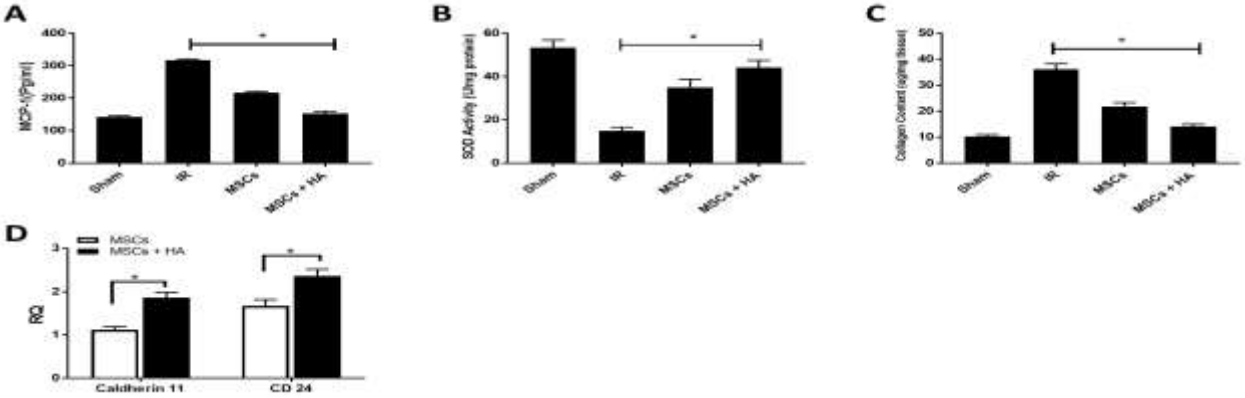

Fig. 4. The effects of MSCs and MSCs/HA treatment on (A) the anti-inflammatory marker MCP-1 values (pg/ml), (B) The antioxidant activity of SOD Antioxidant, (C) Fibrosis level (ug/mg tissue) in all experimental groups at day 7 of surgery (n=6, *P<0.05)

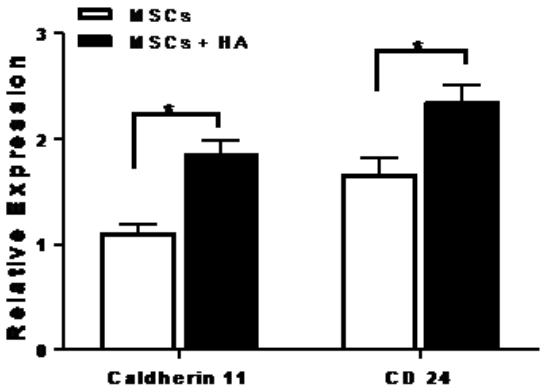

Fig. 5. The expression levels of metanephric markers Cadherin 11 and CD 24 in the treatment group (n=3, *P<0.05)

Gene Expression

The expression levels of metanephric markers Cadherin 11 and CD 24 was significantly higher in MSCs/HA group compared MSCs ($P< 0.05$), the data was normalized to sham group (Figure 4) and presented for the treatment group (Figure 5).

Histological Study of the Kidney

To examine the effect of WJMSCs on the treatment of renal injury, histomorphological examination was performed by H&E staining and the degree of injury was calculated among the experimental groups. The results indicated that the renal injury score increased in all

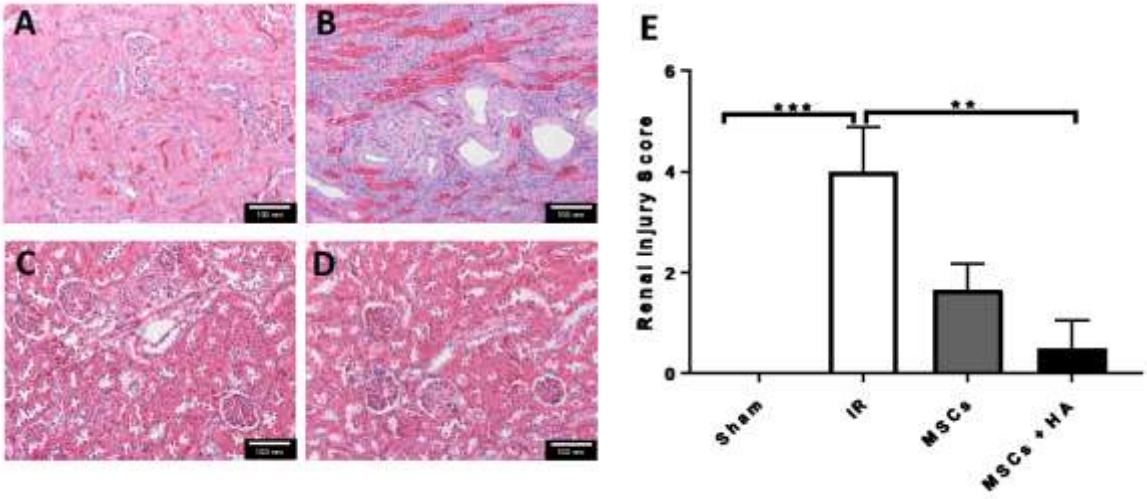

Fig. 6. Histological analysis of Kidney specimens at day 7 showing (A) normal kidney structure of sham group, (B) IR group, (C) MSCs group, (D) MSCs / HA group. scale bare: 50 μm, (E) Degree of renal injury.

groups compared to the sham group, the highest score was observed in IR group. meanwhile, the renal injury score of MSCs/HA was significantly decreased compared to IR group (Figure 6).

Discussion

Kidney diseases, including acute and chronic diseases, are still a challenging health problem for patients all over the world. Since these diseases eventually induce renal failure, the patients with end stage renal diseases is increasing annually. Stem cell therapies offer a promising option for kidney failure treatment due to their ability to differentiate into multiple cell lineages, in addition to their ability to decrease the inflammation and oxidative stress in injured tissue. In this study, MSCs were isolated from Wharton's jelly tissue and expanded invitro. Wharton's jelly tissue is considered an important alternative source for MSCs because it utilizes unused tissue to get viable cells. The isolated cells showed high cell viability and proliferation; moreover, these cells were able to exhibit MSCs feature such as expression of mesenchyme marker, ability to differentiate into multiple cell type (such as osteocyte and adipocyte), and the ability to modulate the immune response during allogenic transplantation. To assess the ability of stem cells to treat kidney diseases, an acute kidney injury model was established by IR injury. Due to the fact that IR injury causes significant increase in serum creatinine and BUN with significant reduction in creatinine clearance, the clinical parameter was confirmed by histological examination, which showed increase in the renal tubular injury in positive control group. These finding agrees with previous studies [23-25].

Renal function returned to its normal level at day 7 post-surgery in all groups, even though faster recovery occurred in both treatment groups (MSCs and MSCs/HA) compared to the positive control group. Histological examination of kidney tissue displayed minimal tubular and interstitial damage with signs of regeneration in the treatment groups. These findings corroborate previous studies that demonstrate the efficacy of stem cell in renal failure treatment [26-32]. Additionally,

MSCs preconditioned with HA demonstrated faster renal function recovery than non-treated MSCs, thus the use of HA along with MSCs increase the efficacy of treatment by enhancing the cell proliferation and recruitment in the injured tissue, regulation of cell–cell interaction and cell-matrix adhesion these finding agreed the previous studies demonstrated that HA enhance the stem cell therapy. [33,34].

Although the mechanism of tissue repair by stem cells is not well understood, our result suggests that some cells engrafted into the injured tissue start to differentiate into metanephric mesenchyme, while other cells provide renoprotection through secretion of some paracrine factors with regenerative, anti-apoptotic, antioxidant and anti-inflammatory effect. These finding were in accordance with previous studies [35-39].

Conclusions

This study evaluates the improvement of renal function of acute kidney injury model induced by IR using MSCs derived from Wharton's jelly tissue. WJMSCs offer alternative source for adult MSCs able to improve the renal function. Our results suggested that WJMSCs were able to enhance tissue repair by promote the differentiation of MSCs into metanephric mesenchyme and provide renoprotection by reducing the inflammation and oxidative stress resulted from IR injury. Utilizing MSCs along with hyaluronic acid enhance the ability of WJMSCs to repair kidney tissue injury. Further studies are required to address the underlying mechanism behind the effect of HA on MSCs.

Conflict of interest statement. None declared.

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Original article

Sociodemographic Determinants of Kidney Disease in Egyptian Tertiary Health Center

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Abstract

Introduction. Chronic kidney disease (CKD) is increasingly recognized as a public health problem, and is linked to the risk of development of cardiovascular disease (CVD) with their accompanying morbidity, mortality and increased healthcare costs. The study aims to outline a planned control strategy for renal diseases.

Methods. This study was conducted among CKD Egyptian patients (n=556) in the nephrology outpatient clinic of Kasr Al Ainy hospital. Personal and family socio-demographic characteristics, present history, habitual drug intake, family history of kidney diseases, laboratory findings and pattern of care in the outpatient clinic were obtained.

Results. Among the participants, diabetes mellitus (DM) and hypertension were the most common causes of CKD (56% and 40%) respectively. Older age and male sex are associated with low estimated glomerular filtration rate (eGER) (P <0.001). Patients with middle and high sociodemographic status were significantly associated with higher eGFR than those with low sociodemographic status (P <0.001).

Conclusions. Old age, female gender, illiteracy and low sociodemographic status were significantly associated with low eGFR. On the other hand, smoking, habitual intake of analgesics, residential exposure to chemicals, family history of CKD and lack of compliance for regular follow up were not significantly associated with low eGFR in Egyptian CKD patients.

Key words: chronic kidney disease-diabetes mellitus-illiteracy-morbidity-socio-demographic status

Introduction

Chronic kidney disease (CKD) is one of the most widespread non-communicable disease (NCD). CKD is consistently associated with enormous medical, social, and financial burdens for individuals, their families, and national health systems [1]

CKD definition encompasses all grades of reduced renal function associated with poor outcomes, repeated hospitalization, and increased risk of morbidities as anemia and cardiovascular complication and mortality [2].

The epidemiological pattern of chronic kidney disease widely differs among the societies, however it is not well established due to the lack of national renal registries and sufficient representing data specifically in developing countries and eventually in Egypt [3]. CKD prevalence in US escalates with age (4% at age 29-39 y; 47% at age >70 y), more in blacks [4] while in the Australian AusDiab kidney study, the prevalence of impaired GFR was 11.2% and increased with aging (from 0.01% in the 25 to 44 y age group to 54.8% in patients with age >65 y) [5].

The Fogarty International Center (FIC) of U.S. has reported that the global burden of renal disease confers to ~830 000 demises per year and 18 867 000 disability-adjusted life years (DALY) [6] and this rank of high mortality and disability is similar across World Bank regions, particularly East Asian and Pacific regions [7].

Aside the well-recognized etiological factors of developing CKD such as diabetes, hypertension and glomerular disorders, there are the socio-demographic aspects (age, sex, education and occupation), thus assessing these aspects are of the utmost importance.

No adequate data on the different clinical patterns of renal disorders in Egyptian populations are present owing to the scarcity of research, sparsity of renal regional registries, medical records and filing systems inadequacy. An Egyptian study has concluded that CKD and acute kidney injury were the dominant causes of hospital admission. Sepsis, hyperkalemia, and HTN are common risk factors of mortality in Egyptian patients with kidney disease [8].

The aim of the study was to outline the sociodemographic profile, highlighting the various pattern of renal diseases among attendants to outpatient clinics of Kasr Al Ainy hospital and to determine the potential risk factors and related outcomes for planned control strategy.

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Materials and methods

Study design and sampling

This is descriptive cross-sectional study. A purposive nonprobability sample was taken consecutively from chronic renal disease patients who attend the nephrology out-patient clinic of Cairo University Hospital. The study was carried out from January 2016 to April 2017. The total number of the participants was 556 patients. Post-transplant patients and those who were clinically unstable and mentally non cooperative (demented) were excluded from the study.

The study protocol conformed to the ethical guidelines of 1975 the Helsinki declaration and was approved by the Medical Research Committee in the Internal Medicine Department at Faculty of Medicine Cairo University. Informed consents were obtained from all enrolled participants

Data Collection Tools

An interviewing questionnaire (to overcome the illiteracy of patients) was designed to collect data from renal patients about demographic characteristics, cause of renal failure, habitual analgesic intake and family history. A pilot study was done on 30 patients to check the validity and clarity of the structured questionnaire. Most of the questions were close ended and were precoded prior to data collection to facilitate data entry and analysis.

The questionnaire included questions about the following data.

1. Personal and family socio-demographic characteristics: e.g. age, sex, occupation, educational status residence, smoking [For calculating Cigarettes life quarters, we multiply the number of cigarettes smoked per day by number of years of smoking by 365 (days of the year) to get the whole number of cigarettes smoked all through life then divide the patients according to smoking habit into 4 categories [never smoked, extreme low (<25^{th} percentiles), middle (25^{th}-75^{th} percentiles) and extreme high (>75^{th} percentiles)].
2. The sociodemographic status was classified into 3 classes as high, middle and low. Crowdedness index is evaluated according to the number of individuals per room, the score ranges from 1 to 5 the higher score (5) means <1 /per room, while the score weighs 1 means ≥4 / per room [9]
3. Present history: including diseases and conditions affecting kidney functions e.g. hypertension, diabetes, etc.
4. Habitual drug intake.
5. Family history of kidney diseases, hypertension, diabetes, similar renal disease.
6. Laboratory findings (hemoglobin and serum creatinine levels).
7. Estimation of GFR by using Modification of Diet in Renal Disease (MDRD) Study equation [10] eGFR (mL/min/1.73 m^2)= 175 x (Serum creatinine in mg)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if African American).

According to the eGFR, the patients were classified into diseases stages to present the severity and affection of renal function as follows:

Stage 1 (eGFR>90): Normal kidney function but urine findings or structural abnormalities or genetic trait
Stage 2 (eGFR 60-90)
Stage 3 (eGFR 30-60)
Stage 4 (eGFR 30-15)
Stage 5 (eGFR <15) either on dialysis or not.

Data management and Statistical analysis

All collected questionnaires were checked for completeness and consistency. Pre-coded data were entered in the computer using "Microsoft Office Excel Software" program for Windows. Data was then transferred to the Statistical Package of Social Science Software program, version 15 (SPSS) to be statistically analyzed. Data were summarized using mean and standard deviation for quantitative variables and percentage for qualitative variables. Comparison between groups was done using independent samples t-test and analysis of variants (ANOVA) for quantitative data, chi square test for qualitative variables, P values equal to or less than 0.05 were considered statistically significant.

Results

This study involved 556 chronic kidney disease patients with an age range from 15 years to 85 years and mean age of 43±11. There were 307 males (55.3%) with an age range (15-85) and mean 45.4±12 and 249 females (44.7%) of age range (17-75), mean = 45±13. The e GFR by MDRD ranged from 9.3 to 42.34 ml/min/1.73m^2 with mean value of 20.3±5.58 ml/min/ 1.73m^2. The mean level of Hb was 9.9±2.2 gm/dl and serum albumin 3.7±0.4 gm/dl. BMI was 23.5±3.1 kg/m^2.

The socio-demographic data were summarized in Table 1.

Table 1. Socio-demographic, medical and laboratory parameters among the studied patients

Variables		Frequency	Percentage %
Age(years)	(below) 30	102	18.3
	30-	163	29.3
	40-	174	31.3
	50-	104	18.7

	60+	13	2.4
Sex	Male	307	55.3
	Female	249	44.7
BMI*%	<18.5 kg/m2	28	5
	18.5-24.9 kg/m2	389	70%
	>25 kg/m2	139	25
Marital status	Single	52	9.3
	Married	396	71.3
	Widow	96	17.3
	Divorced	11	2
Residential exposure to chemicals	No	428	77
	Yes	127	23
Residency	Rural	393	71%
	Urban	163	29%
Educational status	Illiterate	167	30
	Can read and write	83	15
	Basic education	137	24.7
	Average education	143	25.7
	High education	26	4.7
Social level	Low	273	49
	Middle	140	25.3
	High	143	25.7
Cigarette life categories	Non -smoker	349	62.7
	Extremely low 25%	59	10.7
	Middle 50%	98	17.7
	Extremely high 25%	50	9
Renal disease causes	Diabetes mellitus	313	56.3
	hypertension	222	40.0
	connective tissue disease	101	18.3
	Obstructive uropathy	46	8.3
	UTI	35	6.3
	Gouty nephropathy	32	5.7
	Unknown	48	8.7
NSAIDS$^{\alpha}$ intake	Infrequent (or prescribed by physician)	35	6.3
	Monthly	93	16.7
	weekly	196	35.3
	Daily	232	41.7
Perceived Health Education	Nutritional	526	94.7
	Life style	524	94.3
	Drug	511	92
	Follow up	528	95
	Reg. on follow up	369	66.3
Hospital admission		267	48
+ve consanguinity		239	43
Family history	Hypertension	341	61
	Diabetes Mellitus	343	62
	Connect tissue diseases	35	6.3
	Renal diseases	110	19.7
Referral	From Kasr Al Ainy	161	29
	from other health centers	395	71
CKD$^{\propto}$ Stages	Stage 2	0	0
	Stage3	26	4.7
	Stage4	437	78.6
	Stage5	93	16.7
Dialysis sessions (3/week)	Health insurance	56	10
	State-funded dialysis	500	90%
	Private sector	0	0
Crowdness index	Up2 per room	256	46
	>2 / room	300	54
Family size	1-4 individuals	236	42.4
	>5 individuals	320	57.6
Working	Not working	275	49.5%
	working	225	40.5
	Retired	56	10

*BMI: Body mass index, αNSAIDS: Non steroidal anti-inflammatory drugs, ∝CKD: chronic kidney disease

As regard the morbidities, results of the current study revealed that total numbers of cases were not mutually exclusive due to combination of different diseases in some patients.

The present study found that e-GFR of patients <30 years is significantly higher than that of the other age groups. And significantly higher in males than females with high education and socioeconomic level as shown in Table 2.

Table 2. Statistical comparison of estimated GFR among the studied patients in relation to their demographic characteristics

Risk factors	Frequency	Estimated GFR* Mean ± SD (mL/min/1.73 m^2)	Significant test F ratio	Significant test t-value	P value
Age					
<30*	102	24.74±6.22	11.53		<0.001
30-	163	20.49±4.81			
40-	174	18.86±4.94			S$^{\alpha}$
50+	117	17.77±4.18			
SEX					
Male	307	23.04±5.42		6.59	<0.001
Female	249	17.73±4.38			S
Educational Level					
Illiterate	167	18.43±5.11	3.44		<0.02
Read and write	83	19.37±5.21			S
Basic education	137	20.49±5.63			
Secondary and higher education**	169	22.15±5.62			
Social level					
Low	273	18.35±4.70	8.07		<0.001
Middle	140	21.08±5.02			S
High	143	22.40±6.35			

*GFR : Glomerular filtration rate, αS : Significant

Table 3. The association between the different etiologies of CKD and the sociodemographic parameters

Variables		Hypertensive nephropathy	Diabetic nephropathy	Connective tissue disease related nephropathy	Obstructive uropathy	Infective nephropathy	Gout	Unknown etiology
Age	X^2	35.66	11.04	10.66	6.86	12.29	6.15	16.13
	p-value	< 0.001(HS)	0.05(S)	0.05(S)	>0.05	>0.05	>0.05	< 0.001(HS)
Sex	X^2	0.13	1.14	15.60	0.95	0.95	0.18	0.82
	p-value	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
Social level	X^2	2.08	1.63	9.75	7.22	4.18	2.15	0.11
	p-value	>0.05	>0.05	0.008(S)	0.04(S)	>0.05	>0.05	>0.05
Smoking	X^2	9.35	8.18	13.56	0.89	3.96	3.93	5.15
	p-value	0.03(s)	0.04(S)	0.004(S)	0.83	0.27	0.27	0.16
Drug intake	X^2	2.27	1.61	33.18	5.24	0.35	1.7	8.17
	p-value	0.52	0.66	<0.001(HS)	0.75	0.23	0.64	0.04(S)
Residential exposure to chemicals	X^2	1.64	0.01	0.70	0.39	1.44	7.42	0.52
	p-value	>0.05	>0.05	>0.05	>0.05	>0.05	0.006(S)	>0.05
Consanguinity	X^2	0.81	0.86	0.01	0.92	1.63	0.75	2.33
	p-value	>0.05	>0.05	>0.05	>0.05	>0.05	0.002	>0.05
Family history of renal diseases	X^2	0.00	0.74	3.47	5.80	8.07	6.82	0.98
	p-value	>0.05	>0.05	< 0.001(HS)	>0.05	0.01(s)	0.01(S)	>0.05
Crowdness index	X^2	0.77	0.35	0.39	0.53	0.74	0.1	0.17
	p-value	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
Working	X^2	0.02	0.86	0.16	0.2	0.63	0.88	0.24
	p-value	0.05(S)	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05

There is no statistically significant difference among the studied patients regarding their smoking habits, habitual drug (analgesics) intake, residential exposure to chemicals, presence of family history of renal diseases or compliance of the patients regarding periodic follow-up.

The current study stated that the government funded 90% of our patients for the treatment.

The association between the different etiologies of CKD and the sociodemographic parameters showed that age and smoking are associated with hypertensive and diabetic nephropathy, whilst connective tissue disease related nephropathy is significantly related to age, drug intake, history of familial renal disease as shown in table 3.

The current results found that there was an inverse significant correlation between hemoglobin level versus age, creatinine, (r-value :-0.507, -0.558) respectively with p-value (<0.01, <0.01) respectively using Pearson calculation, moreover hemoglobin was negatively correlated to smoking, hypertension duration and connective tissue disease related nephropathy duration (correlation coefficient = -0.396, -0.251 and -0.449) respectively, with p-value (< 0.001, 0.001 and 0.009) respectively using Spearman's Correlations.

On the other side creatinine level was positively related to smoking, DM duration, hypertension duration and connective tissue diseases duration (correlation coefficient = 0.298, 0.198, 0.348 and 0.420) respectively, with p-value (0.001, 0.002, <0.001 and 0.015) respectively using Spearman's Correlations.

About 72.2% of connective tissue disease related nephropathy patients had CKD stage 5 while 27.8 % had CKD stage 3 and 4 (X^2 =5.27 and p-value < 0.02). About 58.3% of total gouty nephropathy were at CKD stage 5 with 41.7% were at stage 3 and 4 (X^2 =4.08 and p-value <0.05). There is no statistically significant association among the studied patients between CKD stages and diabetes mellitus, hypertension, obstructive uropathy or urinary tract infections.

Discussion

Old age, female gender, illiteracy and low social level are significantly associated with low GFR as shown by the current study results, however smoking, habitual intake of analgesics, residential exposure to chemicals, family history of CKD and lack of compliance for regular follow up are not significantly associated with low GFR.

Based on the fact, of increasing the prevalence of renal disease and being a medical, social, and economic problem, the current study was carried out aiming at exploring the sociodemographic pattern of kidney diseases among attendants to Kasr Al Ainy nephrology outpatient clinic as a provisional guideline for priority setting and research concerning this national problem.

The current study revealed a predominance of male affection (55.7% versus 44.3%) and this is matched with American [11] and Spanish [12] cohorts. African studies done in Nigeria [13] and Ghana [14] had reported male preponderance (65.3% vs 34.7%) and (55% vs 45%) respectively. The mean age of Egyptian patients was 43±11. The majority of patients were less than 60 years (77%) while above 60 years represent about (2.4%). Increased prevalence of CKD in young males is likely explained by increased estimates of smoking and hypertension as risk factors of CKD among them.

Diabetes and hypertension affect large scale of Egyptian populations particularly adult age group [15] and these diseases are the main territories of renal impairment and end stage renal disease [16]. Our study revealed that patients with diabetic nephropathy were (56.3%) followed by hypertensive nephropathy (40%) whilst the idiopathic, urinary tract infection and gouty nephropathy the least common causes (8.7%. 6.3% and 5.7%) respectively. This pattern is found to be in agreement with the pattern observed in USA as diabetes mellitus or hypertension are responsible for more than 70% of cases of late-stage (stage 5) CKD in Americans and 15% of patients have other or unknown causes [17]. Also, In the Delhi study, 63% of the CKD were due to diabetes and hypertension [12], as well as Nichola had found the higher proportion of CKD patients were either diabetic or hypertensive, along with our data [18] a study had been done on Egyptian elderly kidney patients at Ain Shams University and showed CKD of unknown origin in (13.1%) while diabetic nephropathy patients represented (28.2%) and hypertensive nephropathy (25.5%) [19].

The majority of participants were of rural residency (71%) and lower frequency of urban participants (29%) and this may be attributed to poor health access in the rural area and financial factors.

Low socioeconomic strata and denial of education are believed to have a surrogate impact in perceiving renal diseases, growing the CKD epidemic, aside the inability to attain adequate health care resulting in to increase the burden of CKD complications. Thus, socioeconomic and educational disadvantaged subjects are vulnerable to renal disease.

Herein, there is trend towards the illiteracy (30%) whilst highly-educated subjects are the least percent (4.7 %), approximately 50% of the studied population are classified socio-economically low. It was found to be in agreement with Sweden study which demonstrated that low socio-economic status is associated with an increased risk of CKD [20].

A high crowdedness index was observed in (54%) patients in accordance with the family size (≥5) represent (57.4%),

Most of our patients had perceived health education data regarding the nutrient, life style, and drugs but may be

poorly accomplished. Thereby the main issue of health education is to apply the perceived information.

The current study reported that unemployment proportion was high (49.5%). Unemployment has a financial impact with poor adherence to medications. Loss of employment may be a sequence of the renal disease progression and the resulting asthenia and fatigability.

Our results described that low socioeconomic, high odds of unemployment and inadequate education were associated with advanced CKD stages (4 and 5) (95.3%); and this is common in the developing countries as demonstrated by many cohorts [21].

CKD has adverse financial effect on individuals, their families and consequentially on their societies; it is like crisis that diffuses globally [21]. About 60% of the study patients receive their therapy and dialysis sessions through a channel of government-funded treatment, which presents a heavy economic burden upon the state, decreasing the health quality services.

In the current study, the CKD `1 was not associated with smoking habit, habitual drug (analgesics) intake, residential exposure to chemicals, presence of family history of renal diseases or compliance of the patients regarding periodic follow-up.

Physical and medical complications of renal disease were widely varied [22] Anemia- associated chronic illness was encountered in our study as the mean hemoglobin level was 9.9 ±2.2 gs/dl and its frequency was (75%). Low hemoglobin level is linked to cardiovascular events, increased frequency and duration of hospital admission and poor quality of life.

Regarding eGFR, it was found that the eGFR was significantly lower among old age group. Similar findings were found by Cirillo revealing inverse significant association between age and estimated GFR [23]. The same findings were observed in the study of Ain Shams University [19]. As observed in USA, the prevalence of impaired GFR (<60 mL/min/1.73m^2) was more common in adults ≥ 60 years of age (0.6% at age 20–39 years; 4.4% at age 40–59 years; 28.1% at age 60 years or older in 2003–2006) [24]. The prevalence of impaired GFR increased with increasing age [25].

Females were significantly associated with low estimated GFR. It was found to be in contrary with El Salvador study which revealed that a significant association between male sex and kidney damage [26]. It might be explained by certain socio-demographic criteria as Egyptian females are most commonly overburdened with other medical conditions and more exposed to NSAID.

Moreover, in this study, it was found that patients having connective tissue diseases and gout are significantly (P <0.05) more susceptible for impending dialysis stage (eGFR <15 ml/min/1.73 m^2). The current study findings could be explained by delayed diagnosis of patients suffering from connective tissue diseases and gout who deal with analgesics primarily for long time before specialist consultation thus lead to delay in diagnosis and more kidney damage.

We should mention some points of limitations first, the small sample size, secondly, the study encounters certain spectrum of Egyptian population who attend the Kasr Al Ainy only not addressing the different classes.

We recommended ascertaining the establishment of a health facility based screening system for early detection of renal dysfunction, tracing them, improvement of the facilities for CKD and ESRD management and building up a national adequate center for medical records under the supervision of the Ministry of Health and Epidemiology surveillance institutes and finally providing an integrated preventive controlling programs.

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Conflict of interest statement. None declared.

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Original article

Nutritional Habits of Hemodialysis Patients

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Abstract

Introduction. Nutrition for patients in end-stage renal disease (ESRD) is one of the the most restrictive, owing to the numerous limitations in consuming certain foods, micronutrients as well as restriction in fluid intake. In the following study, we investigated dietary habits of hemodialysis patients and their changes after nutritional education.

Methods. 101 patients undergoing maintenance hemodialysis (HD) were included in the investigation. During the first educational visit every patient received individual recommendations for nutritional intake, necessity for enteral nutritional supplement or for phosphate binders (PB) depending on the anthropometric and laboratory assessment. Two months later, a questionnaire was carried out in order to identify if any changes in food intake were present after this specific nutritional and medical education.

Results. Of 101 patients who completed the initial nutritional screening and education, 76 patients who had all the required data were included in the final analysis. 77,6% of patients stated to had breakfast every day, while 22,4% of them had their first meal at lunch time. 79% of patients ate during or immediately before/after HD, while 18,42% refused a meal. The most common reasons for refusing a meal during HD were nausea and hypotension. 46% of patients had three meals a day, 21% ate only twice a day. In general, patients undergoing HD had three to four meals a day (including snacks). Only 23,7% of patients ate meat products every day, while 22,4% of them consumed meat twice a week. The significant correlation was found between the average age of patients and meat consumption-patients with low meat intake (once or twice per week) were significantly older (average 68.4 years) in comparison to patients with regular meat consumption (four or more times a week; average age of 53.8 years) ($p<0.01$). Regarding the use of PB, 72,4% were aware of their prescription, but despite the educational program, 4% of the patients were taking the medicine between meals, while 2% of patients took PB at any time during the day.

63,2% of patients answered positively when asked whether they attempted to change their eating habits after nutritional education was carried out. 36,8% of them did not even try. When asked to mark the most disturbing problem they need to deal with on maintenance HD, 33% of patients stated blood pressure regulation. 14,5% of patients highlighted poor appetite as their largest problem.

Conclusions. The main intention of nutritional education should be raising the awareness among patients and helping them correct numerous disorders arising from inadequate nutritional intake such as hyperkalemia, hyperphosphatemia, excessive fluid intake, and protein-energy malnutrition. Continuous evaluation and adjustments of medical and nutritional therapy are needed along with permanently repeated aims of this specific treatment.

Keywords: hemodialysis, nutrition, habits, education, phosphorus

Introduction

Patients with end-stage renal disease (ESRD) have one of the most restrictive diets especially those who are diabetics also. Besides the restrictive intake of water, their nutrition should have low potassium and phosphorus content, but should be protein-rich. This aim is not easy to achieve while majority of food with high protein-content is also full of phosphorus [1]. Different therapeutic approaches are available for controling hyperphosphatemia, such as dietary restrictions, adequate dialysis and use of oral phosphate binders [2]. However, despite these approaches, normalization of serum P levels is often difficult and frequently not obtained. Dialysis patients often have numerous comorbidities such as cardiovascular diseases, diabetes, chronic inflammation and infections. They are often with low income, have low level of physical activity and inadequate

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social support. Many ESRD patients have poor appetite especially when hemodialysis is not adequate. All these factors may negatively influence food intake and nutritional status. Nutritional guidelines suggest daily energy intake higher than 30-35 kcal/kg ideal b.w. and daily protein intake higher than 1.1-1.2 g/kg ideal b.w. [3,4]. The assessment of food intake is, together with anthropometric and laboratory evaluation, an important part of the management and treatment of ESRD patients [5,6]. It can help recognize patients with problems and individualized the approach in solving them.

In our study, we assessed the dietary habits and nutritional status in a cohort of stable hemodialysis patients treated in our institution.

Materials and methods

One hundred-one hemodialysis patients were included in this prospective study. All patients gave their informed-consent for participation in the investigation. Patients were treated with hemodialysis for at least three months, two to four times a week with biocompatible synthetic membranes. All patients were seen individually by a nephrologist and a registered dietician. The seven-day recalls were collected by interviews. During the first educational visit every patient received individual recommendations for nutritional intake, necessity for enteral nutritional supplement or adequate use of phosphate binders depending on the anthropometric and laboratory assessment.

Patients' data were obtained through questionnaires that were specifically designed for this study. The questionnaire consisted of items corresponding to socioeconomic status, level of education, dietary habits of the patients, namely breakfast, number of meals per day, number of meals containing meat and number of skiped meals.

Two months later, a questionnaire was carried out in order to identify if any changes in food intake were present after this specific nutritional and medical education.

Descriptive statistics are given as mean ± standard deviation. Statistical analysis was performed by Student's t test for unpaired and paired data. Linear correlation analysis was performed by Pearson's test. Differences were considered statistically significant when $p < 0.05$.

Results

Patients' characteristics

Of 101 patients who completed the initial nutritional screening and education, 76 patients who had all required data were included in the final analysis.

57 were male (56,4%) and 44 were female (43,6%) patients, with mean age of 60,8±16,15 years. The leading cause of ESRD was chronic glomerulonephritis (27,7%), followed by diabetic nephropathy (21,8%) and nephroangiosclerosis (14,8%). The mean time spent on HD was 96,03±102,521 months/weeks?, with a minimum treatment time of 3 hours for 2-4 times a week, blood flow rate was 290.8 (250-350) ml/min and average Kt/V 1.32. Bicarbonate HD and ultrapure dialysate fluid with a flow rate of 500 ml/min was used for all patients, as well as high-flux polysulphone dialysers. Baseline characteristics of the study population (*n*=101) are given in Table 1.

Table 1. Baseline characteristics of the study population (*n*=101). Values are presented as mean±SD and percentage

Characteristics	
Demographic variables	
Mean age (yr)	60.8±16.15
Men (%)	56.4
Arteriovenous fistula (%)	62.37
Renal residual function > 300 ml/d (%)	44.55
Type of primary kidney disease (%)	
Glomerulonephritis	27.72
Diabetic nephropathy	21.78
Nephroangiosclerosis	14.85
Polycystic kidney disease	8.92
Pyelonephritis	2.97
Other	23.76
Mean hemodialysis variables	
Vintage (yr)???	96.03±102.521 ???
Sessions per week (%)	
2	8.91
3	88.12
4	2.97
Mean dose (Kt/V)	1.320±0.295
Duration (%)	
3-3.5 hours	34.65
≥ 4 hours	65.34
Blood flow rate (%)	
200-250 ml/min	10.89
270-300 ml/min	71.29
> 320 ml/min	17.82
Ultrafiltration (kg)	2.637±0.941
Decreasing body weight during hemodialysis (%)	3.857±1.435
Mean laboratory values	
Hemoglobin (g/L)	107.594±12.233
Leucocytes (*10^9/L)	6.240±2.078
Creatinine (μmol/L)	771.089±198.317
Urea (mmol/L)	20.895±5.415
Triglycerids (mmol/L)	1.747±0.934
Cholesterol (mmol/L)	4.176±1.135
Phosphate (mmol/L)	1.434±0.439
Potassium (mmol/L)	4.913±0.660
C-reactive protein (mg/L)	8.159±12.753
Iron (μmol/L)	11.802±4.835
Total iron binding capacity (μmol/L)	40.257±8.196
Ferritin (μg/L)	388.327±189.198

Nutritional habits

46% of the patients had three meals a day, 21% ate only twice a day. In general, patients undergoing HD had three to four meals a day (including snacks) (Figure 1).

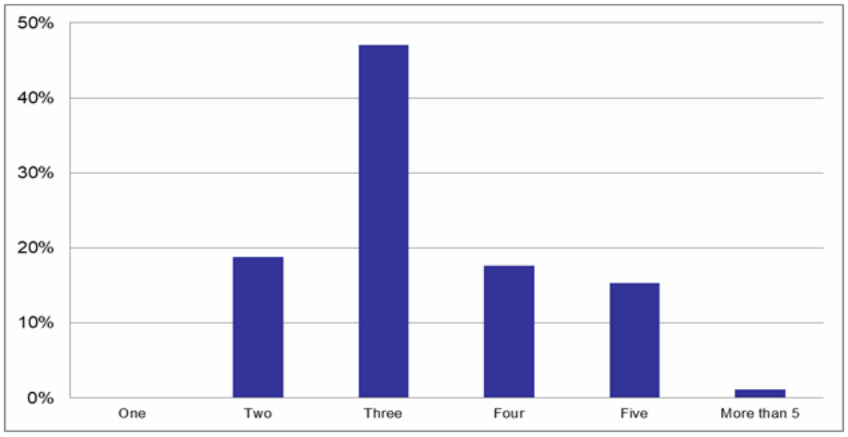

Fig. 1. Number of meals per day.

77,6% of patients stated to have breakfast every day, while 22,4% of them did not eat until lunch time. 79% of patients ate during or immediately before/after HD, while 18,42% refused a meal. The most common reasons for refusing a meal during HD were nausea and hypotension. Only 23,7% of patients ate meat products every day, while 22,4% of them consumed meat twice a week (Figure 2).

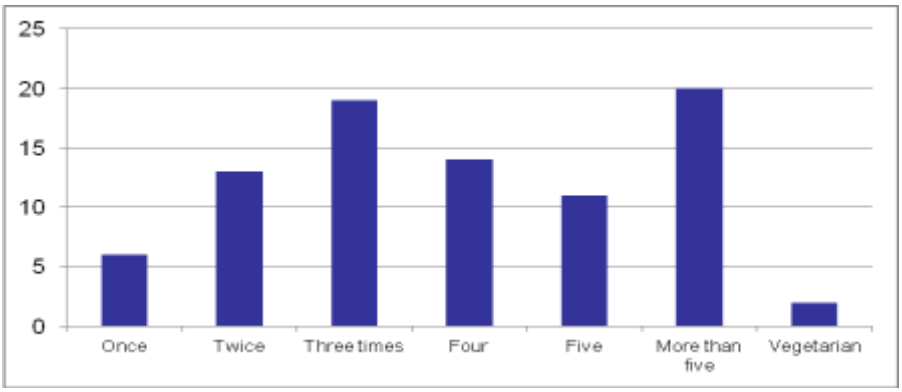

Fig. 2. Consumation of meat-containing meals over 7 days (%)

The significant correlation was found between the average age of patients and meat consumption-patients with low meat intake (once or twice per week) were significantly older (average 68.4 years) in comparison to patients with regular meat consumption (four or more times a week; average age of 53.8 years) ($p<0.01$).

Regarding the use of phosphate binders, 72% were aware of their prescription, but despite the educational program, 4% of patients were taking the medicine between meals, and 2% of patients took phosphate binders at any time during the day (Figure 3).

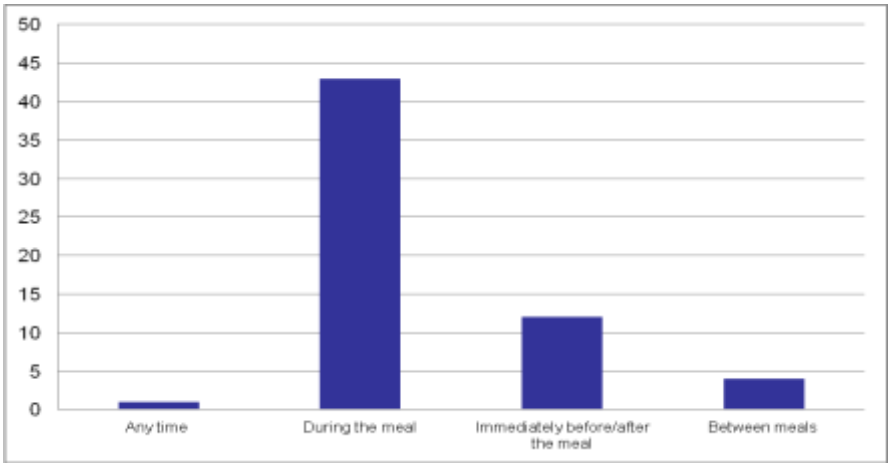

Fig. 3. Use of phosphate binders. % is missing

When patients were asked to mark the most disturbing problem they need to deal with during maintenance HD, 33% of them stated blood pressure regulation. Afterwards followed hyperphosphatemia (27%), hyperkalemia (22%) and excessive fluid intake (22%). Interesting to note is that 15% of patients highlighted poor appetite as their biggest concern (Figure 4).

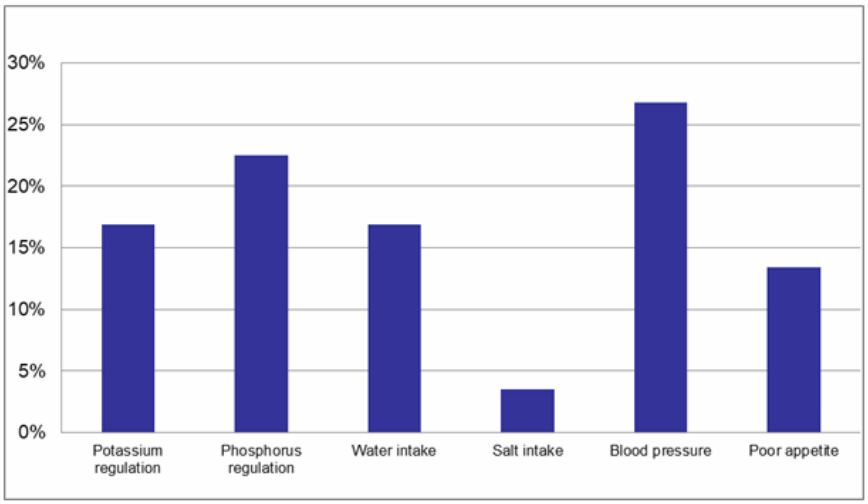

Fig. 4. Self-percieved major health problems

Oral nutritional supplements (ONS) were prescribed for 101 patient. However, only 51% of patients used them as prescribed. Among the reasons which they gave for not using ONS were forgetfulness (10 patients) and barriers from their general practitioners restricting prescriptions (14 patients). Many of them were unable to pick the necessary ONS from the pharmacy due the lack of caregiver (12 patients). Other patients refused to use ONS (dull taste, bowel problems).
We further evaluated their attitude after the specific nutritional education which involved a dietitian and a nephrologist. 63% of patients answered positively when asked whether they attempted to change their eating habits after nutritional education was carried out. However, 37% of them did not even try. Their explanation was that they did not consider nutrition as an important part of their treatment. There was no correlation in regard to the level of education with other parameters.

Discussion

This study showed inadequate nutritional habits in hemodialysis patients. Our data came from the whole cohort of dialysis patients, and not only from those who were in stable condition and free from severe comorbidities. It is well known that severe comorbidities as well as acute complications negatively affect dietary intakes and nutritional status. Thus, many studies on nutrition in maintenance hemodialysis patients are confined? from important biases [7].
78% of our patients had breakfast every day and 19% refused a meal during or immediately after the hemodialysis session. Just 24% of patients ate meat-containing products every day, while 22% of them consumed meat twice a week. There was a strong correlation of meat intake with age which is in concordance with other studies. Namely, available population studies have demonstrated a decline in food intake with aging, predominantly due to a decrease in fat intake [8-10].
Regarding the use of phosphate binders, 72% were aware of their prescription, but despite the educational program, 4% of patients were taking the medicine between meals, and 2% of patients took phosphate binders at any time during the day. In a two-months study of 135 hemodialysis patients, about half of patients were adherent every week, but over the entire 8-week period, only 22 % were totally adherent [11].
Oral nutritional supplements (ONS) were prescribed for 101 patient. However, only 51% of patients used them as prescribed. Among the reasons which they gave for not using ONS were forgetfulness (10 patients) and barriers from their general practitioners restricting prescriptions (14 patients). Many of them were unable to pick the necessary ONS from the pharmacy due the lack of caregiver (12 patients). Other patients refused to use ONS (dull taste, bowel problems).
We further evaluated their attitude after the specific nutritional education which involved a dietitian and a nephrologist. 63% of patients answered positively when asked whether they attempted to change their eating habits after nutritional education was carried out. However, 37% of them did not even try. Their explanation was that they did not consider nutrition as an important part of their treatment.
Recent studies have highlighted the contribution of socio-economic inequalities in health and mortality [12]. Patients with lower socio-economic status have higher serum phosphate concentrations and higher likelihood

of hyperphosphatemia. These data suggest that a low socio-economic status is a novel risk factor for increased serum P concentrations in ESRD [13].

Conclusion

The main intention of nutritional education should be raising the awareness among patients and helping them correct numerous disorders arising from inadequate nutritional intake such as hyperkalemia, hyperphosphatemia, excessive fluid intake, and protein-energy malnutrition. Continuous evaluation and adjustments of medical and nutritional therapy are needed along with permanently repeated aims of this specific treatment. A multidisciplinary team consisted of nephrologists and nutritionists along with other medical specialties, represents a constant need in every dialysis center and should not be perceived as luxury.

Conflict of interest statement. None declared.

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Case report

Mechanical Ventilation, Intravenous Liquid and Bicarbonate Infusion, Fomepizol and Hemodialysis Treatment in Serious Methanol Intoxication

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Abstract

Methyl alcohol is a type of alcohol commonly used in the industry. It can also be used illegally in manufactured drinks. Methanol poisoning is a clinical condition that can cause severe illness and death. A 47-year-old male patient who had complaints of abdominal pain and altered consciousness was brought to the emergency room by his relatives. They reported that he took methyl alcohol approximately 48 hours before admission in the emergency department. The patient was hospitalized as methyl alcohol poisoning. He was with severe acidosis for which NaHCO3 at 1 mEq/kg was given and hemodialysis was performed. Fomepizole was given at a loading dose of 15 mg/kg, and a maintenance dose of 10 mg/kg every 12 hours up to three times was followed. After seven days of intensive care, the patient was discharged without any complications.

Key words: methanol poisoning, fomepizole, hemodialysis

Introduction

Methanol is used predominantly in industrial chemical solvents because of its organic solvent nature. It is a colorless, toxic substance in liquid form at room temperature. Methanol poisoning is often caused by ingestion of illegally produced beverages, as well as by accident or suicide [1]. The metabolites of methanol are very toxic. Methanol is first metabolized to formaldehyde and then formic acid by the alcohol-dehydrogenase enzyme. These metabolites are responsible for metabolic acidosis, blindness, cardiovascular instability and toxicity that can cause death [2]. Because methanol intoxication is not common, the reported number of cases is limited. In this article, we present a 47-year-old man with pH: 6.7 due to methanol intoxication.

Case

A 47-year-old male patient was admitted to our emergency room by his relatives because of a change in his consciousness. At first examination of the patient, the temperature was 36.6^{o}C, blood pressure was 70/40 mmHg, pulse rate was 78 /min, respiratory rate was 22/min. The laboratory findings of the patient were as follows, pH: 6.7, PCO2: 30 mmHg, PO2: 60 mmHg, HCO3: 7 mmol/L. Glaskow coma scale was calculated as 8 points, afterwards the patient was intubated and taken to the mechanical ventilator support. The rest of the biochemistry and complete blood count were as follows, glucose: 166 mg/dL, creatinine: 1.5 mg/dL, AST: 24 U/L, ALT: 11 U/L, Na: 136 mmol/L, K: 5.06 mmol/L, WBC: 46,000 x 10^9/L, HGB: 15,6 gr/dl, PLT: 312 x 10^9/L. The relatives of the patient reported that he took methyl alcohol approximately 48 hours before admission in the emergency department. The patient was assessed and methanol intoxication diagnose was confirmed due to unconsciousness, history of fake alcohol intake, pH and bicarbonate values in terms of deep metabolic acidosis. The blood methanol level of the patient could not be measured. Bicarbonate supplementation, hemodialysis and antidote therapy (3 vials of fomepizole) were applied to the patient as medical treatment. Extubation was performed 48 hours after the start of medical treatment and the patient was discharged 1 week later.

Discussion

Methanol poisoning often carries a high risk of death due to late admission in the hospital and sometimes delayed diagnosis. The general treatment approach of methanol poisoning includes gastric irrigation, ethanol and fomepizole administration, hemodialysis, folic acid and thiamin administration [1,3]. Stomach irrigation should be done in the first hour after intake, since our patient has arrived 48 hours later, no stomach irrigation was performed. Since active charcoal does not adequately bind methanol, it has no place in these poisonings. We

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have not given any active charcoal since our patient did not have any other ingestionsbesides methanol. Ethanol is used in the classical initial treatment of methanol poisoning and can be given by oral, IV or nasogastric tube. 10% i.v. ethanol is used in 5% Dextrose. When used intravenously, loading dose is 10 ml/kg, maintenance dose is 1.6 ml/kg. Orally, 20-30% ethanol is used, with loading dose 0.6-0.8 g/kg, and maintenance dose 0.11 g/kg. If the patient is alcohol-dependent, the loading dose should be adjusted to 15 g/kg [1,2]. Fomepizole is a competitive inhibitor of alcohol dehydrogenase, inhibiting the conversion of methanol to formic acid, the major metabolite. Fomepizol administration is also recommended as follows, 15 mg/kg-loading dose, either intravenously or orally, independent of alcohol concentration, followed by intermittent 10 mg/kg-doses every 12 hours until alcohol concentrations <30 mg/dL [4]. If fomepizol administration is shortly after intakeit can prevent ethylene glycol-related renal failure and methanol-related visual and neurological injuries [4]. Each maintenance dose of fomepizole can be given with slow i.v. infusion within 30 minutes. We have applied fomepizole administration to this case by first loading and then completing the treatment with maintenance dose. In a patient with methanol poisoning, dialysis should be performed if there is evidence of visual symptoms and signs of SSS dysfunction, peak methanol level above 25 mg/dL, severe metabolic acidosis, or more than 30 mL of methanol intake. The blood methanol level of the patient could not be determined because it is not performed in our hospital. Three sessions of hemodialysis were performed to correct the acidosis with increased anion gap confirmed in the arterial blood gas analysis. The pH level of the patient at first consultation is important in terms of prognosis. Severe acidosis and coma indicate poor prognosis. It is good prognostic sign that the patient's consciousness is open? and hyperventilation is possible. Fomepizole is thought to be able to remove the need for hemodialysis if it is applied before the onset of major acidosis or organ injury [4]. When dialysis is indicated, continuous infusion of 1 mg/kg/h is recommended to compensate for elimination through the dialyzer's membrane [4]. Fomepizole is contraindicated in individuals who are allergic to pyrazoles and is not recommended during pregnancy.

Conclusions

Since antidotal therapy is available, it is important to recognize methanol poisoning immediately [5]. The presence of metabolic acidosis associated with an increased anion and osmolal gap is an important laboratory clue. Fomepizole is an effective and safe first-line antidote for methanol intoxications.

Conflict of interest statement. None declared.

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Case report

Paradoxal Diuresis after Vasopressin Administration in Hemodialysis Patient with Bleeding

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Abstract

Uremic bleeding is a well-recognized complication in patients with renal failure. The most common agent used in uremic patients with active bleeding is desmopressin. Desmopressin doses for uremic bleeding are approximately 10-fold higher than doses used fin diabetes insipidus. Oral form of desmopressin was used for treatment of haematoma in the right upper thigh in hemodialysis patient. Residual urine output was 100-200 ml/24 hours in the past couple of years. The second day after desmopressin administration, patient experienced suprapubic painful distension. Urinary catheter was placed and 900 ml of clear liquid was collected?.
In the following days, duiresis continued between 600-800 ml per day. Scientific explanation for this phenomenon is not found. This question can be answered by a prospective trial of the effect of vasopressin in dialysis patients.

Keywords: uremic bleeding, desmopressin, diuresis

Introduction

Uremic bleeding is a well-recognized complication in patients with renal failure [1].
It was described by Reisman almost 100 years ago, in two patients with renal failure caused by Bright's disease (the term is no longer used, but it is described as acute or chronic nephritis) who experienced severe and generalized bleeding [2]. It has been known for many decades that uremic bleeding and platelet dysfunction increases the risk of general bleeding in these patients. The exact mechanism for this emains largely unknown, aldo it seems to be multifactorial.
Important factors contributing to uremic bleeding are dysfunctional vonWillebrand factor (vWF), increased levels of cyclic AMP (cAMP), increased levels of cyclic GMP (cGMP), uremic toxins and anaemia [3-6]. Patients with uremic bleeding typically present ecchymosis, purpura, epistaxis and bleeding from venepuncture sites. These patients can also
present gastrointestinal or intracranial bleeding [7,8]. Treatments for uremic bleeding target the various factors that seem to have a role in platelet dysfunction. The most common agent used in uremic patients with active bleeding is desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP]) [10-12].

Case report

Twenty eight years old female patient has been on haemodialysis from July 2007. The primary cause for renal failure is unknown. As ayoung girl, she had frequent urinary infections. When she was 6, she was wounded by shrapnel in the abdomen and right thigh, and by a bullet in her right shoulder. From the start of dialysis treatment, creation of arterio-venous fistula (AVF) was repeatedly attempted, but it was not successful. Over the years, a central venous catheter was used as a vascular access. In 2010, she received living kidney transplantation from her father. On the second postoperative day, there was an acute humoral rejection. Further in the postoperative period an extensive gastrointestinal bleeding and multiple organ dysfunction developed, and the patient was put on artificial ventilation for a month.
Aftherwards a graft nephrectomy was performed and she was reinstated on intermittent haemodialysis three times per week. Anticoagulant therapy used was low molecular weight heparin (LMWH), Enoxaparin in dose 0.7 mg/ kg before hemodialysis. Residual urine output was100-200 ml/24 hours over the past couple of years. She did not use diuretic therapy. Rutine ultrasound showed small kidney, size 6 cm, modified by type of chronic renal insufficiency. The bladder was with echosonographic normalm features. The patient remained stable until December 2015, when her wellbeing was complicated with pain and swelling in the right upper thigh.
CT scan was performed and showed voluminous musculature of the rear lodge of the right leg as a whole, in

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comparison with the left side, and small fluid collections that had extended the muscle fibres (hematoma). The hematoma was punctured and 50 ml of coagulated blood was evacuated. She remained hemodinamicly stable and mobile, without any decrease in the level of hemoglobin. In February 2016, swelling and pain in the right thigh occurred again. The patient was hospitalized in the Department of Orthopaedics and Traumatology of the Clinical Centre in Sarajevo. Urgent ultrasound was performed and the computed tomography angiography (CTA) verified a large hematoma in the same or similar location as before, located in the m. adductor magnus semimembranosus and semitendinosus in the right leg, polycyclic in form; the dimension of the transverse cross section was about 83X55 mm, and length about 160 mm. The main blood vessels were in order. In the delayed post-contrast stage, extravasation of contrast was recorded in the central and peripheral trace forms. Laboratory findings were as follows: WBC 9.0 x 10^9/L, RBC 2.34 x 10^{12}/L, HGB 7.6 g/dL, HCT 21.4%, PLT 186 x 10^9/L prothrombin time 0.72% (0.64-1.20), prothrombin time PT? 1.17 (INR 0.90-1.40), APTT 51.85 sec (22-38), APTT ratio 1.67 (0,84-1.46), thrombin time 16.9 sec (14.0 to 24.0), activity of fibrinogen 4.1 g/L (1.5 - 4.0) , ECLT > 2 h (> 2), factor VIII 0.52 (0.50 1.80), adhesion PLT 7.7 (>7.5) aggregation and adhesion PLT 630 (>900).

The patient was givenconcentrated filtered red cells and fresh frozen plasma, and was treated with antibiotic Clindamycin 600 mg every 6 hours.

The emergency radiologist performed punctuation of the hematoma and 400 ml of fresh blood was evacuated. Later she developed acute compartment syndrome and was surgically treated, by ligature of artery femoris profunde (APF).

The next day, the patient suffered less pain, leg circumference was smaller and there was no further decline in haematological data.Control CTA showed the state after ligation: APF right with visible air collection of postoperative nature. APF directly distal to the ligation was filled with contrast and well opacified, including its branches. No certain CTA signs of extravasation of HP? from blood vessels were recorded. There were signs of cellulitis with a distinct progression in the size of the hematoma compared to the previous CT, with propagation to the distal third of the back of the legand to the right (Figure 1).

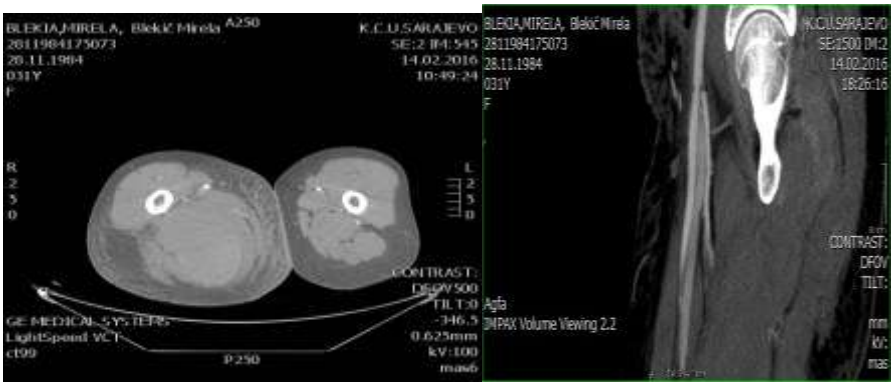

Fig. 1. CTA showed progression in the size of the hematoma with propagation to the distal third of the back of the leg, to the right

Regular haemodialysis treatments were carried out at regular times, 3 times per week in duration of 4 hours, with controlled ultrafiltration, without anticoagulation and with 4% citrate lock in the cathether. After each dialysis, beta erythropoietin was administered at a dose of 4000 IU iv. During the third day of hospitalization, the patient again felt strong pain in the upper thigh, with an increase in the scope; also pain and swelling of the left upper arm and left breast. Ultrasound was performed in the left axilla and it verified polycyclic liquid collection, located next to the artery, 54x25 in diameter. In the superolateral caudal quadrant of the breast there was a hematoma withliquid and sediment component, about 44x17 mm in diameter. The ultrasound of the leg showed a slight regression in the size of the hematoma. The size of the liquid component was about 8 x 30 x 3 cm.Since coagulation factor inhibitors were suspected, during the fourth day of hospitalization, plasmapheresis was performed with plasma volume of 2500 ml of FFP. In the afternoon, there was a further decrease in haematological findings: RBC 2.2 x 10^{12}/L, HBG 6,8 g/dL, HCT 0.20, PLT 222 x 10^9/L, WBC 10.6 x 10^9/L.

Since we did not have desmopressin in parenteral form, we decided to parenterally administer tranexamic acid in a dose of 10 mg/kg, and the same dose was repeated after 48 hours.

Due to the severity of the general condition and the further decline in haematological data, the next day we introduced an oral preparation of dezmopresin, Minirin tablets, 3x2 mg (the fifth day of hospitalization), although oral administration of desmopressin is not included in the guidelines for treatment of uremic bleeding. The second day after the introduction of desmopressin, the patient complained of suprapubic tension, clinically verified as painful distension. After placement of the

urinary catheter, 900 ml of clear liquid was collected in the urinary bag. Since the patient was practically anuric over the last few years, analysis of the resulting content was performed, which showed that it was urine. Analysis of the content were: yellow, Ph 7.0, the relative density of 1.010, 1 g protein/L, glucose negative, negative ketones, bilirubin negative, negative nitrites; the sediment showed 6-8 leukocytes, erythrocytes 20-25, epithelial cells plates and some bacteria. Creatinine in the sample was 1042 ?mmol/L, BUN 24.0 mmol/L, calcium 1.57 mmol/L. During the seventh day of hospitalization, the patient was stable, with slight pain in the upper leg and hand. Ultrasound showed no further progression of the hematoma and the hemogram was stable. Laboratory findings verified thrombocytosis, with a slight increase in LDH. A small dose of LMWH Enoxaparin 20 mg was administered before haemodialysis treatment, while desmopressin was excluded. Desmopressin therapy was orally administered over three days, at daily dose of 3 x 2 mg.
Laboratory findings showed further decline:WBC 7.42 x 10^9/L, RBC 2.72 x 10^{12}/L, HGB 8.72 g/dL, haematocrit 25.7%, PLT 409 x 10^9/L, Na 137 mmol/L, K 6.8 mmol/L, Ca 2.18 mmol/L, CI 105mmol/L, BUN 20,9 mmol/L, creatinine 1007 ?umol/L, LDH 295, INR 0.99, aPTT 32.7.
The patient continued to have dieresis in the following days, between 600-800 ml per day. After one month, her diuresis is between 300 and 400 ml per day.

Discussion

Desmopressin (DDAVP) is a synthetic analogue of vasopressin, the hormone that reduces urine production. It may be taken nasally, intravenously or as an oral or sublingual tablet. There are certain benefits of desmopressin in adults who have problems with night time urination and in treatment of central diabetes insipidus (DI). It is used to replace endogenous antidiuretic hormone (ADH) in the central nervous system in disorders where there is decreased production of of ADH from the posterior pituitary. The most common agent used in uremic patients with active bleeding is desmopressin (1-deamino-8-Darginine vasopressin [DDAVP]). Desmopressin doses for uremic bleeding are approximately 10-fold higher than doses used r in diabetes insipidus, and range from 0.3 ug/kg to 0.4 ug/kg administered intravenously or subcutaneously as a single injection. Desmopressin should not be administered for more than three days [10,11]. To our knowledge, no trial has ever evaluated the oral use of DDAVP in uremic bleeding. Oral administration of DDAVP might be as beneficial as intravenous therapy, but there are currently no data to support this [13,14]. Although not in accordance with treatment guidelines, due to lack of parenteral medication, we administered desmopressin orally to our patient, in total duration of three days. After examining the available literature, we did not find a case in which urine output in haemodialysis patients was increased after treatment with desmopressin. The study Meinders and associates from 1975 showed a paradoxical increase in diuresis in patients with diabetes insipidus after using DDAVP. After an immediate and transient antidiuresis, a single intravenous bolus injection of lysine vasopressin was given during treatment with chlorpropamide. Followed by continuous intravenous infusion of chlorpropamide with lysine vasopressin, carbamazepine or clofibrate and resulted in increased water diuresis for 12-24 h or longer. It is suggested that the antidiuretic action of chlorpropamide, carbamazepine and clofibrate is localized at the receptor site for ADH in the distal renal tubular cell [15]. In a large multi-centre study of 778 patients who had septic shock, Gordon *et al*, found that vasopressin compared to norepinephrine was associated with a trend to reduced creatinine over time, reduced progression to renal failure/loss and reduced mortality. As a result, fewer patients treated with vasopressin in comparison with norepinephrine required renal replacement therapy. These results are consistent with previous small studies, showing that vasopressin compared to norepinephrine increased urine output and creatinine clearance [16]. Study Holmes CL *et al*, showed that vasopressin markedly and significantly increased MAP, did not change PAP, markedly increased urine output and decreased pressor dosage significantly in this retrospective case series of patients receiving vasopressin for severe septic shock [17]. Urine output significantly increased by 4 h, but this effect was not sustained over 24 and 48 h. The paradoxical diuretic effect of vasopressin has been observed in patients with hepatorenal syndrome and congestive heart failure [18], yet the mechanisms remain unexplained. There are three possible explanations of vasopressin's diuretic effect. Firstly, the renal vasculature seems to be relatively resistant to the vasoconstrictor effects of vasopressin [19]. At low doses, there is some renal efferent arteriolar vasoconstriction, relatively sparing the afferent renal arterioles, which therefore increases renal perfusion pressure [20]. A vasodilatory effect of vasopressin on the renal vasculature is present at low doses (0.02 U/mil), which can be blocked by L-NAME [21], suggesting that the effect is mediated by nitric oxide. Secondly, oxytocin has a natriuretic and diuretic effect, due to inhibition of sodium reabsorption at the proximal and distal tubules [22]. Vasopressin may be directly activating oxytocin receptors, causing natriuresis and diuresis. Thirdly, vasopressin releases atrial natriuretic peptide [23], which may be an indirect mechanism of its diuretic effect.

Conclusions

To conclude, in this case, vasopressin was administered for uremic bleeding which resulted in increased

urine output in previously oliguric patient on haemodialysis. Safe scientific explanation of this phenomenon was not found. This question can be answered by a prospective trial of the efffect of vasopressin in dialysis patients.

Conflict of interest statement. None declared.

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Case report

Recurrent Cathartic Use and Acute Kidney Injury

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Abstract

Introduction. Oral sodium phosphate containing (OSP) cathartics are used for bowel cleansing in medical practice. They are generally accepted as safe. However, these agents may cause renal injury in some susceptible patients.
Case report. We present 2 patients suffering from acute kidney injury that could have been prevented easily. The first patient had undergone colonoscopy for chronic diarrhea. The second patient had undergone colonoscopy for iron deficiency anemia and colonic polyps. Both patients presented with nausea and vomiting. Fortunately, they recovered with hemodialysis and supportive measures.
Conclusions. Phosphate containing cathartics have the potential to cause prerenal azotemia or acute phosphate nephropathy. However as rarely seen, clinicians frequently neglect this entity. Even so OSP cathartics must be used cautiously in susceptible individuals. Preventive strategies should be implemented in all of these patients instead of management after renal injury occurs.

Keywords: cathartic, colonoscopy, nephropathy, phosphate

Introduction

Various drugs may cause acute kidney injury (AKI). Oral sodium phosphate (OSP) containing cathartics used for bowel cleansing are among these drugs. In addition to the risk of acute prerenal azotemia, transient hyperphosphatemia, volume depletion exacerbated by concurrent renin-angiotensin system blockers and diuretics, and elevated distal tubular phosphate and calcium concentrations may contribute to the renal injury named as acute phosphate nephropathy (APN) [1,2]. Patients with chronic kidney disease are more susceptible for APN, especially if they are using medications like angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, diuretics, or non-steroidal anti-inflammatory drugs [3]. Some simple measurements can be implemented in order to prevent AKI in these high-risk patients. Proper hydration, stopping risky medications and using safer alternatives to phosphorous-containing formulations are useful. Herein we present two of our recently detected AKI cases in order to increase the awareness about this issue.

Case 1

A 59 year old male admitted to our clinic with nausea and vomiting that started 2 days after a colonoscopy procedure. On physical examination, skin and mucous membranes were dry. No abdominal tenderness was present. Arterial blood pressure was 110/60 mm/Hg. Pulse was 96/min.; Some laboratory parameters were as; urea: 88 mg/dl, creatinine: 3,6 mg/dl, Na: 142 mmol/L, K: 3,1 mmol/L, Ca: 9,8 mg/dl and P: 12,5mg/dl. He was hydrated intravenously for suspected prerenal AKI. But as he was oliguric despite hydration for more than 24 hours, hemodialysis was performed via a jugular catheter. His urine output began to increase at the 3rd day after two dialysis sessions. Hemodynamic parameters and electrolyte levels were followed up closely and corrected rapidly. After 7 days, he was cured completely. Serum phosphate and creatinine levels decreased (Figure 1). Renal biopsy was not performed as healing occurred.
On history, the patient was learnt to be on clinical follow-up for acromegaly after hypophyseal adenectomy 23 years ago. He had also hypertension which was regulated with valsartan and thiazide combination. He had non-bloody, loose diarrhea for a nearly 4 weeks duration. He was scheduled for colonoscopy in part of investigation for his chronic diarrhea. On laboratory before bowel preparation; some parameters were as; urea: 20 mg/dl, creatinine: 0,6 mg/dl, Na: 142 mmol/L, K: 3,1 mmol/L and Ca:10,1 mg/dl and P: 2,6. He was administered a solution including 63.8 g monobasic sodium phosphate monohydrate and 24.3 g dibasic sodium phosphate heptahydrate for bowel preparation. Bowel was accepted as inadequately cleaned after the first cleaning attempt. So he was iven an additinal solution including 900 mg sennosides A and B calcium.?

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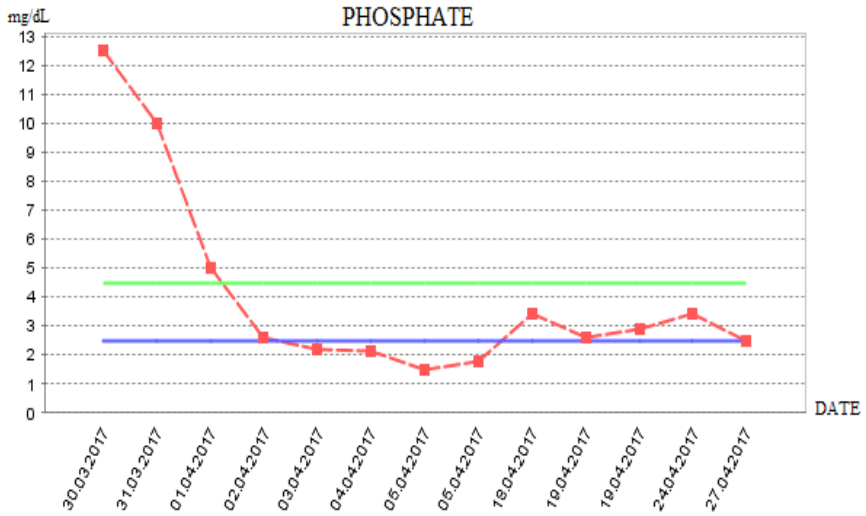

Fig. 1. The serum phosphate and creatinine level graphics of the first patient

Case 2

A 51 year old female consulted to our emergency clinic with nausea, persistent vomiting and fatique one day after a colonoscopy procedure. Arterial blood pressure was 110/60mm/Hg. Pulse was 64/min. On laboratory; some parameters were as; urea: 69 mg/dl, creatinine: 4,4 mg/dl, Na: 140 mmol/L, K: 4,7 mmol/L, Ca: 8,5mg/dl and P: 11,7 mg/dl. She was hydrated intravenously for suspected prerenal AKI but she was oliguric for 12 hours. Hemodialysis was performed via a jugular catheter as she had persistent nausea and vomiting. Her urine output began to increase at the 2nd day after only one dialysis session. Hemodynamic parameters and electrolyte levels were followed up closely and corrected rapidly. After 12 days, she was cured completely. Serum phosphate and creatinine levels decreased. (Figure 2) Renal biopsy was not performed as healing occurred.

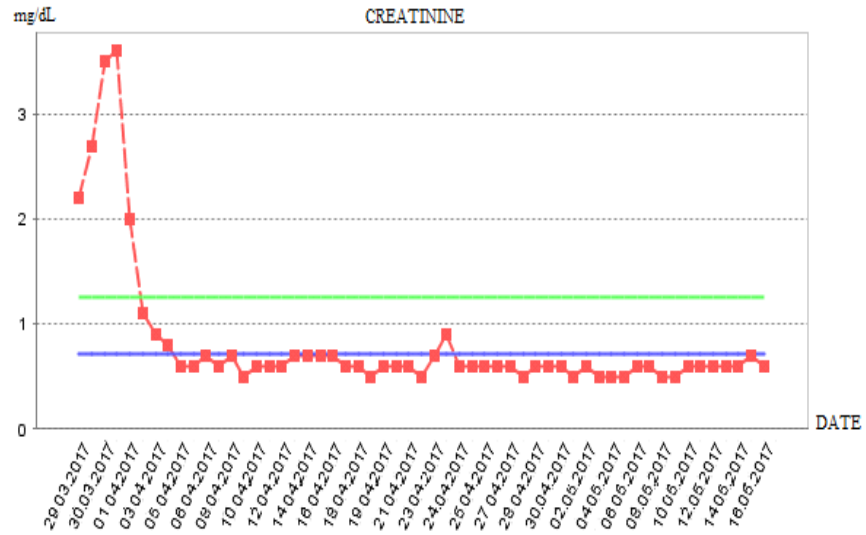

Fig. 2. The serum phosphate and creatinine level graphics of the second patient

On history, this patient was learnt to be under investigation for Cushing's syndrome. She was diagnosed to have bilateral functioning adrenal adenoma. Bilateral adrenalectomy was performed 1 year ago. After the operation, she was on prednisolone 10 mg/day and fludrocortisone 50 mg/day. She was on follow-up for type 2 Diabetes Mellitus and hypertension which was regulated with valsartan/thiazide, amlodipine and nebivolol combination. She was also under investigation for iron-deficiency. Colonoscopy was performed. Colonic polyps were detected. Colonoscopy operator was learnt to fail to finish the procedure because of patient intolerance. Thus biopsy was postponed to another colonoscopic intervention. She was scheduled again for colonoscopy and another preparation with OSP was performed. On laboratory before bowel preparation; some parameters were as; urea: 44 mg/dl, creatinine: 0,5mg/dl, Na: 146 mmol/L, K: 3,2 mmol/L, Ca:

9,1 mg/dl and P: 3,5. She was administered a solution including sodium dihydrogen phosphate and disodium hydrogen phosphate three times for bowel preparation. In addition she was given a solution including 900 mg sennosides A and B calcium. The patient had taken 127.6 g monobasic sodium phosphate monohydrate and 48.6 g dibasic sodium phosphate heptahydrate.

Discussion

Adequate pre-procedural bowel cleansing is essential for colonoscopy. Some oral phosphate containing agents are used effectively for this purpose. Hypovolemia resulting from the preparation procedure may facilitate development of prerenal azotemia especially in patients with chronic kidney disease. Non-steroidal anti-inflammatory drugs (NSAIDs), diuretics and renin-angiotensin system (RAS) blockers that decrease glomerular filtration rate may facilitate renal injury if they are used concurrently with these agents.

In addition to the risk of prerenal azotemia, APN has been reported to occur after exposure to sodium-phosphate (NaP) bowel-cleansing solutions. Intestinal absorption of oral phosphate containing solutions may cause hyperphosphatemia and hypocalcemia [4]. APN is a type of renal injury characterized by tubulointerstitial damage due to deposition of calcium and phosphorus [5]. Clinically, some patients may present with acute kidney injury and very high phosphorus levels. Besides, the renal injury may occur after several weeks or months [6].

The renal injury in APN may recover in some patients but the damage may sometimes become permanent. The most influential marker for prognosis is baseline renal function. Female gender, diabetes mellitus, older age and Caucasian race are other risk factors [2].

The baseline renal filtration function of our first patient was normal. However he was nearly 60 years old and he was taking valsartan/hydrochlorothiazide that may increase the risk of both prerenal azotemia and APN. His medication should be shifted to a safer agent temporarily during bowel-cleansing. A waiting period could be implemented before using the cathartics for the second time in a short time period. Oral hydration should also be motivated. Serum biochemistry tests should also be performed after the first procedure, in order to detect any renal or electrolyte abnormalities.

Our second patient was female. She was diabetic and also on valsartan/hydrochloride treatment. Her baseline renal filtration function was also normal. Her medication was not changed to a safer drug during bowel-cleansing. A waiting period was not implemented before repeating the cathartics for the second time. Oral hydration was not motivated. Serum biochemistry tests were not performed after the first procedure.

They were assessed as euvolemic on physical examination. In addition, despite effective hydration they needed dialysis. So we got away from the preliminary diagnosis of prerenal acute renal injury and acute tubular necrosis due to hypovolemia. Besides all these, they had very high serum phosphate levels on laboratory examination. So we strongly suggested their diagnosis to be APN. Healing occurred. So renal biopsy was not performed as it would be unethical.

Both creatinine and phosphorus improved promptly in the first patient but not in the other patient where creatinine and serum phosphorus remained elevated after 10 days. This may be related to possible different mechanisms of renal injuy acting simultaneously. For example the first patient might have suffered from prerenal injury more, but the second might have suffered from acute phosphate nephropathy more.

Both patients had history of endocrine disease. But their diseases have different impacts on normal human physiology and they were under good control. So a possible coincidence or a tendency to acute renal injury were not suggested to be.

Conclusions

Acute kidney injury due to dehydration or toxic effects of phosphate is a frequently ignored complication of colonoscopy. Clinicians may overlook the diagnosis as a result of variable APN courses. No specific therapy is available, if renal injury occurs once. But prevention is possible with simple measurements. Thus APN must be kept in mind before bowel cleansing procedures.

Conflict of interest statement. None declared.

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Case Report

Idaricuzumab Treatment in Severe Gastrointestinal Bleeding and Renal Insufficiency Due to Dabigatran Overdose: Case Report

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Abstact

Currently, new generation oral anticoagulant drugs are frequently prescribed. Although routinely do not require coagulation test monitoring, new generation anticoagulants may cause overdose in patients with renal insufficiency. Bleeding due to dabigatran overdose may be life-threatening and should be treated immediately. In this article, treatment strategies of a patient with severe gastrointestinal bleeding and renal insufficiency due to dabigatran are discussed.

Keywords: dabigatran, gastrointestinal bleeding, idaricuzumab

Introduction

Until recently, Vitamin K antagonists such as warfarin have been used primarily in patients with atrial fibrillation to prevent thromboembolic complications [1]. However, the use of warfarin in atrial fibrillation has significant limitations such as the need for frequent coagulation tests and interaction with other drugs and foods [2,3]. New generations of anticoagulants (dabigatran, apixaban, rivaroxaban, edoxaban, betrixaban) are frequently used in daily practice and are claimed to be more effective and safe than vitamin K antagonists and they do not need monitoring with coagulation tests. Dabigatran is a direct inhibitor of thrombin and has proven to be more effective than warfarin in stroke and systemic embolism [4]. Idaricuzumab has been reported to be effective and safe inhibitor of dabigartan in two randomized clinical trials [5]. In this article, the use of idaricuzumab in the management of a patient with renal insufficiency and severe gastrointestinal bleeding probably due to dabigatran is discussed.

Case Report

An 86-year-old female patient who was admitted to the emergency department with signs of melena and fatigue within the last hour. She was treated with dabigatran. The vital signs of the patient at the time of admission to the clinic were as follows: temperature 36.6^{o}C, arterial blood pressure 108/70 mmHg, heart rate: 120/min and respiratory rate: 22/min. Fresh blood was detected on rectal examination. The rest of the physical examination was normal. Blood biochemistry and whole blood tests were as follows: glucose: 111 mg/dl, creatinine: 2.1 mg/dl, AST: 21 U/L, ALT: 12 U/L, Na: 136 mmol/L, K: 5.6 mmol/L, Cl: 109 mmol/ L, Ca: 7.4 mg/dl, WBC: 11.200 x 10^9 / L, Hb: 4.3 g/dl, PLT: 118 x 10^9 / L, INR: 4.7, APTT: 58, 7 sec, PT: 42.7 sec. The patient was transferred to the intensive care unit because of the instability in the general clinical situation. Mucosal bleeding points were detected in colonoscopy. Detailed medical history of the patient revealed the use of dabigatran due to non-valvular atrial fibrillation. Before the administration of dabigatran the patient was treated by warfarin that was discontinued because of gingival hemorrhage. Dabigatran was immediately discontinued and fresh frozen plasma and whole blood were given to the patient. However, the low hemoglobin levels and the unstable vital signs persisted after blood transfusion. At this stage, the patient received idaricuzumab at the dose of 5 grams as rapid intravenous infusion. The patient's active bleeding stopped two hours after the infusion of idaricuzumab whereas no further reduction of hemoglobin level was observed. The glomerular filtration rate of the patient increased to 38 ml/min/1.73 m^2 and then returned to the baseline values and the patient was transferred to the ward because of lack of evidence of active bleeding and stable clinical situation.

Discussion

Dabigatran is an oral anticoagulant acting via direct inhibition of thrombin that prevents strokes in patients with non-valvular atrial fibrillation. Before the administration of the new generation of anticoagulants, the renal and liver function tests should be carefully evaluated [4]. Dabigatran overdose can lead to life-threatening bleeding, especially in elderly patients. Idaricuzumab is a monoclonal antibody that specifically binds

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to dabigatran. In particular, it inhibits aDabiFab [6]. Idaricuzumab was approved by the FDA in 2016 and it is found in vials of 2.5 gram. Idaricuzumab can be given as intravenous infusion for 15 minutes or as fast intravenous injection of 2 vials [5].

Conclusions

Dabigatran has low affinity for plasma proteins and is considered to be dialyzable. Prior to administration of idaricuzumab overdose of dabigatran was treated by hemodialysis. Currently, hemodialysis and hemodiafiltration can be used in patients with dabigatran overdose who do not respond to idaricuzumab.

Conflict of interest statement. None declared.

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Case report

Eculizumab for Treatment of a Patient with Atypical Hemolytic-Uremic Syndrome Caused by Mutations of Complement Factor B, Factor H and Membrane Cofactor Protein after Renal Transplantation

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Abstract

Atypical hemolytic uremic syndrome (aHUS) is a rare disease related to genetic mutations in the alternative complement pathway. The risk of aHUS manifestation is increased after renal transplantation.

We present a case of a 47-year-old female who had biopsy-proven thrombotic microangiopathy. Genetic analysis revealed a rare synonymous variation (R381R) of complement factor B. She was also heterozygous for the CFH H3 haplotype and heterozygous for the CD46 (membrane cofactor protein). In April 2016 she received a renal allograft from the deceased donor with eculizumab therapy, tacrolimus, mycophenolate and steroids. The first attempt to prolong the interval between eculizumab dosing had resulted with acute rejection. She had continued with eculizumab for one year when therapy was further denied by the hospital pharmacy committee due to the economic concerns. However, her allograft function remained stable without any signs of hemolysis.

In conclusion, patients with multiple complement factor mutations may be at increased risk for complement activation and may require prolonged or even life-long treatment with eculizumab.

Keywords: Atypical hemolytic uremic syndrome, complement factor B, eculizumab

Introduction

Atypical hemolytic-uremic syndrome (aHUS) is a complex multigenetic complement-mediated disease [1]. The risk of aHUS manifestation is increased after renal transplantation because of the simultaneous occurrence of numerous additive risk factors, including the use of immunosuppressive drugs, infective complications and activated endothelial cells. Eculizumab is a complement C5 inhibitor which specifically blocks terminal complement activation. It is effective in prevention and treatment of aHUS after renal transplantation [2-4]. Duration of treatment remains uncertain. Thus, despite the awareness of the unpredictable disease course, which may be prevented by eculizumab treatment, many patients discontinue eculizumab therapy. We herein report a female with combined mutations associated with aHUS, who received renal transplant with eculizumab treatment.

Case report

A 47-year-old female was diagnosed by biopsy with thrombotic microangiopathy in 2009, and was treated with plasma exchanges and corticosteroids. Despite the 144 plasma exchange procedures and treatment with rituximab, she developed end stage renal disease and had started with hemodialysis in 2012. The last therapeutic plasma exchange was performed in July 2013. Analysis performed at the Sammelweiss University in Budapest revealed ADAMTS13 activity 60 (ref: 67-147%), total complement activity, classical pathway (hemolytic test): 72 CH50/ml (ref range 48-103 CH50/ml), total complement activity, alternative pathway (WIELISA-Alt): 87 % (reference range 70-105%), complement C3: 0,97 g/L (reference range 0,9-1,8 g/L), complement C4: 0,52 g/L (reference range: 0,15-0,55 g/L), factor H antigen: 434 (reference range 127-447 mg/L), complement factor I antigen: 95 % (reference range 70-130%), complement factor B antigen: 87 % (reference range 70-130%), anti- factor H IgG autoantibody: negative (96 AU/mL, ref <110), anti-C1q IgG 3 AU/mL (ref <52), C1q antigen 135 mg/L (ref 60-180), sC5b-9 (terminal complement complex) 173 ng/mL (ref 110-252), C3a anaphylatoxin 89 ng/mL (ref 70-270), C3-nephritic factor 7 % (ref: <10%).

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A genetic analysis found our patient to be heterozygous for a rare synonymous variation (**R381R**) of complement **factor B**. She was **heterozygous** for the ***CFH* H3** haplotype (involving the rare alleles of c.-331C>T, Q672Q and E936D polymorphisms). Additionally she was found to be **heterozygous** for the *CD46* rs2796268 and rs1962149 (membrane cofactor protein).

In April 2016, renal transplantation from the deceased donor was performed. Eculizumab was used for induction, with tacrolimus, mycophenolate and steroids for maintenance. Seven days posttransplant, a surveillance biopsy revealed mild vascular rejection in one of four sampled small interlobular arteries. By electron microscopy, the glomerular endothelial cells were mildly activated. The C5b-9 immunohistochemistry showed very little staining. She received 4 doses of eculizumab (900 mg each) every seven days. The final dose of 1200 mg was planned to be administered two weeks later. However, the first attempt to prolong the interval of drug application had resulted with biopsy proven acute rejection Banff IIA. She immediately received 1200 mg of eculizumab with three steroid boluses (500 mg each). Eculizumab was continued on weekly basis for six months, and then every two weeks for the following six months post-transplant. Besides the regular follow-up at outpatient clinic, disease activity was monitored closely at home by means of urine dipstick testing for hemoglobin. Interestingly, elevations in serum LDH and free-hemoglobin correlated with menstrual bleeding.

Laboratory findings during the post-transplant follow-up are presented in Figure 1.

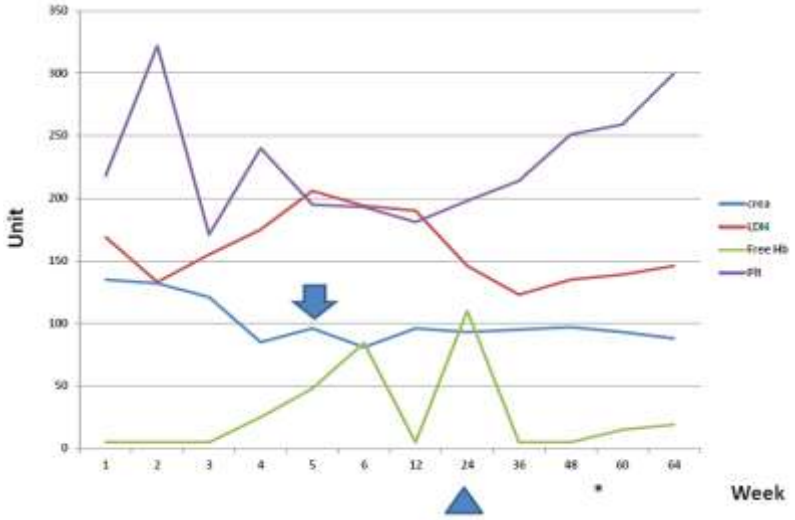

Fig. 1. Parameters of disease activitiy and treatment with eculizumab. Arrow indicates episode of acute rejection after the first attempt to prolong eculizumab dosing interval. Triangle indicates time point at which eculizumab was used every two weeks until the time point indicated by the asterixis. Crea, serum creatinine in µmol/L; LDH, lactat dehydrogenase IU/L, Plt, plattelets; Hb, hemoglobin

Due to economic concerns further eculizumab therapy was discontinued by the hospital's pharmacy committee. Allograft function remained stable with serum creatinine 90 µmol/l, 18 months after the therapy discontinuation without any signs of disease activity.

Discussion

There is very limited data on the post-transplant outcome recurrence of aHUS in patients with different mutations while some of them are very rare. In a meta-analysis which involved 259 patients, the most common mutation was CFH (50%) followed by CFHR1 (35%), MCP (22.8%) and CFI (16.6%) [5]. Mutations of complement factor B are very rare. Several cases have been described recently [6,7]. We report the first case of renal transplant outcome in a patient with CFB mutation.

A potential relationship between the type of complement mutation identified and the risk of subsequent clinical manifestations of aHUS has been suggested. According to the current data, patients with CFH mutations appear to have increased risk for disease manifestations [8]. Patients with a mutation in exons 19 or 20 of the CFH may be more prone to recurrence. Thus it seems that eculizumab therapy discontinuation may be feasible in some but not all patients with a CFH mutation. Although previous studies considered patients with CFH or thrombomodulin mutations to be associated with worst outcomes, whereas MCP mutations were associated with the least severe consequences [9], novel data suggest that the risk of new aHUS manifestations were comparable regardless of the mutation [10]. In the both French study and the study of Noris *et al*. the risk of relapse was approximately 40% [9,10]. Furthermore, French study showed that 82% of relapses in adults occurred during the first year, with

the risk of relapses after the first year decreasing to approximately 25% [10]. Therefore, tapering of the therapeutic strategy to prevent relapses could reasonably be considered.

Another issue is how to follow patients with aHUS. Measurement of complement proteins in plasma was found to be of limited value. In patients with proven genetic mutations reduced C3 levels have been found in only 30–50% of cases [9].

In the meta-analysis of Krisnappa et al. mortality rate decreased with the use of eculizumab significantly (P=0.045) compared to non-eculizumab group and there was no change in mortality rate with the use of plasma exchange therapy (P=0.760) compared to non-plasma exchange group [5]. However, despite this facts and the recommendation of the European Medicines agency which supports life-long treatment with eculizumab therapy for patients with aHUS unless discontinuation is clinically indicated [11] many patients discontinue treatment. Data on eculizumab discontinuation in renal transplant recipients is scarce. The currently available evidence suggests unpredictable course. More data is available from patients with aHUS affecting native kidneys. Out of 52 patients who discontinued eculizumab treatment, 31% had a subsequent disease relapse. Complications occurred irrespective of identified genetic mutation, high risk polymorphism or auto-antibody. In another series, out of 61 patients who discontinued treatment 12 patients developed aHUS complications. According to the data from the global aHUS Registry 296 patients receiving eculizumab until the end of August 2014. Of adult patients, 27% discontinued treatment and 10% subsequently restarted because of the aHUS relapse [12].

Conclusions

This is the first report on outcome of renal transplantation in patient with a very rare CFB mutation in cluster with CFH and MCP mutations. Use of eculizumab during the first year enabled successful outcome 20 months after the transplantation. Although it is too early to claim that eculizumab provides safe post-transplant course for patients with multiple complement factor mutations, our case indicates that isolated kidney transplantation may be a good therapeutic option in this group of patients. However, it requires support of eculizumab which may be needed for prolonged period after renal transplantation with critical period within the first post-transplant month.

Conflict of interest statement. None declared.

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Case report

Leucocytoclastic Vasculitis in a Renal Transplant Recipient with Multiple Primary Malignancies – A Case Report

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Abstract

Skin changes are frequent finding in renal transplant recipients. Besides the skin malignancies, many other skin pathologies may be found requiring skin biopsy for establishment of the diagnosis.
We describe a case of renal transplant recipient with history of breast cancer that developed leucocytoclastic vasculitis associated with planocellular and basocellular skin cancer.

Keywords: leucocytoclastic vasculitis; paraneoplastic; renal transplantation; cancer

Introduction

Renal transplant recipients have up to 100 times higher incidence of skin cancer when compared to the general population [1,2]. Nonmelanoma skin cancers make up to 90% of all skin cancers in transplant recipients, most of them being either squamous cell carcinoma (SCC) or basal cell carcinoma (BCC) [3-6].
Leukocytoclastic vasculitis (LCV), also known as hypersensitivity vasculitis, is primarily a histopathologic term commonly used to denote a small-vessel vasculitis [7]. It is characterized by a spectrum of cutaneous lesions, but palpable purpura is most common [9]. While about 50% the cases are idiopathic, LCV may be caused by medications, infections, collagen-vascular disorders or malignancies [8-10]. Infections, drugs, foods, as well as constitutional and local factors may play some part in the initiation or perpetuation of the disease [11-15]. In patients with malignant diseases or cryoglobulinemia, LCV usually presents as a recurrent palpable purpura of the lower extremities [9]. However, determining the true cause may prove to be difficult, particularly if several possible etiologies may be involved. Herein, we present a patient with histologically proven LCV associated with multiple primary malignancies.

Case report

A 77-year-old female with end-stage renal disease of unknown etiology underwent deceased donor kidney transplantation in September 2010. The long-term maintenance therapy consisted of cyclosporine, mycophenolate mofetil (MMF) and prednisone. In March 2014 she was diagnosed with the left-sided breast carcinoma and was treated with mastectomy. According to the pathohistological examination it was an invasive form of breast carcinoma (NOS-G1). Tamoxifen was induced in September 2014 and her immunosuppressive therapy was changed to everolimus, MMF and prednisone. Allograft function remained stable with creatinine levels 55-70 μmol/L, urea 3.8-5.1 mmol/L, glomerular filtration rate 60 ml/min/1.73m^2 and the peak proteinuria of 1.54 g/dU (occurring after everolimus introduction). In October 2016 she presented with painful purpuric-necrotic skin lesions on both legs which were most prominent on her shins. These lesions spontaneously disappeared in June 2017. In October 2017 the necrotic lesions reappeared on both legs in different sizes, starting as an erythematous livid papule and progressing into purpuric infiltrates and ulcerations covered with dry crusts (Figure 1).

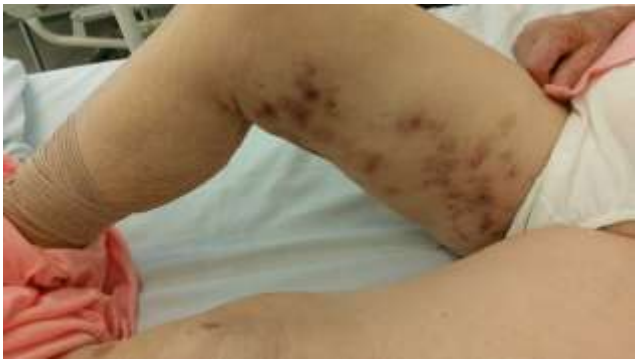

Fig. 1. Necrotic skin lesions on lower extremities.

A nonhealing ulceration on the nasal apex occurred. Meticulous medical examination was performed. La-

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boratory results were as follows: SE 25, hemoglobin 125 g/L, leucocytes 9, CRP 1.2, AFP 3.3 ug/L, CEA 2.4 ug/L, CA 125 73.1 kIU/L, CA 19-9 49.5 kIU/L, CA 15-3 33.0 kIU/L, NSE 15.75 ug/L, serum proteins 66 g/L, A/G ratio 1.14 with polyclonal peak of immunoglobulin A. Viral infections were excluded as potential cause (HBV, HCV, HIV, CMV, EBV, HSV 1 and 2 and Parvovirus were all negative), as was tuberculosis. Immunological tests were all negative (C3 1.66 g/L, C4 0.24 g/L, ANA negative, ANCA negative) and no cryoprecipitate was found. Breast ultrasound found no recurrence of the breast carcinoma. Multislice computerized tomography scan of the thorax, abdomen and pelvis showed no signs of metastatic carcinoma. Skeletal scintigraphy reflected no alterations of in the metabolic activity of the bone. Peripheral pulses were palpable and limb pletismography revealed normal ankle-brachial index (ABI; 1.03 on the right side and 1.05 on the left), color Doppler of veins was normal and without signs of deep vein thrombosis. Parathyroid hormone (PTH) level was within normal range, as were serum calcium and phospate levels (Ca 2.35 mmol/L, P 1.01 mmol/L). A neck ultrasound showed diffuse changes in the echo structure of the thyroid gland (clinical presentation of chronic thyreoiditis with euthyreosis) with several colloid cysts in the lobes. There was neither enlargement of parathyroid glands nor suspicious lymph nodes. The skin biopsy was taken from the both shins and revealed partly necrotic epidermis covered by crust with cellular debris of neutrophils. Upper dermis was partially necrotic containing large amounts of extravasated erythrocytes, neutrophils, eozinophils and mononuclear cells. Capillaries were filled with fibrin. These features were consistent with a diagnosis of leukocytoclastic vasculitis. Calcyphylaxis was excluded. According to the oncologist, tamoxifen was an unlikely cause of these changes. Biopsy of the nasal apex was also performed and revealed a combined basal cell and planocellular skin carcinoma. In January 2018 surgical excision along with lobe reconstruction was performed. Her last follow up was in April 2018 with normal kidney function and apparent withdrawal of the previously present vasculitic skin changes.

Discussion

LCV is defined histologically as a predominantly neutrophilic perivascular infiltrate affecting cutaneous postcapillary venules with fibrinoid deposits in and around the vessel wall, endothelial swelling, and extravasation of red blood cells [16]. The incidence of LCV is 4.5 per 100 000 per year, rising with age of diagnosis and does not differ between male and female patients [17]. It is characterized by a spectrum of cutaneous lesions, but palpable purpura is the most common [9]. While about half of the causes are idiopathic, LCV may be caused by medications, infections, collagen-vascular disorders or malignancies [8-10]. In patients with cryoglobulinemia and malignant disease, LCV usually presents as recurrent palpable purpura of the lower extremities [9]. Initial therapy for LCV can be conservative. Bed rest, warming, and elevation of the lower extremities, nonsteroidal anti- inflammatory drugs (NSAIDs), analgesics, and antihistamines are used to treat symptomatic complaints such as pruritus and/or burning. The diagnosis of LCV is set primarily by exclusion of other underlying systemic disease so it is crucial to regularly monitor patients' clinical status and laboratory findings. Patients with long term immunosuppressive therapy may have another underlying chronic disease covered by the therapy [16]. Many possible causes of the skin lesions were to be found in our patients' medical history since she has cardiovascular disease, basocellular and planocellular skin cancer, surgically removed breast cancer treated with tamoxifen, transplanted kidney and chronic immunosuppression. Since there were no findings of recurrent breast cancer or metastases on CT scans and scintigraphy that was excluded as a possible cause. Immunological illnesses were excluded by negative ANCA, ANA and normal serum complement concentrations. Caciphylaxisis was another possible cause excluded by pathohistological examination and normal serum calcium and PTH levels. Vascular examinations were without significant pathology. From the medications that she was taking, everolimus was found to be associated with LCV [18,19]. However, appearance and disappearance of the lesions was not in connection with its use.

Three months after the surgical removal of skin carcinomas, follow-up examination showed significant improvement regarding the lower extremities skin lesions that finally disappeared. Since other causes of the skin lesions were excluded, we have concluded that PCC and BCC were the most likely causes. Regarding the fact that other possible causes of LCV are present in this patient, regular follow-up must be performed.

Conclusions

Skin changes in renal transplant recipients require pathohistological examination for the proper diagnosis.

Conflict of interest statement. None declared.

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Abstract Book

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Oral presentations

OP-01 AKI and SIADH in patient with hemorrhagic fever and renal syndrome (HFRS)

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Introduction. Hemorrhagic fever with renal syndrome (HFRS) is a rodent borne disease, which is manifested with elevated temperature, headache, abdominal back pain, hypotension, multisystem bleeding, and acute kidney injury-AKI. The HFRS most commonly passes through five clinical stages, such as: febrile status, hypotension, oliguria, polyuria phase, and recovery phase. Those who survive the illness may develop chronic renal failure. Studies show that severe neurological manifestations such as encephalitis or meningitis can occur in HFRS. Some authors have described rare cases of pituitary gland and pituitary insufficiency in patients with HFRS.

Case report. Male patient, aged 27, admitted to the intensive treatment unit with high febricity, headache, abdominal and lumbar pain both sides, nausea, vomiting, bilateral conjugal effusion, hemorrhagic diastase from the nasal mucosa. At admission oliguric, with macroscopic hematuria. Thrombocytopenia and AKI were observed-serum creatinine level 776 µmol /l. Initially, there was doubt about the HFRS diagnosis, since it was winter time (January) and seasonal characteristics of the HFRS in Montenegro has distribution of the disease during the summer and early autumn. After admission, serological testconfirmed HTN (Hantaan) serotype. He had a positive socio-epidemiological anamnesis, drinking forest water and professional exposure to rodents in his working environment. He was treated with polysymptomatic therapy and diuretics, and in the next seven days there was a recovery of renal function with appropriate diuretic and normalization of serum concentrations of nitric waste products, as well as platelet counts. On the eighth day of hospitalization heavy polyuria began to develop - 8 liters of diuresis in 24 hours, with simultaneous hyperkaliemia (8.7 mmol/l), followed by the development of quadriplegia. Serum and urine analyzes (osmolarity, osmolality, and electrolyte concentration) indicated SIADH syndrome-an inadequate excretion of antidiuretic hormone. The MRI (magnetic resonance) of the endocranium showed hemorrhages in the pituitary gland, followed by pituitary necrosis. The patient was treated with RRT-hemodialysis and there was recovery of the diuresis, electrolyte status and acidosis status. He had a transient leap of serum liver enzyme activity. Further monitoring of the patient showed a consequential damage to the renal function with the development of chronic renal failure (CRF) with creatinine clearance of 0.68 ml/s and presence of proteinuria. The control pituitary MRI, after year and a half, had finding of an empty sella syndrome with a normal hormonal status. Patient was under continuous control of endocrinologists and nephthalmologists.

Conclusions. Some patients have severe neurological manifestations and severe pituitary insufficiency within the HFRS. After such Hantaan virus infection, some patients may require lifelong hormone substitution therapy and all patients with HFRS should be closely monitored with regard to endocrine complications.

OP-02 General characteristics and predictors of acute kidney injury due to leptospirosis in Albanian population

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Introduction. Acute kidney injury (AKI) is common in leptospirosis. It is usually characterized by hypokalemia and non-oliguric forms of AKI. Low urine output and hyperkalemia are associated with poor outcome. The aim of this study is to investigate predictors of oliguric AKI in leptospirosis and identify characteristics of this condition in the Albanian population.

Methods. A retrospective study enrolled 119 consecutive adult patients diagnosed with leptospirosis, admitted at Infection Diseases and Nephrology Department of University Centre "Mother Teresa" Tirana, Albania from 2010-2015. Patients who developed AKI were analysed. The markers of oliguria were analysed by receiver operating characteristic (ROC) curves.

Results. Age range comprised patients from 15-78 year, mean age 48+15.4. 92% were male and 8% female. LOS was 14.1+7.4 days. 95 patients developed AKI. Among them, 18.9% were oliguric and 81.1% non-oliguric. ROC curves were used to assess the prediction for developing oliguria. AUC for albumin on admission was 85.4%, with sensitivity of 90% and specificity of 71.1% at cut-off value <2.7 g/dl. AUC for creatinine on admission was 76.9%, with sensitivity of 83.4% and specificity of 64% at cut-off value ≥3.84 mg/dl. AUC for HCO_3 on admission was 76.9%, with sensitivity of 68.7% and specificity of 79.1% at cut-off value <18.4mEq/L. Almost 50% of the analysed population developed severe AKI (AKIN III 51% RIFLE 48%). 9.2% of the total population received renal replacement therapy. Mortality was 8.4%.

Conclusions. AKI is very frequent in leptospirosis. It is a complication associated with high mortality, 8.4% in our cohort. In our study hypoalbuminemia, elevated serum creatinine and low serum levels HCO^{3-} on admission we-

re indicators for oliguric AKI. Every effort should be made to prevent and treat AKI induced by leptospirosis.

OP-03 Health-related quality of life and associated factors in Albanian patients undergoing hemodialysis

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Introduction. Quality of life is an important indicator of a person's health and well-being as well as a parameter to calculate person's illness and survival. Diminished health-related quality of life (HRQoL) is common among hemodialysis patients. In this context, identification of factors that affect the quality of life of these patients takes on particular importance. Purpose: There is currently little data on the health related quality of life (HRQOL) of Albanian ESRD patients undergoing HD and this study sought to examine the patterns of HRQOL and its associated factors within this population.

Methods. This is a cross-sectional study involving 110 patients who had over three months of hemodialysis. KDQoL-36 questionnaire was used to assess their health-related quality of life. Clinical and laboratory data were collected for each patient. These data were analysed in relation to the five components of KDQoL-36.

Results. Out of 110 patients included in this study, 70 of them (64%) were males and 40(26%) females. Their average age was 54.5±12.3 and on the average 4±4.7 years on dialysis. The average values for the five components of KDQoL-36 resulted respectively: SF-12 physical component 40.47; SF-12 mental component 42.70; Burden of chronic renal disease 22.16; Symptoms and Problems 81.29; The effect of chronic kidney disease 60.40. There was a statistically significant correlation between all five components of KDQoL-36 and Diabetes Mellitus, hemoglobin levels and both Symptoms/Problems, SF-12 mental component, gender and Symptoms/Problems also Burden of chronic renal disease.

Conclusions. Our study demonstrated that Albanian HD patients have very low average value of the component "Burden of chronic renal disease" and a satisfactory average of the component "Symptoms and Problems". Factors associated with poorer HRQoL included female gender, DM, anemia. Other modifiable factors should be further investigated to improve HRQoL for HD patients.

OP-04 Patient with deep vein thrombosis and acute renal failure-case report

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Case report. A 70-year-old female patient, was sent to the Clinic of Internal Medicine for suspected deep vein thrombosis. The patient noticed the swelling of the left leg a few days before hospital admission. Clinical examination found that she was febrile 38.8° C and hypotensive 90/60 mm Hg. Laboratory findings showed an increase in D-dimer and nitrogen compounds in serum; urea 15.5 mmol/L, creatinine 338 μmol/L and a mass of leukocytes and bacteria in urine. Color Doppler sonography of the left leg revealed the thrombus at the beginning of the deep femoral vein with propagation in the pelvic veins as well as the superficial femoral vein that was completely thrombosed up to the distal third of thigh. The thrombus also propagated into the great saphenous vein to the half of the thigh. The abdominal ultrasound showed normal results. Upon admission to the hospital, anticoagulant therapy and infusion of fludis had been administered as well as antibiotic therapy after urine culture findings. The fourth day of hospitalization there swasregression of nitrogenous compounds in the blood and gradual correction of renal function; urea 12.6 mmol/L, creatinine 215 μmol/L. During hospitalization urinary catheter was inserted. After anticoagulant therapy, local status was improving and the patient left the hospital clinically stable and normotensive with the normal values of nitrogenous compounds and adequate diuresis.

OP-05 Glycated albumin as predictor of cardiovascular mortality in hemodialysis patients with diabetes mellitus

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Introduction. Glycated albumin (GA) is three-week marker of glycemic control in the patients with diabetes mellitus (DM), while pathophysiological aspect of protein glycosylation represents the cause of the most serious diabetic complications. Since the level of glycosylated hemoglobin (HbA1c) has a controversial effect on mortality, data from the literature suggest a possible predictive role of GA on morbidity and mortality in hemodialysis patients with diabetes. The aim of this study was to explore the possible predictive role of glycated albumin on cardiovascular (CV) mortality in hemodialysis diabetic patients.

Methods. This prospective study included 40 diabetic patients on chronic hemodialysis. The CV mortality of these patients was followed during 5 years. GA was determined by ELISA. In addition to these indices of protein glycosylation and quality of glycoregulation, following parameters were analysed: BMI, waist circumference, previous CVD events, HD adequacy (Kt/V), wESA dose.

Results. According to ROC analysis, the values of GA> 10% and HbA1c>6.5% signified an unsatisfactory glycemic control. During 5 years follow-up period, 86% patients who died due to cardiovascular reason had GA> 10%, and 57% HbA1c>6.5%. In Cox regression hazard model, after adjustment for age and HD duration, it has been shown that the patients with GA>10% had 2.6 times

higher cardiovascular mortality risk than those with GA<10%, and patients with HbA1c>6.5% had 1.4 higher mortality risk, than those with HbA1c<6.5%.
Conclusions. Our study confirmed that glycated albumin is a predictor of cardiovascular mortality in diabetic patients who are on maintenance hemodialysis. Tight glycemic control is of imperative in order to reduce DM related complications.

OP-06 Kidney transplantation in elderly patients
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Introduction. Increasing number of elderly patients are receiving RRT and lack of donors led to establishment of "senior" program within Eurotransplant in 2000. Program anticipates organ allocation from donor older than 65 to recipient in the same age group. It is obligatory for donor, but not for recipient meaning elderly recipient can receive kidney from younger donor. We bring results for kidney transplantation in elderly patients since our Center is a part of Eurotransplant.
Methods. We retrospectively reviewed data of patients transplanted in University Hospital Center Zagreb from 2007 to date.
Results. 118 patients aged ≥65 years received kidney transplant in our Center since 2007. There were 41 female, and 77 male patients. Average age of recipient was 69.55 years with the youngest patient being 65.05 and the oldest 77.35 years old. Average age of donor was 56.67 years, with the youngest donor being only 18 and the oldest 78 years old. There were 56 female, and 62 male donors. Average cold ischaemia time was 13.4 h and 22.8 min (range from 2h 05 min to 23 h 05 min). They all received standard triple immunosuppressive therapy, with basiliximab or Thymoglobuline as induction. 9 patients (7.6%) died, and the average survival is 48.9 months with the longest being 126 months.
Conclusion. Age itself is not a contraindication for kidney transplantation. The approach should be strictly individualized. Extended criteria donors should be taken into a consideration for these patients.

OP-07 The influence of MDR1 gene polymorphisms on kidney graft function
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Introduction. MDR1 gene polymorphisms are connected with calcineurin inhibitors' pharmacokinetics, but little is known about the relationship between MDR1 genotypes and kidney graft function. The aim of this study was to examine the association between the three most important single nucleotide polymorphisms (SNPs) of MDR1 gene (C1236T, G2677T/A, C3435T) and kidney graft function.
Methods. The study included 61 kidney transplant recipients who received cyclosporine based immunosuppressive protocol. DNA was isolated from whole blood samples. Detection and analysis of MDR1 gene polymorphisms were performed using PCR method. During the first two years after transplantation kidney graft function measured by serum creatinine and creatinine clearance, was followed.
Results. According to our results, genotype frequencies were: C1236T-CC (19.7%), CT (80.3%); G2677T/A-GG (22.9%), GT (59%), TA (6.6%), TT (11.5%); C3435T-CC (26.2%), CT (59%) and TT (14.8%). No difference was found among genotypes related to gender and age. Recipients with wild alleles for C1236T polymorphism had significantly lower creatinine level at the 1st (p=0.007), 3rd (p=0.013) and 24th (p=0.014) month after transplantation than heterozygotes. Patients with GG genotype for G2677T/A SNP had better graft function measured by creatinine level than GT and TT patients at the end of the 1st (p=0.02), 3rd (p=0.04), 12th (p=0.03), and 24th (p=0.02) month. CC alleles for SNP C3435T had lower creatinine level that CT and TT alleles at the end of the first year after transplantation (p=0.03). Better allograft function, measured by creatinine clearance, patients with CC alleles had at the end of the 1st year after transplantation for C1236T (p = 0.046) and C3435T (p = 0.047) SNP.
Conclusions. Our study showed that patients with wild alleles for all three SNPs of MDR1 gene had better function during the first two years after transplantation than heterozygotes or variant alleles.

OP-08 Chronic antibody-mediated rejection and treatment in renal transplant recipients: a single center experience
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Introduction. Chronic antibody-mediated rejection (AMR) among kidney transplant recipients is a major unresolved problem which often causes the loss of renal allograft. We aimed to examine incidence, demographics and treatment properties of chronic AMR in our renal transplant patient population.
Methods. We retrospectively examined renal transplant recipients, who have undergone renal allograft biopsy from January 2011-June 2018 and observed at Renal Transplantation Unit of Ankara University Faculty of Medicine. Biopsy results and demographic features, treatment and outcome of chronic AMR were investigated.
Results. 133 renal allograft biopsies were performed to 107 patients kidney recipients: 33(24.8%) acute AMR, 26(19.5%) acute T-cell mediated rejection, 20(15.0%) borderline changes, 8(6.0%) calcineurin inhibitor toxicity, 8(6.0%) recurrent or de novo glomerulonephritis, 5(3.8%) chronic AMR were diagnosed. Five patients with chronic AMR had never experienced an acute rejection episode

and all were under maintenance immunosuppressive treatment (Table 1). The mean time between rejection episodes and the transplant was 146±52 months (min: 84, max: 216). All patients with chronic AMR had histologic evidence of chronic humoral rejection and extensive C4d staining in peritubular capillaries. Donor-specific antibodies (DSA) were evaluated in recipients and positive in four patients. Different treatment modalities were administered. Three patients (60%) were refractory to treatment and lost their transplants, one of whom was DSA negative and treated with plasmapheresis, intravenous immunoglobulin and rituximab. Two patients (40%) had stable renal functions after 3 and 14 months follow-up, one of them took no rescue treatment due to severe interstitial fibrosis and tubular atrophy in renal allograft biopsy. No relationship between treatment regimen and graft survival was observed.

Conclusions. Chronic AMR is becoming clinically critical and a major cause of allograft loss because this form of rejection is usually unresponsive to current treatment protocols. More extensive understanding of pathogenesis of antibody induced injury and development of new therapeutic approaches are needed to improve the outcomes of chronic AMR.

Table 1. Patients with chronic AMR that never experienced an acute rejection episode

Patient	Recipient age and sex	İmmunosupresive treatment	Time to chronic AMR diagnosis (months) and sCr at diagnosis (mg/dl)	Presence of DSA	Presence of C4d in renal transplant biopsy	Treatment	Outcome
1	31, Male	CS, MMF, Tac	216, 3.04	Positive Class II MFI: 1957	Positive	Pulse CS, ATG	Stable renal function
2	44, Female	CS, MMF, Tac	84, 2.52	Negative	Positive	PPH, IVIG, RTX	Graft loss
3	26, Male	CS, MMF, Tac	180, 2.81	Positive Class II MFI: 7530	Positive	No induction therapy	Stable renal function
4	30, Male	CSA, EVE	120, 7.49	Positive Class I MFI: 10690 Class II MFI: 4312	Positive	Pulse CS	Graft loss
5	51, Male	CS, MMF, Tac	132, 3.24	Positive Class II MFI: 10424	Positive	Pulse CS	Graft loss

Abbreviations: AMR, antibody-mediated rejection; ATG, anti-thymocyte globulin; CS, corticosteroids; CSA, cyclosporine; DSA; donor specific antibody; EVE, everolimus; IVIG, intravenous immunoglobulin; MFI, mean fluorescence intensity; MMF, mycofenolate mofetil, PPH, plasmapheresis; RTX, rituximab; sCr, serum creatinine; Tac, tacrolimus

OP-09 Therapeutic Effect of Plasmapheresis, İntravenous Immunoglobulin and Rituximab in Kidney Transplant Recipients with High Panel- Reactive Antibody Levels: A Single Centre Experience

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Introduction. High Panel Reactive Antibody (PRA) levels, limits patients access to kidney transplantation, from potential living donor candidates and decreases renal graft survival by causing acute antibody mediated rejection (AAMR). İn this article, we report our experiences the efficiency of plasmapheresis in reduction of serum PRA levels in renal transplantation candidates and in patients with AAMR.

Methods. We examined retrospectively 47 patients with high levels of PRA (18 for desensitization and 29 with AAMR) from 2008-2018 in Ankara Faculty of Medicine. We evaluate the reduction in PRA class 1 and PRA class 2 levels before and after plasmapheresis, intravenous Immunoglobulin (İVİG) and rituximab therapy

Results. The mean plasmapheresis session was 4.13±2.05. Mean reduction in PRA class 1 was 25.7±6.66% to 19.7±6% ($p<0.05$). In desensitization group; mean reduction in PRA class 1 was 28±9.10% to 22.1±8.14%. ($p<0.05$).

Conclusions. Plasmaferesis is a successful method in reducing PRA levels in renal transplantation candidates and in patients with AAMR.

OP-10 Biopsy proven non-diabetic nephropathy in diabetic patients - single center experience

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Introduction. Kidney biopsy is not the first diagnostic option in patients with diabetes mellitus (DM) and proteinuria. The reason for this is because the slow progression of kidney function decline is thought to be from

diabetic nephropathy (DN), particularly if diabetic retinopathy is present. However, literature data have shown that primary glomerulopathy (PGN) may be interfered with DN. The aim of our study was to analyse histopathological findings and relevant clinical data in DM patients who underwent kidney biopsy.

Methods. In accordance to the current guidelines, we performed kidney biopsy in cases with short history of DM, marked nephrotic syndrome, progressive renal failure, persistent hematuria and/or retinal changes. From 2009-2016 we performed 153 successful kidney biopsies (age 49.8±16.2; 75 men). Out of all, 40 biopsies were performed due to acute kidney injury and for lupus nephritis staging and these were excluded from analysis. Remaining 113 biopsies were performed due to nephrotic syndrome, urine sediment disorders or deterioration of kidney function.

Results. Out of all analysed biopsy data (patients' mean age 51.6±16.6; 62 men), DM was present in 21 (18%; 11 men) and mean duration of diabetes was 4.98±4.38 years (1-15 years). Compared to patients without (w/o) DM, DM patients had statistically higher daily proteinuria (10.0 vs 6.8 gr/24h; p=0.023), and age (55.8 vs 50.7 years; p=0.216) and there were no difference in serum cholesterol (6.7 vs 6.3; p=0.412) and creatinine levels (138 vs. 158 µmol/L; p=0.433) between two groups. Histopathological findings revealed that 13 out of 21 patients (62%) had DN. In remaining 8 patients, the findings were membranous nephropathy in 4, focal-segmental glomerular sclerosis in 2 patients; one patient had IgA nephropathy and one had amyloidosis. Binary logistic regression had shown that males with DM had OR 15.75 (CI 1.42-174.2; p=0.025) for developing non-DN kidney disease. Those with confirmed non-DN PGN were referred for standard immunosuppressive regimen.

Conclusions. Non-diabetic kidney disease was present in 38% among our diabetic patients who underwent kidney biopsy (membranous nephropathy, FSGS, IgA nephropathy, amyloidosis). Male genderwas significant risk factor for non-DM PGN.

OP-11 Graft survival in patients with renal transplantation due to FMF-renal amyloidosis

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Introduction. AA amyloidosis is most commonly caused by FMF in our country. Amyloidosis caused secondary due to FMF is an important cause of end stage renal failure. Renal transplantation is an alternative treatment comparing with hemodialysis in these patients. The present study aimed to show the results of long-term follow-up of graft survival in patients with renal transplantation due to secondary amyloidosis caused by FMF.

Metods. Twenty-seven patients who underwent renal transplantation from 2005-2017 at the University of Ankara Medical Faculty, İbni Sina Hospital were included retrospectively in the study. End-stage renal failure in all of these patients was renal amyloidosis secondary due to FMF.

Results. Twenty-two patients (81.5%) were treated with triple immunosuppressive therapy consisting of MMF+Tac+ Steroid and 5 patients (18.5%) were treated with triple immunosuppressive therapy consisting with Tac+AZA+ Prednol. Acute cellular rejection in 3 patients (11.1%), acute cellular and humoral rejection in 1 patient (3.7%) occurred. In follow-up, graft loss due to acute cellular rejection was observed in only 1 patient. In 1 patient, after 3 years of follow-up, urosepsis and cardiac arrest associated functional graft were observed.

Conclusions. The long-term results of renal transplantation due to FMF-associated amyloidosis cases are quite successful.

OP-12 Results of kidney transplantation program in Montenegro

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Introduction. Preparation of all necessary conditions for the beginning of transplantation program in Montenegro started in 2006 with different activities including public, legal, medical, educational and international cooperation aspects. The first kidney transplantations from living donors in Montenegro were performed on 25th and 26th September 2012.

Methods. data referring to the outcome of kidney transplantation program in Montenegro.

Results. In the period from 2012 until now, 37 kidney transplantations from living related donor were performed and one kidney transplantation from deceased donor in Clinical Center of Montenegro. In the period of five years of follow up, all patients with kidney transplant were in good condition and without serious complication in the post-transplant period. There was complication in two kidney recipient in perioperative period who had delayed graft function. In one recipient there was urinoma; in one patient deep venous thrombosis; and in one patient episode of acute pancreatitis after sirolimus introduction in the immunosuppressive therapy protocol. In one patient we had lymphocele treated by marsupialization, and in one patient kidney graft calculi, successfully treated. Serum creatinine level in the follow up period was in referent values in recipients as well as in donors. There were no episodes of hyperacute and acute rejection and there were no episodes of complications due to immunosuppressive therapy. All kidney donors are followed up carefully in our center; their serum creatinine level was in reference values and there was no evidence of impairment of residual kidney function.

Conclusions. The development of transplantation system improved many medical fields and continuous education of medical staff. Our next steps are improvement of deceased organ donor transplantation and achievement of higher rate of deceased donor kidney transplantation and kidney transplantation program with incompatible blood groups.

OP-013 New anticoagulant therapy and vascular calcification in chronic renal failure: control of outcome ??

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Introduction. Calcified Uremic Arteriolopathy (CUA), clinically manifested by necrotic lesions of the skin and subcutaneous tissue. The pathohistological substrate of insufficient tissue perfusion and ischemia are microvascular stenosis due to calcification of small arterial and arterioles media, endovascular fibrosis and venous thrombosis. Etiopathogenetic, CUA is most commonly associated with calcium and phosphate metabolism disorders in chronic renal failure and co-existence of cardiological and vascular pathology-the main indications e for use of anticoagulant therapy (iatrogenic inactivation of vitamin K dependent vascular calcification inhibitors (ucMGP)).

Methods. 50 years old, obese female patient, treated with PD for 18 months (Kt/V-2,2), delayed parathyroidectomy (dg.SHPTH) due to DVT (excluded thrombophilia), after month of ambulatory follow-up by vascular surgeon and the use of antagonist K and low molecular weight heparin, was hospitalized due to vertigo, hypotension and massive necrotic inflammatory lesions of the skin.

Results. PH findings in the dermal/subdermal blood vessels, in addition to the typical changes in CUA, were due to the dominance of thrombins of fibrin and erythrocytes, with minimal calcified deposits and with extensive inflammatory infiltrates (Ly, PMN, eosinophils) in the marginal necrosis zone. The finding of anti-Heparin/PF4 antibodies does not exclude sensitivity to LMWH (HIT). Parathyroidectomy, an attempt to transition to HD, directing to direct thrombin inhibitors (argatroban) instead of LMWH, surgical lesion treatment and infection prevention, have caused local regression of change and recovery.

Conclusions. CUA, "external" vasculopathy, indirectly points to the risk of iatrogenic calcifying vascular lesions in chronic renal failure and the necessity of legislative availability of new anticoagulants (direct thrombin inhibitors, FX inhibitors). The recommendations on prescribing are missing (indications, clinical scores of risk assessment and dosing).

OP–14 Treatment options for BK nephropathy-single center experience

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Introduction. BK nephropathy is a known complication of novel potent immunosuppressive (IS) protocols in kidney transplant recipients. It occurs in up to 10% of renal transplant patients, and it can cause allograft failure in 7.5%. BK nephropathy is treated by reduction and modification of IS therapy, administration of immunoglobulins (IVIG) and cidofovir. There is no preferred protocol for BK nephropathy management. Here we present our data on biopsy proven BK nephropathy management protocols.

Methods. We analyzed medical records of 1960 patients in our transplant center. Data included from newly transplanted patients that underwent our screening protocol and all other cases that were assessed for BK virus (B/U) when signs of graft deterioration were found. We selected patients that had biopsy proven BK nephropathy, and retrospectively assessed the course of their treatment.

Results. Three percent of our patients had BK virus reactivation and 14% of those patients had biopsy proven BK nephropathy. In patients with BK nephropathy we identified two major treatment groups, one in which solely IS therapy was modified and the other where in association with IS protocol modification IVIG was administered. We applied IVIG in patients with BK viruria that exceeded 10E4 of virus copies in blood. In 57% of patients with BK nephropathy we introduced mTOR inhibitors in their IS protocol. Patients in both groups had a decrease in the number of BK virus copies in blood after therapy.

Conclusions. BK nephropathy is an important factor for graft and patient survival. Prevention by screening for BK reactivation is currently the most efficient way of managing BK nephropathy. Our analysis has shown that BK nephropathy management is highly patient specific.

OP-15 Quantifying Microvascular Abnormalities of Diabetics Patients with Chronic Kidney Disease

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Introduction. Chronic kidney disease (CKD) is strongly associated with cardiovascular disease and there is an established association between vasculopathy affecting the kidney and eye.

Optical coherence tomography (OCT) angiography is a novel, rapid method for high-definition imaging of the retina and detecting infraclinical lesions in parafoveal capillaries. Its use in patients at high cardiovascular disease risk remains unexplored.

Methods. We used the new OptoVue OCTA (Optical coherence tomography angiography) machine, AngioVue system (Optovue Inc., Fremont, CA, USA) to examine superficial and deep capillary plexuses (SCP and DCP) on macular OCTA scans (3×3mm) centered on the fovea in a prospective cross-sectional study in? 24 diabetics with different stages of CKD and diabetic retinopathy (DR), 8 diabetics without CKD or DR and 8 matched healthy controls. Qualitative analysis concerned morphological ischemic capillary alterations. Quantitative analysis measured foveal avascular zone (FAZ) size, parafoveal capillary density, microaneurysms, neovasularisations, percent area of

nonperfusion (PAN), and adjusted flow index (AFI). The same, masked ophthalmologist carried out each study. Plasma C-reactive protein, nitric oxide (NO) and endothelin-1 (ET-1), as measures of inflammation and endothelial function, were also assessed.

Results. All OCTA parameters showed a significant linear correlation with DR and CKD severity ($P<0.05$) in the univariate models except for AFI measured in the SCP and these correlations remained significant after correcting for covariates. Compared to the other capillary layers, the AFI at the DCP decreased significantly with DR and CKD severity. When comparing individual disease severity groups as categories, eyes of subjects with CKD and DR had significantly increased PAN and AFI in the SCP compared to healthy subjects ($P<0.05$). Foveal avascular zone (FAZ) size, parafoveal capillary density, microaneurysms, neovascularisations, percent area of nonperfusion (PAN) were associated with increased circulating C-reactive protein ($r=-0.57$, $P=0.0002$), and ET-1 ($r=-0.44$, $P<0.01$). Finally, decreased NO was associated with parafoveal capillary density, and inflammation and arterial stiffness only in the presence of renal impairment.

Conclusions. Retinal and choriocapillar vascular nonperfusion in OCTA is correlated significantly with disease severity in eyes with DR and CKD. Higher flow rate in the SCP may be an early marker of diabetic microvascular changes before clinical signs generalized atherosclerosis characteristic of CKD. OCT-A could be a new noninvasive tool to quantify microvascular damage in the retinal capillary network to study kidney disease in patients with diabetes. Similarly, the associations with arterial stiffness, inflammation, and endothelial dysfunction warrant further examination.

OP-16 Clinical development of women with X-linked Alport Syndrome

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Introduction. The X-linked Alport Syndrome (XLAS) is caused from mutations to the A5 chain of collagen type IV (COL4A5) and it causes sensorineural hearing loss, keratoconus, and progressive loss of renal function that follows in almost all the heterozygotes men from young age to end stage renal disease (ESRD). Up to recently women were simply considered "carriers" but it is now known that they also can have complete phenotype of the disease as man, and some of them may progress to ESRD. Aim of this study was to investigate the development and the prognosis of CKD in women with transmute to COL4A5.

Methods. We studied 7 families with different transmute. Globally, 48 members of families (18 men and 30 women) were investigated, and in 30 were found carriers of mutation to COL4A5 (8 men and 22 women). Seven from the 22 were submitted to kidney biopsy before performing genes analysis. The female patients were followed for at least 5 years and all clinical information were collected by the medical files.

Results. The age of 22 heterozygotes females ranged from 7 to 78 years (intermediate age 32 years). From the 7 patients with kidney biopsy only in 2 a diagnosis of Alport syndrome was confirmed, two had diagnosis of focal segmental glomerulonephritis (FSGS), one thin basement membrane glomerulonephritis, one postinfectious glomerulonephritis and one IgM nephropathy. The big majority of patients (54%, ages from 7 until 46 years) presented only with hematuria without CKD. However in 18% CKD was present (impairment of renal function or proteinuria >1gr, ages from 7 until 60 years) and 27% had ESRD (from 20 until 70 years). The mutation c.4688+5G>A in gene COL4A5, has not been described in the bibliography, however it is found in region of gene where the changes are pathogenic, have not been found in physiologic individuals, and concern intensely maintained nucleotide in the limit intronsexons, fact that likely influences the splicing process. Finally it is located only in the suffering members of family and no in healthy.

Conclusions. The kidney biopsy in patients with XLAS usually is not diagnostic without the use of electron microscope. The XLAS should not be considered as a non-malignant disease for the heterozygous women of our population In 27% leads to ESRD and in particular that roughly half of the cases are present in relativly young age, similar with men. The more likely explanation for the above phenomenon is asymmetrical de-activation of X chromosome or the existence of modification genes.

OP-17 Prognostic factors for risk assessment in sepsis-induced acute kidney injury (s-AKI) patients

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Introduction. Several prognostic scores and biomarkers have been assessed for risk stratification in septic patients with AKI. Serum lactate is a routinely used biomarker for the management of patients with sepsis and correlates with hypoperfusion and fluid resuscitation. Procalcitonin (PCT) is a bacterial infection marker and its kinetics indicates the response to antimicrobial management. There is insufficient data comparing these two markers regarding outcome prediction. The aim of our study was to compare the prognostic accuracy of lactate and PCT and the combination of them in s-AKI patients population treated with hemodialysis in a tertiary hospital.

Methods. This is an observational cohort study of adult patients with confirmed sepsis or septic shock. All patients had PCT and lactate measurements on admission and during follow-up. We used logistic regression and area under the curve (AUC) as a measure of discrimination of lactate and PCT with in-hospital mortality.

Results. The in-hospital mortality rate of the 91 included patients (mean age 68.7 years) was 21.9% (95% CI=19.6.2 to 25.9%). Concerning prognosis, the initial lactate level was a better mortality predictor (AUC 0.71) compared to PCT (AUC 0.56). For follow-up measurements, PCT (AUC 0.78) showed better discrimination than lactate (AUC 0.71). When looking at biomarker kinetics, PCT increase was more strongly associated with fatal outcomes compared to initial levels alone (AUC 0.81) and was a better predictor compared to lactate kinetics (AUC 0.61). A joint logistic regression model combining follow-up measurements of lactate and PCT kinetics showed a superior prognostic accuracy (AUC 0.80) compared to these markers alone.
Conclusions. Both biomarkers, PCT, and lactate provide prognostic information in s-AKI patients treated by hemodialysis, primarily when analysing kinetics.

OP-18 T cell cytokines in the pathogenesis of histological lesions in different types of podocytopathies

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Introduction. Different T cell subtypes infiltrate glomeruli and through the production of different cytokines are directly involved in the pathogenesis and evolution of histologic lesions in most types of primary glomerulonephritides. We evaluated the role of Th1, Th2 and Treg cytokines in three forms of primary podocytopathies.
Methods. Seventy nine patients with nephrotic syndrome due to: Primary Membranous Nephropathy (PMN) (n=22, M/F 10/12, age 58.2±12yrs, Scr=1.2±0.53mg/dl, Upr=6.3± 3.3g/24h), Focal Segmental Glomerulosclerosis (FSGS) (n=36, M/F 22/14, age: 41.9±17yrs, Scr=1.7±0.8mg/dl, Upr=4.7±5.5g/24hr), and Minimal Change Disease (MCD) (n=21, M/F 5/16, age: 41.4±15yrs, Scr=1±0.4mg/dl, Upr= 7.9±9.3g/24hr) were included in the study. Renal biopsies were re-evaluated regarding obsolescent glomeruli, presence of FSGS, severity of tubular atrophy, interstitial fibrosis and vascular hyalinosis. In first morning urine samples collected at the day of renal biopsy, Th1 (IL-2, IL-12, GM-CSF, INF-γ, TNF-α), Th2 (IL-4, IL-5, IL-13) and Treg (IL-10) cytokines were measured simultaneously, using Luminex technology, and results were correlated with histological parameters and renal function outcome.
Results. In PMN urinary IL-5 levels were correlated to the presence of secondary FSGS (p=0.03), while IL-4 and IL-10 with the severity of tubular atrophy (p=0.05 and p=0.04 respectively). In FSGS, urinary IL-12 levels were the only independent factor correlated with the severity of chronic histologic findings (obsolescent glomeruli, p=0.009 and interstitial fibrosis, p=0.02), as well as impairment of renal function at the end of follow up (p=0.03). In MCD the whole cohort of Th2 cytokines (IL-4, IL-5, IL-13) were significantly increased in patients with multiple relapses (p=0.05, p=0.001, p=0.03 respectively).
Conclusions. Th1 cytokines are implicated in the pathogenesis and progression of FSGS, while Th2 and Treg cytokines seem to be involved in PMN and MCD. In contrast to primary FSGS, secondary FSGS observed in PMN, is correlated to Th2 production, suggesting a different pathogenesis of FSGS in the two entities.

OP-19 Correlation between diabetes mellitus, intima media complex and diastolic dysfunction

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Introduction. Diabetes mellitus is the leading cause of chronic kidney disease (CKD). Cardiovascular disease (CVD) is the main factor affecting prognosis in CKD patients whose morbidity and mortality is 10 to 20 times greater than in the healthy population. The aim of the study is to determine correlation between diabetes mellitus and intima media complex (IMC) thickening in the carotid artery wall, biomarker of heart failure (B-type natriuretic peptide-BNP, N-terminal pro BNP (NTproBNP) and diastolic dysfunction of left ventricle (DDLV) in CKD patients.
Methods. This prospective study included 100 patients with any stage of CKD and GFR level that did not required active treatment by some form of renal replacement therapy. We examined the connection between diabetes mellitus and IMC, BNP, NTproBNP, DDLV.
Using Doppler ultrasound examination we determine the IMC thickening in the carotid artery wall and presence of plaque. All patients underwent measurements of BNP and NTproBNP in blood using electro luminescence immunoassay according to the gender and age. Dopller echocardiography measurement E/A was used for the assessment of diastolic function of left ventricle. Ejection fraction (EF) was expressed as EF% = UV/EDV.
Results. Diabetes mellitus was diagnosed in 31% (31/100) out of 100 patients. Sex distribution was as follows-58% men, mean age was 56.7±10.6 years. Obesity was present in (29/31) 90.3% of the patients, 6.7% had normal weight. Smokers were present in 54.9% cases. Diabetes mellitus type 2 had 93.5% and type1 6.5% of patients. 93.5% of patients with diabetes mellitus and CKD had thick IMC (29/31) 90.3%, as well as 70% of patients had plaque in the carotid artery wall (22/31), 35.5% had pathological values of biomarkers of heart failure (11/31) and 22.6% of patients had systolic dysfunction of left ventricle and 90% DDLV (28/31).
Conclusions. There is significant positive correlation between diabetes mellitus and changes in carotid artery wall, biomarkers of heart failure and DDLV that points out to increased cardiovascular morbidity and mortality

in CKD patients, even before the initiation of any means of renal replacement therapy.

OP-20 Endemic (Balkan) nephropathy and kidney transplantation

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Introduction. Endemic (Balkan) nephropathy (EN) is characterized by tubulointerstitial damage and increased incidence of upper uroepithelium tumors (UUT). The use of immunosuppressive drugs and an increased risk of malignancy after transplantation imposes a need for regular monitoring for the purpose of early detection and treatment of UUT. The aim of the study was to evaluate the frequency of UUT in patients with EN following kidney transplantation.

Methods. Retrospective analysis of medical documentation of patients with EN transplanted at the Clinical Centre of Serbia from January 2003 to December 2013.

Results. During the eleven-year period, 405 kidney transplantations were performed, of which 62% were from a living donor. Only 9(2.2%) patients, average age of 56±4.7 years, were diagnosed with EN. Patients were transplanted from brain dead donors without prior bilateral nephroureterectomy. Induction consisted of antihyomocyte globulin in eight and basiliximab in one patient, while maintenance therapy was based on tacrolimus, mycophenolic acid and corticosteroids. None of the patients had CMV and EBV reactivation. In the early postoperative period, fatal outcome with functional graft occurred in 4 patients due to surgical complications and infections. One patient had transplantectomy due to renal artery thrombosis. None of the remaining 4 patients was diagnosed with UUT on transplanted or native kidneys, as well as tumors of the urinary bladder. All 4 patients still have a functional graft.

Conclusions. The number of prevalent patients with EN has been stable and relatively low over the past several decades, which partly explains the relatively small number of these patients treated by kidney transplantationtherapy. Although none of the patients in our study have had previously performed protective nephroureterectomy, as some authors suggest, none of them developed UUT.

OP-21 Changing of Immunosuppressive Treatment and Results in Intensive Care Unit: Single Center Experience of Renal Transplant Patients

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Introduction. Renal transplant patients (RTP) are very prone to admission of intensive care unit (ICU) due to several complications including severe infections and sepsis, cardiovascular diseases, and other organ failures. During ICU, although there is no standard protocol for immunosuppressive treatments, the dose and the number of drugs used are generally decreased. The aim of this study is to evaluate the changes in immunosuppressive treatments during ICU and evaluate the results of RTP in ICU.

Methods. We evaluated retrospectively our RTP in ICU from 2012-2017. The immunosuppressive protocols and the result were taken from the ICU documents.

Results. A total of 31 (18 males, 13 females, 10 deceased donors and 21 living related) patients were suitable for the analysis. Mean age was 50±10 years, and mean duration after transplantation was 103.4±102.3 months. The average duration time in ICU was 26±34 days. They were all under the triple immunosuppressive protocol including Tac+MMF+Steroid before the admission. The reason for ICU admission was severe sepsis in all patients. Total follow up period was 90±89 months. During ICU hospitalization, 16 patients (51.6%) died and a total of 10 patient were lost with functional graft. In ICU, change in immunosuppressive treatments was as follows; a total of the 23 patients (74.2%) were given only corticosteroid with the mean 32±23 mg/day for immunosuppressive treatment for the mean duration of 26±34 days, 8 patients (25.8%) were changed from triple to two drugs immunosuppressive treatment. For 5 patients (16.1%) MMF+Steroid, 3 patients (9.7%) were given tac+steroid. Mean creatinine levels during ICU were 2.53 mg/dl and 1.86 mg/dl in admission and discharge, respectively. Acute rejection was not developed in any of the patient. Acute kidney damage developed in 42% (13 patients) of the patients in ICU. However, graft functions were returned to previous levels after discharge.

Conclusions. In our study, we observed that life threating infections were the main cause of ICU admission. Reduction in immunosuppressive treatments are common and reduced dose double or single steroid applications were seem to be safe in these patients. None of the patients developed acute rejection and permanent graft damage.

OP-22 Outcomes of Canakinumab Treatment in Kidney Transplant Recipients with Familial Mediterranean Fever

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Introduction. Familial Mediterranean fever, is the most common cause of secondary amyloidosis in Turkey. With colchicine treatment complete remission rate is 60-65%. Approximately 5-10% of patients are resistant. Canakinumab, anti-interleukin (İL)-1 monoclonal antibody is known to be safe and efficient treatment for FMF when patients have colchicine resistance and/or intolerance.

Methods. In the period of 20102017 we screened kidney transplant recipients with FMF in Ankara Faculty of Medicine. We reported 4 kidney transplant recipients with FMF secondary amyloidosis. All 4 patients had FMF attacks

and end-stage renal disease secondary to amyloidosis despite using regular maximum colchicine dose.
Results. İn 3 patients, canakinumab treatment was started after transplantation, and in 1 patient two months before transplantation. All patients had prior treatment with anakinra before canakinumab. One patient had attacks with anakinra, 3 patients had no attacks with anakinra treatment. No serious side effect were seen with anakinra, in 1 patient caused reactions at the site of injection. All 4 patients continued with canakinumab treatment 150 mg for 4 to 8 week intervals with colchicine, approximately for 2 years. They had no attacks (fever, abdominal pain, arthritis, etc.), serum CRP and serum amyloid A levels were normalized, creatinine and proteinuria were stable under canakinumab treatment. Life threatening infection and graft lost were not seen in this two year period with canakinumab therapy.
Results. Canakinumab treatment is a safe, efficient treatment in kidney transplant recipients with FMF.

OP-23 Kidney transplantation in patient with previous malignant disease

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Introduction. Patients with end stage renal disease (ESRD) who have been successfully treated for their cancer are generally considered to be suitable for renal transplantation. Review of previous reports and especially data on recurrent cancers suggest some general guidelines on waiting time between treatment of specific cancers and renal transplantations. According to some registries 13% of recurrences occurred in patient treated more than 5 years before transplantation. The incidence of colon cancer in renal transplant recipients in not elevated during the first 10 years after renal transplantation. It is recommended to wait at least 5 years before transplantation for patients treated for colon cancer.
Case report. Patient RT, male, 58 years old, was diagnosed with pulmonary sarcoidosis 25 years before. He was on regular prednisolone therapy since then. In time he developed extra pulmonary manifestations of sarcoidosis including bilateral kidney calcifications. He developed chronic kidney disease (CKD) 23 years before. In 2002 he was treated with pyelolithotomy of the right kidney. He had subtotal thyroidectomy in 1986, and total thyroidectomy in 1991 due to medullary thyroid cancer with remaining paresis of recurrent nerve with dysphonia and iatrogenic hypothyroidism. Six years ago he was diagnosed with colon adenocarcinoma staging C2pT3N2B (Astler Coller) with secondary deposits in 6/15 resected lymph nodes. He was treated with chemotherapy after wards (6 cycles of capecitabine) following left hemicolectomy. He also had splenectomy during the same procedure. He was diagnosed 2011 with multi ischemic changes in the brain on brain CT tomography. From 2011 he developed arterial hypertension. In 2011 he developed ESRD. He started hemodialysis treatment in February 2014. He was clinically assessed for treatment with kidney transplantation from living related donor in December 2013. In that period he was diagnosed with diabetes mellitus type 2, probably based on the long time prednisolone therapy complications. Control colonoscopy was performef a year ago. Three polyps were found and removed. Histopathological analyses showed low grade dysplasia. Tumor markers, CT tomography of chest, abdomen and thorax showed no recurrence or progression of malignant disease. MRI examination of abdomen showed the presence of granulomatous sarcoidosis changes in the liver. PET scan of whole body was performed in the last year twice and showed no signs of malignant disease. He also has benign prostate hypertrophy and he is treated with alpha blockers on regular basis. Serum ACE (angiotensin converting enzyme) activity was in referent levels and there was no signs of radiological progression of pulmonary sarcoidosis with regular spirometry parameters.
Conclusions. Patient was presented to the transplantation council. We got oncologist agreement for kidney transplantation. He was treated with living related kidney transplantation. It was transplantation of higher risk due to many present comorbidities prior to transplantation. He was treated with basiliximab in induction therapy and with cyclosporine, mycophenolate mofetil and prednisolone as maintenance immunosuppressive therapy. The cyclosporine therapy was converted to sirolimus regimen therapy three months after transplantation. Perioperative and post-transplant period went out without complications. Patient is under frequent oncology controls. Most patients benefit from a waiting period prior to renal transplantation. In case of some cancers at increased risk of recurrence a longer waiting interval of 5 years should be considered. While these statistics may provide general guidelines, the risk of tumor recurrence has to be balanced against the benefits of renal transplantation for each individual patient.

OP-24 Hepatorenal syndrome in kidney transplant recipient

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Introduction. Hepatorenal syndrome (HRS) is a well-recognized complication of end-stage liver disease. Once thought to be a reversible condition with liver transplantation alone, HRS may directly contribute to the require-

ment for long-term dialysis post-transplant. Type 1 HRS or liver failure accompanied by rapidly progressive renal failure carries a median patient survival of 2 to 4 weeks; patients with type 2 HRS or liver failure associated with a slower deterioration of renal function fare better with a median survival of approximately 6 months.

Case report. Male patient, 51 years old, was treated with kidney transplantation from deceased donor, nine years ago, due to terminal renal failure caused by membranous glomerulonephritis. Renal transplantation underwent without any complications. Afterwards he started with immunosuppressive treatment with tacrolimus, mycophenolate mofetil and steroids. Graft function was stable. He started with alcohol abuse after transplantation and developed alcoholic liver cirrhosis two years ago. On the admission he was diagnosed with acute graft dysfunction, anemia, severe thrombocytopenia, and coagulation disorder. In the short time period he rapidly developed HRS following AKI-and manifestation of hemorrhagic syndrome. He was treated with pulse corticosteroid therapy, beside polysymptomatic therapy, in order to reduce the impairment of renal allograft, without any success in improving renal graft function. In the period of two weeks he developed anuria and end stage renal failure and started treatment with RRT with hemodialysis. All drugs administered in the therapy were dosed according to the degree of hepatic and renal insufficiency. He was treated with hemodialysis in the next period of few weeks, without complication. He was put on waiting list for combined liver and kidney transplantation, but died due to severe gastrointestinal hemorrhage.

Conclusion. Combined liver and kidney transplantation for patients with HRS should be considered.

OP-25 Kidney transplantation and Jeune syndrome

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Introduction. Jeune syndrome (asphyxiating thoracic dystrophy, ATD) is a rare autosomal recessive skeletal dysplasia characterized by a small, narrow chest and variable limb shortness with a considerable neonatal mortality as a result of respiratory distress syndrome. Renal, hepatic, pancreatic and ocular complications may occur later in life. Recently two causal genes mutations were identified in ATD syndrome-IFT80 and DYNC2H1. Progressive kidney disease, the nephronophthisis occurs in about 30% of patients. Progressive renal failure is typical for mild form of asphyxiating thoracic dystrophy. There are several cases of patients with Jeune syndrome treated with kidney transplantation successfully described in the literature.

Case report. Male patient, third child of healthy parents, diagnosed with Jeune syndrome in the age of two, after respiratory distress episode and many episodes of respiratory infections and several episodes of pneumonias. He has normal XY karyotype, not tested for IFT80 and DYNC2H1 mutations. He had growth failure and was treated with recombinant growth hormone, abnormal chest shape and limb shortness. He has narrow thorax with short, broad, horizontally oriented ribs, a typical trident appearance of the acetabular margins. Skeletal radiographs showed a small thorax, brachydactyly of the fingers, short and broad diaphyses, wide metaphyses of the arms and legs, and short iliac bones with spiky protrusions. He was diagnosed with retinitis pigmentosa, complicated cataract of the right eye, treated with pseudophakia. Also pancreatic cysts were presentand had normal hepatic function.. In the age of three he had several episodes of seizures, successfully controlled with anticonvulsants. Radiological examination in the age of two also showed nephronophthisis. He developed CKD with arterial hypertension and renal anemia in the age of five. Treated with intermittent hemodialysis for eight months without complications. Followed by living related kidney transplantation, father was kidney donor. Treated with basiliximab in induction and with maintenance immunosuppressive protocol including cyclosporine, mycophenolate mophetil and steroids. The kidney transplantation was successful, without complications. There was no-delayed graft function (DGF), acute rejection or other complications, with remaining arterial hypertension. He was evaluated thirteen years after transplantation. The level of serum creatinine was 123 µmoll, with creatinine clearance of 0.96 ml/s, and proteinuria level of 0.82 g/day, with anemia controlled successfully with ESA. Arterial hypertension was well controlled with calcium channel blockers and beta blockers. There were no complications of immunosuppressive therapy so far. Without pathological findings on color Doppler ultrasound examination of allograft. Respiratory function test including spirometry and body plethysmography showed general restrictive ventilation disorder, but still well tolerated. Gastrointestinal findings showed several pancreatic cysts with regular hepatic and pancreatic function.

Conclusions. ATD is a genetically heterogeneous multi-organ disease with variable expression, predominantly affecting the thoracic cage with respiratory complications as the main problem, but also with renal complications which leads to the CKD and the need of renal replacement therapy.

OP-26 Rapamycin in etiology of deep venous thrombosis and acute pancreatitis

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Introduction. Evidence indicate that rapamycin may contribute to an increased risk of thrombosis. Researchers found that endothelial membrane remodeling induced by rapamycin is crucial for the adhesion of platelets to en-

dothelial cells and thereby for thrombosis. Many investigations showed that rapamycin induces autophagy of pancreatic cells.

Case report. Male patient, 26 years old, was treated with preemptive kidney transplantation from living related donor. He was treated with thymoglobulin in induction therapy because of donor specific antibodies detected prior to transplantation. Due to surgical complications, he had reperfusion graft injury and delayed graft function. Initial immunosuppressive protocol with thymoglobulin and tacrolimus was converted to rapamycin and dismissal of thymoglobulin. Patient was treated with low-molecular-weight heparin (LMWH) in preparation and after intervention. One month after rapamycin treatment he developed deep venous thrombosis of the right leg. He was treated with intravenous heparin with successful recanalization of venous vessels. Twenty days after rapamycin usage he developed an acute pancreatitis followed by increased serum concentrations of amylase and lipase and urine amylase concentrations. After polysymptomatic therapy, patient recovered its pancreatic function. Finally, rapamycin was removed from the immunosuppressive therapy. Patient was with stabile graft function in the next year of follow up period without thrombosis episodes or episodes of pancreatitis.

Conclusions, All patients treated with rapamycin after kidney transplantation should be carefully monitored for venous thrombosis and pancreatic events.

OP-27 Post-transplant proteinuria as a feature of NODAT

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Introduction. The first consideration in evaluating post-transplant proteinuria is whether it originates from the native kidneys or from the allograft. An increasing proportion of patients do not receive dialysis before transplantation and those individuals may have proteinuria due to their native kidney disease. Proteinuria greater than 1500 mg/d 1 year post-transplant and/or an increase in proteinuria from 3 weeks to 1 year >500 mg/d is indicative of new allograft pathology. The second issue to consider is the type of allograft pathology causing post-transplant proteinuria. Some forms of allograft glomerular pathology, such as transplant glomerulopathy, may be associated with CAN but it has distinct pathogenesis, clinical presentation and prognosis. Second, other forms of non-recurrent glomerular disease, such as focal segmental glomerulosclerosis, are rarely present in patients with CAN and when present defines a subgroup of patients with a distinct clinical presentation and prognosis.

Case report. Male patient, 44 years old, admitted to nephrology department because of nephrotic syndrome, with the level of proteinuria of 7,93 g/d with all other elements of nephrotic syndrome, with slight increase in serum creatinine level. Fifteen years ago he was diagnosed with IgA nephropathy and developed CKD in the next few years. Treated with intermittent dialysis for three years. Treated with kidney transplantation from living related donor ten years ago, without significant complications in the follow up period. He was treated with immunosuppressive protocol with basiliximab in induction and tacrolimus, mycophenolate mophetil and steroids after transplantation, without changes in protocol. The level of urine proteinuria in follow up period was less than 500 mg/day. One year prior to this hospitalization he developed arterial hypertension and NODAT and started treatment with insulin, ACE inhibitors and beta blocker. Color Doppler ultrasound showed no signs of acute rejection or CAN-chronic allograft rejection. We also examined other possible causes of nephrotic syndrome-infections, malignancies and hematological diseases, but without positive findings. We suspected that the cause of proteinuria and nephrotic syndrome could be recurrent IgA allograft nephropathy. The biopsy of the allograft was performed. Pathological examination showed glomeruli with expanded mesangium, thick matrix and the formation of nodules in glomeruli, hypercellular nodules, with segmental duplication of the glomerular basement membrane. In peritubular capillaries deposits of C4d were not found. Changes found on EM and in total matched the changes in the context of diabetic nephropathy. There were no signs of recurrent IgA nephropathy or other glomerulopathies.

Conclusions. Proteinuria is a useful prognostic marker after kidney transplantation. Proteinuria after kidney transplantation identifies recipients with glomerular diseases that may cause graft failure. In patients without demonstrable glomerular pathology, other causes of proteinuria should be considered and investigated, including NODAT. These possibilities deserve investigation for better understanding of the prognostic implications of proteinuria after kidney transplantation.

OP-28 Ultrasound characteristics of blood vessels and successful creation of vascular access in diabetic patients

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Introduction. Patients with diabetic nephropathy who developed ESRD are considered complicated regarding the creation of successful vascular access (VA) for hemodialysis. Surgical failure usually arises due to unfavourable blood vessel morphology. Preoperative echosonographic examination is advised to assess the adequacy of blood vessels and determine the type of preoperative intervention. The aim of the study was to show whether patients

with diabetes mellitus have the same success in creating a VA compared to non-diabetics.
Methods. The study included 239 patients with an ultrasound assessment indicating feasible creation of the first or "after first" VA (all approaches after the first created). Of the above, 90 patients had diabetes mellitus as the underlying disease and they were referred for the first (88.1%) and "after first" vascular access (18.9%) and the groups were compared with the remaining 149 patients without diabetes mellitus. The criterion for a successful VA was adequate hemodialysis over a given VA after the maturation period.
Results. Non-diabetics had a 2.09-fold higher probability of successful VA (OR: 2.09, 95% CI: 1.08-4.05). The use of anti-aggregation agents, oral anticoagulant therapy, statins and ACE inhibitors did not affect the outcome of VA in both groups of patients. Inappropriate colour Doppler parameters (uncompressible vein, deep vein position, accessory veins, adverse venous and arterial morphology) were equally presented in both groups of patients.
Conclusions. Successful creation of VA in patients with diabetes mellitus is less common. Given that there was no significant difference in colour Doppler findings between diabetics and non-diabetics, it is necessary to consider and investigate other risk factors for higher success of VA creation.

OP-29 Influence of hemodialysis and hemodiafiltration on serum superoxide dismutase activity and C-reactive protein levels in end-stage renal disease patients

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Introduction. Recent data suggest that inflammation and oxidative stress are common in end-stage renal disease (ESRD) patients on chronic hemodialysis (HD) treatment. The hemodialysis and hemodiafiltration (HDF) are essential renal replacement treatments in patients with ESRD. The aim of this study was to evaluate the influence of HD versus HDF treatment on serum superoxide dismutase activity (SOD), C-reactive protein (CRP), albumin and uric acid levels in ESRD patients on chronic HD treatment.
Methods. In this cross-sectional, single-center study, a total of 100 patients (60% males, 40% females) with ESRD undergoing chronic HD treatment were enrolled. Their mean age was 54.1±11.8 years, with the duration of dialysis of 91.4±76.2 months. The participants were subdivided into HD group (n=37) and HDF group (n=63) according to the dialysis technique. They underwent regular high-flux HD or HDF for 4 hours, three times a week. Blood samples were taken before the procedure of HD in order to measure the serum levels of SOD, CRP, albumin and uric acid. Serum SOD concentration was determined by an enzyme-linked immunosorbent assay (ELISA) method using a commercial kit. Nephelometry was used to measure CRP plasma levels (normal levels 0-5 mg/L). Serum albumin and uric acid concentration were determined by spectrophotometry method.
Results. Serum CRP level was significantly higher (p=0.006), while albumin concentration was significantly lower (p=0.036) in the HD group compared to HDF group. Patients in the HD group had higher serum uric acid level compared to patients in the HDF group, but the difference was not statistically significant (p=0.062). The groups did not differ significantly in serum level of SOD (p=0.999). Significant positive correlation was only observed between serum albumin and uric acid levels in HDF group (r=0.264; p=0.036).
Conclusions. The significant elevation of serum CRP level together with the decrease in serum albumin level observed in HD group suggests that hemodialysis is more associated with the presence of micro-inflammatory state compared to hemodiafiltration in ESRD patients on chronic HD treatment.

OP-30 Vascular access in elderly-a challenge or a damnation?

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Introduction. The annual increase of the number of hemodialysis (HD)-treated patients is 8-16 % in the 75-plus group. The main aim of our study is recording the vascular access type in HD-patients treated for more than 90 days within a five-year period (from January 1, 2012 to December 31, 2016).
Methods. Eighty three (83) patients with a median age of 59.7±13.98 years (28 females and 55 males) were divided in three groups: A (<45 years)-11, B (45-64 years)-42 and C (>65 years)-30.
Results. The median treatment duration was 681.6 days and no statistically significant differences were found between the groups (p>0.05). The used vascular accesses types were arterio-venous anastomosis (AVA), cuffed catheter (CC) and temporary catheter (TC). The access type distribution at the start of HD treatment was: A: AVA-0, CC-0, TC-11; B: AVA-8, CC-9, TC-25; C: AVA-8, CC-10, TC-12 and the differences between the patients from group A and those from groups B and C was significant (p<0.05). After 90 days of HD-treatment, the vascular access type distribution was: A: AVA-10, CC-1, TC-0; B: AVA-36, CC-6, TC-0; C: AVA-17, CC-13, TC-0 and the differences between the relative share of AVA between the groups A, B, and those from group C was statistically significant (p<0.05).
Conclusion. Based on our data, we conclude that the old age is not a contraindication for AVA creation but vascular access type must be decided individually.

OP-31 Arterial stiffness and circulating angiogenic factors in hemodialysed patients

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Introduction. Arterial stiffness is reported to be a predictor of mortality in hemodialysis patients, and there is also data regarding the association of circulating angiogenic factors, such as vascular endothelial growth factor (VEGF) with chronic kidney disease. The purpose of this study was to assess the potential relationship of arterial stiffness with elements of CKD-MBD, with markers of cardiovascular disease and with VEGF.

Methods. We conducted a single-center cross-sectional study that included 63 CKD G5D patients (hemodialysis for 1-5 years, mean age 60.1±11.8 years). All patients were assessed regarding cardiovascular disease (medical history, echocardiography and ECG), we performed using standard methods blood biochemistry, complete blood count and with enzyme- linked immunosorbent assay method- VEGF, soluble klotho. In every patient we measured aortic augmentation index (AAI) and brachial pulse wave velocity (PWV), using oscillometry.

Results. In the studied patients we found a mean value of PWV of 9.3±1.8 m/s. PWV showed a positive correlation with age (r=0.38, p=0.009). We had also found a statistically significant correlation between PWV and serum calcium (r=0.53, p=0.0003) and serum phosphate (r=0.38, p=009), but there was however no statistically significant correlation with iPTH, alkaline phosphatase, vitamin D, soluble klotho. Arterial stiffness results, expressed using PWV showed no differences between the subgroups of patients with/ without diabetes mellitus, valvular calcification, left ventricular hypertrophy, signs of ischemia on ECG. Regarding serum VEGF (mean value 137.13+/-78.74 pg/ml), with higher values in patients with diabetes (154.2 vs 122.8, not statistically significant). We found no statistically significant correlation of VEGF with arterial stiffness. On the other hand, we found a positive, statistically significant correlation, between PWV and hemoglobin (r=0.48, p=0.001) and with serum albumin (r=0.53, p=0.0003). With regard to dialysis efficiency we found a surprising positive statistically significant correlation between eKT/V and PWV (r=0.36, p=0.01), and also with dialysis blood flow (r=0.49, p=0.0007). It has to be mentioned that we observed an increase of eKT/V with the dialysis vintage (r=0.31, p=0.01).

Conclusions. These data indicate an increase of arterial stiffness with age and an association with elements of CKD-MBD. We found also a positive correlation with serum albumin and hemoglobin. However, our study could not show a relationship of arterial stiffness with markers of cardiovascular disease or with circulating angiogenic factors. Further studies are needed to examine the role of angiogenic factors in CKD.

OP-32 Unusual vascular access for hemodialysis

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Introduction. Arteriovenous (AV) fistula is the best vascular access (VA) for patients requiring chronic hemodialysis (HD) therapy. Repetitive venous punctures in forearms in patient on HD develop venous fibrosis, making impossible subsequent cannulation and creation of more AV fistula. Limiting factor for future creation of AV fistula is also use of central venous catheters (CVC) for initial HD therapy in app 60% of patients. The aim of the study was to describe the creation of unusual VA for HD in patients with limited options that may be a matter of choice to safe and prolong the patient's life.

Methods. We had performed 26690 VA at our Department for VA, Clinic of Nephrology, Skopje in a period of 40 years (1977-2017): 9309 as permanent VA, 7968 AV fistula (85.6%) and 1341 (14.4%) tunnelled catheters (TC) such as femoral, subclavian and jugular. Beside of performing AV fistula, AV grafts and TC, we have also performed some unusual VA for HD. Due to some complications, v. azygos (n=1) was enlarged which gave an opportunity to be used as unusual VA for HD; v. saphena magna and a. femoralis superficialis anastomosis (n=2); a. femoralis was cannulated until patients were prepared for continuous ambulatory peritoneal dialysis (n=4).

Results. We have cannulated v. azygos intentionally for a period of 45 days during cardio surgery performed thrombectomy to right atrium and bypass from v. innominate to right atrium with Dacron graft 8mm and catheter Tesio insertion in v. innominate to right atrium. In 2 other patients we avoid using upper VA due to stenosis at innominate veins and performed v. saphena magna and a. femoralis superficialis anastomosis. One patient was with occlusion of right and left axilar vein and occlusion of both femoral veins. We had to perform HD sessions using catheters in a. femoralis in a period of 45 days until patients were prepared for continuous ambulatory peritoneal dialysis.

Conclusions. Unusual VA for HD may be used as a last lifesaving procedure in chronic renal failure patients in whom conventional accesses failed. Such approach may be of choice as it provides sustainable VA for HD.

OP-33 Paradoxal diuresis after vasopressin administration to hemodialysis patients with bleeding

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Abstract. Uremic bleeding is a well-recognized complication in patients with renal failure. The most common agent used in uremic patients with active bleeding is desmopressin. Desmopressin doses for uremic bleeding are approximately 10-fold higher than doses used for diabetes insipidus. We use desmopressin in oral form in treatment of haematoma in the right upper thigh in haemodialysis patients. Residual urine output was to 100-200 ml/24 hours during the past couple of years. The second day after the introduction of desmopressin to the treatment, patient complained about suprapubic painful distension tension.. Urinary catheter was placed and 900 ml of clear liquid was evacuated. The patient continued to have diuresis in the following days, between 600-800 ml per day. Scientific explanation for this phenomenon were found. We have possible explanations for the diuretic effect of vasopressin: increase of renal perfusion pressure, inhibition of sodium reabsorption at the renal tubules and the release of atrial natriuretic peptide. This question can only be answered by a prospective trial of the effect of vasopressin in dialysis patients.

OP-34 One-year outcome of kidney allograft rejection with microvascular injury: role of HLA and non-HLA antibodies

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Introduction. Microvascular injury (MVI) defined as peritubular capillaritis (ptc) and glomerulitis (g) is one of fundamental, but unspecific features of antibody-mediated rejection (AMR). Preexisting and/or *de novo* donor-specific HLA antibodies (DSA) class I and class II are associated with MVI, accelerated allograft fibrosis and subsequent premature graft loss. AMR may also be caused by non-HLA antibodies (i.e. anti-angiotensin II type 1 receptor [anti-AT1 R], or anti-endothelin receptor [anti-ETAR]), either alone or together with DSA. However, previous studies showed conflicting results regarding prognostic significance of non-HLA antibodies on kidney allograft. Therefore, our aim was to investigate a role of DSA and non-HLA antibodies on the medium-term outcome of kidney allograft rejection with MVI.

Methods. Retrospective analysis included 46 pts who had kidney transplantation (tx), or simultaneous pancreas and kidney tx (SPKT) at Merkur hospital between 2007 and 2016, with MVI on protocol, or indication biopsy (bx). Patients with available DSA data pretransplant and at the time of rejection, as well as non-HLA data at the time of kidney rejection were included. Pts with preexisting DSA were considered as DSA positive at the time of rejection even if the DSAs were not detected at that time. Biopsies were scored using the Banff 2017 classification. All pts received treatment for graft rejection that included corticosteroids, anti-thymocyte globulin (ATG), plasmapheresis, intravenous immunoglobulins (IVIg), bortezomib, and/or rituximab depending on the type of rejection.

Results. Among 46 pts with MVI, borderline rejection was diagnosed in 6 pts, TCMR in 13 pts, and AMR in 27 pts (acute/active 18 pts, and 9 pts chronic active). AMR type I was present in 14 pts, and AMR type II in 13 pts. Median time from tx to rejection episode with MVI in borderline group was 32 days (IQR 6-57), in TCMR group 14 days (IQR 10-105), and in AMR group 54 days (IQR 11-1159) (p=0.14). The three groups (borderline, TCMR, and AMR) were different regarding the degree of MVI (ptc+g score) (borderline 1.5±0.5, TCMR 1.8±1, AMR 3.5±1; p<0.001), and cg score (borderline 0±0, TCMR 0±0, AMR 0.7±1.1; p=0.027). There was no statistically significant difference regarding cv score, IF/TA score, eGFR at the time of rejection, eGFR six and twelve months after rejection among the three groups. One year following rejection death-censored graft survival (DCGS) and overall graft survival (OGS) were not statistically significant according to the Banff groups (borderline 100%, TCMR 84.6%, and AMR 88.9%; p=0.57 respectively).

Antibodies (DSA and/or non-HLA) were associated with MVI in 36 pts. 11 pts had only DSAs (all *de novo* DSA), 12 pts had only non-HLA-Abs (AT1R-Ab in all), and 13 pts had both DSA and non-HLA Abs (preexistent DSA in 4 pts, and *de novo* in 9 pts). Time from tx to the rejection was statistically different between groups (only DSA 109 days (IQR 11.1324), only non-HLA-Abs 9 days (IQR 4.5-40), both DSA (preexisting) and non-HLA-Abs 43 (IQR 20.5-118), both DSA (*de novo*), non-HLA-Abs 463 (IQR 181-1304), and antibody negative pts 13.5 days (IQR10-70) (p=0.02). DCGS was not different between pts without antibodies, only DSA, only non-HLA, and both DSA and non-HLA Abs (77.8%, 90.9%, 100%, and 92.3%; p=0.335, respectively).

Conclusions. Our results showed that patients with microvascular injury and DSAs and/or non-HLA antibodies may not experience poorer death-censored graft survival or overall graft survival within first year of acute rejection when active multimodal treatment is applied.

OP-35 Prooxidant-antioxidant balance, hsTnI and hsCRP: mortality prediction in haemodialysis patients, two-year follow-up

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Introduction. Oxidative stress and inflammation are highly intertwined pathophysiological processes. We analyzed the markers of these processes and high-sensitive troponin I (hsTnI) for mortality prediction in patients on haemodialysis.

Methods. This study enrolled a total of 62 patients on regular haemodialysis. The patients were monitored for two years, and the observed outcomes were all-cause and cardiovascular mortality. Blood samples were taken before one dialysis session for analysis of the baseline concentrations of prooxidant-antioxidant balance (PAB), total antioxidant status (TAS), total oxidative status (TOS), hsTnI, hsCRP and resistin.

Results. The overall all-cause mortality was 37.1% and CVD mortality 16.1%. By univariate and multivariate logistic regression, our findings suggest that good predictors of all-cause mortality include hsCRP and PAB ($p<.05$) and of CVD mortality hsCRP ($p<.05$) and hsTnI ($p<.001$). To evaluate the relationship between the combined parameter measurements and all-cause/CVD mortality risk, patients were divided into three groups according to their PAB, hsCRP and hsTnI concentrations. The cutoffs for hsCRP and hsTnI and the median for PAB were used. Kaplan-Meier survival curves pointed out that the highest mortality risk of all-cause mortality was in the group with hsCRP levels above the cutoff and PAB levels above the median ($p<.001$). The highest risk of CVD mortality was found in the group with hsCRP and hsTnI levels above the cutoff levels ($p=.001$).

Conclusions. Our data suggest that hsCRP and PAB are very good predictors of all-cause mortality. For CVD complications and mortality prediction in HD patients, the most sensitive parameters appear to be hsTnI and hsCRP.

OP-36 Risk assessment of development of contrast-induced nephropathy-case description

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Introduction. Contrast-induced nephropathy is defined as exposure to contrast media to the exclusion of other causes of kidney damage, increase of serum creatinine concentration >44µmol/l (0.5 mg/dl) or relatively >25% from baseline within 24-48 hours after intravenous administration of contrast medium and restore for 1-3 weeks. There are invariable (age, diabetes, existing kidney disease, progressive heart failure, low left ventricular ejection fraction <40%, acute myocardial infarction, cardiogenic shock, kidney transplant) and variable factor of risk (volume of contrast medium, hypotension, anemia and blood loss, dehydration, hypoalbuminemia <35 g/l, nephrotoxic drugs). The aim of the study is to describe the case of a comorbid patient with monitoring risk assessment for a contrast nephropathy after CT angiography endocranium, including seven invariable and variable risk factors with chronic kidney disease and the repeated use of a contrast agent.

Case report. We performed an ambulatory contrast CT angiography of the endocranium at General Hospital in Berane, suggested by a neurologist with the usual volume of contrast agent. Being repeated contrast procedure in male patient with comorbidity we monitored his clinical, laboratory daily before and after the procedure 1 to 12 months. Score for a risk assessment of contrast- induced nephropathy is defined according to the table where stagnant heart failure defined as NYHA III/IV and/or with the data on lung edema, chronic kidney disease as sCR> 133 µmol/l or lower JMF <60 ml/min / 1.73m^2, systolic hypotension <80 mmHg, anemia with hematocrit <36-39%. Scoring for risk of contrasting nephropathy was divided in four groups, small risk with a score <5, 6-10 moderate, medium 11-15 and very high risk with a score >16. In a period of one year, he was monitored by standard laboratory findings with anemia status, serum creatinine before and after contrast procedures and monitoring of diuresis and other specialist examinations, including seven parameters of risk factors for contrast-induced nephropathy. Before contrast procedures his findings were as follows: moderate systolic hypotension <110 mmHg (score 1), heart failure NYHA II (score 2), age 65 (score 2), moderate anemia (score 1), diabetes type 2 (score 1), the volume of contrast 100 ml (score 1), serum creatinine 90 µmol/l (score 1) or JGM 80 ml/min/1.73 m^2 (score 1). The total score was 9 and was on the table in Range score risks in the second of four groups of estimated risk of contrast nephropathy and increased concentrations of serum creatinine by 44 µmol/l and there is a moderate risk for contrast- induced nephropathy and dialysis.

Conclusions. Early detection of patients with increased risk for the development of contrast nephropathy before and after administration of contrast medium is important for optimal status. Euvolemia, avoidance of nephrotoxic drugs, the use of contrast agents with low osmolarity, participation of specialists in the prevention of contrast nephropathy development, shortens the length of hospital stay and cost of treatment.

OP-37 Off-clamp Nephron sparing surgery (NSS) and its impact on postoperative kidney function.

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Introduction. Although minimal invasive approach is preferable for partial nephrectomy (PN), open procedure has sill its own place. Recently introduced mini-flank approach is considered appropriate alternative to laparoscopic or robotically assisted PN regarding cosmetic and functional outcomes. Zero ischemia time PN (ZTPN) was developed in order to minimize renal ischemia and preserve renal function. Our technique of ZTPN with hemostatic suture in running fashion aimed to estimate efficacy of this approach in terms of perioperative complications, operative time and estimated blood loss (EBL).

Methods. We retrospectively analyzed 96 consecutive patients who underwent PN, using supra 11th or supra 12th rib mini flank approach. Patients with solitary tumor, limited to the kidney (T1-T2) were included. Using our technique, EBL was 150 ml and average OT 120.2 min. Postoperative transfusion rate was 2.1% with maximum 2 blood units required.
Results. Surgical resection margins were negative in 100% of cases and none patient developed a local or distant recurrence during follow up period. There was no significant difference between preoperative and postoperative outcomes regarding creatinine and glomerular filtration rate (GFR) (p=0.43 and p=0.51).
Conclusions. We can state that our technique is at least comparable to others, open or laparoscopic, with emphasize on low EBL and good postoperative functional outcome.

OP-38 Drug-related clinical manifestations in elderly patients at a nephrology outpatient clinic

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Introduction. Polypharmacotherapy and inappropriate medication use is known and common in general elderly population. Less is known about potential adverse drug effects, drug interactions and their clinical manifestations in elderly patients with chronic kidney disease (CKD). In our study, we aimed to define the polypharmacotherapy and drug-related clinical manifestations in CKD patients.
Methods. We retrospectively examined the data of 99 elderly CKD patients at our nephrology outpatient clinic. Basic demographic data, comorbidities, concomitant medications, potential adverse drug effects and/or drug interactions were recorded. At the visiting day, patients answered a questionnaire about their pharmacotherapy and possible adverse effects. A clinical history and status were obtained. Clinical manifestations of potential inappropriate medication use were recorded.
Results. We included 99 patients (34 female, 65 male), average age 77 years (range from 65 to 94 years). On average, patients regularly used 6.7±2.9 drugs. Number of drugs used by our patients increased with age (r=0.251; p<0.012). Most commonly prescribed drugs prone to adverse drug effects and/or drug interactions were beta blockers (9.2%), non-steroid anti-inflammatory drugs (8.8%), angiotensin converting enzyme inhibitors (7.6%), antilipemic drugs (7.0%), calcium channel blockers (6.1%), antacids (6.5%), loop diuretics (6.1%), antiglycemic drugs (6.1%), alfa blockers (4.7%) and sartans (4.7%), respectively. No clinically relevant abnormalities in homeostasis of coagulation, electrolytes, lipids and/or glycaemia related to drug prescribing were found. In 44 patients, arterial hypotension was determined, 8 of them had clear clinical manifestations of hypotension.
Conclusions. The results of our study show drug-related, clinically relevant blood pressure overtreatment in CKD patients, resulting in hypotension.

OP-39 Early lesions of focal segmental glomerulosclerosis in a patient with acromegaly

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Introduction. Growth hormone (GH)/IGF-1 axis regulates renal growth and function. Hypersecretion of GH in acromegaly is associated with glomerular hypertrophy, hyperfiltration and higher albuminuria levels.
Case report. We present a rare case of focal segmental glomerulosclerosis (FGSG) in a young patient with pituitary adenoma secreting GH. A 30 year-old male patient with acromegaly phenotype was admitted in our hospital due to nephrotic range proteinuria (7.1 gr/dl). His medical history included surgical removal of a pituitary adenoma secreting GH followed by radiotherapy four years ago as well as diabetes mellitus and arterial hypertension. The patient presented normal levels of urea and creatinine (32 mg/dl and 1 mg/dl, respectively), glomerular hyperfiltration (mGFR 220 ml/min) with enlarged kidneys on ultrasound. Imunological and hormonal testing were normal. He underwent renal biopsy which revealed glomerulomegaly, juxtaglomerular cell hyperplasia and lesions suggestive of early stage of FSGS. Symptomatic therapy targeting strict control of blood pressure was initiated. Three months later proteinuria was decreased to subnephrotic level (3.2 gr/dl).
Conclusions. Hypersecretion of GH is associated with structural and functional renal changes leading progressively to FSGS. Strict control of metabolic and hemodynamic parameters is essential for glomerular protection in acromegalic patients.

OP-40 Balkan endemic nephropathy and malignant tumors of urinary bladder- 40 years of follow up

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Introduction. Balkan endemic nephropathy (BEN) is a chronic tubulointestitial kidney disease prevalent in Serbia, Bosnia, Croatia, Bulgaria and Romania. BEN is often associated with the high concomitant appearance of malignant tumors of the urothelium (MTU), especially with malignant tumors upper urothelium (MTUU). The aim of the paper is to assess the basic epidemiological characte-

ristics of malignant tumors of urinary bladder (MTUB) occurring in Jablanica region in the period of 40 years, and to determine the linear trend of MTUB frequency in region with BEN compared to non-endemic regions.

Methods. The research period lasted from 1978-2017. During the analysis of the frequency of MTUB, we used the operative material of Urology Department, Health Care Center, Leskovac, and Urology Clinic, Clinical Center, Nis. The average annual incidence rate (AAIR) was calculated per 100,000 people. We collected data about our patients regarding their sex, age, place of birth and place of living. Patients were classified by the place of living (A-endemic regions, B-hypo-endemic regions, C-non-endemic urban regions, D-non-endemic rural regions). Finally, we observed groups C and D (non-endemic regions) for MTUB. For practical reasons, this period was divided into two parts, the first one from 1978-1997 and the second from 1998-2017.

Results. From 1978 to 2017, 1208 cases of MTUB (282 female and 926 male-1:3.28) with average age of 62 (the youngest 32, and the oldest 86 years). There were 17 patients in endemic (A), 25 in hypo-endemic (B) and 1166 in non-endemic regions (C,D). AAIR of MTUB was (14.35) in endemic regions, (11,23) in hypo-endemic regions and (11,82) in non-endemic regions. There was five times decline in the relative rate of incidence of MTUB per annum in endemic regions from the first to the second period, while the approximate annual rate for MTUB in non-endemic regions was increased by 3,19 times (288: 920). The linear trend of MTUB in the observed period was statically increased ($y=1.6415x +3,45$; $r^2=0,85$). In the first observed period, MTUB of the Jablanica district in endemic regions was 2.58 times more frequent than in non-endemic ones compared to the number of inhabitants, while in the second observed period it was 1.59 times more frequent in non-endemic regions.

Conclusions. High frequency of malignant tumors of the urothelium, primarily MTUU in the areas with BEN incidence, probably points to the common nephropathogentic and cancerogenic etiological factors and proves the existence of a positive correlation between BEN and MTUU, which is not the case with MTUB.

OP-41Diabetic nephropathy, challenges of treatment

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Introduction. Diabetic nephropathy as a major complication of diabetes represents a progressive structural and functional kidney damage, leading to chronic kidney failure and end stage renal disease (ESRD). Novel protocols of treatment and tight follow up between nephrologist and endocrinologist have showed a huge impact in managing the disease and changing its natural path. Early referral to a nephrologist and screening for microalbuminuria and structural kidney damages is a MUST nowadays. A late referral to a nephrologist dismisses the possibility of optimal treatment and represents on itself the major burden and the biggest obstacle on treatment of diabetic nephropathy, thus increasing morbidity, mortality and hospitalization rate. Late referral leads to unfollowed abnormalities, unnoticed progression of kidney disease, patient and family unawareness and fast kidney damage.

Methods. We present an overview of our inpatient situation during 2016-2017.

Results. We conclude that our patients are referred very late for nephrologist checkup that they usually present with overt diabetic nephropathy, frank proteinuria or macroalbuminuria, decreased GFR and on a great proportion with ESRD, leaving no further choices for treatment except renal replacement therapy. Besides this our patients often show with very severe illness, different comorbidities such as: cardiac failure, sepsis, pulmonary failure, cerebrovascular insult etc., lowering the chances of treatment and poor survivor rate.

Conclusion. Nowadays diabetic nephropathy is the leading cause of ESRD in our country and our scope is to work harder and target early stages of the disease in cooperation with primary care units, endocrinology and cardiology departments!

Poster presentations – dialysis

Poster presentations – dialysis

PPD-01 The arterio-venous anastomosis in present days (Analysis of the last 100 arteriovenous anastomoses)

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Introduction. Arterio-venous anastomosis (AVA) continues to be the "gold standard" for vascular access in patients with chronic kidney disease (CKD) undergoing hemodialysis. The purpose of this retrospective study is to analyze the causes that led to CKD, the type of native AVA and its localization as well as their patency.

Methods. The study included the last 100 consecutive and random AVAs constructed in our clinic. 68 men of average age 62.3 (±10.8) years and 32 women of average age 59.9(±15.8) years were operated. The main causes that led to CKD were: chronic glomerulonephritis-33%, hypertensive nephropathy-24%, diabetic nephropathy-20%. The overweight patients were 33% and smokers were 30%. AVA has been successfully constructed in 82% of the patients on left hand and in 18% on the right hand.

Results. A distal, latero-terminal, radio-cephalic fistula was constructed on only 8% of the patients. The most common type of anastomosis was a latero-terminal radio-cephalic in the forearm-58%, followed by a latero-terminal brachio-cephalic fistula-19% and latero-lateral radio-cephalic in the forearm-14% of the patients. The extra-early (up to 7-th day) fistula patency was 95%, early (up to 3-rd month)-80%, one-year cumulative patency for 70 patients was 94%, the remaining 10 patients did not have 1 year of surgical intervention.

Conclusions. The analysis of our results showed that the relative share of the overweight and diabetes population is increasing today. In practice, solutions for the construction of primary forearm anastomosis are increasingly common.

PD-02 Hypokalemia as a marker of poor outcome in peritoneal dialysis – related peritonitis

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Introduction. Determine association between hypokalemia and clinical outcome in patients with peritoneal dialysis-related peritonitis (PDRP).

Methods. We retrospectively evaluated the records of all patients with PDRP who were treated in our hospital in period from 2016-2017. The influence of hypokalemia on the clinical features of peritonitis was assessed. Hypokalemia was defined as a serum potassium level <3.5 mmol/l. Diagnosis of peritonitis was made based on standard criteria. The demographic and laboratory characteristics, pathogens of peritonitis, method failure and mortality rate were analyzed.

Results. We analyzed 42 patients treated with standard PD solutions. We identified total 22 episodes of peritonitis (2 episodes were culture negative) in 17 patients. A single Gram+organisms were founded in 65% and single Gram-organisms were founded in 35 % of the positive culture cases. We verified complete resolution in all cases of Gram+peritonitis and loss of catheter and transfer on HD in 1 case of Gram-peritonitis (14,29%). There were not cases of fungal or multibacterial peritonitis or lethal outcomes. The overall peritonitis rate was 31.6 patient-month per episode. Hypokalemia occurred in 29,41% (5/17) patients with PDRP. Gram-microorganisms were lead pathogens responsible for 80% (4/5) episodes of PDRP in hypokalemic group. This group had significantly higher serum CRP ($p<0.01$), lower serum albumin ($p<0.05$) and PD catheter removal rate ($p<0.05$). There were no significant difference in age, gender, duration of dialysis and mortality between two groups.

Conclusions. Hypokalemia is a marker of poor outcome in peritoneal dialysis-related peritonitis, associated with a high frequency of gram negative causer's infection, malnutrition, inflammation and PD catheter removal rate.

PPD-03 Microinflammation as a risk factor for a development of a cardiovascular disease in hemodialysis patients

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Introcuction. C-reactive protein (CRP)-a reliable marker of microinflamation(MI) in CVD.

- sCRP is <5 mg/l- normal,
- sCRP>10 mg/l signify the microinflammation(MI) of ACC

MI on hemodialysis(HD) in 30- 50% of patients

HD and MI:

- biocompatibility of dialysis membrane,
- the conventional solution for hemodialysis,
- ultrafiltration feedback,
- latent or clinically manifest vascular access infections.

I- the traditional risk factors(TRF)- II-HD-hemodialysis

1-hypertension, 1-biocompatibility
2-hyperlipidemia, 2- endotoxins
3-diabetes mellitus, 3- the solution for hemodialysis
4- cigarette smoking,
5- obesity,
6-uremia (oks.LDL, free radicals ROS, hyperhomocysteinemia, infection, acidosis)

The aim of the study:

I - in hemodialysis patients
II- in the control group
1. to determine hs-CRP (high-sensitivity high-sensitivity CRP)

2. compare hs-CRP in HD and in the control group,
3. comparable hs-CRP in patients with and without cardiovascular complications (CVD) and to determine the incidence of cardiovascular disease on hemodialysis compared to traditional risk factors(TRF).

Methods.

- I- HD-
- group of 20 patients
- 15 males and 5 females
- mean age 57.5 years,
- 15 males with an average age 58.6 years, a group of five women's average age of 54.8 years,
- treated by repeated dialysis treatment in the General Hospital in Berane in 2012 and 2013 made a general overview to the exclusion of acute inflammatory diseases,

II- Control

group of 10 subjects (8 males and 2 females),

- mean age 50.7 years,
- while 8 of them were male with an average age 52.75 years,
- while two were female with an average age 42.5 years, who belong to a healthy population.
- From the medical documentatio 10 patients had developed cardiovascular complications, with an average age of 66.6 years, 9 males average age of 65.67 years, one female, age 76 years with coronary heart disease and all done CRP.

Results.

n 20 patients on hemodialysis,

-the mean concentration was hs-CRP-67±20.8 mg/l (baseline CRP<5 mg/l, while hs>10 mg/l) was significantly higher than in the reference value in the control group ranged 16.2±3.9 mg/l, and between these two groups there was a statistically significant difference ($p<0.01$). For groups of 10 hemodialysis patients with cardiovascular complications, the mean concentrations of hs-CRP was 75.3±31.78 mg/l, with the remaining 10 patients on dialysis without complication was conc. hs-CRP 82.45±24.65 mg/l between these two groups there was no statistically significant difference ($p>0.05$) .Followed compared to traditional risk factors, 10 hemodialysis patients with cardiovascular complications of 100% have hypertension, hyperlipidemia 30%, 20% of the patients with diabetes, 30% of the smoking and obesity have 30%.

Conclusions.

-The concentration of hs-CRP In HD-significantly increased compared to the control group(CG), which belongs to the healthy population.

- The concentration of hs-CRP in HD with cardiovascular complications was not significantly elevated compared with no complications.

The incidence of cardiovascular complications inHD and action on traditional and non-traditional risk factors can reduce the incidence of complications.

PPD-04 Primary kidney disease does not affect L-carnitine supplementation effects in hemodialysis patients

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Introduction. There is a growing body of evidence that the long-term hemodialysis (HD) leads to disturbances of carnitine homeostasis but the results of L-carnitine supplementation in HD patients have been conflicting. In the present prospective study we investigated the effectiveness of intravenous L-carnitine in mitigating dialysis-related protein-energy wasting (PEW).

Methods. Fifty patients (46% male, mean age 63±18.28 years, HD vintage 37.5 (7-288) months) received 1 g L-carnitine intravenously at the end of every HD session for 12 months. Clinical data were obtained from the medical records and charts. Laboratory parameters were measured prior to supplementation and controlled in 6-months intervals. Anthropometric measurements were performed prior to HD session. Malnutrition-inflammation score (MIS) was used as a scoring system representing the severity of PEW.

Results. A significant increase in total cholesterol, predominantly on the account of LDL was found ($p=0.005$). Simultaneously, HDL decreased ($p=0.001$) while triglyceride levels remained unchanged. Although the rise in serum prealbumin could be observed, lean tissue index (LTI) decreased and fat tissue index (FTI) increased which resulted in reduction of the LTI/FTI ratio ($p=0.002$). Multivariate regression analysis showed that higher FTI after introduction of L-carnitine led to greater hemodynamic stability (OR 1.709, 95% CI 1.006-2.905, $p=0.048$). Primary kidney disease had no influence on neither nutritional parameters nor on L-carnitine supplementation effects.

Conclusions. Our results show significant effects of L-carnitine supplementation on lipid metabolism. Although at first these changes could be claimed as undesirable they led to significant amelioration of MIS and were linked tomuch better appetite. Furthermore, FTI increase led to lesser number of intradialytic hypotension episodes. As there was no differences in HD treatment characteristics, primary kidney disease or residual diuresis we could conclude that positive energy balance (with an increase in prealbumin and FTI) eventually led to better hemodynamic stability.

PD-05 Survival of patients on hemodialysis with erectile dysfunction

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Introduction. In patients on hemodialysis, erectile dysfunction is an independent mortality factor. We investigated the impact of erectile dysfunction on survival rate of patients on hemodialysis.

Methods. During a seven-year period, erectile dysfunction was identified among the mortalities reported in pa-

tients receiving chronic hemodialysis. The study covered 70 patients of mean age 57±6.7 years. During the examined period, 42(60%) patients died, the study was completed by 28(40%) patients. Laboratory, demographic, anthropometric and clinical characteristics were recorded using standard methods.

Results. Statistically significant differences between the two groups of respondents were found concerning dialysis duration ($p<0.001$), number of leukocytes ($p=0.003$), adequacy of hemodialysis ($p=0.004$), intima media thickness of the carotid artery ($p<0.001$), presence of cardiovascular disease ($p=0.03$), residual diuresis ($p=0.04$), and hemodiafiltration ($p<0.001$). Hemodialysis adequacy (B-9.634; $p=0.017$), intima media thickness (B 0.022; $p=0.003$), residual diuresis (B-0.060; $p=0.007$), and lower rates cardiovascular disease (B 0.176; $p=0.034$) were significant survival predictors among our patients with erectile dysfunction.

Conclusion. Predictive survival parameters for such patients are residual diuresis, high quality hemodialysis, a low incidence of cardiovascular diseases, and less intima media thickness of the carotid arteries.

PPD-06 Encapsulating peritoneal sclerosis

Pesic S

Introduction. Damage to the peritoneal membrane induced by long-term peritoneal dialysis, can leads to serious, often life-threatening complications as is encapsulating peritoneal sclerosis (IPS). The incidence of IPS-e is about 2.5%, and increases with the duration of peritoneal dialysis. The pathogenesis of sclerosing peritonitis is multifactorial, most commonly the result of an association of inflammatory stimuli and damage of the peritoneal membrane. Mortality is extremely high about 40%.

Case study. Patient K. N. age 62, from Belgrade, on chronic peritoneal dialysis treatment 9 years. After observed ultrafiltration weakness and the occurrence of sterile peritonitis, IPS was diagnosed. The Tamoxifen therapy was introduced and patient was switched to hemodialysis. On several occasions, the patient was hospitalized due to suboclusion and in 2016 athesiolysis with resection of the small intestine was performed together with jejunal-ileal anastomosis. Postoperatively patient expressed signs of malnutrition, fever with an increased markers of inflammation. The twentieth postoperative day he expired.

Conclusions. Immunosuppressive therapy may be effective in the control and prevention of disease progression as well as timely surgical treatment. Finding of early markers for the diagnosis of IPS-e and timely transfer of these patients to other treatment modality for renal replacement function can contribute to a better outcome and reduced mortality in these patients. It may be important to consider regular CT diagnostic procedure after long-term PD for timely diagnosis and surgical intervention.

PPD-07 Treatment of congestive heart failure with sequential dialysis

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Introduction. The advanced congestive heart failure (CHF) may provoke functional kidney disturbances with insufficient and resistant to conservative therapy water excretion. The treatment of chronic renal failure (CRF) with active dialysis related to ultrafiltration (UF), may overcome the renal diuretics resistance with diuresis restoration and edema withdrawal. The aim of the study was to define the indications for active, discontinued UF in setting of the CHF refractory to drugs, especially in the treatment of edema.

Methods. We investigated 12 patients, mean age 62.4±5.3 years, with incipient renal failure, but advanced congestive heart failure. Seven of them were males and 5 females. The indication for discontinued UF, was the severe expressed heart failure, reduced diuresis and initial renal insufficiency. In all investigated patients, before and after each UF procedure, the serum sodium and potassium level, blood urea nitrogen (BUN), creatinine and osmolality were checked. The body weight, abdominal and crural parameters were noted before and after dialysis.?

Results. The recovery was achieved in 10 patients with CHF, but 2 patients out of 12 did not demonstrated satisfactory response to UF. The biochemical features encountered to CHF patients suggest chronic hyponatremia, hypokalemia and hypovolemia. Proteinuria range from 1.2 to 3.6 g/l, and was present in 6 patients. The clinical data were performed with edema formation, reduced diuresis and dyspnea. Mean UF rate achieved after several dialysis was 12.4±7.6L.

Conclusion. Chronic heart failure in chronic renal patients, with severe edemas is an indication for UF therapy, even if the levels of BUN and creatinine are not increased. Reduction of the body weight and the extracellular volume, contributed for improved survival in these patients. However the risk of complications is high and not always with successful treatment.

PPD-08 Incidence, types and complications of vascular accesses in patients on chronic hemodialysis in Clinic for Nephrology, Clinical Centre of Serbia

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Introduction. Hemodialysis (HD) is the most frequent type of renal replacement therapy for patients with end stage renal disease (ESRD) in Serbia. Appropriate vascular access is essential for good and quality HD. The aim of our study is to present the incidence and types of vascular accesses for hemodialysis in patients with ESRD and to show complications regarding the type of vascular accesses.

Methods. Study included 153 patients admitted in Clinic of nephrology, Clinical Center of Serbia for creating vascular access prior to hemodialysis due to ESRD, need

for immediately start hemodialysis due to uremic syndrome and patients whose vascular access was malfunctioning. Clinical and demographic data were collected from medical records.

Results. The most often vascular access was primary arteriovenous fistula (AVF) (68.7%), REDO AVF was done to 11.1% patients, while permanent dialysis catheter (Hickman) was implanted to 15% and arteriovenous graft (AVG) to 3.9% patients (p<0.001). Patients with Hickman catheter were significantly older (72±13.6 vs. 63±15.3 vs. 62±17.2 respectively, p=0.043) and had a higher mortality rate (17.4% vs. 2.5% vs. 12.5%, respectively, p=0.008) compared to patients with AVF and AVG. Vascular access thrombosis was the most common complication (80%). Central venous catheter (CVC) for HD was placed in 19.6% patients due to nonexistent vascular access and in 23.5% CVC was used until the maturation of vascular access. Mortality rate was significantly lower in patients with prior created vascular access compared to uremic patients with CVC as first vascular access been CVC (3.3% vs. 13.3%, p=0.026).

Conclusions. AVF is the most common vascular access for HD. Predominant complication of vascular access is its thrombosis. Elective creation of vascular access for HD significantly reduces mortality rate.

PPD-09 Malnutrition Inflammation Complex Syndrome in Hemodialysis Patients- Implications in Cardiovascular and Vascular Access Outcomes

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Introduction. Malnutrition Inflammation Complex Syndrome (MICS) is frequently encountered in maintenance hemodialysis patients. The cause of this syndrome appears to be multifactorial (including inflammatory cytokine overload, nutrient wasting, uremic toxin accumulation, volume overload). The implications of this syndrome are vast, leading to poorer cardiovascular outcomes, higher intrahospital mortality and lower erythropoietin responsiveness. Our study aims to assess which MICS component correlates with 1-year cardiovascular outcomes, mortality and vascular access patency.

Methods. We retrospectively analyzed 155 chronic maintenance patients for whom we recorded demographics, subjective global assessment (SGA) score, comorbidities, biochemical parameters (hemoglobin, iron status, albumin, CRP, phosphorus, calcium, iPTH), dialysis quality parameters (kt/V, membrane type, membrane surface) and vascular access in January 2017. The outcomes for our patients recorded after one year, in January 2018 were: all-cause mortality, cardiovascular-cause mortality, myocardial infarction, stroke, arteriovenous fistula thrombosis, central line dysfunction.

Results. All-cause mortality was directly and significantly correlated with underweight status (r=0.21, p=0.01) and higher SGA score (r=0.2, p=0.01). Cardiovascular mortality was correlated directly with: age (r=0.2, p=0.01), dialysis vintage (r=0.2, p=0.02), underweight status (r=0.23, p=0.003), higher SGA (r=0.2, p=0.02), lower kt/V (r=-0.2, p=0.01). For new myocardial infarction, the direct, significant correlations with MICS components were: age (r=0.17, p=0.03), underweight status (r=0.19, p=0.01), SGA score (r=0.24, p=0.004), ferritin levels (r=0.2, p=0.009), and lower kt/V (r=-0.24, p=0.002). Concerning vascular access dysfunction, we obtained the following results: higher SGA score correlates directly with AV fistula thrombosis (r=0.37, p=0.05), as well as with central line dysfunction (r=0.22, p=0.004).

Conclusions. Malnutrition Inflammation Complex Syndrome assessment components are associated with higher all-cause mortality, cardiovascular mortality and vascular access dysfunction in our lot of patients, showing the need for better tertiary prevention regarding this subject.

PPD-10 Relationship between leptin level and nutritional status in chronic hemodialysis patients

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Introduction. Malnutrition is frequent and associated with increased risk of mortality and morbidity in hemodialysis (HD) patients. Detecting malnutrition early and treating is of vital important. Various parameters and anthropometric measurements are utilized, but none can provide definite information on their own. Leptin is peptide hormone, involved in the regulation of appetite, and might have a role in the development of anorexia in uremia. Several studies showed significant association between leptin and nutritional parameters, such as serum albumin, prealbumin and total cholesterol.

Methods. The aim of the study was to analyze nutritional status depending on leptin level and relationship between leptin, laboratory parameters and anthropometric measurements in predicting malnutrition in HD patients.

Results. Patients with low leptin level had poorer nutritional status (albumin 36.36±3.42 vs. 41.02±2.78 vs 41.66± 3.11, p< 0.001; total cholesterol 3.75±0.71 vs. 4.35±1.10 vs. 4.99±0.98, p< 0.001; transferrin 1.26±0.29 vs. 1.58±0.38 vs. 1.64±0.27, p<0.05; BMI 19.09±1.24 vs. 22.83±7.92 vs. 27.92±3.80, p<0.05). Patients with normal and high leptin level had good nutritional status. A statistically significant direct correlation was found between leptin level and Body Mass Index and reverse correlation between leptin and total cholesterol. In the malnutrition prediction, leptin showed good sensitivity (0.89), and specificity was similar as other parameters (0.45 for leptin vs. 0.65 for BMI

vs. 0.44 for serum albumin vs. 0.48 vs. 0.50 for transferrin and 0.44 for total cholesterol).
Conclusions. Our results showed that patients with low leptin had malnutrition. With increase of leptin level the nutritional status was improved.

PPD-11 Correlation between testosterone levels in male hemodialysis patients and cardiovascular risk parameters

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Introduction. Low serum testosterone levels in hemodialysis patients have recently been associated with cardiovascular risk factors and increased mortality. Testosterone deficiency is a common finding in hemodialysis patients, most probably as a result of altered sex-hormone metabolism. Low testosterone levels were associated with endothelial dysfunction and atherosclerosis. Low testosterone level is associated with poor nutritional status and increased inflammation in hemodialysis patients.
Methods. The aim of the study was to examine the correlation between the testosterone levels and structural and functional changes of the heart in hemodialysis patients. Cardiac structural and functional disorders were measured by echocardiography indexes.
Results. Sixty four hemodialysis patients were enrolled in this study (33 males and 31 females), mean age 56.47±11.79 years and had undergone dialysis for 72 to 6491 days. We got statistically significant low levels of total, bioavailable and free testosterone in large percentage male patients (87.7%). We found statistically significant negative correlation between tota, free and bioavailable testosterone levels and fractional shortening of left ventricle (FSLV). We also found statistically significant negative correlation between total and free and bioavailable testosterone levels and ainterventricular septal thickness (IVST) and also significant negative correlation between total and free and bioavailable testosterone levels and the thickness of posterior heart wall.
Conclusions. Correlations found in this study indicate the importance of testosterone levels and hypogonadism in male hemodialysis patients and represent a new field of research of treatment and prevention in these patients. Increasing testosterone levels may improve other pathophysiologic pathways that are related to the elevated mortality risk of hemodialysis patients.

PPD-12 Higher ultrafiltration rate may predict intraocular blood pressure in hemodialysis patients

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Introduction. Ocular problems have been reported to exist in patients with end-stage renal disease (ESRD). Changes in intraocular pressure (IOP) are an eye problem among hemodialysis patients, about which there is controversy in the literature. Most studies have shown an increase or no changes in IOP during hemodialysis, but some describe a decrease in IOP during session. This study aimed to evaluate the effects of a one session of hemodialysis on IOP and its relationship with ultrafiltration rate.
Methods. This cross-sectional study was carried out on 67 patients, 35% females, (134 eyes) who were under conventional intermittent hemodialysis for at least 3 months. Patients under glaucoma treatment, with corneal abnormalities, history of corneal surgery, allergy to topical anesthetic agents, or a current eye infection were excluded. Measurements were made at 2 time points, using a pneumotonometer with the patient in a seated position: approximately 15 minutes before starting hemodialysis (T1), and approximately 15 minutes after ending hemodialysis (T2). Blood pressures were also measured at these times. Echocardiographic studies were performed prior to and 30-60 min following the dialysis session. Mean inferior vena cava diameter (IVCD) was expressed as IVCD in inspiration+IVCD in expiration/2. IVCD was adjusted for body surface area (BSA).
Results. Mean age of the patients was 53.2±11.5 years. Laterality of the eyes (right or left) had no significant effect on the predialysis and post dialysis IOP values. Significant increase in intraocular pressure and decrease in plasma osmolarity, SBP, IVCD was found post dialysis.

PPD-13 The role of epicardial fat tissue at cardiovascular risk assessment in hemodialysis patients with nutritional disorder

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Introduction. Protein-energy malnutrition (PEM) is one of the most important risk factors in terms of morbidity and mortality in patients with end-stage renal disease (ESRD) receiving hemodialysis therapy (HD). In this population it is important to evaluate the nutritional status and body composition correctly. Our aim was to compare epicardial adipose tissue (EAT) thickness in HD patients with and without malnutrition. Our second objective was to determine whether the role of EAT in HD patients can be used to determine cardiovascular risk factor in HD patients with malnutrition.
Methods. Fifty-six patients who were receiving HD therapy for ESRD were included in the study. Mini Nutritional Assessment (MNA) was administered to determine the nutritional status of the patients. According to MNA

scores; patients were divided into two groups as PEM+ PEM risk group (group 1, n=25, score <24) and group well-nourished (group 2, n=31, score ≥24). In addition, Tanita SC 330, a body composition analyzer, was used to evaluate the body composition of patients. Blood biochemistry was evaluated retrospectively. Transthoracic echocardiography was performed to determine EAT.

Results. Of the 56 patients included in the study, 31 were male and 25 were female. EAT values were significantly different between the two groups (p=0.032). EAT value was higher in Group 2 than in Group 1. Phosphate (p=0.01) and calcium x phosphate product (p=0.02) values were significantly higher in Group 1. In addition, fat mass (p=0.011), visceral fat percentage (p<0.001), muscle mass (p<0.001), metabolic age (p=0.01), lean body mass (p<0.001) and basal metabolic rate (p<0.001) was significantly higher in Group 1. The highest positive correlation with EAT value was found with visceral fat ratio (r=0.600, p<0.001). There was also a moderate correlation with age (r=0.594, p< 0.001), metabolic age (r=0.501, p<0.001) and low correlation with CRP (r=0.402, p=0.002), fat mass (r=0.388, p=0.003), BMI (r=0.398, p=0.002).

Conclusions. Low EAT level in patients with malnutrition has led to questioning the role of EAT in assessing the risk of CVD in HD patients. Because malnutrition is a frequent problem in the HD population, it is important to know whether patients have malnutrition in order to be able to evaluate EAT as a cardiovascular risk factor in this patients group. As a result, we think that EAT can be used as a risk factor for KVC in patients without malnutrition.

PPD-14 Recurrent thrombosis of AV fistulas in patients with Alport syndrome

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Introduction. The maintenance of adequate vascular access is crucial to patient survival on hemodialysis. Complications related to vascular access account for 20 to 25% of all hospitalizations in dialysis patients. Thrombosis is the leading cause of arteriovenous fistula and graft failure. Thrombophilias are inherited or acquired predispositions to thrombosis and have been suggested as a possible cause of dialysis access thrombosis. Studies to date have been conflicting, with some suggesting a significant association whereas others have not. There are few cases of Alport syndrome as underlying chronic kidney disease (CKD) with diagnosed genetic thrombophilia described in literature.

Case study. Male patient, 25 years old, presented with hematuria and non-nephrotic range proteinuria in childhood, age of two years. At the age of eleven years old he presented with elevated levels of serum creatinine and urea for the first time. Kidney biopsy was performed and Alport syndrome diagnosed. Patient developed severe bilateral hypoacusis also in early childhood. Six years ago the progression of CKD was noticed. He developed end stage chronic renal failure at the age of 24, and was started with RRT, hemodialysis. Patient had multiple recurrent thrombosis of all AV fistulas created in the following period of three years, and with recurrent thrombosis of central venous catheters used as vascular accesses while AV fistulas were maturing. He was treated with anticoagulation therapy all the time, beside the dialysis anticoagulation. By the time he developed thrombosis of all vascular accesses, treatment with CAPD was started in the age of 25. The hematological evaluation was performed and the antiphospholipid syndrome was proven. Genetic analyses on inherited thrombophilias showed that the presence of homozygosity in C667T polymorphism and heterozygosity in A1298C polymorphism in MTHFR gene. Mutation in PAI-1 4G/5G gene in homozygous status was also proven. Polymorphisms for factor V Leiden, in factor II prothrombin mutation and mutation in factor II genes were not detected. He had thrombosis of last AV fistula, although treated with acenocoumarol as anticoagulant therapy with low molecular weight heparin (LMWH) during hemodialysis. He was switched to peritoneal dialysis because of accesses failure.

Conclusions. The presence of thrombophilia is associated with hemodialysis access thrombosis. In patients with Alport syndrome inherited thrombophilias disorders should be diagnosed in every case of first vascular access thrombosis and earlier than in other groups of CKD patients in order to prevent the thrombosis of next hemodialysis vascular accesses with proper anticoagulant therapy.

PPD-15 GF-1 and cognitive functioning in CKD patients

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Introduction. Prevalence of cognitive function decline in end stage renal disease (ESRD) patients undergoing hemodialysis is higher than in general population. We analyzed risk factors for cognitive function decline in those patients.

Methods. This study included 93 ESRD patients undergoing hemodialysis two or three times a week in Center for hemodialysis, Clinical center of Montenegro and two regional centers for hemodialysis in Montenegro. The cognitive status of patients was assessed using the Mini Mental Score Examination (MMSE) test. Laboratory data about risk factors for cognitive function decline was obtained in Center for clinical-laboratory diagnostic in Clinical center of Montenegro.

Results. All 93 patients have been divided into three groups according the results of MMSE. Patients in first group had severe cognitive impairment and MMSE score below 17(26.88%), patients in second group with MMSE score 18-23 had moderate cognitive impairment (40.86%) and third group of patients have MMSE>24 and no cog-

nitive impairment (32.26% of patients enrolled in study). There were no significant differences between groups for gender, smoking habits and level of parathyroid hormone. Level of education was significantly different between groups of patients ($p<0.001$). Laboratory markers observed in this study with significant differences between groups were: IGF 1, IGFBP 3, erythrocytes and hemoglobin ($p< 0.001$, $p=0.004$, $p<0.001$, $p=0.002$ respectively).
IGF 1 proved to be of great importance for evaluating cognitive status in our study. This marker was statistically different between groups ($p<0.001$) and Tukey post hoc analysis showed significant differences between all three groups (first and second group $p=0.045$, second and third group $p=0.015$, first and third group $p<0.001$).
Conclusions. Our data suggest that IGF 1 can be considered as novel biomarker for assessment of cognitive functioning in CKD patients what can be of huge clinical importance. This can be important and the particular new significance of this survey in relation to other studies.

PPD-16 Ultrasound characteristics of blood vessels and success in vascular access creation

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Introduction. Preoperative ultrasound mapping of blood vessels before the surgical creation of a vascular access (VA) for hemodialysis is a useful diagnostic procedure that provides not only diameter of the arterial and venous blood vessels but also dynamic parameters. Such examination provides the higher percentage of successful AVF and AVG creation. The aim of the study was to show the effect of ultrasonic color Doppler parameters on success in creating VA.
Methods. The study included 239 patients (154 males, 85 females) with an ultrasound assessment indicating feasible creation of the first or "after first" VA (all approaches after the first created). Out of all, first VA was created in 176 (73.6%) and "after first" VA was created in 63 (26.4%) patients. Success in creating VA was correlated with ultrasound parameters and applied therapy. The criterion for a successful VA was adequate hemodialysis over a given VA after the maturation period. Results: With each increase in venous blood vessel by 1mm, probability of successful creation of VA increased by 2.98 times (OR: 2.98, 95% CI: 1.42-6.24). There was no statistically significant influence of vein morphology, arterial morphology, vein compressibility and depth on the success of the creation of the first and "after first" VA. The absence of accessory veins carries a significantly greater success of creating "after first" VA ($p = 0.04$).
Conclusions. A greater success in VA creation was observed with use of antiaggregant therapy and if vein diameter increased. Satisfactory ultrasound characteristics of blood vessels are not always a prerequisite for successful creation of VA and other factors of influence should be considered.

PPD-17 Insulin like growth factor 1 (IGF1) as a potential biomarker for assessment of cardiovascular status in end-stage renal disease (ESRD) patients undergoing hemodialysis

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Introduction. Cardiovascular diseases (CVD) are the leading cause of mortality in hemodialysis patients. There are many factors that increase cardiovascular morbidity and mortality in those patients. Chronic kidney disease (CKD) leads to malnutrition, of which the main consequence is a catabolic state. Catabolism induces malnutrition/inflammation syndrome as a key factor leading to CVD.
Methods. The survey was conducted from March 2017 to January 2018, covering 104 ESRD patients on the Chronic Hemodialysis Programme. All relevant ultrasound examinations were performed in Clinical Center of Montenegro.
Results. In the analyzed group of 102 patients we found that the serum levels of IGF1 had a negative correlation with cardiac indexes, including left ventricular mass index (LVMI), the thickness of the septum (SW) and the last wall (LW) and the ejection fraction of the left ventricle (EF), all of which were analyzed in our research. Statistically significant correlations between serum levels of IGF1 and the fractional shortening of the left ventricle (FSLV) and the time since the start of hemodialysis were not verified.
Conclusions. This study has shown a statistically significant correlation between serum levels of insulin like growth factor 1 and the following cardiac indexes: the ejection fraction of the left ventricle (EF), left ventricular mass index (LVMI) and the thickness of septum and the last wall.

PPD-18 Oxidative stress parameters and cardiovascular risk in hemodialysis patients

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Introduction. Beside traditional cardiovascular disorders (CVD) risk factors, microinflammation and oxidative stress have very important role in CVD pathogenesis. The role of inflammation in the propagation of atherosclerosis and susceptibility to cardiovascular (CV) events

in ESRD is well established. Together oxidative stress and inflammation contribute to development and progression of CKD and the associated complications including atherosclerosis, CVD, EPO resistant anemia, immune deficiency, cachexia and others. Among many inflammatory biomarkers that have been studied, high-sensitivity C-reactive protein (hsCRP) has received the most attention in screening and as a predictor of risk and clinical response in this population.

Methods. The aim of the study was to examine the correlation between the different parameters of oxidative stress and microinflammation and correlation between these parameters and structural and functional changes of the heart in hemodialysis patients.

Results. Sixty four hemodialysis patients were enrolled in this study (33 males and 31 females, mean age 56.47 ±11.79 years and had undergone dialysis for 72 to 6491 days. The presence of systemic inflammation was found in 594% patients. Compared with the measurements in the normal hs-CRP group, the interventricular septal thickness (IVST) measurements in the increased hs-CRP group were increased, whereas the left ventricular ejection fraction (LVEF) significantly reduced in this group. We found statistically significant correlation between elevated levels of hs-CRP and interventricular septal thickness (IVST). We also found statistically significant correlation between high levels of hs-CRP and reduced LVEF. There was statistically significant positive correlation between hs-CRP and left atrial pressure of the heart. There was statistically significant positive correlation between levels of creatinine before and after hemodialysis with levels of homocysteine. There was statistically significant positive correlation between levels of serum albumins and level of homocysteine. There is statistically significant correlation between myeloperoxidase (MPO) activity and right ventricle pressure. We found statistically significant correlation between interleukin 6 (IL-6) and fractional shortening of left ventricle, reduced LVEF and left atrial pressure. We also found statistically significant correlation between testosterone level and fractional shortening of left ventricle.

Conclusions. Thickening of the cardiac wall was observed in addition to the manifestation of reduction in heart functioning of patients with elevated proinflammatory parameters. The changes in cardiac structure and function may be caused by the microinflammatory state in hemodialysis patients and changes in hs-CRP levels may be an important cause of the changes. Correlations found in this study indicate the importance microinflammation and condition of chronic oxidative stress in hemodialysis patients and represent a new field of research of treatment and prevention in these patients.

PPD-19 B cell immunity in chronic renal failure, alterations following initiation of renal replacement treatment

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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 pre- and six months post-dialysis ESRD patients.

Methods. B cells (CD45+ CD19+) and their subsets B1a (CD19+CD5+), naive (CD19+ CD27-), memory (CD19+ CD27+), CD19+ BAFF+ and CD19+ IgM+, were quantified using flow cytometry in the peripheral blood of 27pre-dialysis and 11 post-dialysis patients. The results were compared to healthy control group.

Results. ESRD patients had reduced lymphocyte count (1606±655μ/L vs.2459±520μ/L, $p<0.001$) and B cell (CD19+) count (82.7±54.9μ/L vs.177.6±73.8μ/L, $p<0.001$) compared to controls. Likewise, whereas the percentages of B cell subsets were not particularly affected, except for B1a subset which presented a significant increase (4.1± 3.8% vs. 0.7±0.7% $p<0.001$), 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: 55.6±46.6μ/L vs. 97.2±46.6μ/L, $p=0.004$, Memory: 27.1± 15.6μ/L vs. 83.5±56.8μ/L, $p<0.001$, CD19+BAFF+: 69.5± 47.5μ/L vs. 154.7±74.6μ/L, $p<0.001$, CD19+IgM+: 58.1± 42.7μ/L vs.117.9±58.94μ/L, $p=0.001$). In 11 patients who had a follow-up 6 months after starting on renal replacement treatment no differences were found, apart from CD19+IgM+ (74.7±7.4μ/L vs. post 66.9±14.7μ/L, $p=0.041$) and B1a percentage (3.0±2.4% vs. 1.0±0.8% $p=0.038$), which further decreased.

Conclusions. Significant reduction was noticed in B cells subpopulations in patients with ESRD on pre-dialysis stage, and in some of them further reduction was noticed in post-dialysis stage, and these changes may be implicated in clinical manifestations, such as frequent infections or impaired response to vaccination.

PPD-20 Consequences of chronic kidney disease and hemodialysis modalities in T lymphocyte immunity

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Introduction. End stage renal disease (ESRD) is associated with alterations in immune response. The aim of this study was to assess changes in the T cell repertoire within ESRD patients on pre-and six-monthspost-dialysis state.

Methods. T cells subpopulations, namely CD3+CD4+, CD3+CD8+, Natural Killer cells (CD4+CD16+56+), Tregs (CD4+CD25+FoxP3+), CD8+CD28+, CD8+CD28- and CD4+CD28- cells, were isolated from whole blood samples using flow cytometry in 27 pre-dialysis and 12 post-dialysis patients. The results were compared to 13 healthy controls.

Results. ESRD pre-dialysis patients had reduced number of total lymphocytes (1456±624μ/L vs. 2197±478μ/L, $p< 0.0001$), CD4+ cells (697.9±365μ/L vs. 1135.9±360μ/L, $p<0.0001$), NK cells (238.3±141.2μ/L vs. 277.3±83.8μ/L) and Tregs (48.3±27.9μ/L vs. 69.5±24.6μ/L, $p=0.02$) compared to healthy controls. CD4+CD28- were increased among patients on ESRD (66.5±107 vs. 51.9±47μ/L), as were CD8+CD28- (237±207 vs. 202±136).

Fourteen patients had a follow up sample after 6 months in renal replacement treatment, 8 in hemodialysis (HD) and 6 in continuous ambulatory peritoneal dialysis (CAPD). No difference was evident between patients at time of initiating renal replacement treatment. After being for 6 months on HD, patients had significantly increased lymphocyte count ($p=0.009$), NKs, CD4+CD28- and CD8+CD28- ($p=0.05$, $p=0.04$, $p=0.01$ respectively), and reduced Tregs ($p=0.02$). In contrast, patients who were commenced on CAPD had no such differences and T cell subtypes remained stable.

Conclusions. Significant alterations within ESRD patients were noticed, with reduction in CD4+, and Tregs, and increased expression of CD4+CD28- and CD8+CD28-cells. After being on hemodialysis for 6 months further reduction in Tregs and increase of CD4+CD28- and CD8+CD28- cells were noticed, while T cell subpopulations were stable in CAPD, and even tended to return to normal.

Poster presentations- clinical nephrology

PPCN-01 Severe hypothyroidism and renal failure

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Introduction. Hypothyroidism and hyperthyroidism affect renal function by direct renal effects as well as systemic, hemodynamic, metabolic and cardiovascular effects. Most of renal manifestations of thyroid manifestations are reversible with treatment.

Case report. A 66-years-old male was admitted to our hospital with a history of generalized fatigue. He referred weight gain, cold intolerance, dry skin and constipation. There was sudden onset of peri-orbital, facial and generalized leg swelling associated with muscle ache and pains. He had no past medical history, but failed to do regular checkup. On clinical examination he was overweight with peri-orbital edema, facial swelling and dry skin. Laboratory results revealed very high TSH value: TSH 145 mUI/l (NR 0.35-4.75); FT4 0.3 ng/ml (NR 0.89-1.75); Ac anti TPO 15029 U/L (NR<70), urea 100 mg/dl; creatinine 1.7 mg/dl; GFR 51 mL/min. Full blood count was normal and urine analysis showed no evidence of blood or protein. Creatinine kinase was elevated at 235 U/l (0-170) with a normal electrocardiogram and heart ultrasonography. Renal ultrasonography showed normal kidneys and no other abnormalities. A diagnosis of autoimmune thyroiditis was made and the thyroxine replacement was started. After two months the renal and thyroid function were in the normal range.

Conclusions. The cause of the renal failure in hypothyroidism is due to decreased renal plasma flow owing to the hypodynamic state in hypothyroidism. Since there is an important link between thyroid function and renal function we suggest to evaluate the thyroid function in all patients with impaired renal function.

PPCN-02 A case of C3 glomerulonephritis triggered by a respiratory infection

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Introduction. C3 glomerulonephritis (C3GN) is a rare glomerular disease. Uncontrolled activation of the alternative pathway of complement's cascade leads to glomerular deposition mainly of C3 protein with little or no immunoglobulins.

Case report. We present a case of C3GN followed an infection of the respiratory tract. A71 year-old male patient was admitted in our hospital due to an infection of the lower respiratory system. During his hospitalization he presented acute renal failure (urea 143 mg/dl, creatinine 2.9 mg/dl) with full-blown nephrotic syndrome (6.3g/24 hours), microscopic hematuria and arterial hypertension. Immunologic testing revealed the presence of autoantibodies (ANA 1/640, Ra-test 24.8 IU/ ml) and low levels of complement's protein C3 (2 mg/dl, normal 82-175 mg/dl). The kidney biopsy showed interstitial inflammation, mild mesangial expansion and massive granular deposits of C3 in the glomerular basement membranes without deposition of immunoglobulins. Specific treatment with cyclosporine and methylprednisolone was initiated. Two months later the patient had normal renal function, proteinuria 222 mg/24 hours while C3 levels were 62 mg/dl.

Conclusions. C3 GN should be taken in consideration for differential diagnosis in patients with post-infectious acute renal injury. Cyclosporine-based regimen may lead to early remission.

PPCN-03 Hypercalcemic acute renal failure as primary manifestation of non-secretory myltiple myeloma

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Introduction. Non secretory multiple myeloma (NSMM) is a rare variant of multiple myeloma (MM), characterized by lack of monoclonal immunoglobulin or monoclonal heavy or light chains in the serum and urine. Despite the high incidence of osteolytic lesions, hypercalcemia is not common, due to preservation of renal function and renal tubular calcium homeostasis. Combination of hypercalcemia and acute renal impairment in NSMM is quite unusual.

Case report. We present a case hypercalcemic acute renal failure and lytic bone lesions as primary manifestations of NSMM. A 66-year-old female patient was admitted to our hospital due to intense sciatic nerve pain. Radiography and spinal CT scanning revealed osteolytic and mixed osteoporotic and osteosclerotic lesions of the vertebrae and loins. Laboratory investigations showed normochromic normocytic anemia (Hct 33.3%, Hgb 11.4g/dL, MCV 90.7fL, MCH 31.1pg), acute renal failure (urea 89 mg/dL, creatinine 2.23 mg/dL) and hypercalcemia (calcium 14.9mg/dL). Serum and urine protein electrophoresis were normal. Bone marrow biopsy revealed infiltration of monoclonal plasma cells (70%), CD138, MUM1, EMA and CyclinD1 positive, compatible with low-intermediate grade of Bartl-Frisch classification of plasma cell myeloma. The patient received a two-round treatment with bortezomib sc., dexamethasone iv. and cyclophosphamide iv. She was discharged at the 48th day of hospitalization presenting normal serum calcium levels and normal renal function.

Conclusion. Non secretory multiple myeloma should be considered for the differential diagnosis in patients with osteolytic lesions, hypercalcemia and acute renal failure. Treatment should include bortezomib and cyclophosphamide.

PPCN-04 Fibromuscular dysplasia (FMD)-Case report

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Introduction. Fibromuscular dysplasia (FMD) is a segmental, non-inflammatory, non-atherosclerotic disorder of the musculature of arterial walls, leading to stenosis of small and medium-sized arteries.

Etiology is unknown and according to the recent reports estimated incidence in the general population is 2% to 3%. Renal arteries are mostly affected (bilateral disease involvement in 39% to 64%) but FMD changes of cerebral and/or carotid arteries were found in 15% of cases. FMD lesions have been also reported in limb, digestive and coronary arteries.

Case report. Female patient, born in 1979 smoker (20 cig/day), normal BMI.

In 2006, at age of 27 years hypertension (150/100 mmHg) was verified during the second pregnancy (no edema, no proteinuria). In 2011 she was admitted to our department after hypertensive emergency (BP 220/140 mmHg). Bilateral renal artery stenosis was diagnosed. Digital subtraction angiography (DSA) revealed left renal artery (RA): the ring of FMD with non-significant (20% lumen) stenosis; the right RA: in the distal third of RA hemodynamically significant stenosis- the type of medial fibroplasia. The patient was treated with percutaneous transluminal renal angioplasty (PTRA) of the left RA. After intervention her BP was controlled with trandolapril 0.5 mg, amlodipine 10 mg and nebivolol 2.5 mg and kidney function was normal. In 2012 she was admitted to the hospital again after hypertensive emergency and neurological symptoms (headache, disorientation)-subarachnoid hemorrhage + aneurism of the right ACI, aphasia of the right PCA were verified on CT. Embolization of the right ACI was performed. At renal Doppler ultrasound no changes were found at RA. Later on in 2013 she was treated three more times with "coiling" due to recurrent aneurysms in the basin of right ACI and its branches, BP was normal. In 2016 BP became uncontrolled (24h ABPM 157/94 mmHg) without neurological symptoms. DSA verified the restenosis of the right RA ("string of pearls") plus recurrence of aneurysm at right ACI. She was treated with balloon dilatation (RA) and stent-embolization (ACI) after which the BP was controlled (nebivolol 2.5 mg, amlodipine 5 mg) with normal kidney function. In 2018 BP and kidney function were normal, renal Doppler showed no signs of stenosis and neither new changes no new aneurisms on brain MRI.

PPCN-05 Clinical implications of monoclonal gammopathy in patients with diabetes mellitus

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Introduction. MGUS is asymptomatic pre-malignant disorder and is characterized by clonal proliferation of plasma cells. The etiology of this disease is unknown. It is often a result of idiopathic rearrangements of immunoglobulin genes, which causes the production of the M paraprotein followed by production of monoclonal light chains (FLC). MGUS can cause kidney damage. In the nephrons, FLC pass through glomerular epithelial fenestration when their quantity overwhelms the capacity of the renal reabsorption, causing nephrotoxicity and renal function impairment. Production of monoclonal FLC and disturbed ratio κ/λ are predictors of progression of MGUS in the subsequent phases, such as multiple myeloma.

Case report. Patient male, age 64, a longtime diabetic on insulin therapy, hypertonic for many years, surgical and radiotherapy treated for cancer of the vocal cords 20 years ago, with no signs of recurrence, with established chronic renal insufficiency, with creatinine clearance of 0.64 ml/s, presented with nephrotic syndrome after an episode of bronchopneumonia. In laboratory findings persisted accelerated SE 120, anemia, with proteinuria of 12 gr/24h, elevated beta 2 microglobulin 13800 (up to 2400 ref. value), increased serum concentrations of IgM, kappa and lambda serum increased, normal ratio. On ultrasound liver was regular size, spleen voluminous. Bone marrow biopsy was performed by hematologists and findings on histopathologic analysis and IHH (immunohistochemistry analysis). Obtained findings showed regular cellularity, represented all three myeloid lineage, regular cell maturation and proper ratio. Immunohistochemical findngs showed polyclonal plasma cells (part of kappa + lamda). The conclusion was that the morphological findings with immunohistochemical staining corresponds to nonspecific reactive changes. In a sample of bone marrow there was no element of lymphoproliferative disorder. The values of nitrogen compounds in serum ranged from a maximum of 340 µmol/l. Urine kappa and lambda chains had regular concentration and ratio. The findings of serum protein electrophoresis described the presence of paraprotein in the gamma region. Quantitative analysis of urinary proteins demonstrated a non-selective glomerular proteinuria and renal hematuria. The immunology findings showed very high rheumatoid factor, with low consumption values of C4 complement component; form that is usually seen in immunoproliferative malignant hematological diseases. Indirect laryngoscopy excluded recurrence of cancer of ORL region. We excluded the existence of solid organs malignancy (tumor markers normal, CT examination without pathological changes suspected tumor changes). Not verified bone lesions in the skeletal system. Testing on sarcoidosis and neuroendocrine tumors was also negative. Congo red staining of bone marrow for amyloidosis was negative. The patient underwent kidney biopsy. The findings of biopsies showed glomeruli with expanded mesangium with heavy matrix and the proliferation of mesangial cells, with duplication of GBM, with subepithelial deposits. The majority of glomeruli obtained global, cellular or fibrocellular crescents; 40% interstitial fibrosis accompanied by showing atrophy of tubules. Focal mononuclear cell infiltrates were present in the binder, arterioles with concentric hialynosis of intima. The findings of immunofluorescence along the GBM obtained focal and segmental abundant, granular deposits of IgM and kappa light chains, granular deposits of IgG, fibrin, C3 and lambda light chains, IgA and C1q were negative. Findings indicated a proliferative glomerulonephritis with monoclonal IgG deposits. The patient did not met current CRAB criteria for the diagnosis of multiple myeloma and was under constant supervision of hematologists and nephrologists. In the follow up period of 6 months he developed multiple myeloma.

Conclusion. Patients with diabetes and chronic kidney disease are more prone to the development of immunoproliferative hematological malignancies. In such patients, precancerous conditions such as MGUS have faster progression to overt malignancies such as multiple myeloma. Therefore, should be closely monitored and diagnostic processed for a potential hematological disorders. The emergence of proteinuria, especially in nephrotic range, in patients with diabetic nephropathy may not be due only to diabetic glomerulosclerosis, but it can be a manifestation of concurrent malignant and systemic diseases.

PPCN-06 Referral to nephrologist, initiation of hemodialysis and care of advanced CKD patients in western Romania

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Introduction. Referral of CKD patients to nephrologists and initiation of chronic dialysis therapy are frequently debated issues. Both are dependent of the initiation guidelines and many regional specific factors. The aim of this study was to investigate referral and dialysis initiation in advanced CKD patients in a HD center in western Romania.

Methods. We evaluated patients who initiated HD therapy between 2014-June 2017, in a hospital HD center from Western Romania (N=228, 41.6% female, mean age 59.6 ±13.7 years). The patients' data have been retrieved from their hospital and GP files. Early referral to nephrologist (ER) was considered >12 months and late referral (LR) 7ml/min/1.73m^2 and late initiation (LI) GFR 4.5mg/dl) was present in 82.4% of the cases. Patients' survival was negatively influenced (Cox regression analysis) by age >65 years (P<0.001), lack of pre-dialysis monitoring by a nephrologist [P = 0.01, hazards ratio (HR) = 0.8], severe anaemia, lack of erythropoetin treatment (P< 0.001, HR = 0.6), and co-morbidity, e.g. cardiovascular diseases (P<0.001, HR = 1.8) and diabetes mellitus (P<0.001, HR = 2.2).

Conclusion. Early referal to the nephrologist was associated with a longer predyalisis period. Further evolution implies strategies of prevention, based on national surveys, supported by the Romanian Renal Registry.

PPCN-07 Renal function in early postoperative period after open surgery repair of abdominal aortic aneurysm

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Introduction. Acute kidney injury is a common complication after surgical treatment of abdominal aortic aneurysm. Open surgery is most common surgical technique for treatment of abdominal aortic aneurysm. The aim of the study is to present changing of kidney function in early postoperative period after open surgical treatment of abdominal aortic aneurysm.

Methods. This prospective study included 146 patients who needed elective treatment of abdominal aortic aneurysm. Clinical and laboratory parameters were obtained during the early postoperative period.

Results. Average age of patients admitted in this study was 67±7.1 years with dominant male gender (89.7%). Prevalence of patients with preexisting chronic kidney disease was 21.2% and ventricular ejection fraction was 52.6±10.4%. Autotransfusion with cell saver substitute 580ml of blood after average bleeding of 1300ml per intervention. It was 1142±525.9 ml of colloids and 2393 ±750.3ml of crystalloids infused during the surgical procedure. eGFR increased during first four days after intervention (77±34.3ml/min, 79±37 ml/min, 80±37.5 ml/min, 83±42.8 ml/min, 85±45.6 ml/min, respectively p=0.023).

Conclusions. Renal function enhanced after open surgery repair of abdominal aortic aneurysm. Appropriate volume replacement is necessary for prevention of acute kidney injury.

PPCN-08 Comparison of GFR values measured by the camera method and by the MDRD formula and the relative functions of each kidney measured in DTPA scintigraphy in patients with or suspected obstructive uropathy

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Introduction. In our study, we compared the GFR values measured by the gamma camera method and the e-GFR method calculated by the MDRD formula in patients who underwent DTPA dynamic renal scintigraphy for suspected obstructive uropathy. Also, we evaluated the role of DTPA scintigraphy in the follow-up of these patients by comparing the relative functions of each kidney by means of GFR values measured in DTPA scintigraphy.

Methods. A total of consecutive 59 patients were included in this retrospective study. Patients' serum creatinine, age, gender, and race information were used in the MDRD formula to calculate the e-GFR value. According to the e-GFR results, patients were divided into 3 groups: above 90 ml/min (Group 1), 60-90 ml/min (Group 2), and below 60 ml/min (Group 3). The groups were compared in terms of GFR measuring methods, % reduction in relative renal function, and pathologic findings detected in radiological imaging methods.

Results. There were 33 patients in Group 1, 18 patients in Group 2 and 8 patients in Group 3. There was no significant correlation in group 1 (p=0.437, r=-0.140) when comparing both GFR measuring methods (e-GFR and camera method). On the other hand, we found high correlation both in Group 2 (r=0.006, p=0.006) and Group 3 (p=0.043, r=0.723). When the groups were evaluated in terms of decline in relative function (below 10, 10-20, 21-30, and above 30), the number of patients with a decrease in relative renal function greater than 30% was 16(48.5%) in group 1, 6(33%) in group 2 and 5(62.5%) in group 3. When the reduction in relative function of 15 patients with normal radiological examination (CT and USG) was evaluated, there was a decrease of 10% in 7 patients, a decrease of 10-20% in 2 patients, and a decrease of 30% in 6 patients.

Conclusions. Our study showed that patients with normal e-GFR may also have a relative decrease in renal function in DTPA renal scintigraphy in addition to patients with decreased e-GFR. This suggests that decrease in e-GFR is later than the development of a renal dysfunction due to compensatory mechanisms. Demonstration of markedly decreased relative renal function in the radiologically normal kidneys shows that DTPA dynamic renal scintigraphy is an important follow-up method for patients with suspected or proven obstructive uropathy.

PPCN-09 Membranoprolopherative glomerulonephritis secondary to hepatitis C infection

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Introduction. HCV infection should be regarded as a systemic disease, involving various systems. Membranoprolipherative glomerulonephritis (MPGN) is the main histopathologic type of renal involvement. Direct antiviral antibiotics (DAA) have achieved elimination of infection but their effect to secondary complications is not clarified yet. Aim of the study is to present clinical and histological findings of glomerulonephritis secondary to HCV infection, and to assess efficacy of DAA treatment in renal implications.

Methods. Forty eight patients were diagnosed with MPGN during 2000-2016, from whom 6 (M/F 2/4, age 37-68yrs) had hepatitis C.

Results. All patients presented with nephritic syndrome, Screat>2mg/dl, Uprot 4-18g/24hr, and 4/6 required hemodialysis at diagnosis. All patients had reduced C3 and C4 levels and 3/6 had positive cryoglobulins, presented with alveolar hemorrhage (1/3) acute renal injury (3/3) and hemorrhagic rush (3/3). Two patients had mucosa-associated lymphoid tissue (MALT) lymphoma at presentation. Renal biopsy showed endo- (6/6) and extra-capillary

(4/6) proliferation, double contour (6/6), FSGS (4/6), mild tubular atrophy and severe interstitial infiltration. Three patients were diagnosed before 2010, treated with interferon, and had no response. Three were diagnosed after 2010, started on DAA and had a complete recovery of renal function. Simultaneous treatment with plasmapheresis and steroids were applied for cryoglobulinemia. Despite recovery of renal function repeated biopsy showed elimination of inflammation but advanced chronic lesions.
Conclusions. Apart from curing hepatitis C, DAA treatment has beneficial effect on extrahepatic manifestations, although chronic lesions remain in glomeruli.

PPCN-10 Unexpected fatal outcome of treatment membranous lupus nephritis-a case report

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Introduction. The aim is to show the fatal outcomes in patients with type V lupus nephritis (LN) due to the presence of parasitosis of the digestive tract.
Case report. S.Z., 65 old years female patient, in the last 5 years treated for sicca syndrome with a positive ANA, anti SSA and anti SSB Antibody. She was admittied in nephrology unit with acute renal failure due to Clostridium difficile colitis, previously thoroughly gastro-intestinal tested including endoscopy. Immunological findings (C3 lowered -0.76; easily elevated ANA SSA- 33.7 and 47.3 ANA-SSB) conditioned for renal biopsy to be performed. The findings were as follows: the prime lupus nephritis type V Activity Index 10 and Chronicity 3. Standard treatment for LN was initiated (3 pulse doses of methylprednisolone, followed by corticosteroids per os in dose 0,5-1 mg/kg body weight +6 pulses cyclophosphamide in dose 0,5-0,75mg/BSA). After 3 months partial remission was detected (complete recovery of renal function with GFR: 106.64 ml/min, reduction of proteinuria from 11.7 to4.0 g/24 h, the normalization of the urine sediment, C3-0.45, C4 0.01, cryoglobulins and other immunoglobullins were normal). However, the numerous side effects of therapies were registered: steroid diabetes, reactivation of Clostridium difficile colitis, depression and moniliasis of the digestive tract with a strong digestive discomfort and deterioration of patients with purpura. Gradually stopping the immunosuppressive therapy and control gastroscopy was performed with findings that pointed to the existence of Strongyloides stercoralis gastritis with the presence of adult worms in the lumen of dilated glands. The patient urgently was hospitalized at the Clinic for Infectious and Tropical Diseases University Clinical Ceter of Serbia where she died after a few hours.
Conclusions. A rare and unusual case with fatal outcome is presented in patients with unrecognized parasitic disease of the digestive tract and lupus nephritis type V. Despite the necessity and effectiveness of the treatment of glomerulopathy, immunosuppressive therapy has resulted with severe adverse effects including the activation of parasitic disease of the digestive tract. Therefore, before starting immunosuppressive therapy check the possible presence of comorbidities that may further compromise the primary disease.

PPCN-11 Treatment of isolated renal amyloidosis

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Introduction. Amyloidosis is a rare heterogeneous group of diseases characterized by extracellular deposits of amyloid, causing organ dysfunction. It has a wide range of clinical manifestations, depending on which organs are affected, including the nephrotic syndrome, hepatosplenomegaly, congestive heart failure, carpal tunnel syndrome. Abbreviations which are used for different types of systemic amyloidosis are: AL (primary-the deposits immunoglobulin light chain), AA (reactive-secondary), and Aβ2M (β2 consequence of microglobulinemia associated with dialysis). AL and AA represent about 95% of all cases of amyloidosis. The treatment of amyloidosis is complex, and the prognosis uncertain.
Case report. Patient male, age 55 years with no previous history of the disease, presented with nephrotic syndrome, and creatinine level of up to 130 μmol/l. Clinical evaluation of the patient excluded secondary causes of nephrotic syndrome; ruled out systemic connective tissue diseases, malignancy, infection, TB. Sarcoidosis was also excluded. Patient underwent bone biopsy with immunophenotyping in which all three hematopoietic cell lineage were obtained with regular maturation, without elements of myeloma/ multiple myeloma or lymphoproliferative disorder; Congo red staining for amyloidosis was negative. The patient subsequently underwent percutaneous renal biopsy. Histochemical areas of mesangium were PAS negative, with positive Congo red staining, with typical birefringence in polarized light. Findings fit in renal amyloidosis with predominant renal glomeruli abstraction and occasionally blood vessels. Patient underwent adipose tissue biopsy and biopsy of rectal mucosa with Congo red, which were negative with no evidence of amyloidosis. In order to exclude secondary amyloidosis patient underwent PET scan of the whole body, without verified malignant lesions. It was concluded that it was a kidney amyloidosis with no signs of the affection to other organs. Patient underwent treatment of chemotherapy with high dosage-CyBorD protocol (cyclophosphamide, bortezomib, and dexametha-

sone) through 8 cycles, high-dose chemotherapy with melphalan, and transplantation of autologous stem cells.
Conclusions. In patient the treatment was performed with 8 cycles of therapy CyBorD protocol with prophylactic therapy with no significant clinical complications. The findings in evaluation after four cycles of therapy obtained values of nitrogen compounds in serum urea 5 mmol /l, serum creatinine 104 µmol/l, with the rank of proteinuria 1.6 gr/24h and creatinine clearance of 1.15 ml/s. The patient was also treated with autologous stem cell transplantation successfully, with stabile renal function and decreased level of proteinuria.

PPCN-12 Therapeutic plasma exchange in treatment of devic disease
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Introduction. Neuromyelitis optica (NMO) is a rare inflammatory and demyelinating autoimmune disorder of the central nervous system characterized by recurrent attacks of optic neuritis and longitudinally extensive transverse myelitis (LETM). Recent studies have shown that NMO has more frequently a relapsing course. Particular pathological features of NMO as prominent IgG and immune complex deposition and complement activation provide the rationale for the early initiation of plasma exchange in acute exacerbations of NMO.
Case report. Female patient, 52 years old, was diagnosed NMO at neurology department a year ago. After many attacks of bilateral optic neuritis and without clinical criteria for MS-multiple sclerosis, she was tested for anti-aquaporin 4 water channel IgG antibodies (anti AQP4 antibodies) and was seropositive. Patients had a relapsing NMO form with repetitive attacks of unilateral and bilateral optic neuritis and myelitis with minor brainstem signs as nystagmus, nausea, diplopia and dysphagia with no MRI detected brain lesions and confirmed lesions of spinal cord. Patient had four acute attacks in the previous year and all relapses were resistant to corticosteroid therapy and other immunosuppressive agents used in prophylactic treatment. All four attacks were treated with therapeutic plasma exchange (TPE) with 5 % albumin as replacement fluid and with 1.5 blood volume exchange. We used peripheral veins as vascular access and citrate anticoagulation. Every attack was treated with series of five plasma exchanges every other day. After first two TPE we got a mild clinical improvement, but after the last two TPE we got a significant clinical improvement in disappearing of symptoms and recovering neurological state. In last two TPE sessions the clinical improvements started to appear quickly, after two plasma exchanges. We had mild complication of TPE presenting with transient electrolyte imbalances and without coagulation disorders.
Conclusions. In case of unresponsiveness to steroids, early initiation of a rescue therapy with plasmapheresis is a method of choice of treatment of patients with NMO. Removal of antibodies, immune complexes and activated complement from circulation contribute to decrease the inflammatory response and may provide rapid functional recovery.

Poster presentations- transplantation

PPTX-01 Recurrence of focal segmental sclerosis after kidney transplantation from diseased and living donor
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Introduction. In focal segmental glomerular sclerosis (FSGS), the success of renal transplantation may be impaired by the frequent risk of recurrence of the disease on the allograft. In the first kidney allograft, 20 to 30% of patients develop recurrence of FSGS. Second grafts, in those who have had recurrence in their first graft, are generally accompanied by a further recurrence.
Case report. Male patient, 32 years old, was diagnosed nephrotic syndrome and CKD in 27th year. He is from family with ADPKD. In the same year he developed ESRD and started with hemodialysis treatment. In 29th year he was treated with kidney transplantation from deceased donor. He developed multiple complications afterwards: delayed graft function, proteinuria, vein graft stenosis and ureteral obstruction treated with ureteral stent and ureteroneocystostomy. He was treated with plasmapheresis without success. He underwent 4 graft biopsies with recurrent FSGS findings with elements of acute rejection and acute tubular necrosis. He was also treated with rituximab and intravenous immunoglobulins. Due to many infection episodes and complications in the next period he underwent graftectomy one year after. He was treated with kidney transplantation from living related donor in 2014 without complications in postoperative period. Four months after transplantation he presented with proteinuria of 30 grams per day. After biopsy of transplanted kidney recurrent FSGS was pathologically confirmed. Patient was treated with plasmapheresis, corticosteroids, intravenous immunoglobulins and rituximab. Proteinuria was reduced to 0.4 grams per day and graft function was preserved.
Conclusion. Recurrence of FSGS after transplantation is relatively frequent in patients who lost a previous transplant from recurrence. In the case of living donation, the possibility of recurrence and its consequences should be clearly exposed to and discussed with the donor and the recipient.

PPTX-02 Pregnancy in renal transplant recipients
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Introduction. Women of childbearing age with end-stage renal disease requiring renal replacement therapy have almost tenfold lower fertility rates compared to the general population. A live birth rate consistently ranges between 72% and 80% what is comparable to the general population. However, renal transplant recipients experience overall higher rates of cesarean sections, preterm (<37 weeks) deliveries with babies of small gestational age and low birth weight. Herein, we present data on pregnancies recorded in two transplant centers in neighboring countries.

Methods. All pregnancies which occurred in renal transplant recipients who are in follow-up at University hospital center Zagreb or Clinical center Montenegro were recorded. Complications and type of delivery, live birth rate, gestational age and weight of the newborns were evaluated.

Results. Twenty-four spontaneous pregnancies were recorded (in 21 patients), 16 from UHC Zagreb (12 successful, and 4 spontaneous abortions), and 8 from KCCG, one of them being twin pregnancy. Pregnancies occurred 2 to 12 years after the transplant. Two patients from Montenegro died twenty years ago, after the delivery (one from sepsis in local hospital two months later, and one during the pregnancy). Both patients received transplants in Bombay, India and were not regularly followed up. All patients underwent Cesarean section. Live birth rate was 79%. Newborn gestational age ranged from 32 to 39 weeks (mean 34 weeks), with weight 2400 to 3400 g (mean 2800 g). Immunosuppressive protocol included cyclosporine (16 patients) or tacrolimus (5 patients), azathioprine and steroids. One patient had ABO incompatible transplantation. Allograft function remained stable in all patients.

Conclusions. Pregnancies in renal transplant recipients are relatively rare and are considered "high risk" while both mother and offspring may develop complications related to immunosuppressive therapy, suboptimal allograft function as well as by their primary kidney diseases. Relatively high number of transplantations in Montenegrin patients may be explained by younger age of patients and cultural differences which force pregnancies.

PPTX-03 Relapse rates and outcomes of idiopathic membranous nephropathy post kidney transplantation

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Introduction. The aim is to study the frequency of relapse and long-term outcomes of idiopathic membranous nephropathy (IMN) after kidney transplantation (KTx) in patients who ended up in ESRD due to it.

Methods. We retrospectively reviewed the medical charts of all patients with IMN as primary disease, who were transplanted in our hospital from 1990-2016. All patients had biopsy proven IMN in their native kidneys. Demographics and characteristics related to the donors and the recipients at the time of KTx were recorded, including, dialysis time, immunosuppressive schemes, histocompatibility data, acute rejection episodes, patient and graft survival, and eGFR at the end of the follow up time. All relapses of IMN were recorded in conjunction with the treatment which was given and the related response. Patients with KTx incompatible for the ABO system were excluded as well as patients with major surgical complication during the 1st month or adherence problems. All patients with relapse were initially treated with an ACE inhibitor (fosinopril) and depending on the response or not were treated with the Ponticelli protocol, as 2nd line therapy, or more recently with rituximab.

Results. 18 patients, who ended in ESRD due to IMN, received a graft in our hospital from 1990-2016. The mean age at the time of KTx was 47±11.5 years and 13(72.2%) of them were males. The mean time in dialysis was 63.2(±51.5) months, the graft was from deceased donors in 13 cases (72.2%), with a mean donor age of 46(±15.5) years. During a follow up time of 84.97(±57.6) months, 7 patients (38.8%) experienced at least one episode of IMN relapse. Time to relapse was 45.6(±42.7) months from KTx and 24-hour proteinuria was 4.1(□2.9) grams. Two patients experienced acute rejection, one of them during the relapse of IMN. At the end of the follow up time, patients survival was 100%, graft survival was 88.9%, with a mean serum creatinine of 1.8(±0.23) mg/dl, eGFR of 60.84 (±27.3) ml/min/1.73m^2 and mean 24-hour proteinuria of 0.75(±0.58) grams.

Conclusions. Relapse of IMN in the graft is not rare, but in most occasions is responsive to therapy, either with inhibition of the renin angiotensin system, either with enhancement of immunosuppressive treatment, and generally it does not affect long term graft survival.

PPTX-04 Kidney transplantation in patients with inherited thrombophilia

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Introduction. Early allograft loss, due to acute thrombotic complications, remains a constant and proportionally increasing complication of renal transplantation. Most recently the evolution of thrombophilia research has established the potential for inherited hypercoagulability to predispose to acute allograft thrombosis. Inheritance of the factor V Leiden (FVL), prothrombin G20210A mutation, or the presence of antiphospholipid antibodies (APA) or other hypercoagulable states such as hyperhomocystinemia or the C677T polymorphism of the methylene-

tetrahydrofolate reductase gene (MTHFR) may increase the risk of renal allograft thrombosis.

Case reports. First patient, male, 34 years old, treated with kidney transplantation from deceased donor for the first time 5 years ago, with primary cause for ESRD was polycystic kidney disease and FSGS focal segmental glomerular sclerosis. In early post-transplant period he got graft vein thrombosis causing DGF delayed graft function and hemodialysis requirement after transplantation. Graft survival was one year and he was returned on chronic hemodialysis treatment. In preparation for second transplantation, he was tested for thrombophilia and prothrombin G20210A mutation was detected accompanied with C677T polymorphism. Second patient, male, 29 years old, treated with preemptive living related kidney transplantation in the age of 26, unknown etiology of ESRD. Patient developed graft artery thrombosis after kidney transplantation and deep venous thrombosis in the period of follow up, beside therapy with low weight molecular heparin in preparation for transplantation and after surgery. He also developed bilateral avascular necrosis of femoral head in the next period, treated with total hip arthroplasty. He was tested for thrombophilia and prothrombin G20210A mutation was detected. Second kidney transplantation in both cases with higher doses of anticoagulant therapy in preparation and afterwards underwent without thrombotic complications.

Conclusions. Identifying patients with thrombophilia before transplantation and defining their management presents many challenges. The risk of allograft thrombosis must be weighed against the risk of perioperative bleeding and the need for long-term anticoagulation.

PPTX-05 Kidney donor with factor XII deficiency

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Introduction. Factor XII deficiency is usually discovered in patients with a prolonged activated partial thromboplastin time (aPTT). While homozygous individuals have undetectable levels, heterozygous have levels between 25% and 50%. It was found to be associated with myocardial infarction, coronary artery disease, miscarriage, and coronary stent thrombosis. However, most reports of factor XII deficiency and thrombosis document arterial-side thrombosis. Herein we present a kidney donor with factor XII deficiency.

Case report. A 55-year-old female was admitted for evaluation as a potential kidney donor for her husband. She had three pregnancies which passed without complications. At the initial evaluation for kidney donation her aPTT was found to be 74.0 s (normal range 26-37), prothrombin time 14.2 s (11-14), INR 1.2 and thrombin time was 19.1 s (14-21). Broad coagulation examination was performed. Results revealed factor XII deficiency -25.5% (70-150), AT III was 83.8% (79.4-11.5), protein C 74.1% (70-140), with normal values for factors II, V, and XI, but with decreased activity of protein S 53.7% (58-127.5), F VII 59.1% (70-120), F X 52.4% (70-120) and increased F VIII >15% (70-155) and F XIII 146.6% (70-140). vWF activity and lupus anticoagulant were within the normal range. Based on these findings patient preoperatively received enoxaparin-sodium 0.4 ml. Fresh frozen plasma was prepared for treatment of eventual bleeding. Nephrectomy passed uneventfully.

Conclusions. Our case demonstrates that patients with F XII deficiency are suitable candidates for kidney donation. In our patient, combination of deficient and increased activity of different clotting factors probably enabled uneventful pregnancies, as well as post-nephrectomy course.

PPTX-06 DiGeorge Syndrome and kidney transplantation

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Introduction. DiGeorge syndrome is a syndrome caused by the deletion of a small segment of chromosome 22. While the symptoms can be variable they often include congenital heart problems, specific facial features, frequent infections, developmental delay. Associated condition include kidney problems, hearing loss, and autoimmune disorders such as rheumatoid arthritis or Graves disease. Congenital kidney and urinary tract anomalies are present in approximately 30% of the patients with the DiGeorge syndrome.

Case report. Male patient, diagnosed with DiGeorge syndrome and 22q11.2 deletion in early childhood, manifested with seizures do to hypocalcemia in first year of life. Diagnostic investigations of hypocalcemia revealed hypoparathyroidism, absence of thymus and partial T cells immunodeficiency. In the next period he had frequent infections of respiratory and GI tract and the severe hypacusia. He was treated with analogs of vitamin D and calcium preparations. In the age of 23 elevated levels of serum creatinine and urea were firstly noticed. In the next few years he developed chronic kidney disease (CKD) and arterial hypertension. In the age of 33 he developed end stage renal disease (ESRD). He was treated with renal transplantation from living related donor in the age 33, without complications. We used basiliximab in induction therapy and standard protocol with tacrolimus, mycophenolate mophetil and steroids. Although many years of CKD, due to hypoparathyroidism in DiGeorge syndrome, he did not develop CKD MBD or its complications. In perioperative, postoperative period and afterwards, he was treated with calcium preparations and vitamin D supplements. In a year of follow up, until now, his graft function was stable, without rejection or immunosuppression complications.

Conclusions. 22q11.2 microdeletion syndrome (DiGeorge) is a common cause of renal tract malformations, CKD and ESRD and all patients should be monitored for renal

function. They could be also successfully treated with kidney transplantation with adequate follow up.

PPTX-07 Rituximab in treatment of acutisation of chronic antibody mediated renal allograft rejection

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Introduction. Rituximab, which leads to a nearly complete elimination of B-cells, has been shown to be effective in acute antibody-mediated rejections. However, in chronic antibody-mediated rejection, its therapeutic effects are not evident so far. This could be related to the fact that chronic graft damage related to alloantibodies proceeds very slowly in a subclinical manner. In an individual patient, it is not clear when this process was initiated and, thus, the time point of treatment might be too late in order to reverse the already present chronic changes of graft destruction.

Case report. Female patient, 35 years old, treated with kidney transplantation from living related donor in the age of 22, with IgA nephropathy confirmed with prior kidney biopsy, as cause of terminal CKD. She had good graft function, with serum creatinine level of 150 μmol/l, until the switching of immunosuppression regimen between the calcineurin inhibitors tacrolimus and cyclosporin; and conversion of mycophenolate mofetil (MMF) to azathioprine, in preparation for assisted conception treatment; which was unsuccessful. She developed anemia, deterioration of graft function (with serum creatinine level of 397 μmol/l) and proteinuria in range over 1 gram/24h. We performed graft biopsy and got the diagnosis of acute humoral rejection AMR Banff I, ATN like, and diffuse positivity of c4d 2-3+ in peritubular capillares. Donor specific antibodies (DSA) were positive. The treatment consisted of switching the immunosuppressive regimen in introduction of CIN inhibitor back in therapy (tacrolimus) and MMF, corticosteroid pulsatile therapy (500mg of methylprednisolone); five sessions of plasmapheresis and treatment with rituximab in standard dose (375 mg/m²).The result of therapy was the reduction in serum creatinine level to 190 μmol/l and reduction of proteinuria to 0.6 gr/24h. The graft function remained stable on that level in the follow up period.

Conclusions. The reduction or inhibition of the production of DSAs would be an important target in order to reduce alloantibody-mediated chronic graft damage.

PPTX-08 Histopathological diagnoses and management of patients with glomerular diseases induced by medications: A case series

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Introduction. The aim is to study the clinical and histopathological characteristics of patients with drug-induced glomerular diseases and record the outcomes in conjunction with the appropriate treatment, beyond the discontinuation of the offending medicine.

Methods. All cases with any type of biopsy proven glomerular disease, which was associated with administration of a certain medication were studied retrospectively. Demographics and patients' characteristics were recorded along with the related clinical picture, the treatment and the outcome during the follow up time.

Results. Eight patients with glomerular diseases associated with medicines were identified. Six of them were females with a mean age of 59.6(±18.8) years. The renal biopsy was performed within 3-17 days from onset of symptoms which included either nephrotic syndrome (n=4) or nephritic syndrome with acute renal dysfunction (n=4). Patients with acute nephritic syndrome reported general symptoms including fever, arthralgias, fatigue, anorexia and rash. Histopathological evaluation revealed minimal change disease in 3 patients, membranous nephropathy in 1, pauci-immune glomerulonephritis in 2 and lupus like nephritis (WHO Class III, και IV) in 2. The medicines, which were associated were d-penicillamine, tamoxiphen, OH-chlorokine, NSAIDs, propyl-thiouracile, etarnecept, methimazole και infliximab. The median value of serum creatinine was 0.5 (min: 0.5, max: 2.7 mg/dl), the median 24-hour proteinuria was 5530 mg (min: 630, max: 240000 mg) while 4 of the patients had active urine sediment. In patients with nephrotic syndrome discontinuation of the offending drug lead to complete remission within a few weeks. Patients with acute nephritis required treatment with cyclophosphamide and glucocorticoids for 3-6 months, in addition to the removal of the offending drug.

Conclusions. In this small series of patients with glomerular diseases associated with medicines discontinuation of the related drug lead to remission of the nephrotic syndrome within a few weeks while patients with acute nephritic syndrome required treatment with cyclophosphamide and glucocorticoids for 3-6 months, in addition to the removal of the offending drug.

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