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Editorial

BANTAO Association - from Foundation to Present and Future Perspectives

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The idea to establish Balkan Society of Nephrology was born in Skopje, in May 1991, on the eve of the Balkan wars, when the nephrologists from Macedonia (M. Polenakovic), Bulgaria (D. Nenov), Serbia (A. Radmilovic) and Turkey (K. Onen) signed a memorandum in which this idea was articulated. Two years later, on 9 October 1993, at the first Congress of the Macedonian Society of Nephrology, Balkan Cities Association of Nephrology, Dialysis, Transplantation and Artificial Organs (BANTAO) was established 1. Scientific and technical cooperation in the fields of nephrology and artificial organs between the regions on the Balkan Peninsula and the world was highlighted as the main goal of BANTAO. Despite the turbulent times in Balkan Peninsula the I BANTAO Congress was held in Varna from September 22 to 24th, 1995 (President - D. Nenov, Varna), that was an impressive event. Fernando Valderrdbano, Chairman of the EDTA-ERA Registry, reported on that event with a lot of sympathy in the paper entitled "Nephrologists of the Balkan countries meet across political frontiers and war fronts - an example to politicians!" [2].

BANTAO continues to live and to grow: the II Congress of BANTAO was held in September 1997 in Struga, (President - M. Polenakovic, Skopje), the III BANTAO Congress in September 1998 in Belgrade (President - Lj. Djukanović, Belgrade), the IV Congress of BANTAO in Izmir in November 1999 (President - A. Akcicek, Izmir) and the V Congress of BANTAO in Thessaloniki in September 2001 (President - P. Stathakis, Athens) [3]. The number of participants, presented papers and lectures from distinguished guests increased from congress to congress, although the Association did not even had its own statute, nor membership fee. BANTAO has lived and has thrived thanks to the friendship, respect and appreciation among leading nephrologists from BANTAO region, transferred to all other participants. Ch. Stathakis called the links that connect us "spirit of BANTAO" and presented it in the logo of the 5th Congress that became the logo of BANTAO [4]. The next cycle of congresses were held in the same countries as the first five: the VI Congress in Varna (2003; President - D. Nenov), the VII in Ohrid, (2005; President - M. Polenakovic), the VIII in Belgrade (2007; President - V. Nesic), the IX in Antalya (2009; President - A. Basci) and the X BANTAO in Chalkidiki (2011; President - D. Tsakiris) [5]. On the occasion of the twentieth anniversary of BANTAO idea birth M. Polenakovic wrote: "The BANTAO Congress has been established as the major scientific and institutional forum for Balkan nephrologists, with its own journal, indicating our will to communicate, to collaborate, to get to know each other, and to share our difficulties and our successes". [6]. BANTAO journal is an official publication and constitutes the main connection between or a glue sticking together all members of the BANTAO Association. At present, it is published biannually, is incorporated into the public and internet-available databases of DOAJ, SCIMAGO, EBSCO, Google Scholar, De Gruyter Open and we currently consider application into the Medline (Pub Med) database [7].

However, it seems that the history has not been favoring the BANTAO association. After a decade of severe political crisis in 1990s, we are now faced with severe economic crisis. It is clear that the organization of congresses and maintaining positive spirit has been a challenge all previous years. Nevertheless, the BANTAO spirit has surprised even its most persistent and supportive advocates. After circling the Congress between the founding countries, from 2013 the Association was enriched by an initiative of the Romanian nephrologists, which resulted in the organization of a very successful Congress in Timisoara. The next Congress was also moved from the founding countries and was

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successfully held in 2015 in Opatia, Croatia. With a special excitement we do expect the Congress in 2017 when another Balkan country - Bosnia and Herzegovina will join the congress organizers. In this regard, a question that still needs an answer would be how we can explain this positive trend and a large number of visitors at the Congresses during the present economic constraints? Do the centuries-old ties between the Balkan countries still live? Can the hunger for scientific affirmation be met here? Is the Balkans a polygon for training of promising young nephrologists who have difficulties in finding their place at major European and international conferences? Finally, whether the reason might be that people in the Balkans better socialize, laugh, eat, play and sing during the congress social events? Most probably, all together.

So, the question remains - can we do better that this? Our responsibility is not to betray the expectations of the young generation of nephrologists and to persist in goals that have been set in the previous years. Is it a success to keep the tradition despite the years of crisis or we must seek for innovative initiatives within the BANTAO Association? We believe that multicenter studies across the region should be favored since we share the similar medical problems and these studies are a good starting point for obtaining grants. Thus, if we used to have joint CME meetings between the regions, it's reasonable that pharmaceutical companies may support such initiatives in different fields of nephrology.

Many case reports remain forgotten in our institutions but the BANTAO Journal is open to accept them to be published along with the other original scientific contributions and that is certainly an accomplishment of the great spirit of BANTAO. However, we should also try to stick as close as possible to the adopted constitution and validate ourselves as members of the Association, with membership card and growing infrastructure in the years to come. In conclusion, BANTAO has proved to be a new European Medical Association that overcomes political obstacles and boundaries. Neither devastating wars, nor economic crises could have switched off the BANTAO initiative established as a major scientific and institutional forum for Balkan nephrologists communicating and collaborating between each other respecting distinctions but also sharing regional difficulties.

Conflict of interest statement. None declared.

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Review article

Immune Renal Injury: Similarities and Differences Between Glomerular Diseases and Transplantation

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Abstract

Glomerular diseases and renal transplantation are the main fields in nephrology in which the immune system plays a prevalent role. They have for long been considered as independent conditions due to the prominent role of autoimmunity in glomerular diseases and of alloimmunity in renal transplantation.
Moreover, histologic features differ between glomerular diseases and transplantation: in glomerular diseases, histologic damage involves primarily the glomeruli and secondarily the tubulointerstitium and small vessels, whereas in transplantation, allograft injury comprises primarily the tubulointerstitium and vessels and to a lesser degree the glomeruli.
However, recent research has shown that the pathogenetic mechanisms in both conditions share common pathways and that there is cross-reaction between innate and adaptive immunity as well as between auto- and alloimmunity [1].

Key words: glomerular diseases, renal transplantation, adaptive immunity, autoimmunity, alloimmunity

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Innate and adaptive immunity and complement activation

Glomerular diseases have been considered traditionally as autoimmune diseases, since the main pathogenetic mechanism involves (auto-)antibody production and immune complex formation.
In renal transplantation, which is considered as an alloimmune condition, allograft damage is the result of direct reaction of immune cells towards the graft. In this setting, attention has mainly focused on adaptive immunity, since T-cells alone are sufficient to trigger and sustain rejection. T-cells can be sensitized against alloantigens via the direct or the indirect allorecognition pathway. In direct allorecognition, T-cells recognize peptides on the intact donor MHC molecules on the surface of donor cells. In indirect allorecognition, donor MHC molecules are processed and presented as peptides on antigen presenting cells (APCs) of the host.
It has been demonstrated that indirect and direct type of alloresponse play different roles in the physiology of the rejection process. T-cell response via direct allorecognition plays a critical role during the early phase of acute rejection. Once sensitization has taken place, indirect alloresponse may become prominent and further spread and sustain the immune process playing a central role especially in late and chronic rejection episodes [2].
In glomerular diseases, the role of innate immunity was identified decades ago. The innate immunity system provides the first line of defense against infections via cellular and humoral mechanisms. Innate immunity is rapid but specific; it acts through the recognition of pathogens presented by APCs (macrophages, dendritic cells and leucocytes) and their subsequent destruction through opsonization and phagocytosis. Besides APCs, main components of innate immunity are toll-like receptors (TLRs) and the complement system.
The clinical relationship between infection and glomerular diseases is well-known: various types of infections may exacerbate or trigger glomerular diseases as streptococcal infection acute membranoproliferative GN, mucosal infections macroscopic hematuria in IgAN and staphylococcal infections ANCA-associated vasculitis (AASV).
The role of complement activation in glomerular diseases has been thoroughly investigated. Complement can be activated via the classical pathway in immune complex-mediated diseases such as lupus nephritis and cryoglobulinemic nephritis. Former membranoproliferative GN type II, now according to the new classification named "dense deposit disease" and recurrent atypical hemolyticuremic syndrome are both triggered by uncontrolled activation of the alternative complement pathway. Complement activation via the lectin pathway has been implicated in the pathogenesis of IgAN.
In renal transplantation, complement activation plays an important role in ischemia-reperfusion injury with activation of both the classical and the lectin pathway [3]. Complement activation is essential in humoral, antibody-mediated rejection (AMR) where there is depo-

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sition of the C4d component of the classical pathway in peritubular capillaries and glomeruli.
Besides the central role of complement activation both in glomerular diseases and transplantation, there is growing evidence of interaction between innate and adaptive immunity. Innate immunity interferes with dendritic cell maturation, antigen presentation and T-cell activation and can be considered as a major component of the alloimmune response [4].

B-cell activation and antibodies

Circulating antibodies are involved in the pathophysiology of renal damage, both in glomerular diseases and in transplantation. The most typical model of autoantibody-mediated glomerulopathy is idiopathic membranous nephropathy. In membranous nephropathy, recent and former studies have identified several podocytic antigens as targets of autoantibodies. Experimental studies in the late 1950s using rats (model of passive Heyman nephritis) have first identified a large membrane glycoprotein also known as megalin. Another important finding was that activation of complement was also required for the development of proteinuria. The first evidence of in situ immune complex formation was established by Debiec *et al*. [5]. They described a case of neonatal nephrotic syndrome and biopsy proven membranous nephropathy in a newborn whose mother was genetically deficient in an enzyme expressed on podocytes, neutral endopeptidase (NEP). Circulating anti-NEP antibodies from presensitization of the mother during a previous pregnancy crossed the placenta, bound to NEP in fetal podocytes and caused MN in the newborn, which resolved after the clearance of maternal antibodies from the circulation. Autoantibodies directed against other podocytic enzymes as M-Type phospholipase A2 receptor (PLA2R) have been described more recently. Anti-PLA2R antibodies have been further associated with the idiopathic form of membranous nephropathy as well as with disease activity [6].
In renal transplantation, a substantial proportion of acute and chronic rejection episodes are mediated by circulating anti-HLA antibodies, which are either de novo or preformed. Antibodies directed against donor specific antigens (DSA) can cause different types of rejection: hyperacute, acute and chronic antibody-mediated rejection (AMR). Nowadays the occurrence of catastrophic, hyperacute AMR is extremely rare, because of the universal adoption of pretransplantation cross-matching. Acute and chronic AMR due to preformed or de novo DSA still remain one of the leading causes of graft failure. The major mechanism of antibody-mediated injury is activation of the classical complement pathway by the antigen-antibody complex, leading to formation of the membrane attack complex, which results in cellular injury. Antibodies are most commonly directed against human leucocyte antigen (HLA)/major histocompatibility-complex (MHC) class I and II antigens [7]. HLA class I antigens are expressed on all nucleated cells, whereas HLA class II antigens are restricted to antigen-presenting cells (APC) and endothelial cells. However, antibodies can also be directed against other donor specific antigens such as endothelial, MHC-class I related chain A (MICA) or MICB, platelet-specific antigens or molecules of the renin-angiotensin pathway [8].

Evolution of therapeutic approaches

The most commonly used immunosuppressive agents are corticosteroids, alkylating agents (cyclophosphamide), calcineurin inhibitors (CNIs, cyclosporine and tacrolimus), antimetabolites (MPAs, mycophenolate mofetil or mycophenolate sodium and azathioprine) and mTOR inhibitors. They have been used in both glomerular diseases and transplantation. While in transplantation evidence is based on large, multicenter, randomized, controlled trials [9,10], in glomerular diseases most of the evidence comes from small, single center studies [11,12].

Multitarget therapy

A promising trend in the treatment of glomerular diseases, by adopting the model of renal transplantation is multitarget therapy. In transplantation, we use immunosuppressive combinations and not single agents, in order to maximize efficacy and minimize side effects. T-cell activation requires three distinct signals: Signal 1: an antigen at the surface of an antigen presenting cell (APC) triggers T cell activation through binding at the CD3 receptor complex of the T cell. Signal 2: This second signal also known as co-stimulation occurs when CD80 and CD86 on the surface of APC interfere with CD28 on T-cells. Signals 1 and 2 activate several intracellular signal transduction pathways. These pathways enhance the production of cytokines such as interleukin (IL)-2, IL-15 and IL-4. IL-2 binds to CD25 (the IL-2 receptor) and activates the mammalian target of rapamycin (mTOR), providing signal 3, the stimulus for T-cell proliferation.
Immunosuppressive drugs act synergically, blocking different sites of this activation cascade. Corticosteroids are the oldest immunosuppressants and have been used in glomerular diseases and transplantation for decades. Their immunosuppressive action is mediated through a number of pathways, mainly directed towards redistribution of lymphocytes and macrophages to the lymphoid tissue and inhibition of the production of cytokines (IL-1, IL-2, IL-6), tumor necrosis factor-alpha (TNFα) and interferon-gamma (IFN-γ).
Calcineurin inhibitors, cyclosporine and tacrolimus bind to a cytoplasmic receptor, cyclosporine to cyclophilin and tacrolimus to FKBP12 and form a complex that binds to and inhibits the action of cyclophilin. Cyclophilin inhibition results in inhibition of NFATc dephosphorylation (cytosolic Nuclear Factor of Activated T cells) which

subsequently leads to reduced cytokine release, including IL-2. Mammalian target of Rapamycin (mTOR) inhibitors (sirolimus and everolimus) bind to the same intracellular receptor as tacrolimus, FKBP12. Instead of forming a complex with calcineurin, mTORi's, bind to mTOR, interfering with signal 3 of T-cell activation by inhibiting rapamycin, which is a key kinase for the cell cycle, thereby resulting in cell-cycle arrest in the G1-S phase. Antimetabolites include the older drug azathioprine and the newer derivates of mycophenolate acid (MPAs), mycophenolate mofetil (MMF, cellcept) and mycophenolate sodium (myfortic). Azathioprine antagonizes purine metabolism and inhibits synthesis of DNA, RNA and proteins. It may decrease proliferation of B- and T-cells, which results in lower immune activity. The newer antimetabolites, MPAs, are more selective inhibitors of purine synthesis. Mycophenolate inhibits inosine monophosphate dehydrogenase (IMPDH) and suppresses de novo purine synthesis by lymphocytes, thereby selectively inhibiting proliferation of activated T-cells.

In renal transplantation, use of combinations of immunosuppressive agents increases efficacy and reduces drug-related toxicity. The multitarget therapeutic approach has been adopted in glomerular diseases, with promising results. One such case is the use of combination therapy consisting of calcineurin inhibitor (tacrolimus) with mycophenolate mofetil and corticosteroids for the treatment of severe, mixed proliferative and membranous lupus nephritis (class III and V on renal biopsy). After the positive results in the first 40 patients, published in 2008 by Bao *et al.* [13], a large, multicenter, randomized controlled trial (RCT) with a total of 368 patients with proliferative lupus nephritis was published recently, in 2015, by Liu *et al.* [14]. This was one of the largest trials in lupus nephritis. When the same multitarget regimen (tacrolimus, mycophenolate mofetil and corticosteroids) was compared with conventional therapy (intravenous pulses of cyclophosphamide and steroids) for induction therapy of LN, there were significantly higher remission rates in the multitarget therapy group after six months.

Minimization of Immunosuppression

Nowadays, immunosuppressive protocols include more selective and more potent drugs than in the past. Despite enhanced efficacy and use of reduced doses of immunosuppressive agents compared to the past decades, cumulative toxicity of immunosuppression still remains a substantial problem in renal transplantation. Main side effects of calcineurin inhibitors are hypertension, hyperlipidemia and diabetes mellitus, which are all major risk factors for cardiovascular complications. Cardiovascular events are still the leading cause of death in transplanted patients. Moreover, CNIs are nephrotoxic; the nephrotoxicity of cyclosporine was described in the early 1990s. CNI nephrotoxicity can schematically be divided into "acute" and "chronic". Acute, potentially reversible nephrotoxicity i. e. without evidence of histologic damage, or "acute arteriolopathy" results from vasoconstriction of the afferent arteriole of the glomerulus, due to increase of vasoconstrictor factors as endothelin and thromboxane and activation of the renin-angiotensin system (RAS), as well as a reduction of vasodilators like prostacyclin, prostaglandin E2 and nitric oxide (NO). Reversible tubular dysfunction is also recognized as a feature of acute CNI nephrotoxicity. Chronic CNI nephrotoxicity still remains the Achilles' heel of current immunosuppressive regimens [15]. Myers *et al*. were the first who demonstrated in heart transplant recipients, that cyclosporine is associated with irreversible damage to renal architecture [16]. This damage affects all renal compartments: vessels (arteriolar hyalinosis), tubulointerstitium (tubular atrophy and interstitial fibrosis) and glomeruli (thickening of Bowman's capsule and glomerulosclerosis). In the hallmark study by Nankivell *et al.* with protocol biopsies, it was shown that CNI toxicity progresses with time after transplantation and by 10 years CNI nephrotoxicity was seen in virtually all cases [17].

One of the most recent trends in transplantation is "immunosuppression minimization". The efforts towards minimization include two categories of immunosuppressive agents: calcineurin inhibitors and corticosteroids.

CNI sparing protocols comprise:

1. Complete avoidance of CNI. This approach had poor outcomes with unacceptable high rates of early, acute rejection and infection episodes [18].
2. CNI minimization. Combinations of very low doses of CNI in combination with mTORi or MPAs have shown slight improvement of GFR, but histologic damage still occurs.
3. The last approach is CNI withdrawal and conversion to mTORi. Early conversion, from 4 weeks to 1 year post-transplantation is preferable to late conversion. Late conversion is beneficial only in patients with preserved renal function (eGFR>40ml/min) and proteinuria less than 800mg/24hrs [19]. An open label, observational study from our Center showed beneficial effects of late conversion in terms of GFR improvement in selected patients with baseline GFR at conversion > 40ml/min [20].

Corticosteroids, even at low maintenance-doses, have numerous and potentially serious side-effects. Since 2000, many steroid-sparing protocols have been implicated in renal transplantation with good results. Early steroid withdrawal is preferable to late withdrawal [21]. Both steroid- and CNI-sparing protocols must be used with caution in selected groups of stable renal transplant recipients with low immunological risk.

Long-term immunosuppression is used in glomerular diseases, too. The most characteristic glomerular disease, in which cumulative toxicity of immunosuppression is a major issue, is lupus nephritis. Lupus nephritis is an organ and life-threatening disease. Moreover, it has a long course with a high rate of relapses. Given the se-

verity of the disease, the need for long-term, often aggressive immunosuppression and the fact that it affects a patient population comprising of young women at childbearing age, efforts to minimize immunosuppression toxicity have been started early. The first step to reduce cumulative toxicity of cyclophosphamide was the Eurolupus trial, published by Houssiau *et al.* [22]. In a Caucasian population, it showed equal efficacy of a regimen comprising a total of 3g of cyclophosphamide for remission induction of proliferative LN, compared to higher "conventional" doses of iv cyclophosphamide used in the classic "NIH regimen". After the revolutionary study by Chan *et al.* in 2000 [23], which showed equal efficacy of mycophenolate mofetil when compared to cyclophosphamide for remission induction in proliferative LN, the efficacy of MPA's as induction therapy was further confirmed in larger, multicenter studies [24,25]. One successful effort to minimize corticosteroids in lupus nephritis was a randomized, controlled trial, "MyLupus Trial". When reduced-dose steroids were compared to standard-dose steroids, in conjunction with Myfortic as induction therapy in proliferative LN, reduced-dose steroids showed equal efficacy in remission induction [26].
ANCA-associated vasculitis (AASV) is another potential life-threatening systemic disease that affects the glomeruli, causing rapidly progressive glomerulonephritis often with accelerated loss of renal function. It affects predominantly elderly patients with comorbidities, in whom overimmunosuppression may have detrimental effects. Efforts to minimize toxicity have been made by the EUVAS and other groups for the last two decades [27,28].

Targeting therapy

B-lymphocytes play a central role in the pathogenesis of glomerular diseases and are also implicated in antibody-mediated rejection (AMR) in renal transplantation [29]. Besides producing antibodies, B-cells have many other functions: they interact with T-cells, they may act as antigen presenting cells and they clonally expand. A number of monoclonal antibodies that target different receptors and lead to sustained (6-12 months) depletion of B-cells, are currently available. The most commonly used is the chimeric, ligand monoclonal, anti-CD20 antibody rituximab. Rituximab has been used in a variety of conditions in renal diseases, in glomerulonephritis as well as in transplantations. The wide range of the therapeutic implications of Rituximab, has been reviewed by our group in 2013 [30].
After the proof of non-inferiority of rituximab as induction therapy in both RCT's, RAVE and RITUXVAS [31,32]. R/rituximab has been approved as induction therapy for AASV. After the positive results of the MAINRITSAN trial [33], which showed better results of rituximab compared to azathioprine for maintenance of remission, the therapeutic setting has completely changed in this renal-disease category, too.
In lupus nephritis, in our experience, rituximab in combination with MMF is effective as maintenance treatment in patients with proliferative LN [34]. Its therapeutic effect may potentially be related to down-regulation of the T cell costimulatory molecule CD40 ligand [35,36]. In a multicenter RCT, the LUNAR trial, rituximab in combination with conventional therapy (3 g of mycophenolate mofetil and corticosteroids) showed no additional benefit compared to placebo in terms of remission induction [37]. It has shown efficacy in cases of refractory LN, in combination with conventional therapy. In membranous nephropathy, our experience with rituximab in 12 cases showed that it was efficient with sustained remission long-term and minimal toxicity [38]. Similar results have been shown by others, including a very recent French study presented in an abstract form at the last ASN [39,40,41 (abstract)].
One of the more recent fields of investigation is blockade of costimulation, i.e. the second signal of T-cell activation. Both monoclonal antibodies abatacept and belatacept inhibit the CD28/CD80-86 pathway of costimulation. Abatacept (cytotoxic T-lymphocyte associated antigen4-Ig) binds to CD80 and CD86 on antigen presenting cells, blocking the interaction with CD28 receptor on T-cells. It has been approved since 2005 for treatment of moderate to severe rheumatoid arthritis, refractory to methotrexate and anti-TNF treatment [42]. In glomerular diseases, efforts have been made towards use of abatacept in lupus. Two trials of abatacept in active lupus nephritis, given additionally to conventional therapy, failed to prove efficacy [43,44]. In primary glomerular diseases, there is a case series of 5 patients with FSGS (4 with recurrent FSGS after renal transplantation and 1 with primary FSGS) treated with abatacept. All patients had positive immunostaining for CD80 (B7-1) in podocytes of kidney biopsies. Abatacept was given additionally to intensive plasmapheresis and all 5 patients achieved either partial or complete remission [45]. We have treated one patient with massive nephrotic syndrome due to FSGS recurrence after renal transplantation with abatacept in combination with plasmapheresis, unfortunately with negative results. Though the podocyte CD80 pathway seems important in some proteinuric glomerular diseases, further investigation towards use of costimulation blockade in this condition is warranted.
Belatacept, is a derivate of abatacept, which binds with more avidity to CD86 and is preferably used in kidney transplantation. Belatacept in transplantation was evaluated in two, open-label, randomized, multicenter, controlled trials (BENEFIT, BENEFIT-EXT). Both studies showed that belatacept was not inferior to cyclosporine in terms of patient and graft survival and was associated with better renal function short term [46,47]. Though a higher infection rate was observed in the belatacept group, after these trials, belatacept was approved in 2011 from the Food and Drug Administration (FDA) as the first costimulation blocker for use in renal transplantation.

In conclusion, new insights into the pathogenesis of glomerular diseases and renal transplantation have elucidated common pathways of allo-and autoimmunity and links between innate and adaptive immunity, with potential for new therapeutic targets.

Conflict of interest statement. None declared.

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Original article

Correlation of Residual Diuresis with MIS Score and Nutritional Status in Peritoneal Dialysis Patients: A Croatian Nationwide Study

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Abstract

Introduction. Residual diuresis (RD) is an important predictor of mortality and cardiovascular (CV) deaths in peritoneal dialysis (PD) patients, and contributes more to overall survival compared to PD clearance. In this study we investigated the correlation between RD and CV outcomes in PD patients.

Methods. A total of 190 PD patients from 13 dialysis centers, a national representation, were included in this analysis. Biomarkers of anemia, nutritional status [malnutrition inflammation score (MIS), subjective global assessment (SGA), serum albumin, anthropometric measurements including body mass index (BMI)], dialysis dose (Kt/V) and laboratory measurements were determined. RD was estimated using the volume of daily urine.

Results. There were 78(41.05 %) females and 112 (58.95 %) males; aged 57.35±14.41 years, on PD for 24.96±24.43 months. Fifty-six patients had diabetes type II (44 as primary kidney disease). The mean RD was 1170±673.6 ml (range 0-3000 mL). Statistically significant correlations between RD and BMI, hip circumference, time on PD, Kt/V, MIS, SGA, erythrocytes (E), Hemoglobin (Hb), PTH, and serum albumin were observed.

Conclusions. We demonstrated a significant correlation between RD and MIS score, SGA, anthropometry and albumin. Every effort should be invested to maintain RD for as long as possible to achieve optimal treatment results and to decrease CV mortality in PD population.

Key words: peritoneal dialysis, residual diuresis, anemia, nutritional status, CKD-MBD, MIS score

Introduction

Cardiovascular (CV) related diseases are the leading causes of death in dialysis patients; CV issues account for more than 40% of deaths in the dialysis population [1]. Residual diuresis (RD) is an important predictor of both overall and CV mortality in peritoneal dialysis (PD) patients. Maiorca *et al*. were the first group to report a 50% reduction in mortality in peritoneal dialysis (PD) patients who maintained some RD [2]. Diaz-Buxo *et al.* demonstrated strong association between residual renal creatinine clearance and PD patient survival, whereas peritoneal clearance did not affect mortality [3]. These findings have been supported by many additional studies in various countries which have all highlighted the importance of maintaining RD to reduce mortality in PD patients [4-10]. Additional benefits for patients with preserved RD were reported, including improved quality of life and reduced systemic inflammation [11,12]; a reduction in systemic inflammation may reduce the incidence of protein-energy wasting.

Residual diuresis is important for small solute clearance, removal of middle molecular uremic toxins, maintenance of fluid balance, as well as for phosphorus control, the role of the kidney in nutrient homeostasis, vit. D activation, erythropoietin production, minerals, carnitine production, etc. This would set the story as to why one is measuring nutritional markers and status. The decline of RD also contributes significantly to anemia, inflammation, and malnutrition in patients on dialysis, and correlates with valvular calcification and cardiac hypertrophy [13]. However, a decline in RD is inevitable with time on dialysis, demanding an increase in the reliance on PD clearance to compensate for the loss in RD.

Because the kidney has a key role in nutrient homeostasis, in this study we investigated the correlations between RD and nutritional status, and other parameters associated with CV outcomes in Croatian PD patients.

Materials and methods

The PD registry of the Croatian society for nephrology, dialysis and transplantation was utilized to collect data from 190 Croatian PD patients, who are being treated in 13 dialysis centers countrywide, for inclusion into this analysis. This study was approved by the Ethics committee of the University hospital center in Zagreb. All patients treated with PD in Croatia were included

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in the PD registry, and in this investigation. Biomarkers of anemia, nutritional status [malnutrition inflammation score (MIS), subjective global assessment (SGA) score, serum albumin, body mass index (BMI)], anthropometric measurements (skinfold thickness measured at the triceps region, hip and waist circumference) and laboratory measurements (calcium, potassium, phosphorus) were determined. RD, or residual diuresis, was estimated using volume of daily urine. Hypertension was defined as the need for antihypertensive drugs other than a diuretic for the maintenance of blood pressure below 140/90 mmHg. Adequacy of dialysis was determined by the total weekly urea clearance (Kt/V). Transport characteristics were determined by the PET test.

Statistical analysis was performed using commercially available software; Statistic 6.1 StatSoft [StatSoft, Inc. (Dell Software), Tulsa, OK, USA]. The relationship between any two parameters was tested by regression analysis. Statistical differences between parameter values were tested by either the t-test or χ-square test as appropriately. A p value of less than 0.05 was considered statistically significant.

Results

Our study cohort had a mean age of 57.35±14.41 years with mean PD duration of 24.96±24.43 months at study enrolment. Of the 190 patients, diabetes type II was the primary cause of kidney disease in 44 patients. An additional 12 patients developed diabetes after the study period started. Patients' characteristics are presented in Table 1.

The mean RD was 1170±674 ml (range 0-3000 ml). Transport characteristics were as follows: 55(28.95%) patients were considered high average, 63(33.15%) patients were considered low average, 19(10%) patients were considered low and 26(13.7%) were considered high transporters. Data for 27 patients was missing. The mean weekly total Kt/V was 2.42 (range 1.42-4.25). In our regression analysis, RD significantly correlated with Kt/V (r= 0.4374, p<0.001).

Statistically significant correlations between RD and numerous potential CV diseases risk factors were found (Table 2). Namely, positive correlation was observed for BMI, hip circumference, Kt/V, E, Hb and serum albumin, with negative correlation of RD with iPTH, MIS, SGA and dialysis vintage was recorded.

Table 1. Patients' characteristics

Characteristic	Value
Females (No. (%))	78(41.05)
Males(No. (%))	112(58.95)
Age (years; mean±SD)	57.35±14.41
Dialysis vintage (months; mean±SD)	24.96±24.43
Primary kidney disease (No. (%))	
Renovascular	46(24.2)
Diabetes mellitus	44(23.15)
Glomerulonephritis	55(28.95)
ADPKD	17(8.95)
Other	28(14.75)
Smokers (No. (%))	41(21.58)
Hypertension (No. (%))	177(93.8)

Table 2. Statistically significant correlations between RRF and CV disease-related parameters in PD patients (Pearson's correlation coefficient, one-tailed significance level). MIS - malnutrition inflammation score, SGA - subjective global assessment, E - erythrocytes, Hb - hemoglobin, iPTH - intact parathyroide hormone

Variable	Correlation coeficient	P
BMI (kg/m^2)	0.3341	0.000003
Hip circumference (cm)	0.2571	0.0062
PD vintage (months)	-0.3927	0.00000003
Kt/V	0.4374	0.000000007
MIS	-0.4767	0.0000005
SGA	-0.3048	0.0087
E	0.1524	0.0384
Hb	0.1614	0.0282
iPTH (pmol/L)	-0.1816	0.0174
Serum albumin (g/L)	0.2263	0.0022

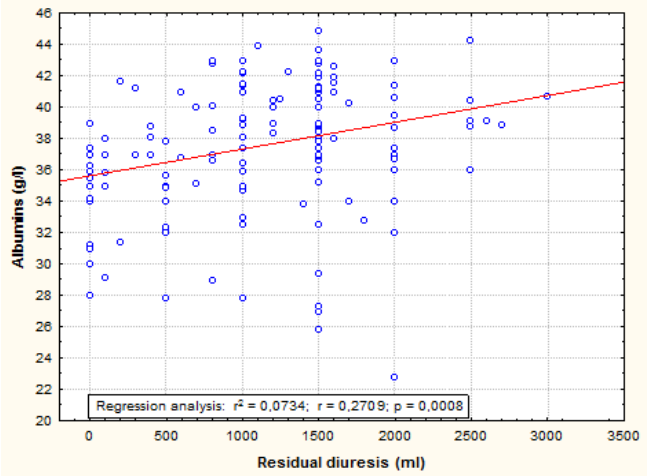

Fig. 1. Correlation between serum albumin and residual diuresis. Patients with lower residual diuresis had lower serum albumin

Residual diuresis correlated with nutritional parameters (albumin, MIS, SGA, BMI and hip circumference) (Table 2). Other anthropometric parameters (neck or brachial circumference) had no significant correlation with RD. Serum albumin was reduced significantly in patients with declining residual diuresis (Figure 1).

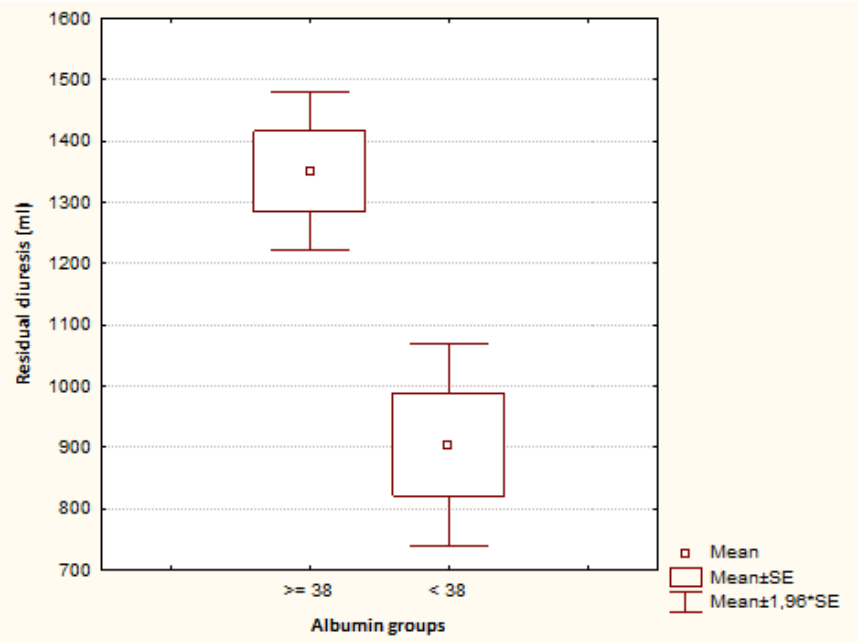

Fig. 2. Patients with serum albumins <38 g/L had significantly lower residual diuresis compared to patients with serum albumins ≥38 g/L

Patients with serum albumin ≥38 g/L had significantly higher residual diuresis when compared to those with serum albumin <38 g/L (Figure 2).

Additionally, low residual diuresis had a negative impact on BMI (Figure 3), and patients with BMI<23 kg/m^2 had significantly lower RD (residual diuresis) than patients with BMI ≥23 kg/m^2 (Figure 4).

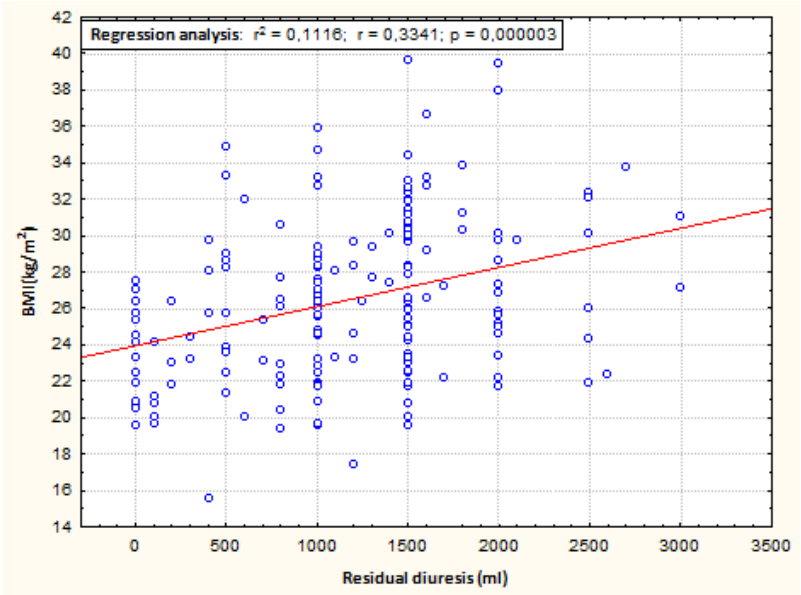

Fig. 3. Correlation between BMI (kg/m^2) and residual diuresis. Patients with lower residual diuresis had lower BMI

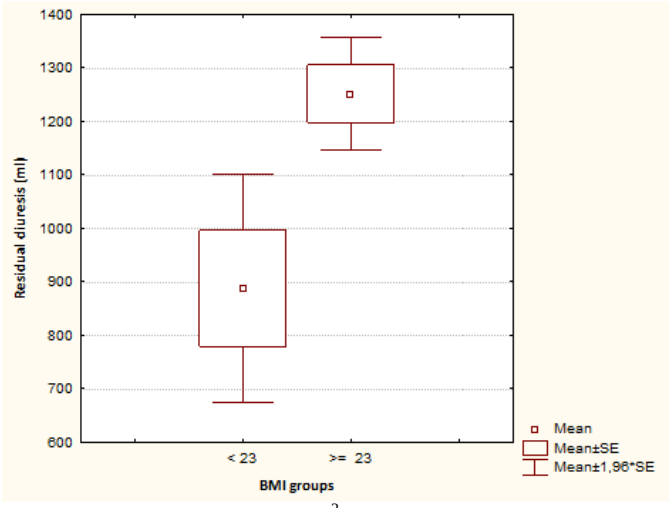

Fig. 4. Patients with BMI ≥23 kg/m^2 had significantly higher residual diuresis than patients with BMI <23 kg/m^2

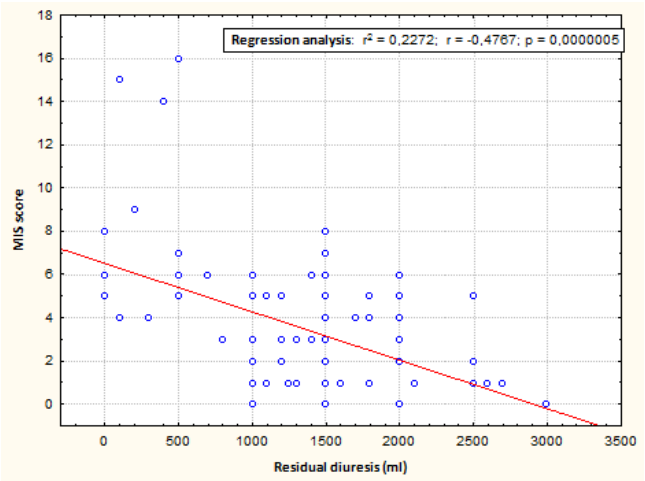

Fig. 5. Correlation between MIS score (kg/m^2) and residual diuresis. Patients with lower residual diuresis had higher MIS score

MIS was available for 101 patients. Both MIS (Figure 5) and SGA (N=48) (data not shown) had significant negative correlation with RD in our cohort of patients.

We further investigated the correlation between anemia and RD. Erythropoietin (EPO) was used for treatment of anemia in 127 patients. Patients with a higher RD had a higher serum hemoglobin level (Figure 6), and required less erythropoietin stimulating agents (ESA) (Figure 7).

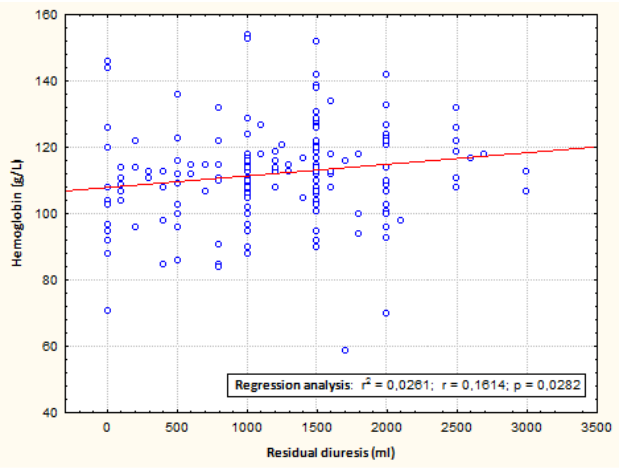

Fig. 6. Correlation of serum hemoglobin with residual diuresis. Patients with higher residual diuresis had higher serum hemoglobin

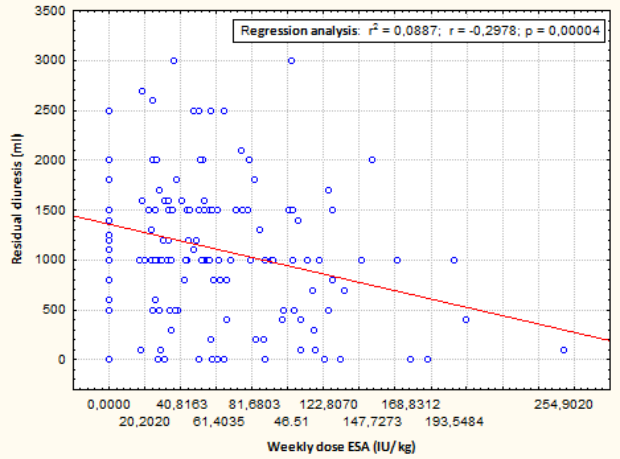

Fig. 7. Correlation of weekly dose ESA and residual diuresis. Patients with higher residual diuresis required less ESA

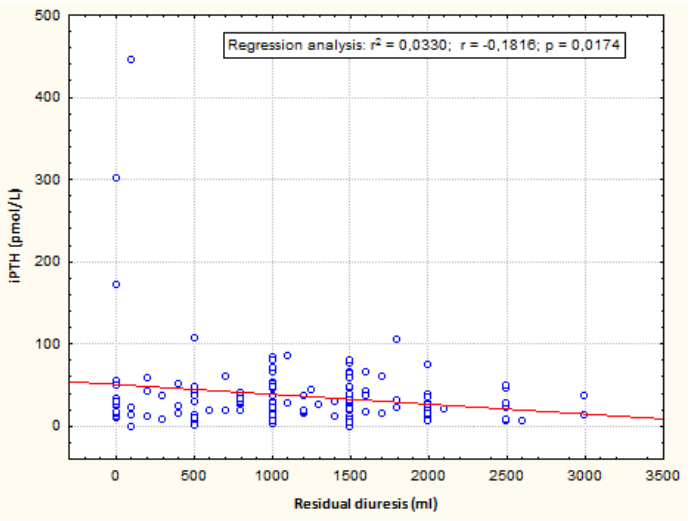

Fig. 8. Correlation of iPTH and residual diuresis. Patients with lower residual diuresis had higher iPTH

Additionaly, RD significantly correlated with iPTH level (Figure 8).

Serum iPTH correlated with age (r=-0.1995, p=0.0081), use of EPO (ANOVA F=-2.9924, p=0.032), weekly dose of EPO (r=0.1934, p=0.0103), and use of bicarbonates for treatment of metabolic acidosis (t=-2.32614, p=0.021242). Phosphorus level had no significant correlation with RD, but significantly correlated with Kt/V (r=-0.2192, p=0.0053). There was no correlation of serum calcium with other parameters.

Based on our definition of hypertension (need for antihypertensive drugs other than a diuretic for the maintenance of blood pressure below 140/90 mmHg) 93.8 % of patients were hypertensive, and required at least one antihypertensive drug in addition to a diuretic. A trend toward lower blood pressure and arterial pulse pressure was observed in patients with higher RD. However, RD was not significantly correlated with either systolic or diastolic blood pressure. Patients with diabetes needed less antihypertensive drugs than non-diabetic patients (t -2.12403, p =0.035018).

Table 3. Statistically significant correlations between use of icodextrin and other parameters in PD patients (t-test or χ-square, as appropriate). EPO - erythropoietin, Hb - hemoglobin

Parameter	Correlation	P
Episodes of peritonitis (No)	2.75086	0.006625
Antihypertensive drugs (No)	1.98222	0.049135
Use of EPO	19.58887	0.00021
Weekly dose EPO	2.13973	0.033855
Transport type (high)	25.41760	0.00001
Nutritive support (yes)	6.067899	0.01377
Hb (g/L)	-2.86562	0.004708
Plattelet (No.)	2.27902	0.023971
Calcium (mmol/L)	-2.46832	0.014607
Phosphorus (mmol/L)	2.16569	0.031788
Creatinine (μmol/L)	2.30323	0.022522
Albumin (g/L)	-3.02474	0.002900
Residual diuresis	-2.28732	0.023463

Forty-one patients (21.58%) were smokers, however, there was no correlation between smoking status and RD. Mean total cholesterol was 5.28±4.75 mmol/L, LDL 3.03±1.12 mmol/L, and HDL 1.20±0.36 mmol/L, with triacylglycerides 2.07±1.19 mmol/L. There was no correla-

tion between total cholesterol, LDL, HDL or triglycerides and RD.
Over half (53%) the subjects were prescribed PD using once daily long dwell exchange, with icodextrin as the principal osmotic agent. Use of icodextrin significantly correlated with various clinically relevant parameters (Table 3).Finally, we investigated the influence of anuria on observed parameters. Twenty-two patients (11.57%) were anuric with daily urine output <200 ml. The median age of anuric patients was 57±19 years, with PD duration 52±39.67 months vs. 21.5±19.25 months in patients with preserved RD (p=0.000000022). Anuric patients had lower Kt/V (1.88±0.31 vs. 2.47±0.37, p=0.0034), lower serum albumins (34.47±3.52 g/L vs. 38.07±4.17 g/L, p=0.000266) (Figure 9), lower BMI (23.65±2.43 kg/m^2 vs. 26.86±6.35 kg/m^2, p=0.041), and lower serum calcium (2.16±0.18 vs. 2,26±0.,17, p=0,014), but higher CRP (9.28±7.98 mg/L vs. 5.19±7.2 mg/L, p=0.015) and MIS score (7.38±3.46 vs. 3.31±2.82, p=0.00022) than patients with RD, respectively. Finally, anuric patients had a significantly higher iPTH (65.64±110.96 pmol/L vs. 32.7 pmol/L, p=0.0012).

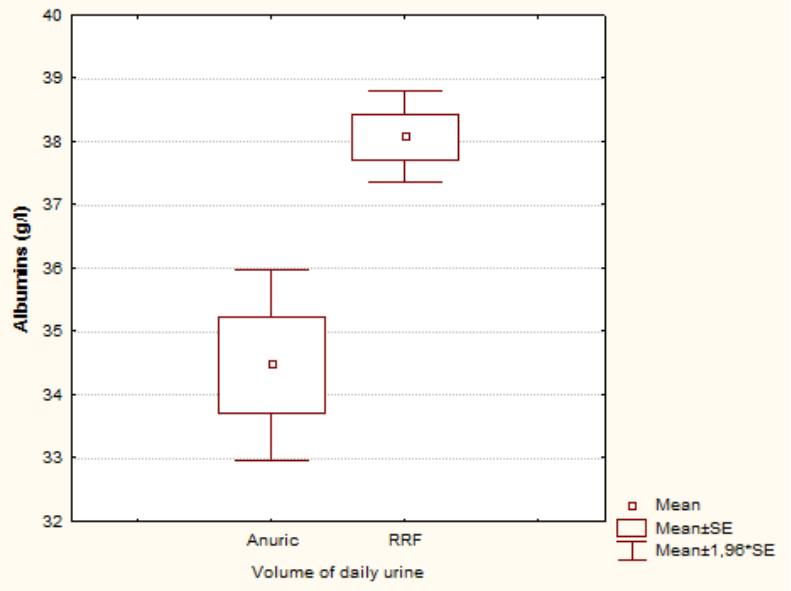

Fig. 9. Serum albumin and residual renal function. Anuric patients had significantly lower serum albumin compared to patients with residual diuresis (RRF)

Discussion

In the present cross-sectional study, we investigated the association between residual diuresis and nutritional status and other potential cardiovascular risk factors in Croatian PD population. All patients on renal replacement therapy with PD in Croatia, from 13 different dialysis centers, were included in this study. This is the first study, to our knowledge, that provides a national overview of the nutritional status of current PD patients.
The mean PD duration was 24.96±24.43 months. A relatively short PD duration is a consequence of the extremely well-developed renal transplant program in Croatia with an average waiting time of less than two years, what causes drop-out of many PD patients very soon after starting with the method.
Hypoalbuminemia is a well-known adverse factor for progressive left ventricular hypertrophy, left ventricular dilation and cardiac failure in dialysis patients, thus contributing to CV mortality in the dialysis population [14-16]. Previous studies have confirmed the importance of urea clearance and nutritional status in predicting the survival of dialysis patients [17-21]. In our cohort, residual diuresis correlated with nutritional parameters (serum albumin, MIS, SGA, BMI and hip circumference), but interestingly, not with waist or brachial circumference. Additionally, anuric patients had lower dialysis adequacy (Kt/V), nutritional parameters (serum albumins, BMI), and higher CRP and MIS, thus having additionally increased risk for CV disease [22], and PEW.
Our results suggest that patients with better preserved RD were significantly less anemic despite having a lower requirement for EPO, which may decrease the risk for developing left ventricular hypertrophy [23], as well as other negative cardiovascular events [24].
Patients with preserved residual diuresis had a lower iPTH; without impacting serum phosphorus in Croatian PD patients. Disordered mineral bone metabolism was not a significant adverse factor for loss of residual diuresis in previous studies [25]. Lopez-Menchero *et al.* analyzed the impact of RD on mineral bone metabolism in 37 PD patients and showed that RD was significantly correlated with serum phosphate levels (r(2)=0.19; beta=-0.594), but not with calcium or PTH [26]. Dong *et al.* found a low prevalence of hyperphosphatemia in those with RD and anuric patients [27]. The main difference between our results and previous studies may be due to the widespread use of phosphate binders, espe-

cially sevelamer, in those studies. In the Croatian PD population, there is a flexible approach to sevelamer use; through our phosphate education program less phosphate binders are used overall as it depends on the phosphate content in foods.

Hypertension is the primary contributory factor to cardiovascular mortality in the dialysis population. There was no correlation between arterial hypertension, smoking status or dyslipidemia with RD in Croatian PD population. Menon *et al.* have shown that residual urine output ($P<0.001$) was an independent risk factor for poor BP control [28]. In a meta-analysis, long-term use (≥12 months) of ACEis or ARBs showed additional benefits of preserving residual kidney function in CAPD patients, with no significant difference on residual kidney function preservation between ARBs and ACEis. Zhang *et al.* concluded that, there is currently insufficient evidence to support the use of an ACEi or an ARB as first line antihypertensive therapy in PD patients because of small number of RCTs with small number of participants [29]. This suggests that the major problem with hypertension control in anuric patients is volume control in peritoneal dialysis [30]. Use of bioimpendance for estimation of potential volume overload might explain lack of correlation between arterial hypertension and RD in our population.

There is evidence of an association between peritonitis episodes and loss of RD [31,32]. This was not found in our population. However, we found a correlation between the number of peritonitis episodes and use of icodextrin, demonstrating the loss of ultrafiltration capacity. Patients using icodextrin were found to have much greater net ultrafiltration (UF) and a lower incidence of negative net UF compared to solutions with different glucose concentrations. A recent Cochrane meta-analysis concluded that whereas icodextrin increased ultrafiltration compared with a standard 2.27 g/L glucose exchange, it had no effect on RD [33]. In the present study, we showed correlations between the use of icodextrin and numerous cardiovascular risk factors (Table 3) such as anemia, hyperphosphatemia and hypoalbuminemia, but not with MIS or SGA.

Many studies have investigated the role of residual diuresis compared with peritoneal clearance and factors associated with its preservation [9-11,34]. All these studies have come to the same conclusion; peritoneal clearance may not substitute the loss of residual diuresis [9,10]. Thus, every effort should be made, by health care professionals, to slow down the decrease in residual diuresis. Results from this study suggest that in order to decrease the rate of RD loss in patients treated with PD, the following has to be done: strict control of blood pressure, avoidance of nephrotoxic agents, optimal control of blood glucose in patients with diabetes mellitus and the use of ACE inhibitors or A-II receptor antagonists, both in patients with diabetic nephropathy and in patients with other causes of kidney failure. Additionally, loop diuretics should be used to increase salt and water excretion, urinary tract infections should be treated, metabolic bone disease should be prevented and treated, and finally, nutritional status should be maintained [13]. Thus, an integrative approach, individualized for each patient's characteristics may decrease the rate of RD loss in PD population, keeping in mind the increased risk for development of cardiovascular diseases in patients with end-stage renal disease [35-37].

MIS is a valuable tool for identifying patients with protein energy wasting [38-40]. The Croatian society for nephrology, dialysis and transplantation has included MIS in the routine screening of dialysis patients. However, MIS is rarely used in clinical practice, and data about its application in peritoneal dialysis patients is scarce [41,42]). To the best of our knowledge, in the present study, for the first time, we demonstrated a correlation between MIS and residual diuresis thus highlighting its additional importance in clinical practice, and the importance of preventing and treating PEW.

The limitation of our study, in addition to the fact that it is an observational study and does not show cause and effect, is our estimation of residual diuresis by volume of residual urine. Clinically, RD is assessed by evaluating 24-h urine clearances and determining the arithmetic average of creatinine clearance (Cl_c) and urea clearance (Cl_u) [43,44]. However, even contemporary methods are all unreliable and either underestimate or overestimate GFR in patients on PD [45,46]. However, this study represents a nation and not one particular clinic, which is its advantage. It provides insight into the clinical practice and current status of peritoneal dialysis in the country, which may influence standard of care and health policy in Croatia.

Conclusion

In conclusion, our study demonstrated a significant correlation between RD (measured as residual diuresis) with MIS, nutritional status and other cardiovascular risk factors in PD patients. By preserving RD and maintaining nutritional status we may possibly decrease cardiovascular mortality which is the leading cause of death in dialysis population.

Practical application: Our results for the first time emphasize the role of MIS in follow-up of patients treated with peritoneal dialysis, and correlates MIS with residual diuresis. Every effort should be invested to preserve residual diuresis, and to lower MIS score.

Conflict of interest statement. None declared.

Reference

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Original article

Kidney Transplantation Program in Montenegro

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Abstract

Introduction. There was no transplantation program in Montenegro until 2012. On the other hand, there were 93 patients with transplanted kidney. These transplantations were performed abroad; 15% in areas of black organ markets (India, Pakistan, Russian Federation). Beside the ethical problems, these transplantations carried a high risk of complications.

Methods. Our health system had to ensure solution for patients with terminal organ failure. Preparation of all neccessary conditions for the beginning of transplantation program in Montenegro started in 2006 with different activities including public, legal, medical, educational and international cooperation aspects.

Results. The first kidney transplantation from living donor in Montenegro was preformed on September 25th, 2012. In the period from 2012 until now 23 kidney transplantations from living related donor were performed and one kidney transplantation from deceased donor in the Clinical Center of Montenegro. In the a two year-follow-up period, all patients to whom kidney transplantation was performed are in a good condition and without serious complications in posttransplant period.

Conclusion. Development of the transplantation program allowed controlled transplantation and safety of patients. Our next steps are development of deceased organ donor transplantation and achievement of higher rate of deceased donor organ transplantation and individualization of immunosuppressive therapy.

Key words: transplantation program, living donor, deceased donor, transplant tourism

Introduction

Kidney transplantation is considered the treatment of choice for patients with end-stage renal disease (ESRD). Advantages of kidney transplantation in relation to dialysis are reflected in the better quality of life and prolonged survival in renal transplant recipients.

Until 25th of September 2012, since we have started transplantation program in Montenegro, patients from Montenegro who needed kidney transplantation, could not undergo this procedure in the institutions of the health system of Montenegro, due to lack of legal, ethical and medical conditions, necessary for transplantation program. In patients who had living related donors for kidney transplantation, transplantations were performed in medical institutions in neighboring countries with existing transplantation program such as Croatia, Serbia, Bosnia and Herzegovina. However, a large number of patients who needed kidney transplantation had no living related donors. Montenegro is one of the states which signed the Istanbul Declaration that strictly prohibits trafficking in human organs. Nevertheless, patients from Montenegro, who aspired to have a better quality of life and who wanted to avoid dialysis complications have decided to purchase necessary organs illegally and to perform kidney transplantation in countries with a black market of organs or to go for a transplantation in states in which it was legally possible for foreigners to be placed on a waiting list for a kidney transplantation. The development of transplantation program in Montenegro is organized and planned through all the necessary segments such as: legislation, international collaboration, education, provision of necessary infrastructure for the development of the program and raising and dissemination of knowledge about the importance of this program in the professional and general population.

In February 2011 Montenegro became a full member of RHDC - Regional Health Development Center, which is part of SEEHN - South East European Health Network, and which regional center is in Zagreb. RHDC is an organization and project supported by the Council of Europe, with aim to develop transplantation medicine in countries of South-Eastern Europe and to establish all necessary conditions for the development of transplantation in South-Eastern Europe. The most important

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issue to be accomplished in the international cooperation was signing of the collaboration agreement between the Ministry of Health of Montenegro and the Republic of Croatia, which happened in April 2012. According to this agreement, Montenegro specialists can fully count on the cooperation with Croatian experts in regard to the education of our staff and performing transplantations. Today Croatia, with its own model of organ transplantation, has become one of the leading countries in Europe, and with the number of kidney and liver transplantations, has became a leading country globally since 2012.

The bilateral agreement on collaboration in the field of transplantation program was signed between Montenegro and Croatia on 23rd of October 2013. In line with this agreement, patients from Montenegro who need organ transplantation from deceased donors, who do not have living related donor, can be placed on waiting lists in Croatia or the Eurotransplant waiting lists. The contract involves reciprocity, i.e. depending on involvement of donation of organs from cadavers and on the number of organs from deceased donors given in the Eurotransplant system, the same number of patients from Montenegro could be put on waiting lists in Croatia for obtaining solid organs such as liver and heart. According to the contract signed between our country and the Ministries of Health, explanted kidneys from deceased donors in Montenegro, stay in Montenegro and transplantations are performed for patients who are on the waiting list for a kidney in Montenegro. If we cannot find a potential recipient who has immunological and medical eligibility for treatment with kidney transplantation, explanted kidneys will go to the Eurotransplant system and will be allocated according to the principles of allocation in the Eurotransplant.

In the present study we evaluate current status of renal transplantation in Montenegro.

Materials and methods

This study includes data about kidney transplantation in Montenegro until 2012, data about kidney transplantations conducted in centers outside the health system of Montenegro, as well as data on renal transplantation since the establishment of the transplantation program performed at the Clinical Center of Montenegro. The observed period of monitoring of patient and graft survival after transplantation covers a period of 13 years, from 2002 to 2015. Standard statistical methods of data analyses were used.

Results

In the period from 2002 to 2012, 95 patients from Montenegro were treated by kidney transplantation in different centers in the region and abroad. Since the establishment of the transplantation program in the health system of Montenegro, a total of 24 kidney transplantations in the Clinical Center of Montenegro were conducted. Distribution of the number of transplantations in the reporting period is shown in Figure 1.

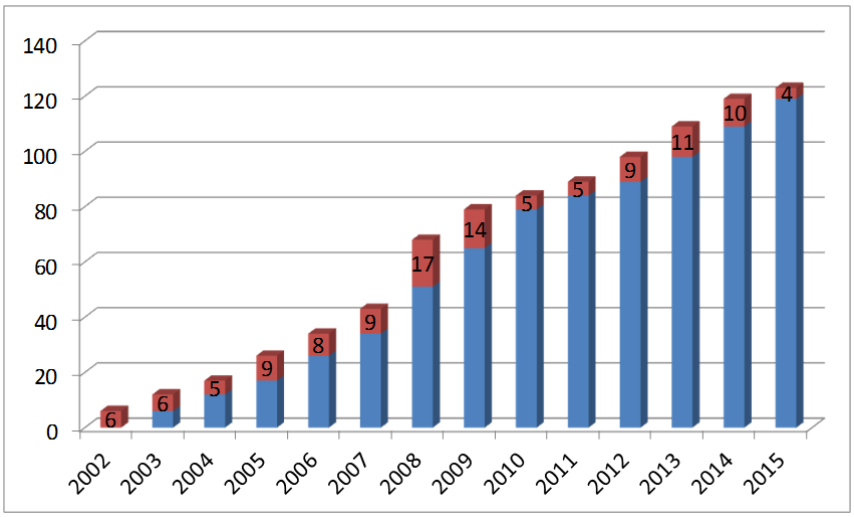

Fig. 1. Number of patients with kidney transplant by year of kidney transplantation (cumulative and new). Upper parts of the bars represent new patients.

According to the type of donor, in the reporting period, 77 kidney transplantations from living related donor were performed (65.2%), 27 kidney transplantations from deceased donors (22.8%) and 14 transplantations (12%) from a living unrelated donor.

The largest number of living related transplantations was performed in clinics of the neighboring countries. The largest number of such transplantations were done in the Clinical Center of Serbia, Belgrade (33), then in the Military Medical Academy, Belgrade, Serbia (11), in the Clinical Center of Rijeka, Croatia (6), the Clinical

Center of Sarajevo, Bosnia and Herzegovina (1), while 2 such transplantations were performed in Paris (France). Since the establishment of organ transplantation in the Clinical Centre of Montenegro 23 kidney transplantations from living related donors have been done. One kidney transplantation from living related donor was done in the Clinical Hospital Center Zagreb, Croatia.

Kidney transplantation from deceased donors of patients from Montenegro in the reporting period were performed in clinical centers abroad where it was possible, according to the applicable legal norms of those countries where those patients could be put on waiting lists with adequate financial compensation. Most of those kidney transplantations were made in Moscow, Russian Federation. In the Federal Medical Biological Agency, University Hospital, 119 - Moscow, Russia in the reporting period, 18 kidney transplantations from deceased donors were performed in patients from Montenegro. In the Hematology Clinical Center of Moscow, Russia two kidney transplantations from deceased donors, and in the Institute NV Sklifosovskog, Moscow, one kidney transplantation from deceased donor was performed. One kidney transplantation from deceased donor was performed in Lyon, France, one in Vienna, Austria, and one in Turin, Italy. Two kidney transplantations from deceased donor, which was actually a double kidney and pancreas transplantation, were performed in the Clinical Center Merkur, Zagreb, Croatia, which had ESRD due to diabetic nephropathy as a consequence of diabetes mellitus type I. Since these patients had a double, Montenegrin and Croatian citizenship, they could be placed on the waiting list of Eurotransplant in Croatia.

Among the patients with kidney transplantation from Montenegro in the reporting period, there are 14 patients in whom kidney transplantations were performed in third world countries, where black market organs exist. In the absence of a living donor and deceased donor transplantation program, searching better quality of life, patients went on the black market of organs (India, Pakistan), where they had kidney transplantation. In this period, kidney transplantations from a living unrelated donor were performed in 12 patients in the Aalil Hospital Lahore in Pakistan and in 2 patients in the New Delhi Star Medical Center in India.

The first realized kidney transplantation from deceased donor in the Clinical Center of Montenegro was carried out on 8th of December 2013. Harvested organs were allocated according to the rules of Eurotransplant within the same network. Liver from deceased donor was allocated in the Clinical Center of Zagreb, and the heart was allocated in the Clinical Center of Ljubljana, Slovenia. After this Montenegro became a part of the Eurotransplant system. Based on the previously signed bilateral agreements on collaboration in the field of organ transplantation between Montenegro and Croatia, kidneys from deceased donors were allocated to patients who were on the waiting list for kidney transplantation in Montenegro, with the highest number of points scoring by the rules obtained by the Eurotransplant. One kidney, unfortunately, could not be used due to previous surgical treatment on that kidney, damaged by a high degree of fibrosis due to nephropexy.

In the observed period of 13 years, there were a total number of 118 patients with kidney transplantation, of which terminal graft dysfunction was found in 6 patients, and they restarted the chronic hemodialysis program while in the same period of follow-up, 6 patients died.

Four patients died with normal graft function (accidental death or due to other diseases), while two patients died after the allograft lost.

Since September 2012, 24 kidney transplantations were performed in the Clinical Center of Montenegro. In 2012, 2 kidney transplantations from living related donors were performed; 9 living related kidney transplantations were performed during 2013 as well as one transplantation from the deceased donor; eight kidney transplantations from living related donor were done during 2014 and four kidney transplantations during 2015.

Discussion

The population of ESRD patients is increasing globally. There were 2,876 million of ESRD patients at end of 2011, with an annual growth rate of 6-7% in the general population [1]. Organ transplantation has been one of the greatest medical achievements of the twentieth century, which has significantly improved the quality of life, prolonged life for hundreds and thousands of patients worldwide [2].

The incidence of transplantation was greater than 30 pmp in 2010 in Western Europe, USA and Australia [3]. Developing countries often have a low incidence of transplantation due to many factors including poor infrastructure and lack of educated medical staff. Organ transplantation is determined by individual national circumstances, which include:

1. legally established principles of transplantation medicine (standard operating protocols testing potential organ donors and recipients);
2. whether it is legally determined to be organ donors from? brain dead person (cadaver) or patients with cardiorespiratory death (NHBD - non-heart beating donors), or there is no regulation and legislation;
3. is there a waiting list of patients for transplantation to the compelling need of various organs;
4. the cost of health care;
5. the availability of organs for transplantation;
6. the level of technical capacity as well as the availability of organs for transplantation [4].

In the early 90s of the twentieth century transplantation tourism was in the focus, as an usual concept in the medical practice [5]. Medical tourism in general refers to patients who travel abroad for the purpose of obtaining

health services. Patients were traveling abroad because in their countries the particular type of treatment was not available or the quality of medical services was not appropriate. Medical tourism is a global phenomenon in the health care system and in 2006 for the purpose of medical tourism $60 million was spent in the world [6]. The problem itself is reflected in the new entities and special forms of medical tourism, such as transplantation tourism. World escalation in the number of patients with renal diseases, the increased demand for kidney transplantation, the lack of organs and dying patients on waiting lists has led to the phenomenon of transplant tourism [7].

The World Health Organization (WHO) in 2004 urged Member States "to take measures to protect the poorest and vulnerable groups from transplantation tourism and the sale of organs and tissues, paying attention to the issue of international sale of human organs and tissues" [8]. In order to respond to urgent and growing problems of organ sales, transplantation tourism in the context of the global shortage of organs the Summit in Istanbul was organized. The conclusions have been defined as the Istanbul Declaration. The basic principles of the Istanbul Declaration are: all states should have a legal and professional framework to govern organ donation and transplantation activities, as well as a transparent and orderly supervision, monitoring activities, which ensure the safety of the donor and recipient and enforcement of standards and prohibitions on unethical practices [9]. Transplant tourism has always been surrounded by controversy: where is the source of authority, care of donors after transplantation and transplant outcome [10]. Within the growing need to increase the number of transplantations, an insufficient number of altruistic transplantation has led to almost legalizing organ market as an incentive of organ donation. Transplant tourism coincides with high surgical complications, acute rejection of transplanted organs, the presence of severe infection as the most common cause of major morbidity and mortality in these patients. Transplant tourism is fueled by several factors, such as: deep gap between rich and poor people, easier way to travel, the globalization of the world as well as difficulties in securing legal principles. As key determinants of transplant tourism should be particularly emphasized the number of patients on waiting lists in developing countries, as well as those patients who are not on the waiting lists; people who mediate transplantation tourism (professionals: doctors, surgeons and unprofessional persons: sellers of organs, brokers, mediators in the sale of organs); countries exporting organs, and organ dealers [11-15]. Graft and patients survival after kidney transplantation performed in countries where there are black organ markets, upon their return, and follow-up in the home center was not significantly less according to most studies that have addressed this issue, but it is fraught with far greater number of serious complications after transplantation [16,17]. Survival of patients and grafts in patients in Montenegro, who had kidney transplantation as a result of transplantation tourism, was not statistically significantly lower compared to the results obtained from other systems and studies (mortality at 13-year follow up to 5.08%). However, it was associated with a large number of different complications that had to be treated in institutions of our health care system, both because of their complexity and seriousness.

Conclusion

The problems of transplantation medicine which have been related to all aspects (legal, medical and ethical) demanded a doctrine for the current period, which is based on the recommendations and principles of the Istanbul Declaration. The Istanbul Declaration seeks to promote and preserve humanity act of organ donation, a well-ordered state, clear legal regulation of the health care system and the need for further development of the best modalities of transplantation medicine guaranteeing a reduction in medical, and thus transplant tourism. Well-organized system of health care will provide the most important premise of scientific and medical postulates of transplantation medicine, which includes: continuing education of personnel, transparent waiting lists and adequate evaluation of the donor and recipient. Implementation of the law, with strict adherence to ethical principles and scientific doctrine and with adequate training of transplant experts are the main prerequisite for the development of modern and sophisticated transplantation medicine.

The establishment of transplantation programs in the health system of Montenegro ensures the safety of patients who need this type of treatment, controlled by the applicable protocols and principles of good medical and clinical practice, and provides avoiding of complications.

In parallel with the development of living related transplantation systematic and intensive work on developing a program to deceased donor transplantation must be organized and implemented, because it is the only solution for patients who do not have a living related organ donors, and for patients who are in the terminal organ failure who cannot be treated with transplantation from a living donor, such as patients with heart or liver failure. A lot has been done to create conditions for the beginning of this complex program in our health care system, but much more remains to be done.

Conflict of interest statement. None declared.

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Original article

Association Between Hypertension and Residual Renal Function in Hemodialysis Patients

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Abstract

Introduction. Cardiovascular diseases are the leading cause of death in hemodialysis patients. The decline of residual renal function increases the prevalence and severity of risk factors of cardiovascular morbidity and mortality in these patients. Hypertension is common in dialysis patients and represents an important independent factor of survival in these patients.

Methods. The study included 77 patients who are on chronic HD for longer than 3 months. Depending on the measured residual diuresis patients were divided into two groups. The study group consisted of patients with residual diuresis >250 ml/day, while patients from control group had residual diuresis <250 ml/day. All patients had their blood pressure measured before 10 consecutive hemodialysis treatments. Collected data were statistically analyzed using SPSS 16.0.

Results. The study included 77 hemodialysis patients, mean age of 56.56±14.6 years and mean duration of hemodialysis treatment of 24.0 months. Of the total number of patients, 39(50.6%) had preserved residual renal function. Hypertension was more common in the group of patients who did not have preserved residual renal function (68.4% vs 25.6%). There was statistically significant negative linear correlation between the volume of residual urine output and the residual clearance of urea and values of systolic blood pressure [(rho=-0.388; p<0.0001); (rho=-0.392; p<0.0005)], values of mean arterial pressure [(rho =-0.272; p<0.05); (rho=-0.261; p=0.023; p<0.05)] and values of pulse pressure in hemodialysis patients [(rho =-0.387; p<0.001); (rho=-0.400; p<0.0005)].

Conclusions. Residual renal function plays an important role in controlling blood pressure in patients on hemodialysis. More attention should be directed to preserve residual renal function, and after the start of hemodialysis by avoiding intensive ultrafiltration with optimal antihypertensive therapy.

Key words: hypertension, chronic renal failure, residual renal function

Introduction

Life expectancy among patients with chronic kidney disease (CKD), especially among those with end-stage renal disease (ESRD) has decreased, and is significantly lower than in the general population. The leading causes of morbidity and mortality among dialysis patients with ESRD are cardiovascular diseases (CVD), reported to be responsible for 50% mortality rate in these patients [1].

In 1995, Maiorca *et al*. were among the first to note an independent relationship between the presence of residual renal function and survival in patients on dialysis [2]. Residual renal function (RRF) is an important predictor of survival in peritoneal dialysis (PD) patients but its role in hemodialysis (HD) patients is less known. Loss of RRF is associated with higher arterial pressure, more severe anemia, greater degree of inflammation and malnutrition, and greater cardiac hypertrophy, all of which contribute to increased cardiovascular events in dialysis patients [3,7]. Thus, patients on hemodialysis (HD) had more rapid reductions in their RRF than those on peritoneal dialysis (PD) [4]. Hemodialysis seems to be worse than peritoneal dialysis (PD), probably because sudden drops in blood pressure are more likely in hemodialysis, since fluid is removed much more quickly during short hemodialysis sessions as compared to the longer treatment cycles in PD. A study conducted in the Netherlands showed an association between intradialytic hypotension/decrease in systolic blood pressure and decline of RRF [4,5]. These findings are corroborated by reported relations between diastolic blood pressure and decline of RRF [5,6]. A correlation between degree of volume expansion and urine output in a recent report has been used as the basis for suggesting that a certain degree of fluid overload may preserve RRF [7,14]. The CHOICE study provides evidence for several beneficial effects of RRF in HD patients. The study demonstrates a strong and independent relationship between a simply obtained urine output assess-

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ment and survival as well as improved QOL, lower inflammation and less EPO use in a national prospective cohort study of 734 incident HD patients [7].
RRF may be measured or estimated. The simplest measure of RRF is urine volume. Despite its shortcomings, urine volume has been correlated to GFR in studies, and most authors defined loss of RRF as estimated urine volume ≤ 200 mL/ 24 hour.
Aim of our stady was was the role of residual renal function in controlling blood pressure in patients with hemodialysis.

Material and methods

The study was conducted as intersection, prospective, clinical, comparative and descriptive study at the Clinic of Hemodialysis, Clinical Center of the University of Sarajevo. The study included 77 CKD patients.
Inclusion criteria: patients who received regular hemodialysis treatment three times a week, were age >18 and <75 years and agreed to participate in the study. The exclusion criteria were patients in hemodialysis treatment for less than three months and uncontrolled blood pressure. All patients provided informed consent for participation in the study. Depending on the measured residual diuresis patients were divided into two groups. The study group consisted of patients with residual diuresis >250 ml/day (n= 39), while patients from control group had residual diuresis <250 ml/day (n=38).
The following clinical and laboratory data of the groups were assessed: systolic blood pressure (SBP), diastolic blood pressure (DBP), length of hemodialysis treatment (LHT), urinary 24-hour volume (UV24hs), hemoglobin (Hb), serum calcium (Ca), serum phosphorus (P), parathormone (PTH), serum albumin (Alb).
All patients had their blood pressure measured before 10 consecutive hemodialysis treatments. The SBP and DBP were immediately obtained before the HD session using the arm opposite the AV fistula and represented the average of the last ten HD sessions. Mean arterial blood pressure (MAP) was calculated using the formula MAP= *(SBP-DBP)/3+DBP* and pulse pressure (PP) was calculated using the formula PP=*(SBP-DBP)*.
The residual urine output (UV) was collected during the interdialytic period. Interdialytic period is the time between two dialysis. (When postdialysis blood is collected for urea measurement, the patients empty their bladder. From this time, all urine collected and brought to dialysis unit when patient returns for the next dialysis).
In patients with residual diuresis residual clearance of urea was calculated using the following formula:

rCl U= (UV x UrU / ID Period) / Mean BUN

Mean BUN = (U1 + U2) / 2

UV -Urine Volume
ID -Interdialytic period
UrU -Urine Urea Concentation
U 2-the BUN just prior to the second dialysis of the week
U1-the BUN just after the first dialysis of the week

Interdialytic weight gain (iWG) represents the difference between body weight immediately after the HD session, and the weight obtained immediately before the next HD session. The iWG value was considered the arithmetic average of the last ten HD sessions. The assessment of adequacy of dialysis was done using the Kt/V index. Kt/V is defined as the dialyzer clearance of urea multiplied by the duration of the dialysis treatment divided by the volume of distribution of urea in the body.
Hypertension was determined according to the WHO criteria (office BP 140/90 and/or the use of antihypertensive therapy).

Blood analyses

All biochemical parameters were measured by commercial kits according to the manufacturer's instructions. Intact PTH was determined by immunoradiometrict assay on the gamma counter at the Institute of Nuclear Medicine, Clinical Center Sarajevo (reference range 10-65 pg/L, approximately three times the value of the upper limit of the reference interval is recommended for patients on dialysis). C-reactive protein CRP (reference range 0-5 mg/l) was measured by nephelometric method (quantitative measurement), and Hb-Hb (ref. range 138-175 g/L), serum calcium Ca (ref. 2 interval, 10 to 2.55 mmol/L, phosphorus P (ref. range 0.81 to 1.58 mmol/L) and serum albumin -Alba (ref. range from 35.0 to 50.0 g/L) were performed at the Institute of Clinical Chemistry and Biochemistry by standard laboratory procedures.

Statistical analysis

Measurements for normally distributed variables are reported as mean + standard error; median values and interquartile range are used to describe non-normaly distributed variables. Difference between the groups was assessed by the Student's t-test or Mann-Whitney U test. Values lower than 0.05 were considered significant. Spearman's correlation coefficient was used. Collected data were statistically analyzed using SPSS 16.0.

Results

The research involved 77(100%) hemodialysis patients, of whom 39(50.6%) had preserved residual renal function and residual diuresis >250 ml/24 hour.
The average diuresis of patients with preserved RRF was 1000.00 ml/24H (500.0-1300.00 ml/24H).
There was no evidence of a statistically significant difference in gender distribution of patients in comparison to other groups (p> 0.05).
The average age of patients in the study was 56.56±14.6 years. The average duration of hemodialysis treatment was 24.0 months (12.0 to 43.5 months). The average age

of patients with preserved RRF was less but not statistically significant compared to the average age of patients without preserved RRF. The median duration of hemodialysis treatment in the group of patients with preserved RRF was significantly lower than the mean value of the duration of hemodialysis treatment in the group of patients without preserved RRF. Average interdialytic weight gain in the group of patients with preserved RRF was also decreased significantly with respect to the average weight gain in the group of patients without preserved RRF (Table 1).

Primary renal diseases that led to the end-stage of renal failure in both groups were hypertension and diabetes mellitus, taking into concern that the group of patients without preserved RRF had more frequent hypertension, but not statistically significant (18 vs. 34%) (Table 1).

Table 1. Gender distribution, age, duration of hemodialysis treatment, interdialytic weight gain and primary renal disease in the observed group of patients

	With RRF		**Without RRF**		**p<**
	n	**%**	**n**	**%**	
Total	39	100	38	100	
Female/male?	25	64.1	28	73.3	ns
Female	14	35.9	10	26.3	ns
Age (years)	58.0		60.0		ns
Duration of HD (months)	16.0 (7.0-26.0)		38.0 (24.0-69.0)		0.0001
Interdialytic weight gain	2.4 (1.8 – 2.6)		3.5 (3.0 –4.0)		0.001
Hypertension	7	18	13	34	ns
Diabetes mellitus	9	23	8	22	ns
ADPKD	6	15	4	11	ns
GN chr	6	15	6	16	ns
Pn chr	6	15	3	8	ns
miscellaneous	4	10	3	8	ns
unknown	1	3	1	3	ns

Table 2 shows the value of clinical laboratory parameters in serum of hemodialysis patients with preserved and without residual renal function. C-reactive protein (CRP), phosphorus (P) and parathyroid hormone (PTH) levels in hemodialysis patients without preserved RRF were significantly higher compared to the same parameters in hemodialysis patients with preserved RRF. There were no significant differences in the concentrations of albumin, hemoglobin and calcium among patients with preserved RRF and those without preserved RRF.

Table 2. Clinical and laboratory parameters of groups

	With RRF (n=39)	**Without RRF (n=38)**	**p<**
C Reactive Protein (mg/L)	3.2 (1.7 – 7.1)	6.0 (4.1 – 10.3)	0.05
Albumin (g/L)	36.56 ± 0.62	36.03 ± 0.69	NS
Hemoglobin (g/L)	102.0 (98.0 – 112.0)	101.5 (96.5 – 107.0)	NS
Serum Phosphorus (mmol/L)	1.5 (1.2 – 1.9)	2.1 (1.6 – 2.3)	0.0001
Serum Calcium (mmol/L)	2.21 ± 0.03	2.25 ± 0.03	NS
PTH level (pmol/L)	226.24 ± 18.90	504.37 ± 46.01	0.0001

Table 3 presents difference in the prevalence of patients with hypertension and values of hemodynamic parameters in hemodialysis patients with and without preserved residual renal function. In the group of patients without preserved RRF hypertension was frequent (74.4% vs 25.6%) (χ^2*=14.149; p=0.0002; p<0.001).* The values of systolic blood pressure, mean arterial pressure and pulse pressure in hemodialysis patients without preserved RRF were significantly higher than those in the group of hemodialysis patients with preserved RRF. No significant differences in the values of diastolic blood pressure among patients with and without preserved RRF were found.

There was a statistically significant negative linear correlation between the volume of residual urine output and systolic blood pressure in hemodialysis patients (rho= -0.388; p<0.0001).

We also confirmed a statistically significant negative linear correlation between residual clearance of urea and systolic blood pressure in hemodialysis patients (rho=-0.392; p<0.0005).

Table 3. Presence of hypertension and hemodynamic parameters in the observed group

	With RRF (n=39)		Without RRF (n=38)		p<
	n	%	n	%	
With hypertension	10	25.6	26	68.4	
Without hypertension	29	74.4	12	31.6	
Systolic blood pressure BP (mmHg)	130.0(120.0-143.0)		150.0(140.0-160.0)		0.0001
Diastolic blood pressure DBP (mmHg)	80.0(70.0-80.0)		80.0(70.0-90.0)		NS
Mean arterial pressure MAP (mmHg)	95.5 ± 0.9		101.2 ± 2.1		0.05
Pulse pressure PP (mmHg)	57.0(40.0-65.0)		70.0(60.0-80.0)		0.0001

Volume of residual urine output and residual urea clearance did not correlate to the value of diastolic blood pressure in hemodialysis patients [(rho=-0.093; p=0.421) (rho=-0.078; p=0.502)]. In addition, there was a statistically significant negative linear correlation between the volume of residual urine output and the value of mean arterial pressure in hemodialysis patients (rho=-0.272; p<0.05). We also confirmed a statistically significant negative linear correlation between residual urea clearance and values of mean arterial pressure in hemodialysis patients (rho=-0.261; p=0.023; p<0.05).

A strong statistically significant negative linear correlation between the volume of residual urine output and the value of pulse pressure was observed in the analyzed groups (rho = -0.387; p <0.001) (Figure 1).

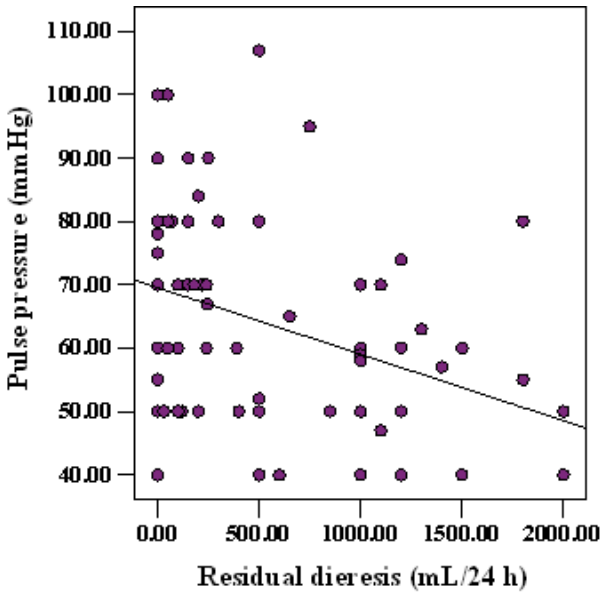

Fig. 1. Correlation between residual diuresis and pulse pressure rho= - 0.387, p<0.001

We also confirmed a strong statistically significant negative linear correlation between residual urea clearance and the value of pulse pressure in hemodialysis patients (rho=-0.400; p<0.0005) (Figure 2).

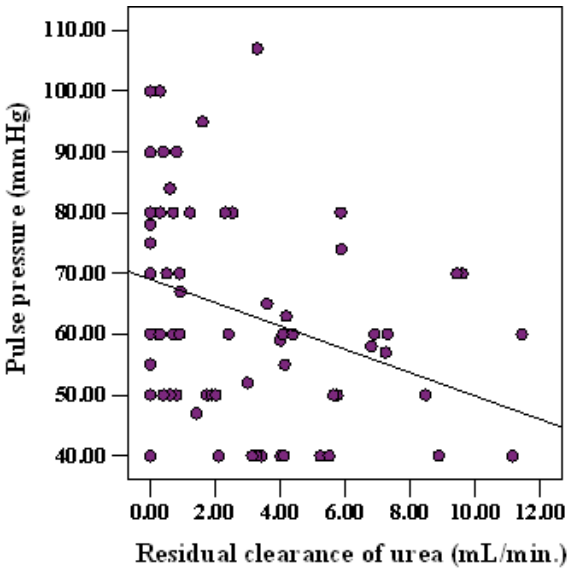

Fig. 2. Correlation between residual clearance of urea and pulse pressure rho= - 0.400, p<0.0005

Discussion

The role and importance of preserving residual diuresis or residual renal function (RRF) is recognized and clearly defined in patients treated by peritoneal dialysis, and residual diuresis is considered the "heart" of peritoneal dialysis. It has been shown that preserving RRF plays an important role in patients on hemodialysis in recent years [3,4,13]. Accurate measurement of RRF in patients with chronic renal failure remains a challenge. The most commonly recommended average value are the sum of creatinine clearance and the clearance of urea [4]. Values of residual urea clearance and diuresis have been used to estimate RRF. If the residual urea clearance was less than 1 ml/min and the daily urine output of less than 200 ml, then RRF was lost, which was supported by other researchers [4,8]. There are various factors that have an impact on the loss of RRF. It is believed that the length of hemodialysis treatment is one of the factors contributing to the loss of RRF [6]. In our study, patients without preserved RRF had significantly longer duration of hemodialysis compared to patients with preserved RRF (38.0 vs.16,0 months, p<0.0005).

One of the important factors in the development of heart disease and vascular disease in patients with CKD is anemia, which occurs in the early stages of CKD. Patients with preserved RRF have better control of anemia [8]. Our research has not found a significant difference regarding hemoglobin of patients with and without preserved RRF. Although the loss of RRF was linked with hypoalbuminemia in the studies of some authors, our study results did not find significant difference in albumin concentrations in the two groups. Hyperphosphatemia is common in dialysis patients. It is associated with the development of vascular calcification, and an increased risk of cardiovascular diseases [10,11]. RRF role in controlling the balance of phosphate is clearly proven in patients on PD and patients on hemodyalisis [9]. In our study there was a significant difference in the level of phosphorus in the observed groups. Patients with preserved RRF had lower values of serum phosphorus in comparison to patients without RRF (1.5 vs. 2.1, p <0.001). In addition to phosphorus, an important factor associated with an increased risk of cardiovascular diseases is secondary hyperparathyroidism. In our study, we showed that patients with preserved RRF had significantly lower levels of parathyroid hormone compared to patients without preserved RRF (226.24 vs. 504.37, p <0.001).
Hypertension is a common finding in patients treated with hemodialysis [11]. Although the causes of hypertension are multifactorial, the significance of the volume status impact in the control of blood pressure [15]. Patients with preserved RRF have better control of body water volume, hence it can be assumed that they will have better blood pressure control. Our research revealed a significant difference in interdialytic weight gain in the dialysis patients with and without preserved RRF (2.4 vs. 3.5, p<0.05), which clearly indicates that patients with preserved RRF have better body water volume control. Since hypertension in the majority of these patients depends on the volume status and considering that blood pressure is alternating between dialysis, there is no consensus of blood pressure (BP) values before and after hemodialysis needed in the diagnosis of hypertension. It is considered that predialysis values of BP exceeding 150/85 mmHg and postdialysis BP greater than 130/75 mmHg may be used as a threshold to define hypertension, with a sensitivity of at least 80% [15]. In our study, hypertension is defined as the value of BP greater than 140/90 mm Hg, measured as average value of blood predialysis pressures in ten consecutive hemodialysis treatments. Taking this into consideration, there is a statistically significant difference in the BP values in the two groups. Hypertension was more frequent in patients without preserved RRF (68.4 vs. 25.6%, p<0.001). Significantly higher values of systolic blood pressure (150 vs 130 mmHg, p<0.001), mean arterial (101.2 vs. 95.5, p<0.05) and pulse pressure (70.0 vs. 57.0, p<0.001) were found in patients without RRF, but not in the values of diastolic blood pressure. There was a positive linear correlation between the volume residual diuresis, residual urea clearance, systolic blood pressure (rho=-0.272, p<0.005; rho=-0.388, p<0.0001), mean arterial pressure (rho=-0.272, p<0.05; rho=-0.261, p<0.005) and pulse pressure (rho=-0.387, p<0.005; rho =-0.392, p<0.005). Pulse pressure per se is a better predictor of CV events and mortality in hemodialysis patients. Pulse pressure increase of 10 mmHg increases the risk of CV events by 22% [11,12].
The results of our study clearly show that patients with preserved RRF have a lower incidence of predialysis hypertension and significantly better control of blood pressure.

Conclusion

Residual renal function contributes significantly to the overall health and well-being of patients on hemodialysis. RRF has been implicated to be important in maintaining the fluid balance of patients on hemodialysis. Loss of RRF is associated with higher systolic blood pressure, higher mean arterial blood pressure and higher pulse pressure. RRF also plays an important role in phosphorus control, and removal of middle weight uremic toxins. Patients without RRF have more severe anemia, greater degree of inflammation and malnutrition. It is therefore crucial to develop effective therapeutic strategies that may preserve RRF in dialysis patients. Assessment of RRF is currently not part of routine hemodialysis care in our country. These results provide a strong rationale for routine monitoring of RRF in HD patients. Furthermore, development of methods to assess and preserve RRF is important and may improve dialysis care. Possible limitation of the study was the small study sample.

Conflict of interest statement. None declared.

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Short Communication

Is there any Gender Difference in the Association between Obesity, Chronic Kidney Disease and Anemia

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Abstract

Introduction. Nowadays, obesity has emerged as one of the most independent risk factors for chronic kidney disease (CKD) in both economically developed and undeveloped countries. The number of patients requiring dialysis as a consequence of obesity-related renal diseases, such as diabetes mellitus and hypertension, is increasing worldwide. Moreover, obesity has been shown to favorize the risk of cardiovascular diseases (CVD) with premature death due to CKD and/or end-stage renal disease (ESRD). The aim of the study was to investigate the association between obesity [e.g. body mass index (BMI)], kidney function [e.g. glomerular filtration rate (GFR)] and renal anemia in CKD patients.

Methods. Retrospectively, data from the register of 315 pre-dialysis patients with different stages of CKD not on erythropoiesis stimulation agents (ESAs) during the period between 1 Jan 2013-30 June 2013 were used to assess the association between the degree of CKD impairment with the degree of obesity and anemia. The stage and/or progression of CKD was calculated by GFR, while the degree of obesity by the body mass index (BMI). CKD was defined as a glomerular filtration rate (GFR) <60 mL/min per 1.73 m^2. Data analysis was performed by means of the simple Microsoft excel program.

Results. Within the study population of 315 CKD patients, 123 were males with mean age of 63.4±1.33 years and 192 females of 57.3±1.2 years. The GFR reduced with the increased BMI in both genders, and majority of patients (n=243) were in CKD stage 3, with a mean GFR of 44.5 ml/min/1.73 m^2. The BMI values in female patients with first and second degree of obesity negatively correlated with GFR ($r=-0.46$, $p<0.05$). Only female patients with second degree of obesity (BMI of 35-39.9 kg/m^2) had a positive correlation between the decreased renal function and reduced Hb levels.

Conclusions. Our study provided an unconditional evidence not only for the presence of an association between the degree of obesity (BMI) and the degree of renal function impairment (GFR), but also an association between the higher BMI and the higher degree of kidney anemia seen in women with second degree of obesity. Further larger scale trials and interventional studies are required to see the effect of body weight reduction on renal function and especially anemia.

Keywords: anemia, body mass index, chronic kidney disease, obesity, renal function

Introduction

Chronic kidney disease (CKD) has recently been recognized not only as a risk factor for end-stage renal disease (ESRD), but also for cardiovascular disease (CVD) which is the leading cause of death in developed countries [1,2]. Besides aging, a number of factors have been associated with CKD such as hypertension, impaired glucose tolerance or diabetes mellitus, dyslipidemia, obesity, and smoking [3,4]. Obesity has also been recognized as a factor related with CKD, but there has been no clear answer to an important question: which is the underlying mechanism of CKD developing in association with increased BMI. It is supposed to be related to the activated renin-angiotensin system, increased sympathetic nerve activity, insulin-resistance or hyperinsulinemia and dyslipidemia [3-5]. A significant association between CKD and BMI was recently found in men but not in women by two epidemiological studies done in Japan and in Singapore [6,7]. Approximate number of overweight persons in 2010 is around 1 billion adults and 475 million of those suffering from obesity [8], similar like worldwide "obesity epidemic". Although the effect of obesity might differ among races, obesity has a significant impact on CKD and ESRD [9]. The increasing number of obesity cases both in the developed and developing countries may be particularly due to the unbalanced diets and sedentary lifestyle [10]. Moreover, obesity is the leading cause of increased mortality worldwide because of the associated inflammatory metabolic disorders such as hypertension, cardiovascular and kidney diseases, dyslipidemia, glucose intolerance, and certain cancer diseases.

In spite of a progressive fall in the incidence of traditional risk factors of cardiovascular morbidity (cigarette smoking, high blood pressure, and hyperlipidemia), there

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is an upward trend in the prevalence of obesity and CKD. Furthermore, there is a strong correlation between BMI and the relative risk of progression of CKD. Predominance of oxidative stress in both obesity and azotemia stimulate synthesis of angiotensin II, which in turn increases TGF-B and plasminogen activator inhibitor-1, thereby propagating glomerular fibrosis. Furthermore, local synthesis of angiotensinogen by adipocytes, leptin activation of sympathetic nervous system, and hyperinsulinemia contribute to the development of hypertension in obesity and CKD. In addition, increased renal tubular expression of Na-K-ATPase and a blunted response to natiuretic hormones in obesity promote salt and water retention. Glomerular hyperfiltration from systemic volume load and hypertension results in mesangial cellular proliferation and progressive renal fibrosis [11]. Additionally, obesity-related kidney damage has been posited to be due to hyperlipidemia, increased oxidative stress, increased salt intake, and activation of the sympathetic nervous system [12].

We used the outpatient data in order to assess the degree of obesity in the cohort of registered patients with CKD, and to examine the possible impact of obesity on the degree of renal function impairment and renal anemia and possible gender difference.

Material and methods

Data of 315 patients with CKD from the outpatient nephrology register centre within the Hospital St. Anna Sofia in the period between 1 Jan. 2013-30 June 2013 were analyzed. All patients included into the study were with various CKD stage, none of them was receiving erythropoiesis stimulation agents (ESAs) or any specific immunosuppressive agents. Various demographic, clinical and biochemical parameters (gender, age, height, weight serum creatinine and hemoglobin levels) were retrospectively collected from patients' database. The body mass index (BMI) and glomerular filtration rate (GFR) were calculated according to the standard estimations and the overweight, first, second and third degree of obesity were defined as having BMI <25-29.9 kg/m^2, 30-34.9 kg/m^2, 35-39.9 kg/m^2 and >40 kg/m^2, respectively. An estimate of GFR was obtained by the four-variable Modification of Diet in Renal Disease (MDRD) equation. Data processing was performed by means of Microsoft excel data analysis for descriptive statistics. Various stratified groups were compared with t-test or Mann Whitney U test, and association between various parameters was assessed with correlation analysis as appropriate. P value <0.05 was considered significant.

Results

Within the study population of 315 CKD patients, 123 were males with mean age of 63.4±1.33 years and 192 females of 57.3±1.2 years. The results for hemoglobin and GFR in various groups of patients stratified according to the degree of obesity, gender and BMI are presented in Table 1.

Table 1. Degree of obesity (BMI) in men and women with values of average Hb levels and GFR (MDRD)

Degree of obesity	BMI	Gender	Number	Hb level (g/l)	GFR (MDRD) ml/min
below physiological values	< 18.5	female	37	127	78
		male	0	-	-
Physiological values	18.5 - 24.9	female	105	128	58
		male	29	131	59
Overweight	25 - 29.9	female	33	129	61
		male	67	130	51
First-degree obesity	30 - 34.9	female	13	129	50
		male	23	130	44
Second-degree obesity	35 - 39.9	female	3	115	33
		male	3	134	35
Third-degree obesity	> 40	female	1	134	80
		male	1	132	61

There were 37 women with a BMI below the physiological values (malnourished), while there was not a single man with BMI in this category. The majority of patients were within the group with physiological values of BMI, 29 males and 105 females. In addition, another group of 100 patients (67 males) were slightly overweight, the first degree of obesity was found in 36 patients (23 males) and only 6 patients (3 males) had the second degree obesity. Only one male and one female patient had the third degree obesity and were not included in the analysis.

Majority of patients (n=243) were in CKD stage 3, with a mean GFR of 44.5 ml/min/1.73 m^2. The BMI values in female patients with first and second degree of obesity negatively correlated with GFR (r=-0.46, p<0.05). Unexpectedly, only female patients with second degree of obesity had a positive correlation between the decreased renal function and reduced Hb levels (Figure 1 and 2). The already known correlation between obesity and renal function was also found among males. Namely, the increased BMI was associated with a reduced GFR but not with Hb levels (Figure 3 and 4).

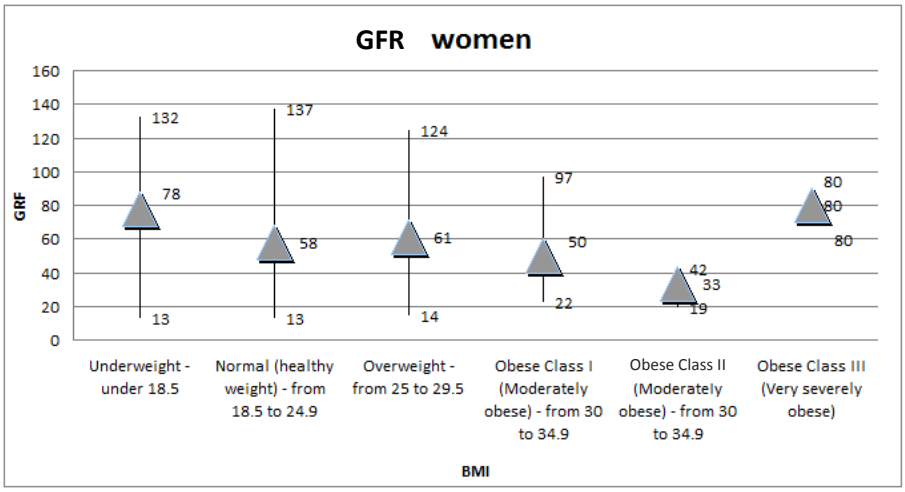

Fig. 1. Glomerular filtration rate (MDRD) and body mass index (BMI) in women

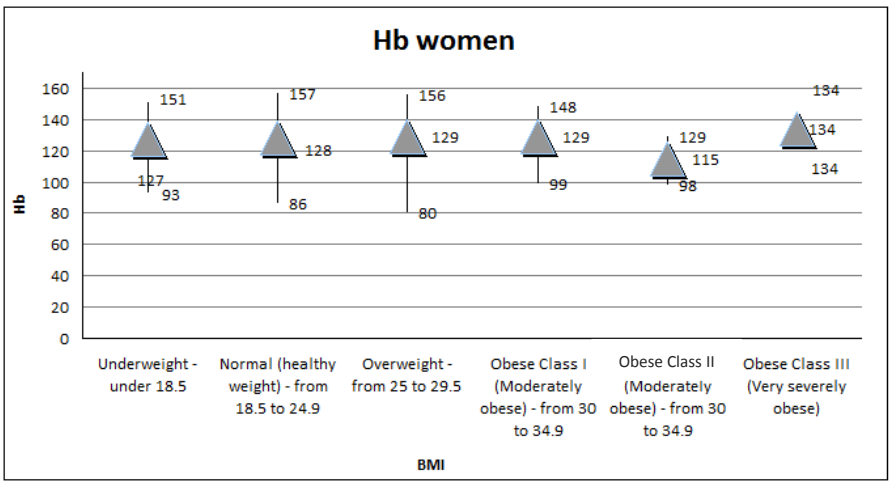

Fig. 2. Average hemoglobin level (g/l) and body mass index (BMI) in women

Fig. 3. Glomerular filtration rate (MDRD) and body mass index (BMI) in men

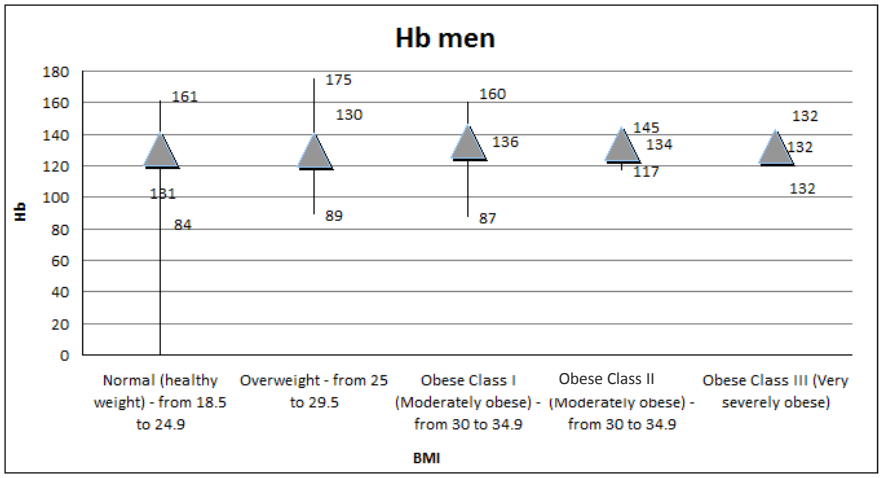

Fig.4. Average hemoglobin level (g/l) and body mass index (BMI) in men

Discussion

This study showed an association between obesity and anemia in female patients with CKD as well as between the degree of obesity and renal function in both, male and female patients. To the best of our knowledge, there are only a few data on the association between overweight and renal function, but data on the association between the obesity and anemia in CKD patients lack in the literature.

Anemia is common in patients with CKD, but not in the earlier stages of CKD. Patients with CKD stage III have a prevalence of concurrent anemia of 5.2%, whereas those with stage IV disease of 44.1% [13], which is in line with the results obtained only for the female patients in our study. Anemia is also with greater prevalence in CKD patients older than 60 years, as compared to the younger patients, most probably secondary to the greater rate of CKD in older individuals and their lower estimated GFR associated with aging [14]. However, our female cohort was younger than 60 years of age, thus the impact of BMI may be even more prominent. In only one study of Karlee JP *et al.* a positive correlation was found between the increased BMI and increased ferritin levels and decreased serum iron and transferrin saturation. Here, despite the involvement of the chronic inflammation in the iron studies, obesity was not found to be associated with anemia [15].

It should be acknowledged that the age of female subjects may be an important factor influencing results of this type of epidemiological studies, because estrogen levels which decline after menopause may exert a protective action on the kidneys. However, BMI in our study was most probably with a greater impact on the impairment of the renal function compared to age, which did not show a significant difference between the various obesity groups. Finally, in the present study, to avoid including CKD secondary to diabetic nephropathy, we excluded subjects with diabetes mellitus or with a fasting blood glucose level of 126 mg/dl or higher. The shortcoming of our study is that the analysis was performed with a relatively low or even statistically insufficient number of subjects. Nevertheless, for the first time in patients not treated with ESAs there was a correlation between obesity and decreased renal function with renal anemia in females with second degree of obesity. The already known correlation between the obesity and renal function in both female and male patients was confirmed.

Conclusions

The GFR reduced along with the increase of the BMI in both genders providing unconditional evidence for the association between the degree of obesity and renal function impairment in CKD patients. In addition, an association between BMI and the average hemoglobin level was found only in females with second degree of obesity. It is necessary to carry out such monitoring on larger scale trials, looking for various hygieno-dietetic regimes, races and cultural beliefs differences. After our pilot observational study examining the cross-sectional relationship between BMI, CKD and renal anemia, further follow-up and interventional studies are required to see the effect of body weight reduction on renal function and anemia.

Conflict of interest statement. None declared.

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Case report

Left Ventricular Cleft Detected by Transthoracic Echocardiography in a Patient with Autosomal Dominant Polycystic Kidney Disease

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Abstract

Recently, the presence of left ventricular clefts has been identified frequently with the advancement of cardiac imaging modalities such as cardiac magnetic resonance imaging and computed tomography. Here we report a rare case of left ventricular cleft that was incidentally diagnosed with the ECG changes that imitated the presence of LMCA stenosis and diagnosed by transthoracic echocardiography in a patient with autosomal dominant polycytic kidney disease.

Key words: policystyc kidney disease, left ventricular clefts, ECG, echocardiography

Introduction

Left ventricular clefts are defined as slit or fissure-like protrusions through the >50% of compact myocardium and tending to occlude with the myocardial contractions. The presence of left ventricular clefts has a higher incidence in patients who has gene mutations related to hypertrophic cardiomyopathy. However, in our case the left ventricular cleft was incidentally detected in a patient who has end-stage autosomal dominant polycystic kidney (ADPKD) disease. Besides this, ADPKD has many cardiac manifestations; association with left ventricular cleft has not been reported previously to the best of our knowledge.

Case report

A 55-year-old woman without any known history of coronary artery disease or family history was referred to our Department due to ischemic ECG changes. She has had ADPKD for 5 years and she was planning to undergo hemodialysis due to end-stage ADPKD. Her blood pressure was 100/60mmhg and the heart rate was 73 bpm. ECG revealed ST elevation in lead aVRand ST depression predominantly in leads DII, DIII, aVF, V4-V6 (Figure 1).

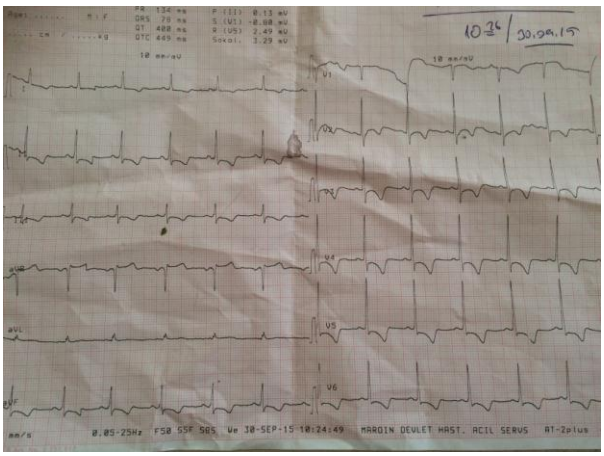

Fig. 1. ECG changes: ST elevation in lead aVRand. ST depression in leads DII, DIII, aVF, V4-V6

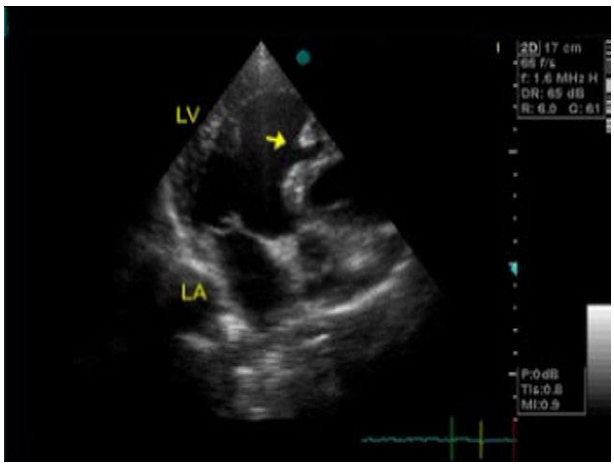

Fig. 2. TTE apical view shows interventricular septal cleft in mid diastolic frame. Arrow points the cleft in mid interventricular septum

Laboratory analyses showed that her mineral status and cardiac enzymes were in normal range. Subsequently, transthoracic echocardiography (TTE) was performed and it showed no wall motion abnormality in parasternal long or short-axis views. In apical 4-chamber view; a U-

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shaped, slit-like appearance with an extension through the compact myocardium was noted in mid interventricular septum (Figures 2 and 3). This fissure-like abnormality was tending to narrow with myocardial contractions which was compatible with the diagnosis of left ventricular clefts. There was no evidence of flow though the myocardial defect with color doppler examination or no pressure gradient by pulse wave examination which helped to distinguish from ventricular septal defects by TTE (Figure 4). Although ECG changes theoretically showed the presence of LMCA stenosis, immediate coronary angiography showed no significant stenosis of the coronary arteries. The patient underwent dialysis program, soon after she was discharged with anticoagulation therapy.

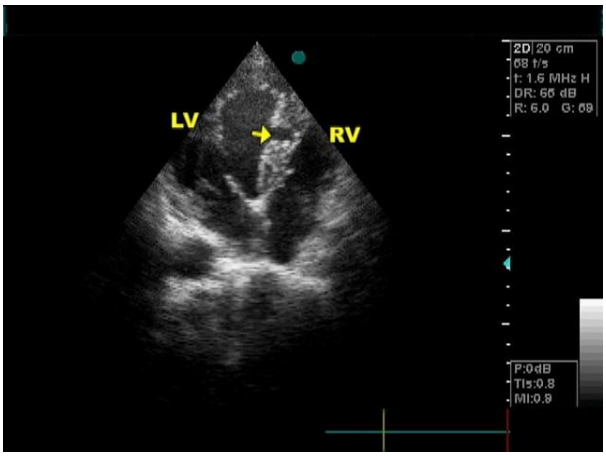

Fig. 3. TTE apical 4C view shows the U-shaped, slit-like appearance of the cleft in mid interventricular septum

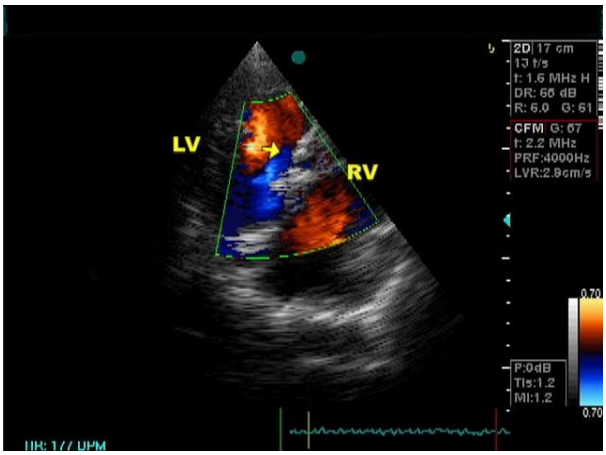

Fig. 4. TTE with color doppler interrogation showing no flow through the cleft
(Abbreviations: TTE: Transthoracic Echocardiograhy. LV: left Ventricle, RV: right Ventricle, LA: Left Atrium)

Discussion

The presence of left ventricular clefts has been identified by CTA and MRI imaging modalities over the past decades. It has been described as V- shaped, slit-like appearance, extending >50 of myocardium and tending to narrow in systole and with a higher prevalence in patients with hypertrophic cardiomyopathy (HCM) gene mutation [1,2]. Petryka *et al*. found higher percentage of left ventricular clefts in patients who were referred for cardiovascular MRI with HCM, myocarditis, and hypertension [3]. The cause of clefts is not known but it is thought to be disarray of myocardium in patients with HCM [4]. Left ventricular clefts should be differentiated from left ventricular diverticulum, which are defined as saccular protrusions beyond the myocardial borders and have a high incidence of thromboembolism. The treatment of left ventricular cleft is done with anticoagulation therapy to prevent tromboembolism. Surgery is usually not needed.
In our case the shape of the fissure-like appearance was compatible with the definition of the left ventricular cleft, but it was in a patient with ADPKD which is a rare coexistence. The detected cardiac manifestations of ADPKD are: left ventricular hypertrophy, heart valve abnormalities, coronary artery dilatation, atrial septal aneurysms, interrupted aortic arch, aortic dissection, dilatation and coarctation [5-7]. But, the presence of left ventricular cleft in patients with ADPKD has not been previously reported. Boutter *et al*. have found that pkd1 and pkd2 gene mutations are associated with ventricular and atrial septation in mice and that could be a possible explanation of coexistence of left ventricular clefts and ADPKD [8,9].

Conclusion

Patients who have ADPKD and with pkd1 and pkd2 mutations may have cardiac septation anomalies such as atrial septal defects, interatrial septal aneurysm, etc. Left ventricular cleft, which is thought to be congenital defect of myocardium, may be detected by MRI or TTE in patients with ADPKD as it was the case with our patient.

Conflict of interest statement. None declared.

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Case report

Idiopatic Systemic Capillary Leak Syndrome Treated Successfully with High-Dose Intravenous Immunoglobulins

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Abstract

Idiopathic systemic capillary leak syndrome (ISCLS) is characterized by a triad of hypotension, hemoconcentration and hypoalbuminemia due to a shift of intravascular fluid and albumin to the extravascular area. We describe a hypovolemic patient with hemoconcentration and hypoalbuminemia who was successfully treated with high-dose intravenous immunoglobulins (IVIG). The purpose of this case report is to discuss the clinical management of idiopathic systemic capillary leak syndrome on the background of relevant literature review.

Keywords: systemic capillary leak, hypoalbuminemia, intravenous immunoglobulins

Introduction

Systemic capillary leak syndrome (SCLS) was first reported by Clarkson *et al.* 55 years ago [1]. This syndrome is a rare condition characterized by unexplained episodic capillary hyperpermeability and by chronic recurrent episodes of a triad of hypotension, hypoalbuminemia and hemoconcentration associated with paraproteinemia. Rare complications of SCLS are renal damage and rhabdomyolysis, ascribable to increased compartment pressure and ischemic myonecrosis, which were seen in our patient [2]. We report the case of a 57-year-old woman with chronic SCLS treated with high-dose intravenous immunoglobulins (IVIG) after she failed to respond to other treatments. The patient was successfully treated with IVIG.

Case Report

A 57-year-old woman came to our hospital presenting with episodes of resting dyspnea, abdominal pain, vomiting, diarrhea, oliguria and anasarca, which had started a week ago. When admitted to the Emergency Department the patient showed hemodynamic instability, and hence she was referred to the intensive care unit.

Systolic blood pressure was 90/60 mmHg, heart rate: 130 beats/min. Her breath and cardiac sounds were normal. The laboratory finding showed hemoglobin: 17.9 g/dL, hematocrit: 51%, leukocytes: 22.500/mm2, platelets: 346000/mm^2, blood urea nitrogen creatinine (BUN/Cr): 33/0.8 mg/dL, total protein/albumin: 5.3/3.2 g/dL, C-reactive protein (CRP): 1.03 mg/L creatinine phosphokinase: 3011 U/L, CK MB: 77.62 ng/ml, troponine: 1.86 ng/ml

Table 1. Laboratuary findings of the patient

Peripheral blood		Biochemistry
White blood cell count:	22.500 K/uL	Total protein: 5.3 g/dl
Hemoglobin	17.9 gr/dl	Albumin: 3.2 g/dl
Hematocrit	51.7 %	Blood urea nitrogen: 33 mg/dl
MCV	87.3 fL	Creatinine: 0.8 mg/dl
Platelet	346 K/uL	Glucose: 111 mg/dl
ESR	4 mm/h	Sodium: 128 mmol/L
Serology		*Potassium: 4.09 mmol/L*
Antinucleer antibody	negative	Calcium: 8.4 mg/dl
C-reactive protein	1.03 mg/dL	Phosphorus: 3 mg/dl
Endocrinology		*AST: 448 U/L*
Cortisol:	17.8 µg/dL	ALT: 186 U/L
Free T3:	4.82 pg/mL	LDH: 1139 U/L
Free T4:	1.28 ng/dL	ALP: 48 U/L
TSH:	0.513 uIU/mL	Creatine phosphokinase: 3011 U/L
		CK-MB: 77.62 ng/ml
		Troponin: 1.86 ng/ml

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(Laboratuary findings of the patient are shown in table 1). Common causes of generalized edema accompanied by hypoproteinemia, such as nephrotic syndrome, liver dysfunction, congestive heart failure and gastrointestinal protein-losing enteropathy, were excluded. We had to exclude acute myocardial infarction (echocardiography was normal and acute ischemic findings were not observed on electrocardiography), rhabdomyolysis, hypothyroidism, adrenal insufficiency, exercise, trauma, using alcohol and drugs were excluded.

Leukocytosis and erytrocytosis of the patient was connected to hemoconcentration since there was no evidence of infection evaluated with physical examination, imaging and laboratory tests. It turned out that she had SCLS 10 years prior to this admission and was being followed up. We considered SCLS exacerbations. Central venous pressure was 4 cm H2O, and aggressive fluid support in the form of 2 litersof i.v. fluids (normal saline) were given over the next 6 hours and saline treatment was continued. Intranenosus metilprednisolone 1 mg/kg daily was started after the intravenous fluid substitution. We also used theophylline, terbutaline, salbutamol, diuretics and calcium antagonists. She did not respond to the treatment because of an increase in cardiac enzymes and CK levels, failure to provide adequate diuresis and continuation of muscle pain. Based on literature reports, intravenous immunoglobulin (IVIG) 0.5 g/kg was administered for 4 days. After this theraphy her blood pressure and CVP returned to normal levels the next day. During the follow-up elevated CK levels up to 20160 U/L decreased after IVIG 193 U/L, and cardiac enzymes returned to normal.

Discussion

SCLS is a disorder which presents with recurrent episodes of hypovolemic shock, due to leakage of plasma to the extravascular compartment reflected by concomitant hemoconcentration, hypoalbuminemia and edema. It is a rare, but life-threatening disorder characterized by unexplained episodic capillary hyperpermeability due to a shift of fluid and proteins from the intravascular to the extravascular space [2].

Actually, the pathogenic mechanisms of SCLS and the cause of the episodes of capillary leakage remain unclear. According to one proposed theory, the origin of the increased susceptibility to vascular hyperpermeability is thought to lie in serum factors, not in the vasculature itself, as endothelial cadherin internalization and disruption of interendothelial junctions with subsequent increased permeability were inducible in human microvascular endothelial cells by exposure to sera from SCLS patients [3]. A study demonstrated that serum taken from patients with SCLS mediated extensive apoptosis and contraction of endothelial cells in vitro [4]. Also, endogenous interleukin-2 (IL) may contribute to the pathogenesis of this syndrome [4]. In most cases of IL-2-induced capillary leak syndrome, however, attacks developed during the IL-2 therapy [5]. Other than IL-2 several factors mediating the increased vascular permeability have been proposed, primarily cytokines, such as interleukins 6, 8, and 12, interferons gamma and alpha, tumor necrosis factor alpha, vascular endothelial growth factor, and C-X-C motif chemokine 10 and chemokine (C-C motif) ligand 2 [6-8].

Standard treatment of SCLS is not yet established. Multiple regimens, based on possible pathological mechanisms, have been tried with various degrees of success, including theophylline, terbutaline, salbutamol, steroids, diuretics, calcium antagonists, and plasmapheresis [9]. In addition to the treatment of the acute phase, several prophylactic therapies have been tried. Recurrence is a notable feature of SCLS, so its prevention is important. Terbutaline and theophylline therapy have been reported to be apparently effective against SCLS recurrence. Although morbidity and mortality rates associated with SCLS are high, the prognosis seems to have improved recently. However, the most successful therapeutic measure during an attack to date is the application of intravenous immunoglobulin [8,10]. Firstly, according to the article which was published by Vigneau and Lambert IVIG were effective against acute-phase of SCLS [11, 12]. IVIG prevent it from mediating tissue damage by scavenging its active components and diverting complement attack from cellular targets.

Based on these promising results, we repeatedly administered IVIG (0.5 gr/kg over 4 days) to our patient. We achieved a milder clinical presentation of acute attacks and dramatically reduced the frequency of recurrence. In conclusion, awareness of SCLS is most important for improving the outcome because early diagnosis and immediate fluid replacement therapy are essential.

Conflict of interest statement. None declared.

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Case report

Primary Amyloidosis Presenting with Nephrotic Syndrome and Atypical Intrahepatic Cholestasis: Report of 2 Cases

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Abstract

Liver is one of the most commonly involved organs in both primary and secondary systemic amyloidoses, but hepatic amyloidosis, manifested as mild to moderate enlargement, is usually not symptomatic nor it is clinically problematic. Rarely, massive hepatomegaly, severe cholestatic hepatitis or liver failure may be encountered in patients with systemic amyloidosis. Two cases with lambda light-chain amyloidosis presenting with nephrotic syndrome and atypical intrahepatic cholestasis are discussed with clinical features, laboratory and kidney, liver and bone marrow biopsy findings in view of the relevant literature.

Keywords: intrahepatic cholestasis, nephrotic syndrome, primary amyloidosis

Introduction

Among the various secondary causes of nephrotic syndrome in adults, systemic amyloidosis comprises an etiologically and clinically heterogenous group of patients (diseases) composed of cases with either primary or secondary amyloidosis, excluding the very rarely seen familial visceral forms. Both primary and secondary systemic amyloidoses may be complicated depending on the organs involved. Liver is one of the most commonly involved organs in both forms, but hepatic amyloidosis, manifested as mild to moderate enlargement, is usually not symptomatic nor it is clinically problematic. Rarely, massive hepatomegaly, severe cholestatic hepatitis or liver failure may be encountered in patients with systemic amyloidosis and light chain deposition disease with less than 50 reported cases [1]. Herein, we report two cases of primary amyloidosis presenting with nephrotic syndrome and atypical intrahepatic cholestasis.

Case 1

A 55-year-old female was admitted to our Nephrology Clinic with pretibial pitting edema for 2 months. History revealed no symptoms of heart, liver or thyroid disease and no drug use. She had no known previous disease but tingling in hands with normal electroneuromyography for 2 years. On admission she was good in general appearance, fully cooperative and oriented. Her tympanic temperature, heart and respiratory rate were normal and blood pressure was 90/60 mmHg. She had 3+ pretibial edema, decreased breath sounds over right lower zone, 6 cm hepatomegaly under subcostal margin on midclavicular line.

Table 1. Laboratory Features of Cases on Admission

Parameter	Case 1	Case 2
BUN (mg/dL)	17	15
Creatinine (mg/dL)	0.87	1
Albumin (g/dL)	1	1.2
24 hour urinary protein (mg/24 hour)	9810	7125
AST (U/L)	45	50
ALT (U/L)	31	28
GGT (U/L)	1733	543
ALP (U/L)	1351	513
Total/direct bilirubin (mg/dL)	0.6/0.2	0.7/0.2
Serum free kappa/lambda (mg/L)	26/384	12/124
Urinary free kappa/lambda (mg/L)	311/634	61/76
IgG/IgA/IgM (g/L)	5.4/2.6/1	2.1/1.6/1.1
Beta-2-microglobulin (mg/L)	3	3.1

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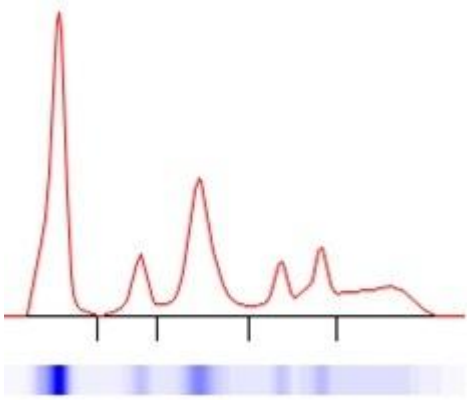

Fig. 1a.

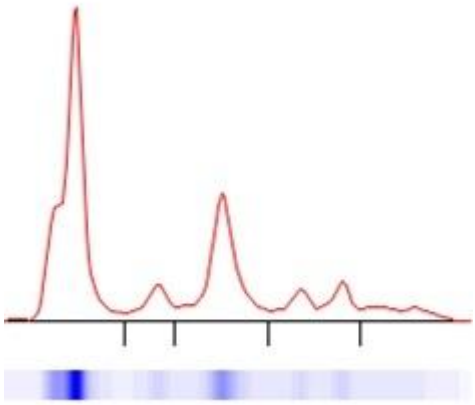

Fig. 1b.
Figure 1. Serum protein electrophoreses of Case 1a and Case 2b

Laboratory examination (Table 1) revealed deep hypoalbuminemia, nephrotic proteinuria, hyperlipidemia and decreased glomerular filtration rate (creatinine clearance = 71 mL/min). Complete blood count and prothrombin time were normal. No laboratory sign of glomerulonephritis was present. Serum protein electrophoresis (SPE) revealed hypoalbuminemia with an irregular gamma and a high alpha-2 band (Figure 1a). Serum and urinary levels of free light chains and immunoglobulins are shown in Table 1. Urinary immune fixation electrophoresis was positive for lambda light chain. Serum autoimmune and metabolic tests of liver injury and markers of viral hepatitis were all negative and no history of hepatotoxic drug use was present. Ultrasonographically kidneys were normal, liver was 161 mm with normal parenchymal appearance, intra- and extrahepatic bile ducts, portal and hepatic veins were normal. A coronal CT scan at the level of portal hilus showing hepatomegaly with normal portal vasculature and no finding of extrahepatic cholestasis is presented in Figure 3. Myocardial hypertrophy with granular echogenicity suggestive of cardiac amyloidosis, thickening of mitral valve leaflets and pleuropericardial effusion were detected echocardiographically. Duodenal and rectal biopsies were negative for amyloidosis. Percutaneous kidney, liver and bone marrow biopsies were performed. Kidney biopsy revealed prominent deposition of amorph eosinophilic extracellular material, showing positive staining with Congo Red and immunohistochemistry identified lambda light chain with positive P component, proving the diagnosis of lambda light chain amyloidosis (Figure 2a). Liver biopsy was also compatible with lambda light chain amyloidosis with the same immunohistochemical features. Importantly, amyloid deposition was more prominent in the perisinusoidal (Disse) space than in the periportal space (Figure 2a). Ten percents of lambda monotypic interstitial plasma cell infiltration was found in the bone marrow (Figure 2b). After the first cycle of melphalan and prednisolone chemotherapy on the 15th day of admission she had acute kidney injury requiring hemodialysis and hyperbilirubinemia developed without further increase in cholestatic enzymes (Table 2). Despite prophylactic anticoagulation she had a possible ischemic stroke with cardiovascular collapse and died. No autopsy was performed.

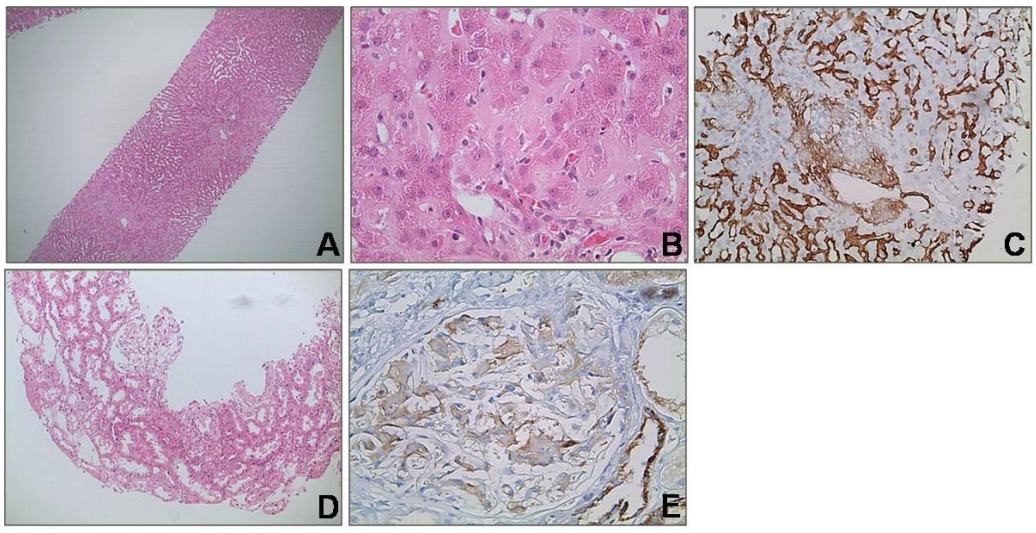

Fig. 2a.

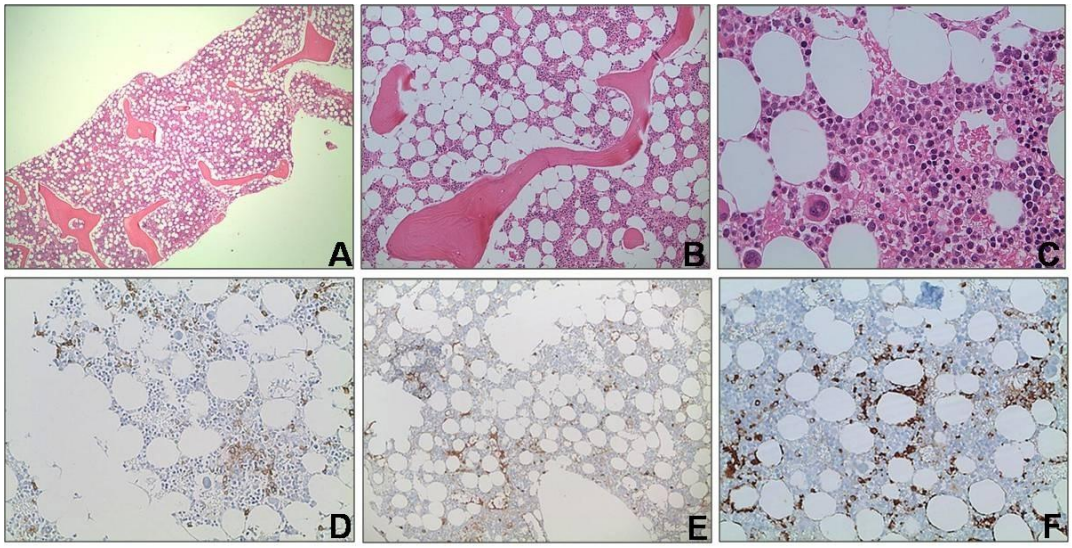

Fig. 2b.

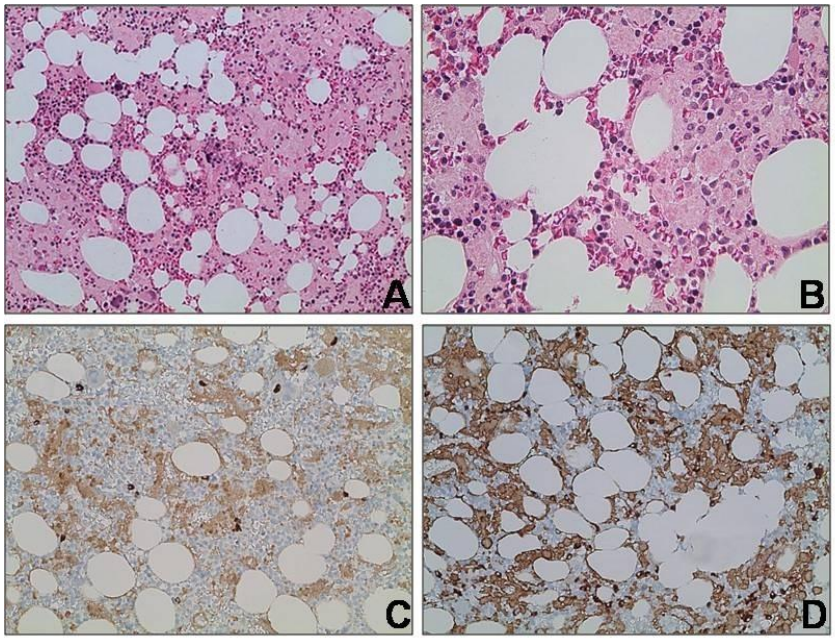

Fig. 2c.

Fig. 2. Liver and kidney biopsy findings of Case 1 (**a**); **A-C**. Amoprh hyaline appearance in Disse space (H&E x25, x400) and immunohistochemical lambda expression (x200). **D-E**. Amorph hyaline appearance due to glomerular amyloid deposition (H&E x100) and immunohistochemical lambda expression (x200). Bone marrow biopsy findings of Case 1 (**b**); **A-C.** Scattered interstitial plasma cells in hypercellular bone marrow biopsy (H&E x25, x100, x400). **D-F**. Immunohistochemical expressions of CD38, kappa, and lambda (x200, x100, x200). Bone marrow biopsy findings of Case 2 (**c**); **A-B**. Extracellular amorph hyaline appearance due to amyloid deposition in bone marrow biopsy (H&E x200, x400). **C-D**. İmmunohistochemical kappa and lambda expression (x200).

Table 2. Chronologic Laboratory Features of Case 1

Parameter	Day 0	Day 15	Day 27	Day 31	Day 33
Creatinine (mg/dL)	0.87	1.98	3.8	2.7	4.9
AST (U/L)	45	35	41	47	47
ALT (U/L)	31	51	57	60	61
GGT (U/L)	1733	2592	2026	1918	1902
ALP (U/L)	1351	2315	1056	1249	1415
Total/direct bilirubin (mg/dL)	0.6/0.2	1.5/0.7	11.9/6.7	6.5/4.6	5.7/3.5
Prothrombin time (second)	10.9	12.2	12	12	12.1

Due to nephrotic loss and replacement, serum albumin is not presented chronologically; Undulations of serum creatinine is due to hemodialysis

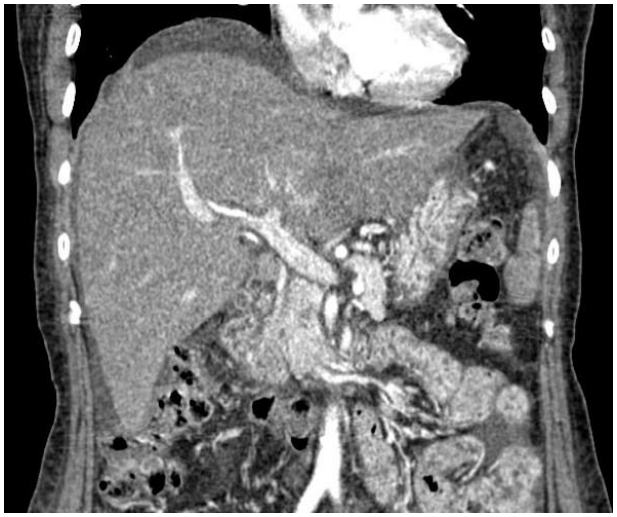

Fig. 3. Coronal CT scan of Case 1 at the level of portal hilus showing hepatomegaly, normal portal vein and no finding of extrahepatic cholestasis

Case 2

A 56-year-old female, being followed in the Hepatology Inpatient Clinic because of hepatomegaly, hypoalbuminemia, ascites and pretibial edema with the initial diagnosis of liver failure, was referred to our Nephrology Clinic because of concomitant nephrotic proteinuria. She had known coronary heart disease but no symptom of cardiac failure was present and echocardiography was normal except for minimal pericardial effusion. She had a surgical release for carpal tunnel syndrome 5 months prior to admission and diagnosed as combined hyperlipidemia at that time. Vital signs and physical examination were normal except for 3+ pretibial edema and mild ascites with 2 cm hepatomegaly under subcostal margin on midclavicular line. Her complete blood count, prothrombin time, serum creatinine and electrolytes were normal. Deep hypoalbuminemia, hyperlipidemia, and nephrotic proteinuria were present. Detailed laboratory examination is shown in Table 1. Her liver was 20 cm with a normal parenchymal density, intra- and extrahepatic bile ducts, and portal and hepatic veins were normal on computed tomographic examination of the abdomen. Tests for viral, autoimmune and metabolic liver diseases were all normal. No laboratory sign of glomerulonephritis was present. SPE was similar to that of Case 1 with more prominent prealbumin and hypogammaglobinemia plus irregularity of the gamma band (Figure 1b). Serum and urinary levels of free light chains and immunoglobulins are shown in Table 1. Ultrasonography of the kidneys was normal. Bone marrow aspiration and biopsy revealed 6% of lambda monotypic interstitial plasma cell infiltration (Figure 2c), almost all of which showed atypia in flow cytometric examination and expressed deletion of both 13q and 17p. Lambda light chain amyloidosis was also evident in bone marrow biopsy with positive staining with Congo Red and immunohistochemical P component and lambda light chain positivity (Figure 2c). She was diagnosed with primary systemic lambda light chain amyloidosis. Due to poor prognostic clinical and genetic features, an autologous hematopoietic stem cell transplantation is planned after remission induction with bortezomib-based therapy and appropriate pre-transplant conditioning regimen.

Discussion

In patients with systemic amyloidosis of both primary or reactive types, the differential diagnosis of cholestasis may be challenging, especially in cases with multisystemic and complicated disease that may lead to cholestatic type of liver injury secondarily due to treatment related issues or systemic infections. Although hepatic involvement is common in patients with systemic amyloidosis of both types, it is usually asymptomatic. Rarely, amyloid infiltration of the liver causes massive hepatomegaly, severe cholestasis and liver failure and prognosis is usually poor in those with survival measured in months [1,2]. In patients with plasma cell dyscrasias cholestasis may be related to light-chain or rarely heavy chain deposition disease, amyloidosis or plasma cell infiltration of the liver. Although metabolic imaging techniques like 18-fluorodeoxyglucose positron emission tomography or serum amyloid P scintigraphy can differentiate between these, the most accurate diagnostic modality is liver biopsy. Interestingly in patients with hepatic amyloidosis serum ALP or GGT elevation may be the only laboratory sign and they can increase to 10 to 50 times the normal with mild or no increase in bilirubin. Later in the course of the disease hyperbilirubinemia ensues [3]. This may be related to the infiltration of the perisinusoidal space fist by the amyloid fibrils causing hepatocellular membrane injury releasing ALP and GGT, then granular deposits in interhepatocellular, pericanalicular and periductal spaces sequentially leading eventually to portal amyloidosis impairing bilirubin transport. After chemotherapy Case 1 had hyperbilirubinemia with a peak of 11.9 mg/dL of total bilirubin on the 27th day of admission, possibly due to superposed intrahepatic cholestatic effect of chemotherapy since hyperbilirubinemia was partially reversible and not accompanied by further increase in cholestatic enzymes (Table 2). Minimal increase in ALT, AST and lactate dehydrogenase and no prolongation of prothrombin time suggested no extensive hepatocellular damage. Some reported cases with light or heavy chain deposition disease without amyloidosis exhibit the same clinical and laboratory features of intrahepatic cholestasis [1]. Such disproportionate pattern of increase in cholestatic enzymes and bilirubin can also be seen in chronic partial obstructive diseases of biliary tree, early in the course of any extrahepatic cholestatic disease, and other infiltrative disease of the liver like lymphomas. In case of amyloidosis, how deposition of extracellular proteins in the granular or fibrillar (amyloid) form causes hepato-

cellular membrane injury in the early course of disease remains to be clarified. Primary biliary cirrhosis, which is rarely reported to be associated with secondary systemic amyloidosis and nodular amyloid deposition in the biliary tree causing extrahepatic type cholestasis should be kept in mind in the differential diagnosis in patients with systemic amyloidosis with cholestasis, making imaging and biopsy an imperative [2-4].

Conflict of interest statement. None declared.

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Case report

A Rare Case of Peritonitis: Streptococcus Salivarius

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Abstract

Streptococcus salivarius is a Gram-positive bacteria that may cause infections like endocarditis and meningitis. However, it has not been reported as a causative agent of peritonitis in peritoneal dialysis patients. In this paper we present a rare case of peritonitis with *Streptococcus salivarius* admitted to our Clinic with abdominal pain, who had been on peritoneal dialysis treatment for 19 months. *Streptococus salivarius* was cultured from the effluent, sensitive to ampicillin and penicillin G. Patient was discharged completely cured. Peritonitis is the most important clinical issue that occurs in patients treated with peritoneal dialysis, and every effort should be invested to determine the causative agent while even rare bacteria as *Streptococcus salivarius* may be found.

Keywords: peritonitis, peritoneal dialysis, streptococcus salivarius

Introduction

Peritonitis is the most important complication of peritoneal dialysis (PD). The most common organisms isolated are *Staphylococcus aureus* and coagulase negative staphylococci [1]. *Streptococcus salivarius* is a Gram-positive, facultative anaerobic bacteria that colonizes gastrointestinal and genitourinary tracts, oral cavity and paranasal sinuses [2]. Although it is regarded to have low virulence, *Streptococcus salivarius* may cause life-threatening infections like endocarditis and meningitis [3], and it has not been reported as a causative agent of peritonitis in PD patients. Herein, we present a case of peritonitis with *Streptococcus salivarius* in a PD patient.

Case report

A sixty-year-old male patient treated with PD for 19 months was admitted to our Clinic due to abdominal pain and cloudy effluent. His physical examination revealed decreased skin turgor, paleness of the conjunctiva and skin, metallic valvular sound, a mild systolic murmur at the apex and diffuse abdominal tenderness. He had increased C-reactive levels without leukocytosis. Cell count of the peritoneal effluent revealed 9800 leukocytes/mm³ (90% polymorphonuclear leukocytes). After culturing the effluent, empiric treatment with intraperitoneal cefazolin and vancomycin plus oral ciprofloxacin was started. Leukocyte count of the effluent decreased to 400/mm³ on the second day and 20/mm³ on the fifth day. Streptococus salivarius was cultured from the effluent, and antibiotic sensitivity test showed that ampicillin and penicillin G were effective. The treatment was continued for a total of 14 days. He was discharged completely cured.

Discussion

Streptococci are Gram-positive bacteria including a collection of species that live in many body organs and range from benign to those causing life-threatening infections. ***Streptococcus salivarius*** is spherical, Gram-positive bacteria and principal commensal bacterium of the oral cavity, and hence colonizes the mouth and upper respiratory tract [2]. The bacteria is considered an opportunistic pathogen; it rarely enters the blood stream during brushing the teeth or dental work. It is found in cases of septicemia, endocarditis and meningitis in patients with neutropenia [3].

Peritonitis is is the most important clinical problem that occurs in patients with end-stage renal disease treated by peritoneal dialysis (PD). The incidence of peritonitis varies from center to center [1]. Many types of microorganisms may cause PD peritonitis. The most frequent pathogens are *Staphylococcus aureus*, Gram-positive organisms and *S. Epidermidis* [4]. A large review of 3366 patients showed that almost 50% of infections were due to Gram-positive organisms and 15% to Gram-negative organisms, 20% were culture negative (sterile peritonitis), only 4% were polymicrobial infections while fungal infection occurred in less than 2% of cases [5]. The most frequent pathogens are Gram-positive organisms, *Staphylococcus*

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aureus and *S. epidermidis*. In the literature there are also case reports about peritonitis due to group B *Streptococcus* [6]. Streptococci which are oral colonizers like *Streptococcus salivarius* are unusual cause of peritonitis in CAPD. This emphasizes the need of appropriate oral hygiene and antimicrobial prophylaxis during dental procedures.

To the best of our knowledge, this is the first reported case of peritonitis due to *Streptococcus salivarius*. As this organism colonizes plaques in the oral cavity, patients should take good oral hygiene especially after tooth extraction.

Conflict of interest statement. None declared.

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Case report

Calcified Double J Stent after Sequential Liver and Renal Transplantation Associated to Primary Oxalosis: Case Report

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Abstract

Hyperoxaluria type I (HPI) is a metabolic disorder secondary to liver alanine glyoxylate aminotransferase deficiency. Renal failure occurs due to the excessive production and precipitation of oxalate in the kidney. Combined liver-renal transplantation is the correct treatment for this condition when end-stage renal failure occurs since in renal transplantation alone the risk of recurrence of the same pathology in the transplanted kidney would be high.
We determined the calcification surrounding the double J stent inserted to the transplant ureter in a short time in a 22-year-old patient who underwent sequential liver and renal transplantation with the diagnoses of oxalosis. In the literature we have not found papers on calcification of double J stent following combined or sequential transplantation. Although after the sequential transplantation the calcification, nephrocalcinosis, and renal stones were practically not of great concern, these patients should be followed up more carefully in terms of stent calcification during the early post-transplant period.

Key word: hyperoxaluria, renal transplantation, double J stent

Introduction

Primary hyperoxaluria (PH) occurs due to an autosomal recessive hereditary disorder of the metabolism of glyoxylate, which causes excessive oxalate production. The most common disorder is due to deficiency of the enzyme alanine: glyoxylate aminotransferase (PH type I), that is specific to hepatic peroxisome [1-4].
The incidence of the disease is at least 1% in the pediatric population with end stage renal disease but it is higher in consanguinious marriages [5].
Considering the higher rate of intermarriages in our country, a higer proportion of such possibility may be considered.
The disease leads to deposition of calcium oxalate crystals in the kidney, nephrocalcinosis, progressive renal failure and systemic deposition of oxalate (oxalosis) [6-8]. Calcium oxalate is not effectively removed by dialysis and isolated kidney transplantation is not the method of choice due to the risk of the recurrence of nephrocalcinosis and nephrolithiasis. Overproduction of oxalate which leads to deposition of calcium oxalate crystals in the kidney continues after isolated kidney transplantation and therefore graft loss occurs frequently [9,10]. Combined liver and renal transplantation (LKT), which has relatively improved graft and patient survival, is the crucial tratment method for patients with PT-1 [11,12]. We present a case of calcification of double J stent inserted to the transplant ureter after a successful sequential liver and renal transplantation in a patient with oxalosis.

Case report

We report a case which demonstrates the disastrous consequences of late diagnosis of hyperoxaluria in a 22-year-old man with nephrocalcinosis, a staghorn calculus and recurrent urinary tract infections. His initial management at another hospital included multiple percutaneous nephrostomies and lithropsies. He had eight siblings. His paternal uncle and one of his eight siblings had renal calculi and were hemodialysis patients. His renal function steadily worsened in the ensuing years and hemodialysis treatement was started when he was 20 years old. In this period due to recurrent severe pyelonephritis total right nephrectomy was performed. The kidney biopsy specimen showed chronic interstitial fibrosis and calcium oxalate crystal deposition was seen in the renal tubules under polarized light microscopy. These findings were consistent with oxalosis. After two years of hemodialysis treatment, he was admitted to our transplant unit for living related liver and renal transplantation from his sisters. They were all healthy; no history of nephrolithiasis and/or no recurrent urinary tract infections. Metabolic evaluation of 24 hour urine collections and genetic analysis were performed. After exclusion of oxalosis from donor candidates sequential transplantation was successfully achieved. Firstly, liver transplantation

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from his sister was performed, and two months later he received kidney transplant from his other sister. Before renal transplantation the patient was underwent intensive hemodialysis treatment (two weeks daily/five hours). During renal transplant operation double J stent was inserted in the transplant ureter. ATG was given as an induction threapy and standard immunsuppressive protocol (maintenance therapy) mainly consisted of triple therapy composed of steroids, a calcineurin inhibitor (tacrolimus) and mycofenolic acid. At the time of discharge, his serum creatinine concentation was 1.4 mg/dl and BUN was 56 mg/dl. Liver function tests were within normal limits. He was admitted to the hospital for removing of the double J stent two weeks later. During the process a calcified stent was detected (Figure 1).

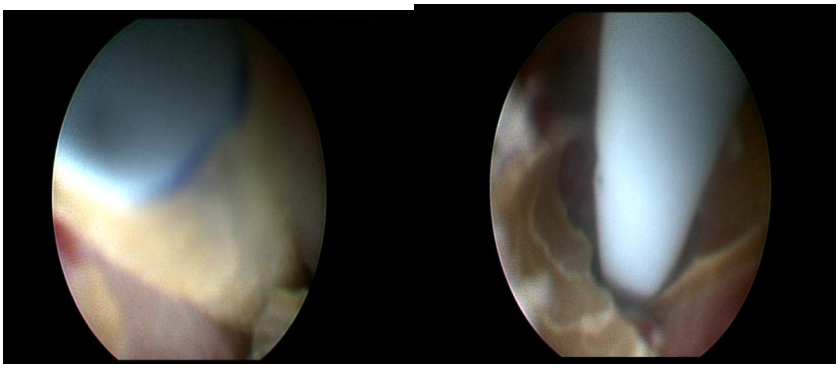

Fig. 1. Calcified double J stent

The stones surrounding the calcified double J stent inserted into the transplant ureter were successfully treated by laser lithotripsy and the stent was removed. The history of renal calculi was not detected during the post-transplant follow-up period. The patient is being still followed-up in the liver and renal transplantion outpatient policlinics and his liver function tests are within normal limits; basal serum creatinine concentation is 1.3 mg/dl.

Discussion

The excess oxalate that is produced in PH is primarily excreted by the kidneys. Urinary calcium oxalate supersaturations occur in the presence of excess urinary oxalate excretion and this suparsaturation leads to crystal aggregation, urolithiasis, and nephrocalcinosis [2]. Calcium oxalate crystals are also deposited within the renal interstitium and renal tubule cells. Nephrocalcinosis or recurrent urolithiasis can cause renal parenchymal inflammation and fibrosis and, if persistent, end-stage renal disease [2]. Other urinary complications associated with urolithiasis, such as infection and obstruction, also contribute to renal damage in affected patients. Intervention is required when stones obstruct the urinary tract. Nephrostomy, ureteroscopy, and ureteral JJ stent are preferred interventions for stone removal. Open surgical removal may precipitate acute renal failure and extracorporeal shock-wave lithotripsy (ESWL) may harm the kidney because of the potential presence of nephrocalcinosis and microlithiasis within the kidney [13]. In our case recurrent nephrolithiasis, nephrocalcinosis, hematuria, urinary infections and rapid development of renal failure are the prominent clinical manifestations. Firstly, the history of renal stone was detected at the age of seven and eleven years and the patient underwent a couple of surgical intervention and ESWL due to the recurrent stones.

The efficacy of treatment in PH is dependent on early diagnosis. Initiation of medical management as soon as possible leads to protection of renal functions, postpones the end-stage renal disease (ESRD) and minimizes nonrenal sequelae [2]. The patient had late diagnosis, after developing all complications when he was 20 years old by microscopic examination of kidney biopsy specimen obtained by total right nephrectomy due to recurrent episodes of urinary tract infection. So he had been already on reguler hemodialysis when he was diagnosed.

The definitive cure for PH type 1 is liver transplantation as the donor liver provides the missing enzyme, which lowers oxalate production to the normal range, but liver transplantation itself has significant complications and potential mortality. It is performed when the glomerular filtration rate is less than 40 ml/min/1.73 m². Sequential transplantation (liver followed by kidney transplantation), are performed in patients with PH type 1 and ESRD [14-16]. The rationale underlying this approach is the initial liver transplant allows intensive dialysis to clear the stores of tissue oxalates, thereby reducing the risk of kidney injury after renal transplantation [16-18]. In our case, firstly liver transplantation and two months later renal transplantation were performed from patient's two sisters.

The daily oxalate production is approximately 3500 to 7500 micromol in patients with type 1 PH, but the maximal oxalate elimination is 950 to 1440 micromol/day via conventional hemodialysis and also peritoneal dialysis [19]. As a result, standart maintenance dialysis therapy is not sufficient for lowering the plasma oxalate level. Higher plasma oxalate level increases the risk of systemic oxalosis. Intensive dialysis (eg, more than four-hour

daily HD sessions or a combination of PD and HD) is required to minimize plasma oxalate level. However, such intensive treapy is not effective to reduce the daily oxalate load. It should be instituted before renal transplantation in order to decrease the plasma oxalate level and oxalate deposition which leads to injury of the renal allograft [20]. Before renal transplantation the patient was taken to the intensive hemodialysis treatment (two weeks daily/five hours). Double J stent was inserted into the transplant ureter during the surgery but stent calcification of was observed within a short period (two weeks).

Mobilization of tissue oxalate deposits ensues gradually after transplantation and high urinary oxalate excretion may persist even more than two years after transplantation until tissue stores are removed [21].

In our case, double J stent might have been calcified because of the possibility of elevating urinary oxalate excretion.

We should be careful in terms of calcification of double J stent, inserted during the combined or sequential liver and renal transplantation, which is the actual treatment of oxalozis. During the early period after transplantation they should be closely monitored.

Conflict of interest statement. None declared.

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Letter to Editor

High Sensitivity C-Reactive Protein does not Correlate with IL-6 in Patients with Chronic Kidney Disease

Neha Garg, Mrinalini Kotru, Anil Yadav, Meera Sikka and Om Parkash Kalra

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Sir,

High Sensitivity C-Reactive Protein (hsCRP) is an acute phase reactant synthesized primarily by liver after stimulation by various cytokines including IL-6 (Interleukin-6). Hence, levels are elevated in various inflammatory diseases, including CKD (chronic kidney disease) especially in patients on hemodialysis [1]. IL-6 is a 26 kDa protein produced by the Kupffer cells of liver in response to inflammation. Its expression is regulated at gene expression level by interleukin-1 and tumor necrosis factor-α). Its levels are found to be elevated in CKD patients due to decreased clearance as well as increased production [2]. It is a strong inducer of CRP both in vitro and in vivo and its serum levels closely reflect CRP levels[2]. Hence, hsCRP and IL-6 are strongly correlated in most of the clinical conditions.

In our study of 77 clinically diagnosed patients with CKD (Stage 3, 4 and 5) no correlation was seen between hsCRP and IL-6. The mean age (±SD) of patients with CKD was 49.6 (±14.0) years. The mean duration (±SD) of CKD was 20.6 (±18) months.

The inflammatory parameters analyzed in this study were ESR (Erythrocyte Sedimentation Rate), hsCRP and IL-6 as shown in Table 1.

Table 1. Inflammatory parameters in CKD patients (n=77)

Parameter	Mean±SD	Range
hsCRP (mg/L)	63.78±84.26	1.0-254.0
IL-6 (pg/mL)	33.80±32.30	3.5-145.0
ESR (mm in 1st hr)	74.86±39.24	5.0-160.0

hsCRP-High sensitivity C-reactive protein; IL-6-Interleukin-6; ESR-Erythrocyte Sedimentation Rate

All the patients had elevated IL-6 (normal <2.97 mg/L). HsCRP was also increased [63.78 (±84.26) mg/L], however, 20.07% (17/77) patients had normal hsCRP (<6 mg/L). ESR was high in majority (96.1%, 74/77) of patients. A positive correlation was seen between hsCRP and ESR (r=0.493, p=0.000). However, no correlation of IL-6 was seen with hsCRP (r=0.157, p=0.172) or ESR (r=0.167, p=0.147). This is in contrast to various studies which show a positive correlation between hsCRP and IL-6 as IL-6 is a known inducer of hsCRP [3]. In contrast, Enocsson *et al.* in their study demonstrated that hsCRP levels do not correlate with IL-6 levels in lupus nephritis patients [4]. They explained this on the basis of activation of type 1 IFN (Interferon) system which inhibits IL-6 mediated hsCRP induction or due to hsCRP polymorphism. However, our study group was heterogeneous with hypertension and diabetes mellitus being the most common etiological factors for CKD and only 3.8% (3/77) patients with lupus nephritis. However still, the factors explained by Enocsson might have existed in our study group, too. Polymorphisms hsCRP are being increasingly studied in CKD patients and could be a contributing reason for the lack of correlation between IL6 and hsCRP [5].

Additionally, CKD patients may have numerous other factors which contribute to inflammation causing different expression of various proinflammatory cytokines.

To conclude, in the present study, levels of IL-6 did not correlate with hsCRP reflecting that factors other than IL-6 were governing the levels of hsCRP in our study group. These findings need validation in larger studies.

Conflict of interest statement. None declared.

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In memoriam

In Memoriam- Acad. Vladisav Stefanovic (1943 - 2015)

*Momir Polenakovic and Goce Spasovski

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Acad. V. Stefanovic unexpectedly left his loved ones and us, his friends, in October 2015. However, his work, vision and friendship will remain permanently with us and will show us the future directions of our work.

Acad. Stefanovic received his excellent education in France, and he was an extraordinary physician and an eminent researcher, with many friends among the nephrologists in the world. He was the key figure in the realization of the idea of scientific development of the Department of Nephrology at the Medical Faculty, University of Nish. With his numerous works he became one of the most productive scientists in the field of medicine in Serbia, and beyond in the Balkans and Europe. He pointed out to the need for professional development based on research results and he was an uncompromising fighter for the quality of the published papers.

We shared the same ideas about the need for research in nephrology, especially in the area of the Balkan endemic nephropathy (BEN). Together with our partners we have published several papers in the field of BEN, with participation of colleagues from the Bulgarian Academy of Sciences and the Macedonian Academy of Sciences and Arts. Some papers and ideas were among the first in the scientific community in the field of BEN research.

He was very active in the work of the Serbian Medical Society, the Nephrology Association of former Yugoslavia and in the Balkan Association of Nephrology, Dialysis, Transplantation and Artificial Organs (BANTAO), as well as in the European and the International Society of Nephrology. He was a member of the Editorial board of the BANTAO Journal.

He was modest in his life, and with immense energy and unprecedented enthusiasm in his work with patients, students and colleagues.

He will remain a model pioneer in the study of nephrology.

M. Polenkovic and G. Spasovski

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In memoriam

In memory of Prof. Dr. Cengiz Utas (1959 - 2015)

Turkish Society of Nephrology

"You only live once, but if you do it right, once is enough". Mae West

Prof. Utas delivering **his address as Congress Secretary at ERA-EDTA 42nd Congress President's Dinner in Istanbul, 2005**

The sudden and very untimely loss of former ERA-EDTA Council Member Prof. Dr. Cengiz Utas at 56 years of age after a heart attack came as a great shock to the entire Turkish Nephrological Community as well as his friends in ERA-EDTA and elsewhere in the world.

The late Professor Utaş was a prominent member of the Turkish Society of Nephrology (TSN). He served as TSN Executive Board member for 11 years (2000-2011) and also as Vice-President of the Society for 3 years (2008-2011). He headed various TSN Committees responsible of Congress & Meeting Organization, of Publications, of Scholarships and of International Scientific Relations. He also served for 14 years (1994-2008) as Editor in Chief of TSN's Official Publication the "Turkish Journal of Nephrology Dialysis Transplantation (TNDT)". He has regularly contributed to TSN annual National Congresses as lecturer, panelist, symposium member, Congress Secretary and Congress President. He was also actively involved in TSN's many Educational and Training Courses both as organizer and member of teaching faculty. In fact, he was the initiator of the very successful yearly TSN Winter Schools, now in their 13th year.

Professor Utas was not only a good clinician and a successful academician, but also an outstanding administrator. In 1993 he founded the Erciyes University Medical Faculty's Department of Nephrology in Kayseri, Turkey, which he chaired until 2004. He later served as the Vice Dean (1996-2000) and then the Dean (2000-2002) of the same Faculty. He then was elected and served as President (Rector) of the Erciyes University (2004-2008) a large Central Anatolian State University comprising 18 Faculties, 12 Colleges, 7 Institutes, 38 research centres and a total number of 60.000 students. During his rectorship term, he made significant contributions to Erciyes University on structural, technical, social, and most importantly academic grounds. From 1993 up to 2014, he authored and co-authored 123 international publications related to Nephrology. He edited four textbooks on Nephrology and Dialysis in Turkish and authored or co-authored many chapters in Turkish textbooks in the field.

Within a time span of seven years, Professor Utas has served as Congress Secretary to two different ERA-EDTA Congresses which were organized both in Istanbul: the 42nd Congress in 2005 and the 50th Anniversary Congress in 2013. In both occasions, he has contributed greatly to the local organization and social program including the organization of Pre-congress Council Meetings, Opening Ceremonies and Presidential Dinners and thus played a crucial role in the unquestionable success of both congresses. In 2005, he became Editorial Board Member to the NDT journal and remained so for many years. From 2005 to 2008, Professor Utaş worked as elected member of the ERA-EDTA Council. He genuinely enjoyed his Council term and with his well proven creative and innovative managerial and organizational skills together with his exceptional aptitude for collaborative scientific and administrative team work, we have every reason to believe that during this term he made a worthy positive contribution to the work of ERA-EDTA concerning the development and advancement of Nephrology in Europe. We also think that his work for ERA-EDTA as Congress

Secretary and then a Council Member greatly fulfilled his long-standing aspiration for the better integration of Turkish Nephrology to European and World Nephrology.
Professor Utas was also a very active member of the TSN Peritoneal Dialysis Study Group (also known as TULIP) that engaged in many peritoneal dialysis-related multicenter research projects nationwide and also at the international level resulting in many international publications. As such, he quickly became known in the ISPD circles and was appointed to preside the 2008 ISPD Congress in Istanbul which, thanks to his efforts turned out to be one of the most successful ISPD Congresses ever.
Professor Utas who always gave primordial importance to the advancement of Nephrology in South-Eastern Europe and the Balkans was also an esteemed member of BANTAO. As such, he assumed the role of Congress Secretary and worked very hard for the social and scientific organization of the legendary 2009 BANTAO Congress held in Antalya, Turkey.

His fellow TSN Executive Board Members who worked with him during his 11 years of service on the TSN Board will remember him as "the Planner", "the Organizer", and "the Driving Force" behind many leaping achievements of TSN and Turkish Nephrology in the past decade.
Most importantly, he was a loving and dedicated husband to his wife Serap Utas, a Professor of Dermatology, and a devoted and caring father to his son Alper Utas, a successful lawyer at one of the top law firms in Istanbul.
To his friends, he will remain a very warmhearted, caring and larger-than-life person to be always remembered for his good deeds. May God bless his benevolent soul and give solace to his loving friends and family.
Rest in peace, our beloved friend Cengiz. Your contributions to the Turkish and the European nephrology will always be remembered.

Turkish Society of Nephrology

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