# BANTAO Journal

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Renal best practice guidance/guidelines and implementation controversy

Spasovski Goce and Polenakovic Momir

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Keywords: guidance; guidelines; implementation

A clear need for guidance in all areas of medicine has been recognised over the last decade aiming to assist practitioners in clinical decisions about best medical care and outcome of treatment for their patients. The term "guidance" should not be understood as imposed standard, but statement which is considered as an important component of the application of medical knowledge to medical practice. A variety of guidelines have been created ever since by various societies, associations and initiatives all over the world [1-3]. These guidelines were supposed to be entirely based upon the best possible current evidence. This particular question was especially important in view of the complexity of CKD patients and difficulties in measuring hard outcomes which are directly attributed to a specific guideline related change in the patient outcome [4]. In this regard, there is still a continuing medical debate as to whether guidelines and their development process actually impact patient outcomes.

The European Renal Association–European Dialysis and Transplantation Association (ERA-EDTA) has a decade of tradition of producing guidelines [2]. Being aware that the nephrology guidelines often lack high level of evidence, and in the presence of a biased perception of the medical community in case of low evidence guidelines, the ERA-EDTA Council nominated advisory board for defining the future of European Best Practice guidelines (EBPG). The members of the board decided that European nephrology guidelines issued by the ERA-EDTA should be published as "guidelines" only in the case of high-level evidence; otherwise they should be named "recommendations" or "position statements". Due to this substantial change in philosophy, the name of the initiative was changed from EBPG to European Renal Best Practice (ERBP) [5]. The main purpose of this initiative was to help increasing the visibility of European Nephrology guidance and to enhance the quality of European and world-wide nephrology practice. In addition, this process was considered as standard for judging the quality and providing a cost-effective clinical care via implementation of the issued recommendations and position statements.

Once successfully disseminated, a guideline perception from the practicing nephrologist is equivalent as for a tool to reduce variability in diagnostic and treatment strategies, trying to provide best possible patients' outcome linked to the particular guideline implementation. Moreover, it should serve to ideally optimize the limited health care resources by ensuring "best practices". However, after production, major difficulties to encompass the whole process of guidance arise when introducing the evidence and clinical guidelines into routine daily practice, which appears as frequently neglected issue. Here, development of implementation tools (various forms of educational materials for clinicians and patients) and protocols (algorithms) to be followed would be necessary to complete the crucial step of translation into the clinical practice [6].

A present knowledge and thinking about approaches to changing medical practice (implementation) is still not precisely defined [7]. The uptake of evidence is influenced by three basic issues: attributes of evidence, barriers and facilitators to changing practice, and effectiveness of dissemination and implementation strategies. Taking into account various attributes of evidence (type/chronicity of the topic, method of analysis, complexity and quality of the evidence) that are in part non-modifiable, it could in turn improve the effectiveness of implementation. Barriers and facilitators to changing practice have shown that obstacles can arise at different stages in the health-care system (at the level of the patient, the individual professional, the health-care team, the health-care organisation, or the wider environment) [8]. Naturally, appropriate understanding of such obstacles to develop an effective intervention is essentially important [9]. The effectiveness of dissemination and implementation strategies depends on the type of evidence, i.e. whether it is based on professionally-oriented interventions, or towards any organisational or the patient's issues [7]. Here, various educational strategies (educational mate-rials, systematic reviews of guideline implementation strategies, CME activities, small group interactive education with active participation, use of local opinion leaders, audit and feed-
back, reminders, mass media campaigns, etc.) might be employed in accordance to particular guideline, clinical and current environmental setting. Finally, the economic assessment of performance strategies is scarce, as is the information on patients’ outcomes, which should be viewed as a challenge for future research.

In summary, the professional development of implementation strategies needs to be built into daily patients’ care, taking place at the point of time with clinical decision support tools and frequent patient-specific reminders to help medical practitioners to make the best decisions. On the other hand, the obstacles to changing practices are not only in the professional setting but also in the patient, the organisation of care processes, resources, leadership, and the political environment [10]. Hence, not only generation of guidelines, but also additional measures and actions at the level of teams or organisations are considered of paramount importance when developing plans for change in clinical practice. None of the approaches for transferring evidence to practice is shown to be superior to all changes in all situations. Hence, a continuous and dedicated clinical practice, facing the main difficulties and measuring the success of implementation progress based at regular intervals will be certainly helpful. Finally, there is a lot to be done in order to enhance and globalise the quality of European and worldwide nephrology practice. Nevertheless, once the problem is noted, a kind of solution should follow.

Conflict of interest statement. None declared.

References:


Clinical characteristics and renal survival of focal segmental glomerulosclerosis morphologic variants

Grcevska Ladislava, Dzikova Sonja, Gordana Petrusevska and Gjore Zografski

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Abstract

Background. A number of morphologic variants of primary and secondary focal segmental glomerulosclerosis (FSGS) are now recognized. Histological variants may have specific clinical characteristics and prognosis. Our study utilized a large cohort of FSGS patients to determine if the pathologic variants defined by the Columbia proposal are distinct clinico-pathologic entities.

Methods. It was a single center study, 115 adult patients with biopsy proven FSGS were included. Renal biopsies were reviewed by two pathologists. Demographic and clinical data were obtained by charts. Statistics included One-way ANOVA, Kruskal-Wallis and Mann-Whitney tests.

Results. The frequency of FSGS variants was as follows: collapsing 15 (13%), tip lesion 24 (20.8%), perihilar 28 (24.4%), cellular 40 (34.8%) and not otherwise specified (NOS) 8 (6.9%) patients. Tip patients were younger (age 28.67±3.84), compared to perihilar (p=0.000), cellular (p=0.007) and NOS (p=0.012). Diastolic blood pressure was the highest in perihilar variant, significantly higher comparing only to tip variant (p=0.05). There was not noted difference in serum creatinine levels at biopsy among the variants (p=0.091). Plasmaproteins level was significantly lower in collapsing variant (55.13 ± 2.68g/l) and cellular (57.6 ± 1.92g/l) compared to perihilar (66.21 ± 1.24g/l) and NOS (66.25 ± 1.83g/l), p=0.02. The mean value of proteinuria was as follows: collapsing 7.35 ± 1.7g/d, tip lesion 4.76 ± 0.77g/d, perihilar 2.6 ± 0.4g/d, cellular 5.16 ± 0.75g/d and NOS 1.7 ± 0.41g/d, the difference among the groups was significant, p=0.000. We also noted differences in survival of patients. 5-year survival rate of collapsing variant was 25%, NOS variant 45%, perihilar 55%, tip lesion 63% and patients with cellular variant 67%.

Conclusion. We can conclude that FSGS variants are with different histopathological and clinical features and different outcome of the disease.

Keywords: collapsing nephropathy; focal segmental glomerulosclerosis; glomerulonephritis; nephrotic syndrome; proteinuria

Introduction

A pattern of focal segmental glomerulosclerosis (FSGS) may result from diverse pathogenetic mechanisms including heritable mutations of podocyte-specific proteins (nephrin, podocin, alpha actinine 4) [1-6], infections, especially viral (HIV, parvovirus B19) [8-11], drug toxicities and adaptive responses to reduced functioning renal mass [12-14]. For most patients with FSGS who present with nephrotic syndrome or heavy proteinuria, no secondary cause is identified and then we can use the term “idiopathic FSGS” [15-19]. But, data from the literature present different clinical and pathological features and different outcome of the disease. Idiopathic FSGS is clinically and pathologically heterogeneous, and these variants display variable renal outcomes [20-22]. Widely accepted Columbia FSGS Classification [22-26] recognizes five variants of FSGS, as follows:

Fig. 1. Collapsing variant of FSGS: glomerular capillary tuft collapse, podocyte hypertrophy and hyperplasia
1. **Collapsing variant (COLL)**
At least one glomerulus with defining features (glomerular capillary tuft collapse, overlying podocyte hypertrophy and hyperplasia), other glomeruli may have segmental lesions of any subclass. Tubulointerstitial changes are severe. COLL FSGS has a more aggressive clinical course, with fewer remissions and more frequent end-stage renal disease.

![Fig. 2. Tip lesion FSGS: segmental lesion of glomerular capillary tuft, confluence with origin of proximal tubule](image)

2. **Glomerular “tip” lesion (TIP)**
Collapsing and perihilar lesion has to be excluded. At least one glomerulus must have defining features (segmental lesion involving 25% of glomerular tuft, adhesion or confluence of glomerular lesion with origin of proximal tubule, segmental lesion may be foam cells or endocapillary hypercellularity). Less expressed tubulointerstitial changes. Severe nephrotic syndrome is present in most of the patients, but the response to steroid treatment is good, as well as the survival of the patients.

![Fig. 3. Cellular variant of FSGS: segmental endocapillary proliferation, foam cells are visible](image)

3. **Cellular variant (CELL)**
Collapsing and tip lesion must be excluded. At least one glomerulus must have defining features (segmental endocapillary proliferation, segmental endocapillary foam cells with occlusion of capillary lumina). Other glomeruli may have segmental sclerotic lesions. Severe nephrotic syndrome is the common, the response to treatment and renal survival is poor.

![Fig. 4. Perihilar variant of FSGS: segmental occlusion of glomerular capillaries with matrix accumulation and hyalinosis](image)

4. **Perihilar variant (PH)**
Collapsing, “tip” lesion and cellular variant must be excluded. More than 50% of glomeruli must present segmental occlusion of glomerular capillaries by matrix accumulation and hyalinosis. The lowest frequency of nephrotic syndrome and the highest frequency of hypertension are characteristics of this pattern. The response to steroid treatment is poor, but on the other hand the survival is the best.

![Fig. 5. NOS variant of FSGS: non-specific segmental capillary tuft lesion](image)

5. **Not otherwise specified (NOS variant)**
Other variants have to be excluded. Any number of glomeruli may be involved, segmental glomerular tuft lesion is necessary, capillary tuft collapse may be found, but without podocyte hyperplasia. Patients tended to have clinical and pathologic parameters that were intermediate with respect to the spectrum of findings in the other distinctive variants. Hypertension is frequent, but nephrotic syndrome, too. Complete remission is rare.
In this study, we classified our patients with FSGS according to Columbia Classification of FSGS [22] and compared their clinical characteristics and renal survival. We also tried to compare our results found in each variant with previously reported data about that variant of FSGS.

**Patients and Methods**

We conducted a retrospective, clinicopathological analysis of adult patients (>15yr age at presentation) who had primary FSGS, diagnosed at our Department. The diagnosis of primary FSGS was established when there was no immunopathologic evidence for another primary glomerular disease or pathologic and clinical evidence for a systemic disease associated with secondary segmental glomerular sclerosis (morbid obesity, reflux, HIV infection, nephrectomy, solitary kidney, intravenous drug abuse, family history of renal disease). On the basis of these criteria, we identified a total of 115 patients with primary FSGS during a period of time of 10 years and they were basis of this study.

Renal biopsy tissue was divided and processed for light, fluorescence and electron microscopy. Semi-thin sections were done in all cases, and ultra-thin unfortunately only in 18. Inclusion in this study required a minimum of 8 glomeruli in the light microscopic section. Light microscopic examination of slides stained with hematoxylin/eosin, PAS and methenamine silver-PAS (Jones stain) provided the diagnosis of FSGS and categorization into one of 5 groups, according to previously described criteria of Columbia Classification of FSGS [22]. Tubular, interstitial and vascular changes were not taken into consideration. Renal biopsy specimens were analyzed by two pathologists.

Demographic, clinical and laboratory information at the time of renal biopsy and at follow-up was obtained on each patient. Clinical records were reviewed to determine the patients’ gender, age, blood pressure, level of protein excretion, serum creatinine and serum plasmaprotein at the time of biopsy.

Renal insufficiency was defined as serum creatinine >120 µmol/l. The date of the start of dialysis treatment was the date of the end of renal survival. Nephrotic-range proteinuria was defined as >3g/d protein loss and massive proteinuria defined as >10g/d protein. Hypertension was defined as a systolic BP>140mmHg and a diastolic BP>90 mmHg. Complete remission was defined as a urine protein of <0.4g/d and partial remission was defined as a urine protein between 0.41 and 2.9g/d.

Patients with normal renal function and nephrotic syndrome were treated with steroids, sometimes combined with cyclophosphamide and past 5 years with mycophenolate mofetil. This treatment was also performed in patients with serum creatinine < 220µmol/l. Patients with non-nephrotic proteinuria and renal failure (creatinine > 220µmol/l) were treated with ACE-inhibitors. Renal “death” was defined as need of dialysis treatment.

Statistics included One-way ANOVA, Kruskal-Wallis, Mann-Whitney tests and Kaplan-Mayer survival curves.

**Results**

This pattern was found in 13 patients, aged 35.47 ± 3.89 (M ± SE, mean ± standard error). Diastolic blood pressure (DBP) at renal biopsy was 96.67 ± 2.66 mmHg, serum creatinine 101.93 ± 6.6 µmol/l, daily protein loss of 7.35 ± 1.7g/d and plasmaproteins level of 55.13 ± 2.68g/l. Complete remission was not achieved in any patient, partial in 2/13. All 13 patients developed chronic renal failure during follow-up, and 5-year survival rate was 25%.

**Fig. 6.** Hyperplasia and hypertrophy of visceral epithelial cells with hyaline droplets in collapsing variant of FSGS

**Fig. 7.** Affection of urinary pole of glomerulus in “tip” lesion of FSGS

This histopathological form was diagnosed in 24 patients, aged 28.67 ± 2.38. DBP at start of the study was 90 ± 2.6 mmHg, serum creatinine 106 ± 12.37 µmol/l, plasmaproteins 60.5 ± 2.4g/l and daily protein loss of 4.7 ± 0.76g. Complete remission was noted in 2/24 patients, without relapse during follow-up, partial in 8/24. 14/24 patients developed chronic renal failure during follow-up and 5-years survival rate was 63%.
Fig. 8. Hilar affection in perihilar variant of FSGS

21 patient was diagnosed as perihilar variant of FSGS, aged 41,1 ± 3,89, DBP at biopsy was 100 ± 1,98mmHg, serum creatinine levels of 140 ± 13,43 µmol/l, plasmaproteins level of 66,21 ± 1,24 g/l and daily protein loss of 2,59 ± 0,4g. Summary data of this group presented creatinine level > 120µmol/l and normal plasmaproteins. None of the patients responded to immunosuppressive treatment, and 5-year survival rate was 55%.

Fig. 9. Foam cells in cellular variant of FSGS

This group consisted of 28 patients, aged 36,2 ± 2,06. DBP was 96,12 ± 1,95 mmHg, plasma creatinine 108,9 ± 7,94 µmol/l, plasmaproteins 57,6 ± 1,92g/l and daily protein loss of 5,16 ± 0,75g/d. Complete remission was noted in 3/28 and partial in 10/28 patients. 15 patients developed chronic renal failure during follow-up, but slow progressive and 5-year survival rate was the best: 67%.

NOS variant

8 patients were not classified in previous groups, but presented focal-segmental changes. They were aged 39,62 ± 3,7, with DBP at start of the study 99,37 ± 5,54mmHg, serum creatinine 111,75 ± 12,66µmol/l, plasmaproteins 66,25 ± 1,83g/l and daily protein loss of 1,7 ± 0,33g/d. Only one patient (with nephrotic syndrome) responded partially to immunosuppressive treatment, the other 7 patients developed chronic renal failure during follow-up. The 5-year survival rate was 45%.

Analyzing clinical data of all groups, it can be seen that “tip” lesion patients was younger comparing to perihilar (p=0,000), cellular (p=0,007) and NOS lesion patients (p=0,012). DBP was the highest in perihilar variant, but the difference was significant comparing only to “tip” variant (p=0,05). There was not noted significant difference in serum creatinine levels at biopsy among different histopathological variants (p=0,091). Plasmaproteins level was significantly lower in collapsing and cellular variant compared to perihilar and NOS (p=0,012), and the difference among the daily loss of proteins of different patterns was also significant (p=0,000). We also noted different survival rates in different histopathological forms.

Discussion

We reviewed the presentation and clinical course of adult patients with primary FSGS to determine the significance of different forms of glomerular histopathological lesions. Glomerular changes were classified according to Columbia FSGS Classification [22]. We can conclude that there was no significant difference in renal function among the groups, nephrotic syndrome was characteristic for collapsing, cellular and tip lesion and hypertension for perihilar and NOS variant. Complete remission was rarely occurred in all groups, some patients with nephrotic syndrome responded to immunosuppressive treatment with partial remission [31,32]. But, partial remissions were more frequent in cellular and tip lesion, only two collapsing variant patients with severe nephrotic syndrome partially responded to therapy. Histopathological patterns with clinical presentation with nephrotic syndrome and more frequent partial and complete remissions (excluding collapsing variant) also presented better survival. It is well known that cellular, collapsing and tip lesion share clinical presenting features of heavier proteinuria, more frequent nephrotic syndrome and shorter duration of symptoms compared to NOS and perihilar variant of FSGS, suggesting that the first three variants reflect acute glomerular injury, or possibly a response to heavy proteinuria [22-28]. Literature data agree that morphologic variants of idiopathic FSGS display significantly different rates of remissions. The outcome is the worst for collapsing variant; this fact was also presented in our study [22-24]. “Tip” lesion patients presented the best outcome in the other series [22,26], they are on the second place in our material, after cellular variant. It is interesting that contrary to literature data cellular variant is frequent among our patients with FSGS, with severe
nephrotic syndrome as dominant clinical feature and the best survival. This difference may due to the fact that tubular atrophy, interstitial fibrosis, interstitial edema, interstitial inflammation and vascular changes were not taken into consideration. The degree of podocyte hyperplasia and hypertrophy in each segmental lesion also was not graded. It is clear that inclusion of tubulointerstitial changes and quantification of glomerular changes may explain the difference in survival and different responses to treatment, but it will be the matter of the other study.

Conclusions

This study confirms that different histopathological variants of FSGS according to Columbia FSGS classification present different clinical features and different outcome of the disease.

Conflict of interest statement. None declared.

References

Prevention of hemodynamic instability during hemodialysis in cardiac-compromised hypotension-prone patients

Kes Petar, Basic-Jukic Nikolina, Sefer Sinisa and Ratkovic-Gusic Iva

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Abstract

Background. Hypotension is the most common complication of hemodialysis (HD). The aim of this study was to investigate the efficacy of hypertonic saline (10%), albumin (20%), and 10% hydroxyethylstarch (HES) on blood pressure (BP) course during HD session in cardiac-compromised hypotension-prone HD patients.

Methods. Fifteen patients (8 female, 7 male), age ranging from 56-80 years, undergoing chronic HD for 6-36 months, were included in the investigation. All patients were cardiac-compromised (NYHA III-IV), with ejection fraction ranging from 23-40%. Intra-dialytic hypotension was experienced in all patients more than once a week. Dry body weight was estimated on clinical basis. The patients were studied during three HD sessions that differed only in the type of intravenous fluid administered. In the randomized order, an intravenous infusion of 12 ml of saline (10 % sodium chloride), 100 ml of albumin (20%) or 100 ml of HES (10%) was administered when systolic blood pressure (SBP) was less than 90 mmHg, or when the SBP decreased more than 30 mmHg.

Results. Systolic BP decreased significantly versus baseline during HD in all three sessions (p<0.05). The decrease was significantly greater when using saline compared with albumin (p<0.05) or with HES (p<0.05). There was no significant difference in SBP decrease between the patients treated with albumin and those treated with HES. Diastolic BP decreased significantly versus baseline during HD and treatment with saline and albumin (p<0.05) but not with HES. Diastolic BP at the end compared to DBP at the start of HD session decreased with saline, increased with albumin, and increased significantly with HES. There was no significant difference in inter-dialytic weight gain after the treatment with hypertonic saline, albumin or HES. Three patients experienced a hypotensive episode when using saline and one patient experienced a hypotensive episode when using albumin. However, ultrafiltration could be continued when the patients were placed in the Trendelenburg position.

Conclusion. Our results demonstrate that SBP was better maintained with albumin (20%) or HES, compared with hypertonic saline. The increase in SBP was greater with HES compared to albumin. It is possible that higher sodium concentration of HES has an additional beneficial effect on the SBP course, without repercussion on the inter-dialytic weight gain.

Keywords: hemodialysis; intra-dialytic hypotension; treatment; prevention; saline; HES; albumin; heart failure

Introduction

Intra-dialytic hypotension (IDH) is the most common complication of hemodialysis (HD) that may induce minor side effects such as dizziness, muscle cramps, nausea, and vomiting, but may also lead to more serious complications, such as subendocardial ischemia, severe arrhythmias or neurological complications [1,2]. Dialysis-associated hypotension is especially frequent in elderly patients and in those with compromised cardiovascular system [3-6]. Pathophysiology and treatment of IDH have been extensively studied, and most of the papers emphasized its multifactorial origin [3,7,8]. The immediate cause of hypotension is reduction of intravascular volume that is most frequently treated by injecting hypertonic saline [9]. However, because of side effects of the hypertonic saline (hypertension, thirst, and inter-dialytic weight gain) this therapy is not without drawbacks. Volume expansion can also be achieved by hyperoncotic infusions, such as dextran and mannitol [10,11], but their use is of limited clinical importance because of side effects [9-13]. An intravenous infusion of albumin or other hyperoncotic fluids further enhance vascular refilling and could improve hemodynamic stability [14]. Recently, an increased risk of death was reported in critically ill patients treated with albumin [15]. Data on the effect of hypertonic saline,
hydroxyethylstarch (HES) and albumin on systolic blood pressure (SBP) course in cardiac-compromised HD patients with frequent hypotensive episodes are scarce. The aim of this study was to investigate the efficacy of hypertonic saline (10%), albumin (20%), and HES (10%) on the blood pressure (BP) course during combined ultrafiltration (UF) and HD in cardiac-compromised HD patients.

**Patients and methods**

**Study Population and Dialysis**

Fifteen patients (8 female and 7 male) undergoing chronic, intermittent HD, were included in the investigation. All patients were cardiac-compromised (New York Hearth Association /NYHA/ classification III-IV) [16], and had a mild-to-severe left ventricular dysfunction (ejection fraction /EF/ of 40% or less), which was determined by the two-dimensional echocardiogram after HD. All the patients experienced IDH more than once a week. Informed consent was provided by all participants. The study was approved by the Sestre Milosrdnice University Hospital Ethics Committee. Dry body weight (DBW) was determined clinically by the nephrologist. The UF rate was prescribed according to the estimated DBW and inter-dialytic weight gain, and was constant during a single HD session. Hemodialyses were performed using the Nipro NCU 10E modules (Nisco Nipro Corporation, Japan) with hollow fiber dialyzers (hemophane membrane - Hospal, France; cellulose diacetate membrane - Pliva, Croatia). The blood flow ranged from 220 to 280 ml/min, with the dialysate flow of 500 ml/min. The dialysate concentrate (H-K DM 10 and H-K 6, Pliva, Croatia) composition was as follows: sodium 100 mmol/L, potassium 2 mmol/L, calcium 1.5-1.75 mmol/L, magnesium 0.375 mmol/L, chloride 105.75 mmol/L, acetate 2 mmol/L. The dialysate bicarbonate concentration was individualized and adjusted to achieve a post-dialysis serum bicarbonate level between 26 and 30 mmol/L. The dialysate temperature was adjusted to the patient’s pre-dialysis body temperature. The dialysate temperature and dialysate composition did not differ between the three treatment sessions.

**Study Protocol**

The ESRD patients were studied on the days of their regular dialysis. Each patient served as his or her own control and was studied during three sessions that differed only in the type of intravenous fluid administered. The study started with the insertion of needles with patient in the supine position during the dialysis session. Intravenous infusion of 12 ml of saline (10% sodium chloride; Croatian Institute for Transfusion Medicine, Zagreb, Croatia), 100 ml of albumin (20% human albumin; Institute of Immunology, Zagreb, Croatia), or 100 ml of HES (10% HAES-steril; Fresenius, Bad Homburg, Germany) was administered at room temperature (22°C) when SBP was less than 90 mm Hg, or when it decreased more than 30 mm Hg in relation to the start of UF and HD, in which case UF was continued at the same rate. The osmolar load of the administered saline (309 mosm/L) was similar to the osmolar load of HES (308 mosm/L). The order of the intravenous infusions was randomized. Measurements of arterial BP were performed just before the start of UF and HD (t=0), when SBP was less than 90 mm Hg or when the decrease in SBP was more than 30 mm Hg versus the start of UF and HD (t=iv); after one (t=1), 5 (t=5), and 30 (t=30) min after t=iv; and at the end of UF and HD (t=end).

**Measurements and Laboratory Methods**

Blood pressure (SBP, and diastolic BP /DBP/) was measured every 30 minutes routinely and every 10-15 minutes if the patient became symptomatic or if BP decreased. Moreover, SBP and DBP were also measured at t=iv, t=1, t=5, t=30, and t=end. Before and at the end of HD, the blood sample was taken to determine the levels of serum sodium and ionized calcium (Chiron Diagnostics, Essex, UK), blood urea nitrogen and creatinine (Beckman CX-I, Brea, USA).

**Dialysis Adequacy**

Dialysis adequacy (Kt/V) in HD patients was calculated using the second-generation formula introduced by Daugirdas [17]. Blood samples for determinations of urea were taken before and immediately after HD.

**Statistical Analysis**

All values are expressed as mean ± SD. The parameters assessed during different treatments were analyzed with paired Student’s t-test and ANOVA. P value lower than 0.05 was considered significant.

**Results**

**Patient Characteristics**

The mean patient age was 70.4 years (range, 56-80 years), and the mean time on HD was 22.1 months (range, 6-36 months). End-stage renal disease was caused by benign nephrosclerosis (7 patients), chronic glomerulonephritis (3 patients), diabetic nephropathy (3 patients), and chronic pyelonephritis (2 patients). The mean residual diuresis was 185 ml (range: 0 to 840 ml/day). Heart failure resulted from one or more myocardial infarctions (6 patients), ischemic heart disease (3 patients), left ventricular systolic dysfunction (4 patients), and dilated cardiomyopathy (2 patients). The mean EF of the patients was 28.7±8.4% (range, 23 to 40%).

The pre-dialysis DBW in the three study treatment sessions (saline, albumin, and HES) were 67.5±12.82, 66.9±12.63, and 66.74±12.69 kg, respectively. The UB rate was 0.92±0.31, 0.86±0.39, and 0.91±0.25 L/h in the three treatment sessions. The differences were not statistically significant. The mean Kt/V was 1.16±0.6, and did not significantly changing during HD sessions. The
dialysate temperature during all three HD sessions was 36.93±0.39°C.

**Changes in Blood Pressure**

Table 1 shows the SBP during HD sessions in hypotension-prone patients treated with three different hypertonic solutions. There were no statistically significant differences in duration of intravenous infusion of saline, albumin, and HES (147±67, 144±58, and 150±76 min, respectively). Systolic BP decreased significantly versus baseline (t=0) during UF and HD in all three treatment sessions (p<0.05). The decrease was significantly higher when using saline compared with albumin (p<0.05) and when using saline compared with HES (p<0.05). There were no significant differences between albumin and HES.

When the values at t=iv with those at t=end were compared, SBP decreased with saline (change in SBP, -8.71±16.63 mmHg; NS), increased with albumin (change in SBP, +8.66±16.61 mmHg; NS), and increased significantly with HES (change in SBP, +16.11±19.37 mmHg; p<0.05). The change in SBP at t=end versus t=iv was significantly greater when using saline compared with HES (p<0.05) and tended to decrease more when using saline compared with albumin (p=0.09). There were no significant differences between albumin and HES.

### Table 1. Systolic SBP course during treatment with three different solutions

<table>
<thead>
<tr>
<th>Variable</th>
<th>SBP (mmHg) Saline (10%)</th>
<th>Albumin (20%)</th>
<th>HES (10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>t=0</td>
<td>128.1±60.6</td>
<td>122.3±58.2</td>
<td>128.2±62.0</td>
</tr>
<tr>
<td>t=iv</td>
<td>84.8±40.0</td>
<td>81.0±38.6</td>
<td>82.3±40.2</td>
</tr>
<tr>
<td>t=5</td>
<td>99.3±47.0</td>
<td>96.2±45.5</td>
<td>96.3±45.5</td>
</tr>
<tr>
<td>t=15</td>
<td>99.3±46.5*</td>
<td>106.9±50.3</td>
<td>105.6±49.6</td>
</tr>
<tr>
<td>t=30</td>
<td>96.8±45.4*</td>
<td>105.6±49.6</td>
<td>103.0±48.1</td>
</tr>
<tr>
<td>t=60</td>
<td>90.9±42.5*</td>
<td>100.8±49.6</td>
<td>98.8±46.0</td>
</tr>
<tr>
<td>t=end</td>
<td>93.4±35.3*</td>
<td>98.8±36.9#</td>
<td>100.3±37.2#</td>
</tr>
</tbody>
</table>

*p<0.05 vs. albumin and HES, # p<0.05 vs. t=0

Diastolic BP decreased significantly versus baseline (t=0) during UF and HD with saline and albumin (p<0.05), but not with HES. When the values at t=iv with those at t=end were compared, DBP decreased with saline (change in DBP, -5.71±16.70 mmHg; NS), increased with albumin (change in DBP, +2.89±10.05 mmHg; NS), and increased significantly with HES (change in DBP, +7.55±10.38 mmHg; p<0.05). The change in DBP at t=end versus t=iv tended to decrease more when using saline compared with HES (p=0.075) (Table 2). There were no significant differences between albumin and HES and between albumin and saline.

### Table 2. Diastolic BP course during treatment with three different solutions

<table>
<thead>
<tr>
<th>Variable</th>
<th>DBP (mmHg) Saline (10%)</th>
<th>Albumin (20%)</th>
<th>HES (10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>t=0</td>
<td>67.7±9.3</td>
<td>65.5±6.0</td>
<td>66.7±5.9</td>
</tr>
<tr>
<td>t=iv</td>
<td>59.3±7.5</td>
<td>57.3±6.9</td>
<td>57.9±6.4</td>
</tr>
<tr>
<td>t=5</td>
<td>64.8±5.6</td>
<td>67.1±5.3</td>
<td>66.5±5.1</td>
</tr>
<tr>
<td>t=15</td>
<td>61.6±6.7*</td>
<td>67.2±4.7</td>
<td>65.3±5.1</td>
</tr>
<tr>
<td>t=30</td>
<td>57.7±5.8*</td>
<td>62.9±4.6</td>
<td>62.3±4.9</td>
</tr>
<tr>
<td>t=60</td>
<td>58.1±7.0</td>
<td>58.9±5.1</td>
<td>60.1±5.1</td>
</tr>
<tr>
<td>t=end</td>
<td>56.5±7.3**</td>
<td>57.3±5.7**</td>
<td>60.0±4.8**</td>
</tr>
</tbody>
</table>

*p<0.05 vs. albumin and HES, & p<0.05 vs. HES, # p<0.05 vs. t=0

### Table 3. Laboratory data before the start of HD and at the end of the HD session

<table>
<thead>
<tr>
<th>Laboratory data</th>
<th>Saline (10%)</th>
<th>Albumine (20%)</th>
<th>HES (10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>t=0</td>
<td>1010±213.4a</td>
<td>1041.6±217.6a</td>
<td>421.4±100.7a</td>
</tr>
<tr>
<td>t=end</td>
<td>401.1±113.3a*</td>
<td>1058.7±220.7</td>
<td>423.6±98.2a*</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>29.3±3.9</td>
<td>7.9±1.1*</td>
<td>29.2±3.4</td>
</tr>
<tr>
<td>t=0</td>
<td>9.7±0.9*</td>
<td>7.9±0.8*</td>
<td></td>
</tr>
<tr>
<td>t=end</td>
<td>7.9±0.8*</td>
<td>7.9±0.8*</td>
<td></td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>138.5±2.0</td>
<td>136.0±2.0*</td>
<td>136.8±1.8</td>
</tr>
<tr>
<td>t=0</td>
<td>135.8±2.2</td>
<td>135.9±1.6*</td>
<td></td>
</tr>
<tr>
<td>t=end</td>
<td>135.9±1.6*</td>
<td>135.9±1.6*</td>
<td></td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>1.24±0.04</td>
<td>1.27±0.03*</td>
<td>1.34±0.02*</td>
</tr>
<tr>
<td>t=0</td>
<td>1.31±0.02*</td>
<td>1.31±0.03*</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.001 vs. t=0, *p<0.05 vs. albumine and HES
The inter-dialytic weight gain after treatment sessions with saline, albumin, and HES was 2.63±0.38, 2.43±0.34, and 2.63±0.71 kg, respectively, with no significant difference between the three treatment sessions. Three patients experienced a hypotensive episode when using saline and one patient experienced a hypotensive episode when using albumin. However, UF could be continued when the patients were placed in the Trendelenburg position.

The laboratory data are presented in Table 3. The change in serum sodium was comparable between the three treatment sessions. During all sessions there was a significant increase in ionized calcium and decrease in BUN. There were no significant differences in change in ionized calcium and BUN between the sessions.

Discussion

Intra-dialytic hypotension is common, occurring in 20 to 30% of HD sessions [1,3,18,19]. The adequacy of intradialytic sodium and water removal plays a pivotal role in preventing both IDH and overhydration. It had been assumed that the primary cause of IDH was induction or exacerbation of intravascular volume depletion by rapid UF. This hypothesis was disproved by the observation by Bergstrom et al. [20] that patients who became hypotensive during HD tolerated the same degree and rate of fluid removal with pure hemofiltration with no diffusive component of solute loss. During conventional HD, the rapid diffusive removal of urea and other small solutes results in a reduction of plasma oncotic pressure, which shifts water into the cells, further depleting the extracellular volume, which has also diminished by UF. It is also possible that the rapid fall in plasma oncotic pressure contributes to the hemodynamic instability, perhaps by interfering with sympatheic responsiveness to the volume depletion [21]. On the contrary, isolated UF does not create the osmotic gradient between the cells and the extracellular fluid, while the removed fluid has the same concentration of small solutes as the plasma. The fall in intravascular volume will raise the plasma protein concentration and therefore the plasma oncotic pressure, drawing water from the extracellular space and the cells into the vascular space, thereby leading to the relative preservation of intravascular volume [22,23].

It has been shown that limiting the reduction in extracellular osmolality by injecting hypertonic fluids could be an efficient treatment of symptomatic hypotension [6]. However, repeated intravenous injections of saline may lead to an increase in the exchangeable sodium pool and, as a consequence of thirst, may lead to an increase in inter-dialytic weight gain and hypertension, which may be of great clinical importance in cardiac-compromised dialysis patients [24,25]. In the present study two hypertonic fluids (HES, 10%, which is also a hyperoncotic fluid), and saline (10%) were compared with albumin (20%), a hyperoncotic fluid with an osmolality between 260 and 280 mosm/L, with respect to their effect on SBP. Saline and HES were administered in such amounts that a similar osmolar load was given. It was found that SBP was better maintained with HES compared with saline, suggesting that it is not only the effect of osmolality, but also the additional oncotic effect of HES that is responsible for the distinct and prolonged effect on SBP course.

It can be expected that hypertonic HES (10%) may be of even greater clinical importance in cardiac-compromised HD patients who often experience IDH. Van der Sande et al. [26] have evaluated the effect of normal saline, 20% albumin, or HES on preservation of blood volume in HD patients [26]. There was no significant difference in SBP among the three groups, but the preservation of blood volume was significantly better with HES and albumin compared with saline [26]. However, the increase in SBP, although not significant, was greater with HES compared to albumin [26]. It is possible that the higher sodium concentration of HES compared to albumin has an additional beneficial effect on SBP. In their second study, van der Sande et al. [27] investigated the effect of hypertonic (3%) saline, 20% albumin, and 10% HES in dialysis patients with frequent hypotensive episodes. Systolic BP was better maintained with HES or albumin, compared with saline [27]. The increase in SBP, although not significant, was greater with HES compared to albumin. Similar osmotic load of HES and saline indicate the responsibility of additional oncotic effect of HES on SBP course. In a randomized, blinded, crossover clinical trial, Knoll et al. [28] evaluated the effect of normal saline and 5% albumine in the treatment of IDH in 72 chronic HD patients. The percentage of target UF achieved was 0.84 ± 0.17 for 5% albumin compared with 0.80 ± 0.16 for saline. The post-dialysis SBP, postdialysis DBP, volume of study fluid used to treat IDH, time required to restore the BP, total nursing time required to manage the hypotensive episode, number of treatment failures (22% vs. 24%), and the frequency of recurrent IDH (36% vs. 36%) were not significantly different when 5% albumin was used compared with saline. It is concluded that 5% albumin is no more effective than normal saline for the initial fluid treatment of IDH in chronic HD patients [28]. Gong et al. [29] compared hypertonic saline solutions with dextran, which also has oncotic effects, and found that SBP response was more prolonged with 23% saturated hypertonic saline and dextran compared with hypertonic saline alone (7.5%). However, the majority of patients needed repeated intravenous infusions to maintain SBP [29]. Nette et al. [30] compared the effect of no infusion with isovolumetric infusion of isotonic and 3% saline, isotonic and 20% glucose, and 20% mannitol, in 6 patients during the first hour of 6 standardized HD sessions with UF. The maximum increase in relative blood volume (RBV) directly after infusion was significantly greater with 20% glucose than with all other infusions. Stroke volume increased and total peripheral resistance decreased significantly after hypertonic glucose infusions. As mannitol has the same osmolarity, molecule mass and charge, the greater increase in RBV following hypertonic glucose appears to be a specific effect, possibly related to a decline in vascular tone. It is therefore uncertain whether the observed increase in
plasma volume during hypertonic glucose infusions will be of clinical benefit [30]. In the present study SBP was better maintained with albumin compared with hypertonic saline, which could be caused by the oncotic effects of albumin. These data are also comparable with the results of previous studies, in which it has been found that SBP, although not significantly, was better maintained with albumin compared to saline [2,26,27]. The effect of HES on BP control was not significantly different when compared to that of albumin. The increase in SBP, although not significant, was greater with HES compared to albumin. It cannot be excluded that the higher sodium concentration of HES has an additional beneficial effect on SBP course. This difference in sodium concentration does not appear to introduce untoward clinical effects, because the change in serum sodium during HD and interdialytic weight gain during the days after treatment were comparable between the three sessions.

By applying conductivity kinetic model to ESRD patients prone to IDH, Locatelli et al. [4] observed a significantly lower reduction in intra-dialytic SBP, and trend toward a reduction in symptomatic IDH, without modifying the dialysate and reinfusate sodium concentration values, or patient's DBW [4]. More recent investigations have suggested that the disparate hemodynamic responses to fluid and solute removal during HD and hemofiltration may be dissociated from changes in osmolality, membrane bioin-compatibility, pyrogen-containing dialysate, thermal stress, catecholamine and other vasoactive hormones release, or venous tone [21,31-33]. In order to evaluate the safety, efficacy, and cost of treatment of HD-associated hypotension, Emili et al. [34] designed a protocol consisting of the stepwise use of saline, mannitol, and albumin. The protocol was evaluated prospectively in 2559 consecutive HD sessions in a total of 442 patients. Hypotension occurred during 24% of sessions, and reversal of low BP was achieved without the need for albumin in 91% of cases [34]. From these data, data from recently published studies [26,27], and from the authors’ results, it is concluded that HES (10%) is an effective solution for maintaining BP in hypertensive-prone HD patients, comparable to albumin (20%), but superior to hypertonic saline. Given the side effects and cost of albumin, HES may be preferred [35].

An integrated approach to HD-associated hypotension would consist of the prevention of reduction in SBP or a symptomatic fall in mean BP by preserving plasma volume (the assessment of an optimal fluid state (DBW), minimizing interdialytic weight gain, sodium modeling, individualizing UF targets), optimizing the cardiovascular function (avoiding food ingestion before and during HD, avoiding acetate containing dialysate, increasing calcium concentration of dialysate, reducing dialysate temperature, using sequential UF followed by isoosmolar HD or HF, using biocompatible dialyzer membranes), and finally, by a protocol-based response if IDH could not be prevented. Perhaps the greatest promise in minimizing this complication lies in technologies capable of adjusting of the dialysate composition and rate of UF continuously throughout the procedure on the basis of real-time changes in parameters that influence vascular refilling. The delivery of HD in this manner allows for adjustments to be made on the basis of minute-to-minute variations in the response of the cardiovascular system to UF.

Conflict of interest statement. None declared.

References


Difficulties in achieving the K/DOQI (NKF) laboratory target values for bone and mineral metabolism in haemodialysis patients

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¹Renal Unit, Athens Medical Group “Dafni” Clinic, Athens, Greece, ²Department of Nephrology and Renal Unit, “NIMITS” Veterans Administration Hospital, Athens, Greece

Abstract

Background. Increased serum phosphorus (PO₄) and elevated calcium phosphorus product (CaxP) levels have been recognized as risk factors for increased cardiovascular mortality in haemodialysis (HD) patients. However, an increasing number of studies report difficulties in meeting K/DOQI guidelines for bone and mineral metabolism, raising questions regarding the management of HD patients. The aim of this study was to evaluate our ability to meet K/DOQI guidelines for bone and mineral metabolism in HD patients.

Methods. We reviewed laboratory parameters of bone and mineral metabolism in 103 patients over a period of 16 months. Serum calcium (Ca) and PO₄ levels were determined monthly using standard assays, calcium phosphorus product (CaxP) was calculated every month and intact parathyroid hormone (iPTH) levels were determined every three months using chemiluminescence immunoassay (CLIA). Patients requiring phosphate-binding agents received calcium carbonate, sevelamer or a combination of these. 76/103 patients required an analog of vitamin D (41/76 received alfacalcidol, 35/76 received paricalcitol).

Results. Serum Ca ranged from 5.8 to 12.4 (mean ± SD; 8.8 ± 0.7) mg/dl, serum PO₄ ranged from 1.7 to 10.9 (mean ± SD; 5.5 ± 1.35) mg/dl, CaxP product ranged from 22 to 101 (mean ± SD; 49 ± 12) mg²/dl² and iPTH levels ranged from 9 to 1750 (mean ± SD; 294 ± 286) pg/ml. The average percentage of serum Ca, serum PO₄ determinations and CaxP product which met the K/DOQI target levels was 64 ± 6%, 52 ± 9% and 74± 7% respectively. In regards to iPTH, 33 ± 8% of the determinations were within the recommended range. Only 8± 7% met all four recommended guidelines simultaneously. In regards to the number of patients who achieved the K/DOQI guidelines for Ca, PO₄, CaxP product or iPTH target levels the corresponding percentages were 55%, 44%, 63% and 12% respectively. Notably, only 3% of the patients met the target for all four parameters simultaneously.

Conclusion. Our data indicate that with current medication the achievement of K/DOQI guidelines for the management of bone and mineral metabolism in haemodialysis patients is very difficult in clinical practice.

Keywords: bone metabolism; K/DOQI targets; chronic kidney disease; secondary hyperparathyroidism

Introduction

Chronic kidney disease (CKD) is linked with increased morbidity [1], is associated with a wide range of causes of mortality [2,3] and recent reports about all cause mortality attributable to CKD, and escalating figures of prevalence and incidence of the disease, raise CKD at the levels of global epidemic [4,5]. Although the percentage of CKD patients who require haemodialysis (HD) treatment (stage 5 CKD) is small, this group is characterised by high rate of morbidity and mortality and much shorter life expectancy [4]. The prevalence of coronary heart disease (CHD) in HD patients is 40%, and in peritoneal dialysis patients 60% [6] while CVD – related mortality in this group is 10 to 30 times higher compared to the general population [7]. The National Kidney Foundation (NFK) – published the Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines for HD patients, regarding bone and mineral metabolism recommending tight control of serum calcium (Ca) and phosphorus (PO₄) levels, calcium-phosphorous product (CaxP) and intact parathyroid hormone (iPTH). These guidelines anticipate adjusted Ca level: 8.4-9.5 mg/dl, serum PO₄ : 5-5.5 mg/dl, CaxP: < 55 mg²/dl² and iPTH: 150-300 pg/ml [8]. These recommended cut-off points and range are in line with the accumulated evidence that the presence of plasma Ca, PO₄ and CaxP product at concentrations greater than, or outside the suggested K/DOQI ranges, is associated with increased all-cause mortality risk, risk for fracture-related hospitalization, and fatal and non fatal cardiovascular events [9-11].
Unbalanced mineral homeostasis, also implicated in the pathogenesis of hyperparathyroidism [12-15] occurring at the very early stages of renal failure. A decrease in 1,25 dihydroxycholecalciferol (the active form of hydroxyvitamin D) accompanied by increased PTH levels are the earliest mineral metabolism alterations occurring in CKD with calcium and phosphorus changes appearing at a later stage [16]. PTH levels are inversely related to glomerular filtration rate (GFR), showing considerable variability at GFR < 60 ml/min [16] while the incidence and severity of secondary parathyroidism increases as renal function is deteriorating [17].

Notwithstanding the clinical importance of maintaining calcium and phosphorus homeostasis and preventing or controlling secondary hyperparathyroidism in patients with CKD, there are an increasing number of reports recognizing difficulties in maintaining K/DOQI guidelines in HD patients despite optimal therapy [16,18-22]. Most of these studies report an alarmingly small percentage of patients that manage to maintain all four guidelines, raising questions about aspects of clinical practice such as treatment strategies and level of patients’ compliance.

In the present study we evaluated our ability to meet K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease and present laboratory results of serum Ca, PO₄, Ca×P product and iPTH in a group of HD patients. In addition the percentage of patients that maintained laboratory values within the recommended ranges was evaluated.

Patients and methods

We reviewed laboratory parameters of bone and mineral metabolism of 103 patients (71 males, 32 females, patient characteristics are presented in Table 1, over a period of 16 months (April 2004 to August 2005). The study was approved by the Institutional Ethical Committee and all patients signed and dated an informed consent form, endorsing access to their medical information. The study was conducted in accordance to the Helsinki Declaration of 1975, as revised in 2000.

Table 1. Demographic characteristics of the study population

<table>
<thead>
<tr>
<th>Patients</th>
<th>103</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65± 15*</td>
</tr>
<tr>
<td>Sex, % (n)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>69 (71)</td>
</tr>
<tr>
<td>Female</td>
<td>31 (32)</td>
</tr>
<tr>
<td>Standard HD/HD (Haemodialfiltration % (n))</td>
<td>61.2 (63)/38.8 (40)</td>
</tr>
<tr>
<td>Diabetes % (n)</td>
<td>33 (34)</td>
</tr>
<tr>
<td>Time on HD* (months)</td>
<td>20 ± 10*</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.4 ± 0.2*</td>
</tr>
<tr>
<td>Calcium dialysate (mEq/L)</td>
<td>3 ± 0.5*</td>
</tr>
</tbody>
</table>

*Data are expressed as mean ±SD values, °HD: Haemodialysis

Patients remained in the haemodialysis unit for a mean of 20.3 ± 10.4 months and received either standard haemodialysis (HD) or haemodiafiltration (HD). Demographic characteristics and medical history of concomitant diseases were recorded. Serum calcium and phosphorus levels were determined using standard assays every month. The level of serum calcium was corrected for albumin. Calcium phosphorus product was calculated every month. Intact PTH levels were determined every three months using chemiluminescence immunoassay (CLIA). There were a total of 1648 determinations for serum calcium, phosphorus and Ca × P and 550 determinations for iPTH. Kt/V was calculated every 5 months. Patients requiring phosphate-binding agents received calcium salts, sevelamer or a combination of these and those requiring vitamin D compounds received alfacalcidol or paricalcitol. The physicians taking care of the patients managed the parameters of bone and mineral metabolism according to standard practice and adhering to K/DOQI guidelines.

Values are presented as means ± SD, except were otherwise indicated. Categorical variables are described by relevant frequencies. Differences between categorical variables over the observed period were analysed using the χ² analysis test. Level of significance was set at p≤0.05.

Results

A total of 103 patients were included in the study. The demographic characteristics of the study population are detailed in table 1. The average age was 65± 15 years; 69% were male and 31% were female. Thirty three percent of patients were diagnosed with diabetes mellitus. Sixty three patients (61.2%) received standard HD and 40 (38.8%) patients received haemodiafiltration. The average time on HD was 20±10 months, the average Kt/V was 1.4 ± 0.2 and calcium dialysate was 3 ± 0.5 mEq/L.

The percentages of patients who received calcium salts, sevelamer, combination of calcium salts and sevelamer, aluminium hydroxide in combination with other phosphate-binding agents were 59%, 30%, 17.5% and 20% respectively. The percentage of patients that required a vitamin D analogue was 73% (76/103) in which 54% (41/76) received alfacalcidol and 46% (35/76) received paricalcitol (Table 2).

Table 2. Phosphate binders and vitamin D analogues treatment of HD patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Frequency</th>
<th>Dose Mean ± SD (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium carbonate</td>
<td>59 (61/103)</td>
<td>1.5 ± 0.5 grams/day (0.5-2.5)</td>
</tr>
<tr>
<td>Sevelamer</td>
<td>30 (31/103)</td>
<td>4±1.6 grams/day (1.6-8)</td>
</tr>
<tr>
<td>Calcium carbonate + sevelamer</td>
<td>17.5 (18/103)</td>
<td>0.5 ± 0.5 / 4 ± 8 grams/day</td>
</tr>
<tr>
<td>Aluminum Hydroxide</td>
<td>20 (21/103)</td>
<td>1.9±0.5 grams/day (0.9-2.8)</td>
</tr>
<tr>
<td>Alfacalcidol</td>
<td>54 (41/76)</td>
<td>2±0.5 mcg/HD°</td>
</tr>
<tr>
<td>Paricalcitol</td>
<td>46 (35/76)</td>
<td>7±2.5 mcg/HD° (2.5 - 12)</td>
</tr>
</tbody>
</table>

°Concomitant administration with other phosphate binders.

°HD: every session of haemodialysis
Serum Ca ranged from 5.8 to 12.4 (mean ± SD; 8.8 ± 0.7) mg/dl, serum PO$_4$ ranged from 1.7 to 10.9 (mean ± SD; 5.5 ± 1.35) mg/dl, CaxP product ranged from 22 to 101 (mean ± SD; 49 ±12) and iPTH ranged from 9 to 1750 (mean ± SD; 294 ± 286) pg/ml, (Table 3).

The average percentage of serum Ca, serum PO$_4$ determinations and CaxP product which met the K/DOQI target levels was 64 ± 6%, 52 ± 9%, and 74 ± 7% respectively (Fig. 1). In regards to iPTH, 33 ± 8% of the determinations were within the recommended range. Only 8 ± 7% of all determinations met all four recommended targets simultaneously (Figure 2).

Table 3. Bone mineral metabolism parameters during the haemodialysis treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium (mg/dl)</td>
<td>8.8 ± 0.7</td>
<td>5.8 – 12.4</td>
</tr>
<tr>
<td>Serum phosphorus (mg/dl)</td>
<td>5.5 ± 1.3</td>
<td>1.7 -10.9</td>
</tr>
<tr>
<td>CaxP (mg$^2$/dl$^2$)</td>
<td>49 ± 12</td>
<td>22 - 101</td>
</tr>
<tr>
<td>iPTH (pg/ml)</td>
<td>294 ± 286</td>
<td>9 - 1750</td>
</tr>
</tbody>
</table>

In regards to the number of patients who achieved the K/DOQI guidelines for Ca, PO$_4$, CaxP product or iPTH the corresponding percentages were 55%, 44%, 63% and 12% respectively. Notably, only 3% of the patients met the target for all four parameters simultaneously (Figure 3). Intact parathyroid hormone levels after 16 months of treatment with phosphate binders were significantly more likely to fall within (150-300 pg/ml) or below (<150 pg/ml) range ($p \leq 0.001$).

Fig. 1. Percentage of laboratory determinations of serum calcium, phosphorus, calcium – phosphate product, and iPTH within K/DOQI targets during the 16 months of HD treatment

Fig. 2. Percentage of laboratory determinations that met all four K/DOQI guidelines during the 16 months of HD treatment

Fig. 3. Percentage of patients who met all four K/DOQI targets during the 16 months of HD treatment

Discussion

A surprisingly low percentage (3%) of HD patients managed to achieve and maintain K/DOQI guidelines for bone and mineral metabolism in the present study. This result is in line with previous, recent observations that...
and 5 CKD patients during 12 months of HD treatment. In this study, the percentage of patients who achieved and maintained K/DOQI guidelines was low. Wei et al. [22] reported that the in-target percentages of patients for Ca, PO₄, Ca×P product and PTH were 46%, 53%, 28% and 28% in HD patients respectively, whereas the percentage of patients with simultaneous achievement of all 4 guidelines was only 4.3%. Similarly low percentages have been reported by Aly et al. [18], who found that 4% of patients managed to achieve K/DOQI guidelines in all four parameters, and Young et al., 4.6% [23], whereas a study from Craver et al. investigated stage 3, 4, and 5 CKD patients during 12 months of HD treatment and reported that patients who had all four parameters within recommended ranges where 34.9%, 18.4% and 21.6%, for stage 3, 4 and 5 CKD respectively [16].

Several factors have been considered to contribute to the increased difficulty seen in attempting to attain guidelines’ cut-off levels and ranges. Simultaneous achievement of serum Ca and PO₄ and maintenance of PTH levels within ranges of normal, in many cases have been proven problematic. Abnormal increases in Ca and PO₄ levels have deleterious effects in CKD patients and play an active role in the pathophysiology of extraskeletal calcification [24]. Hyperphosphataemia for example is one on the main factors contributing to secondary hyperparathyroidism [25], manifested as increased parathyroid hormone secretion and activity, and is also associated with increased risk of all-cause mortality and mortality due to cardiovascular events, such as myocardial infarction and heart failure [11,17]. The recommended clinical approach in treating secondary hyperparathyroidism and hyperphosphataemia, is the administration of vitamin D analogues (calcitriol, paricalcitol, alfacalcidol) and phosphate binders (calcium carbonate, sevelamer, lanthanum carbonate). The main goal of administering these agents is to suppress PTH levels and reduce hyperphosphataemia and so attenuate the systematic stimulus for increased PTH secretion. However, the administration of such agents, especially of calcium based phosphate binders, is associated with a range of adverse events including hypercalcaemia and hyperphosphatemia. Moreover, vitamin D analogues such as calcitriol and paricalcitol have been implicated [24] and may contribute in the in vivo development of vascular calcification [26]. The introduction of calcium free phosphate binders, such as sevelamer and lanthanum carbonate seems to be effective in maintaining parathyroid hormone levels and also to be associated with reduced cardiovascular risk compared to calcium carbonate [27,28] [29,30]. However despite the possible beneficial effects of sevelamer on the progression of vascular calcification, it is still unknown whether this agent is likely to improve the long-term survival outcome of dialysis patients. [31]. This, taken together with reports regarding the financial impact of sevelamer treatment, raises questions about the effectiveness of sevelamer as an anti-hyperphosphataemic agent [32].

Nonetheless, parathyroid hormone seems to be the parameter of bone and mineral metabolism that is the most difficult to control, or the one that presents with the lowest percentages of adherence. Out of range PTH levels are reported to be twice as likely to be below K/DOQI recommended guidelines of 150-300 pg/ml than above [21], suggesting that the employed therapeutic treatment may oversuppress PTH regulation. In our study we observed that after 16 months of treatment, iPTH levels were more likely to fall within or below the recommended ranges (38%, 39%, and 23% for <150 pg/ml, 150-300 pg/ml, and >300 pg/ml respectively, \( p \leq 0.001 \)) than above.

Missing and shortened haemodialysis sessions could potentially be another contributing factor which prevents achievement of recommended guidelines. Wald et al. [33] reported that for each 1% increase in frequency of abbreviated sessions, the odds of consistent control for phosphate and Ca×P product decreased by 2%, while for every missed session the odds for achieving Ca, PO₄ and Ca×P recommendations is decreased by 2%, 4% and 1% respectively. These results suggest that dialysis time is a crucial ingredient for the regulation of mineral metabolism, while extended dialysis times may result in significant decreases in serum Ca, Ca×P and PTH levels [34,35]. Decreased patient-dietician ratio is another recommendation as a means to improve phosphate level control. However results on the impact of such intervention is still inconclusive [33].

Nonetheless, control of bone and mineral metabolism is a difficult task since it requires concomitant modulation of dietary intake, modifications in pharmacological interventions and modified dialysis prescription. The success of these interventions are heavily dependent on patient behavior, the level of awareness of health care providers, the quality of health care provider–patient communication [23] and most importantly on patients’ compliance and adherence to prescribed treatment and dialysis regime. The last has been investigated in a group of HD and PD patients. It was estimated that 16% of the prescribed pills were omitted and this was attributed to the increased burden of patients’ pharmacological intervention with orally administered agents or pill-burden. Overall compliance at the 80% level was as low as 38% and although patients did not differ in respect to serum Ca, PO₄ and PTH, significantly higher doses of phosphate binders were prescribed to non-compliant compared to compliant patients. Moreover, patients who attained and maintained K/DOQI recommendations presented with a lower pill-load compared to non-achievers, suggesting that effective treatment options that lead to fewer pill intake may aid in achieving K/DOQI targets [21].

Recommendations for clinical practice in order to increase rate of achievement of K/DOQI guidelines include prescription of non-calcium phosphate binders, increase of vitamin D analogues and moderation in calcium carbonate administration [36]. In terms of clinical care provision it is reported that a single renal nurse practitioner...
is more likely to adhere to guidelines that are multiple rotating nephrology trainees in a renal-hypertension clinic [37]. This observation was also accompanied by significant lower all-cause hospitalization 12 months after the initiation of dialysis. Despite the delimitations that the above observations may have, it is clear that clinical practice has to be accordingly modified in several aspects in order to improve health care standards and treatment outcomes of stage 5 CKD patients.

Conclusions

In conclusion, despite the above mentioned parameters, which might interfere with treatment goals raising the difficulties in attaining prescribed guidelines, there is also an increased body of data suggesting that sustaining control of bone and mineral metabolism according to K/DOQI guidelines may have positive impact on morbidity and mortality [19,24,33,38]. However our data and others, indicate that with current medication the achievement of K/DOQI guidelines for the management of bone and mineral metabolism in HD patients is very difficult in clinical practice. Moreover, the percentage of HD patients who achieve K/DOQI guidelines is alarmingly small suggesting that there is a great need to expand the available options of pharmacological treatment and standardize procedures in order to better control bone and mineral control in HD patients.

Authors’ contributions

XX and XX conceived of the idea for the project and supervised the project. All authors reviewed and interpreted the statistical analyses. XX wrote the first draft of the manuscript, while all authors contributed to the final version of the manuscript. All authors read and approved of the final version of the manuscript. EC, VM, LP, GS

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References


E. Chelioti et al.


Original Article

L-carnitine level in hemodialysis patients

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¹Institute of Physiology, ²Department of Nephrology, Medical Faculty, Skopje, R. Macedonia

Abstract

Background. Hemodialysis (HD) patients are exposed to homeostasis change. Impaired lipid metabolism, heart failure, anemia, muscle cramps and other disturbances are common for HD patients. L-carnitine is an amino acid which regulates these symptoms. It is related to the energy production in the body and has important role in the glucose oxidation.

Methods. This study included 45 patients on HD (20 male and 25 female) at age of 42±14 years. The controls were 24 healthy subjects. Primary renal diseases of the patients were as following: nephroangiosclerosis (n=20); interstitialpyelonephritis (n=12); diabetes nephropathy (n=4); adult polycystic disease (n=4); Duration of the HD procedure lasted app. 4 hours. The patients were dialysed by both, hemophan and polysulphon membranes, with blood flow of 250 ml/min. Regarding ultrafiltration rate, it was related on certain water lost, determined from the previous HD. Patients were divided in 3 groups concerning HD duration in years: I group (≤5); II group (6-10); III group (≥11). Plasma L-carnitine (mg/L) was determined by the enzymatic UV method (Roche Diagnostic GmbH, Manheim, Germany). Triglyceride (TG) level was determined by enzymatic colorimetric tests Vitros 250 (dry chemistry - Ortho Diagnostic Johnson-Johnson, USA). Urea and creatinine (mmol/L) were examined by Bio Rad, US. Hematocrit (%) was determined by blood counter analyzer AABx Micros 60.

Results. L-carnitine level in HD patients after the HD session showed decreased level which compared to the control group showed significant difference (p<0.05). During the HD session the L-carnitine level was 16% decreased. The decreased levels of urea and creatinin, compared to their levels before the HD session, were also significant (p<0.0001). Hemoconcentration and the increased level of triglycerides were noticed after the HD session, due to the water lost. Proporionally dropped values of L-carnitine in the patients group with longer HD duration were found.

Conclusion. L-carnitine is a small molecule which probably passes through HD membrane, during the HD session. The longer duration age of HD, the lower L-carnitine level was noticed which may cause some HD symptoms.

Keywords: hematocrit; hemodialysis; L-carnitine; triglycerides

Introduction

Carnitine is a conditionally essential metabolite that plays a critical role in cell physiology. It is peptide, produced in liver, kidney, and brain from the essential amino acids: lysine and methionin. Carnitine is necessary for fatty acid transport to sites of beta-oxidation in the mitochondria, where it prevents organic acid accumulation. Because of these key regulatory functions, carnitine represents a crucial determinant of mitochondrial energy metabolism. Its deficiency may lead to metabolic and clinical disturbances. Loss of carnitine through dialytic membranes occurs in maintenance hemodialysis (HD), resulting in potential carnitine depletion and relative increments of esterified carnitine forms [1]. More than a half century L-carnitine has been known as an amino acid that regulate the lipid metabolism. Actually it is produced in the body and it is involved in fatty acid metabolism regarding energy production, realized in the mitochondria. L-carnitine (L-3-hydroxy-4-N-trimethylaminobutyric acid) is also known as vitamin Bt that regulate the entrance of long chain fatty acid into mitochondria, thus is involved in energy production as ATP. It has important role in glucose oxidation [2].

The mechanism of its role is related to the acyl-CoA synthetase with long chains that is located on the outer mitochondrial membrane, while β-oxidation enzymes are located in its matrix [3]. The inner mitochondrial membrane is not permeable to CoA esters, and therefore carnitin palmitoiltransferase I and II as well as carnitine translocase are important for the transport of the activated fatty acids as carnitin esters in mitochondrion during the oxidation process. L-carnitine is normally eliminated through the urine, but in patients undergoing HD its excretion is impaired [4]. In end-stage renal failure,
erythropoietin lack is often combined by decreased L-carnitine level [5,6]. In the study of Reuter SE 2008, it has been suggested that these disturbances in carnitine homeostasis may be associated with a number of clinical problems common in this patient population, including erythropoietin-resistant anaemia, cardiac dysfunction, and dialytic complications such as hypotension, cramps and fatigue [7]. It causes anemia, when it is resistant to erythropoietin therapy at normal iron levels [8,9] due to its lack in red blood cell viability and osmotic resistance, respectively. [10,11]. Its lost causes impaired lipid metabolism by increased blood levels of both, cholesterol and triglycerides [12].

This condition may influence to the chronic morbidity and mortality of these patients. The aim of this study was to examine the L-carnitine level in hemodialysis patients before and after hemodialysis, and to examine its level related to the different HD duration.

Patients and methods

A number of 45 HD patients (20 male and 25 female) at age of 42±14 years was examined and compared to a control group of healthy subjects (n=24), sex and age matched. Primary renal diseases of the patients were as following: nephroangiosclerosis due to hypertension provoked renal insufficiency (n=20); interstitial pyelonephritis (n=12); glomerulonephritis (n=5); diabetes nephrathy (n=4); adult polycystic disease (n=4); Duration of the HD procedure lasted app. 4 hours. The patients were dialysed by both, hemophan and polysulphon membranes, with blood flow of 250 ml/min. Regarding ultrafiltration rate, it was related on certain water lost, determined from the previous HD. The blood from the different duration group patients was taken after HD session. Supplement therapy like EPO, L-carnitine and iron was not given to any of the examined patients, in order not to have the influence on examined parameters. For the blood analysis, plasma samples were taken from the cubital veins from HD patients before and after the HD session. Plasma L-carnitine was determined by the enzymatic UV method (Roche Diagnostic GmbH, Manheim, Germany). Prior the assay, plasma samples were first deproteinised with 0.6 mol/L perchloric acid and with 1.2 M potassium carbonate. The quantity of NADH was measured by its absorption of 340nm. The results are expressed in mg/L. Urea and creatinine (mmol/L) were examined by Bio Rad, USA. Triglycerides (TG) was determined by enzymatic colorimetric tests Vitros 250 (dry chemistry - Ortho Diagnostic Johnson-Johnson, USA) and expressed in mmol/L. Hematocrit (%) was determined by blood counter analyzer AABx Micros 60.

Statistical analysis

For the statistical analysis, Student t-test was used and p value less than 0.05 was considered significant. The results are expressed as mean values ± standard deviations.

Results

| Table 2. Levels of urea, creatinine, hematocrit and tryglicerids in HD patients before and after the HD session |
|---------------------------------|-----------------|-----------------|-----------------|
| Before HD | After HD | p |
| Urea (mmol/L) | 26.70 ± 5 | 8.30 ± 3 | <p>0.0001 |
| Creatinin (mmol/L) | 909 ± 341 | 273 ± 178 | <p>0.0001 |
| Hematocrit (%) | 28 ± 11 | 45 ± 19 | <p>0.01 |
| Triglycerides (mmol/L) | 2.5 ± 1.9 | 4.0 ± 2.6 | <p>0.01 |

The L-carnitine level in HD patients before HD session showed no significant difference when compared to its level in healthy subjects. Nevertheless, L-carnitine level in HD patients after the HD session showed significant difference (p<0.05) (Table 1). During the HD session the L-carnitine level decreased from 5.57 ± 1.6 mg/L to 4.72 ± 1.9 mg/L (p<0.05) (Table 2).

| Table 3. L-carnitine level (mg/L) in HD patients after HD session, concerning HD duration |
|---------------------------------|-----------------|-----------------|-----------------|
| | I group | II group | III group | p |
| | ≤ 5 years | 6-10 years | ≥ 11 years | |
| n = 15 | n = 22 | n = 8 | |
| L-Carnitine (mg/L) | 4.84 ± 1.6 | 4.42 ± 1.97 | 4.29 ± 1.9 | N.S. |

N.S. – not significant
After the HD session, besides L-carnitine, the decreased levels of urea and creatinin were noticed (p<0.0001). Regarding the hematocrit and triglycerides level, hemocoagulation was noticed after the HD session (Figure 1). On the Table 3, no significant difference was found for L-carnitine level in different HD duration groups, although the longer duration, the lower L-carnitine level was noticed.

Fig. 1. Examined blood sample parameters before and after HD session (in %)

Discussion

L-carnitine is considered as "conditionally essential nutrient" or "conditional vitamin" which supraphysiological concentrations in plasma and target organs may exert beneficial effects on several metabolic parameters that have derangements of a common origin (e.g. insulin resistance, type 2 diabetes, dyslipidemia) and which are frequently present in end-stage renal disease patients undergoing dialysis. [13]. In our study, the primary renal diseases of HD patients were nephroangiosclerosis and interstitiopyelonephritis. Significantly decreased L-carnitine level after the HD session in HD patients emphasised the possible lost of this small molecule through the HD membrane. Therefore the structure of HD membrane may determine the quantity of lost L-carnitine. Nevertheless, L-carnitine level before HD rises either by the food intake or by extra renal production, e.g. liver, brain. Higher hematocrit and higher triglyceride level after HD session show hemocoagulation due to the water lost. According to this, L-carnitine is lost even more than our obtained results due to present blood concentration. However, in general, higher triglyceride level was found in HD patients before HD session, when compared to healthy subjects which implicate impaired lipid profile of these patients [14]. In the study of Vernez L et al., 2006, the kinetics of carnitine, individual acylcarnitines and butyrobetaine in patients on HD was investigated. During HD, the plasma concentrations dropped by approximately 80% for all compounds determined. In patients supplemented with 20 mg/kg carnitine, the amount of carnitine removed by haemodialysis equalled 42% of the dose administered [15]. Due to our results, plasma concentration of L-carnitine level was dropped by approximately 16% after the HD session. Regarding the results we obtained, the L-carnitine level proportionally decreases with the HD duration. Although no statistical significance was found, probably because of small number of patient groups, in the group with the longest HD duration, lowest L-carnitine level was noticed, which probably elucidate the fact that longer the HD duration, harder it’s renewed. This means that the capacity of L-carnitine production (endogenous plasma level) decreases with the HD duration.

Although the relationship between dialysis age and carnitine status is poorly understood, there are some studies that examined the relationship between duration of dialysis and plasma and skeletal muscle concentrations of L-carnitine and its esters in end stage renal disease patients. In the study of Evans AM et al., 2004, it is considered that long-term HD treatment is associated with a significant reduction in endogenous plasma, which is in accordance with the results we obtained. In their study, decreased muscle L-carnitine levels and a significant increase in plasma acylcarnitines were found. They have also noticed that the majority of the changes of plasma L-carnitine concentrations occur within the first few months of HD, while muscle levels continue to decline after 12 months of treatment [16]. Therefore, supplementation of L-carnitine is a treatment of choice in HD patients, particularly for those who are resistant to erythropoietin therapy, those who suffer from lipid disturbances, intradalysitic symptoms of cramps, hypotension, etc. In the study of Kazmi WH et al. 2005, patients with cardiovascular disease, defined as hospitalizations for angina, myocardial infarction, arrhythmia, congestive heart failure, cerebral vascular disease or peripheral vascular disease prior to receiving carnitine, and those with anemia and hypoalbuminemia derived the greatest benefit from carnitine therapy. Administration of L-carnitine to chronic HD patients is associated with lower hospital utilization [17]. While the erythropoietin influence is focused on bone narrow pluripotential cells stimulation, L-carnitine improves red blood viability and longevity and therefore low plasma L-carnitine in HD patients causes red blood cell osmotic fragility. L-carnitine supplementation is also registered in children who suffer from HD common symptoms. It is demonstrated that children with chronic renal failure on regular HD suffer from. In addition, L-carnitine plasma decreased level causes dyslipidemia, oxidative stress, and impairment of cardiac functions [18]. Oral L-carnitine supplementation at a dose of 50 mg/kg within 2 months improved their condition [18]. If other factors related to anemia are excluded, the postdialysis parenteral L-carnitine therapy can be considered in selected stable patients, which may improve anemia and may reduce the weekly requiring dose of the rHuEPO and also be cost-effective [19]. In the study of Wanic-Kossowska M et al., 2007 the influence of combined therapy with L-carnitine and erythropoietin on selected blood morphology parameters in patients treated with HD was analyzed. They realized that combined therapy could decrease the requirement for exogenous erythropoietin. The correlation between serum carnitine concentration and erythrocyte osmotic resistance indicates indirectly the beneficial effect of L-carnitine administration on erythrocyte cell membrane stabilization [20]. The review of Hurot JM et al., 2002 suggests a promising effect of L-carnitine on anemia management. However they suggest that the route
of L-carnitine administration should be evaluated because there is no evidence as to the most efficient method of administration in maintenance hemodialysis [21].

Conclusions

In summary, we could conclude that L-carnitine as an essential peptide is decreased in HD patients, especially after the HD session. It is probably lost through the HD membrane during the HD session. Although it is renewed during the period between the two HD sessions, his lack is proportional to the HD duration. This condition may cause some common dialytic symptoms that influence the morbidity and the mortality of HD patients.

L-carnitine is essential peptide that might be lost through the HD membrane which may cause some common dialytic symptoms that influence morbidity and mortality of HD patients. Although it is renewed between the two HD sessions, his lack is proportional to the HD duration. Therefore, L-carnitine substitution therapy might be beneficial improving the life quality and longevity of HD patients.

Conflict of interest statement. None declared.

References

Original Article

The effect of peritoneal dialysis on the development of left ventricular hypertrophy: Is it a risk factor?

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Abstract

Background. Left ventricular hypertrophy (LVH) is the most important factor for the survey of the patients that use continuous ambulatory peritoneal dialysis (CAPD). This group of patients has 80% abnormal echocardiographic signs, and most of them are about LVH. We aimed to find out the risk factors of CAPD patients that affect LVH.

Methods. We studied 57 CAPD patients (29 female, 30 male) randomly selected from the nephrology clinic. Patients were divided into two groups as those with and without left ventricular failure. Echocardiography was performed. Risk factors such as age, hypertension, diabetes mellitus, chronic renal failure duration, and peritoneal dialysis time were noted. Creatinine clearance, weekly Kt/V, and protein catabolism rate (PCR) are studied for all patients. Serum creatinine, albumin, sodium, potassium, cholesterol, triglyceride, uric acid, calcium, phosphorus, CRP, parathyroid levels, and hematocrit were measured. The results were examined for statistical significance by Student’s t-test, Mann-Whitney U test. The Fischer exact test and chi-square test were used for categorical variables.

Results. Hypertension was found in 74% of the LVH group patients, in 54% of the other group, which was not statistically significant. Mean parathyroid hormone level tended to be higher in the LVH group. There was no difference in hematocrit levels between these two groups as well as in other parameters such as chronic renal failure duration, peritoneal dialysis time, Kt/V, creatinine clearance, PCR, creatinine, albumin, sodium, potassium, cholesterol, triglyceride, uric acid, calcium, phosphorus, and CRP.

Conclusion. While hypertension, anemia, hyperparathyroidism, and hypoalbuminemia were important factors in LVH progression found in the literature, it was not found to be of significant difference in our patients with and without LVH. It is concluded that much larger patient group and a longer period of observation are needed in order to reach a significant relationship, but also a lot of other local factors remains to be investigated.

Keywords: continuous ambulatory peritoneal dialysis (CAPD); left ventricular hypertrophy (LVH); uremia

Introduction

Renal transplantation as a treatment of chronic renal failure can be administered to only a small percentage of patients in Turkey. The most commonly utilized method of dialysis in the treatment of chronic renal failure is hemodialysis. However, hemodialysis lowers the quality of life, establishes a dependency on hospitalization thereby disrupting daily activities, and has negative effects on hemodynamics. Additionally, as an expensive method, it is of significant cost on the budgets of the patients and social security institutions.

In the recent years, due to the undesirable effects of hemodialysis, peritoneal dialysis has been applied to an increasing number of patients. Peritoneal dialysis is preferred because it is applicable to patients who are in the risk group for hemodialysis complications preventing their need for prolonged hospitalizations, and because it less costly procedure than hemodialysis itself.

Cardiovascular complications with peritoneal dialysis manifest as hypertension, dyslipidemia, increased atherosclerosis, uremic cardiomyopathy, left ventricular hypertrophy (LVH), and heart failure. LVH may depress contractility of the heart, causing abnormal compliance and heart failure as a result [1]. Additionally, it may exacerbate the clinical manifestations of coronary artery disease, and increase the incidence of sudden death. LVH is shown to be the most important factor determining the survival of the patients under continuous ambulatory peritoneal dialysis (CAPD). Although factors like hypertension, anemia, parathyroid hormone, hyper-volemia, and hypoalbuminemia are accepted as responsible in the formation of LVH amongst CAPD patients, some studies single out uremic toxins as the cause [2].
In this study, we compared the effects of hypertension, parathormone, albumin, calcium, phosphorus, creatinine clearance, uric acid, potassium, and weekly Kt/V on LVH on patients with and without this condition.

Patients and methods

A total of 57 patients were randomly included into the study without any age or sex distinctions, followed up regularly in the Istanbul Training and Research Hospital, Peritoneal Dialysis Unit. Patients who received treatments of CAPD, continuous cyclical peritoneal dialysis (CCPD), and nocturnal intermittent peritoneal dialysis (NIPD), whose dry weight was gained back, and who did not present hypervolemia (Table 1) were recruited to the study and treated for three months. Patients whose dry weight was not gained back due to ultrafiltration deficiency were excluded.

The patients’ reports of disappearance of symptoms were taken as the clinical criterion for the efficacy of the dialysis. Anamnesis, physical examination, venous blood samples, 12-lead resting EKGs, and telecardiographies were investigated. In the EKGs, LVH was evaluated according to the Skolow-Lyon criteria. Transthoracic echocardiography was performed with a Vingmed System FiVe Device transducer probe. Interventricular septal dimensions (IVSd) in diastole, and posterior wall dimensions (PWd) and left ventricular dimensions at end diastole were measured. The left ventricular mass was calculated by the cubic method, with the formulaLVmass=1.05 x (total volume - intracavitary volume) [4]. Left ventricular mass index was calculated by dividing the left ventricular mass by the body surface area.

Blood pressure values over 140/90 were interpreted as hypertension based on WHO/ISH (1999), JNC-VI, BHS (1999) and Turkish Society of Cardiology National Hypertension Treatment and Follow-Up Manual (2000) [5,6,7].

In this cross-sectional study, the patient groups were formed using the biochemical values and echocardiographic evaluations at the time of admission. The patients were divided into two groups as the ones with and without LVH, as indicated by the echocardiographic measurements of IVSd, PWd, and left ventricle mass index (g/m²).

Patients’ age, blood pressures, diabetes mellitus condition, duration of chronic renal failure and peritoneal dialysis have been recorded. Weekly Kt/V ratio and creatinine clearance have been charted and investigated. Blood samples were collected intravenously from the antecubital vein for investigating hematocrit, albumin, creatinine, uric acid, parathormone, cholesterol, triglyceride, sodium, potassium, calcium, phosphorus, and CRP.

To analyze the results, the packet statistical program SPSS for Windows release 10.0 (SPSS, Chicago, IL, USA) was used. In the comparisons, Student’s t-test, Mann-Whitney U test, chi-square, and Fischer’s exact test were used.

Results

A total of 57 (27 females and 30 males) peritoneal dialysis patients were analyzed into the study. The mean age for LVH (+) patients was 44.1±10.9, and 41.8±13.6 for LVH (-) patients, being not significantly different. There was no significant difference with respect to the frequency of hypertension or diabetes mellitus.

Additionally, no significant difference was identified in the mean duration of chronic renal failure and peritoneal dialysis, neither with regard to the type of dialysis.

Groups have been also compared based on hematocrit, creatinine, albumin, sodium, potassium, total cholesterol, triglyceride, uric acid, CRP, parathormone, calcium, and phosphorus values. No difference was found in these parameters as well.

Discussion

Cardiovascular diseases are the main cause of mortality and are responsible for 40% of the deaths [8]. These diseases are more prevalent amongst dialysis patients [9]. Cardiovascular diseases manifest as coronary artery diseases, hypertension, and LVH. It has been found that more than 80% of the dialysis patients present abnormal echocardiographic findings, mainly LVH [10]. In a study conducted with 433 patients, echocardiographic evaluations revealed LVH in 75% of the subjects. LVH in these patients was the main determinant of survival [11]. In uremic patients, cardiac functions are affected by a variety of factors. Some experimental studies show that uremic toxins have a depressing effect on myocardial functions [12].

In dialysis patients, risk factors for LVH are advanced age, hypertension, chronic anemia, hypoalbuminemia, hypervolemia, and the duration of dialysis. In the long term, LVH may depress contractility of the heart, and cause abnormal compliance and heart failure. Additio-
nally, it may increase the clinical manifestations of coronary artery disease and the incidence of sudden death. An increase in the frequency of asymptomatic ventricular arrhythmia and abnormal vasodilator reserve microcirculation are responsible for sudden death [13]. There are various reasons for LVH in CAPD patients. Theoretically, CAPD is hemodynamically advantageous compared to hemodialysis: I) AV fistula does not lead to hypercirculation in CAPD patients; II) CAPD does not cause sudden change in intravenous volume and has no adverse effects on the heart; and III) CAPD results in better blood volume and pressure control.

Hypertension is the main cause of LVH in the general population [13]. The recession of LVH with antihypertensive use has been documented in multiple studies [14,15]. Hence, it could lead us to a conclusion that a sufficient treatment, hypertensive heart disease can be reduced. Leenen et al., in a study including 18 patients with hypertension and LVH, found that LVH worsened only in 1 patient, whereas it showed recession in 15 patients 6-12 months into CAPD treatment [16]. This was associated with the normalization of blood pressure and volume as a result of CAPD. Although this conclusion is supported by other studies, different causes for hypertrophy are investigated.

Eisenberg et al. [17] worked with 27 LVH patients, and the echocardiographic findings showed an increase in hypertrophy from the initial 52% to 76% in 18 months. Diastolic blood pressures taken at the onset and the end of the study revealed no difference; however, systolic pressure was greater in the group with severe LVH. No correlation was found between LVH and renal failure, duration of dialysis, anemia, or creatinine levels. Rambaussek et al. observed an increase in the left ventricular mass in uremic animals submitted to subtotal nephrectomy. This finding has not changed after I) the animals reached a normotensive state with ACE inhibitors, II) sympathetic activity was eliminated with alpha and beta blockers, and III) the preload was decreased by administering high doses of furosemide to the uremic animals [18]. Mall et al. report that in uremic rats with normal blood pressure, interstitial tissue in the myocardium has increased [19]. These studies indicate that not only hypertension, but uremia as well, plays an important role in the formation of LVH.

Our patient group includes subjects who, without hypervolemia, have gained back their dry weight. Hypertension frequency was 70% in the group with LVH, and 54% in the group without hypertrophy. No difference between the groups in hypertension frequency was found. Activated interstitial cells may cause collagen accumulation in the left ventricular myocardium. Changes in mechanical activity due to cardiac contractions, and circulating growth factor levels may play a role in interstitial lesion formation. The changes in the cardiac contractions are connected to a rise in the afterload and shifts in electrolytes. Additionally, prorenin secretion is known to influence on the coronary flow. Circulating and locally secreted renin may play a role in hypertrophy, alongside with growth factors. Moreover, increase in the reticuloendothelial system activation and sympathetic hyperactivity should be considered as well. All these factors may cause LVH. Tumor necrosis factor-alpha (TNF-alpha) is usually discharged through the kidneys. In uremic patients, a rise in TNF-alpha levels due to a residual renal function loss has been observed. It is thought that TNF-alpha plays a role in peripheral neuropathy, malnutrition, erythropoietin sensitivity and LVH pathogenesis [20]. In peritoneal dialysis patients, a correlation between TNF-alpha levels and severity of LVH was found.

Then the question why do these factors affect only the interstitial cells is raised and why there is an increase in the number of interstitial cells and the fibrosis is limited to the heart, not showing up in the other organs? These questions might be answered mainly through the strong local factors responsible for hypertrophy found in the heart.

Parathormone is thought to be a strong uremic toxin [21]. The heart is sensitive to parathormone. Cardiac cAMP concentration, cardiac velocity, and contractile performance are shown as increased after in-vitro addition of parathormone. However, the increase in myocardial calcium has not been studied in humans. On the other hand, LVH progression has not been improved after rats subjected to parathyroidectomy have been rendered normocalcemic via injection of calcium. Even though parathormone levels were higher in the LVH group in our study, statistically significant difference has not been found. We could not find a significant difference in calcium or phosphorus levels in either group as well.

It has been shown that anemia can cause LVH in dialysis patients, and with anemia treatment LVH could have been reduced. Hüting et al. [22], in a study with 55 CAPD patients, observed a direct correlation between LVH regression and mean arterial pressure. They found no correlation among diastolic blood pressure, hemoglobin, parathyroid hormone in serum, and CAPD duration. In our study, we did not find any connection between LVH and hemoglobin concentration as well. Wang et al., after investigating the relationship between residual renal function and left ventricular function in 158 CAPD patients, have reported uremic levels and the residual renal function as key indicators. It has been reported that the decrease in erythropoietin secretion with a loss in residual renal function is one of the reasons causing LVH [23]. In our study, it was shown that patients with further loss of renal residual function had a higher degree of anemia, needed a higher dose of erythropoietin, and presented with more advanced LVH. It was reported in other studies that anemia can cause LVH in dialysis patients, which can only partially respond to anemia treatment [24]. In contrast, Rambaussek et al. showed even though hematocrit levels raised up to 40% via blood transfusion, myocardial hypertrophy could not have been prevented. Though we found lower levels of hematocrit level in our patient group with LVH, this has not been found to be significant.

One of the most critical complications in CAPD patients is malnutrition. Patients treated with peritoneal dialysis lose significant amounts of protein. The level of albumin
loss comprises 50-79% of the total protein loss [25]. In a cross-sectional study, it has been determined that 40% of the patients suffer from malnutrition and 8% have serious protein loss. This is an important risk factor in mortality and morbidity in peritoneal dialysis patients. The reasons for malnutrition are multifactorial. Serum albumin levels are shown to be correlated with protein-catabolism rate (PCR). Nutrition has important effects on the patients’ acid-base balance. A decrease in protein catabolism causes acidosis regression. It has been found that hypoalbuminemia correlates with the LVH, left ventricular dilation, and heart failure [26]. Wang et al. found a correlation between severity of albuminemia and severity of LVH. In our study, we did not find a relationship between LVH, albumin levels, and protein catabolic rate [27]. There was no any statistical association between the LVH and other parameters (uric acid, total cholesterol, triglyceride, CRP, sodium, potassium) as well.

Conclusions

While hypertension, anemia, hyperparathyroidism, and hypoalbuminemia were important factors in LVH progression found in the literature, it was not found to be of significant difference in our patients with and without LVH. It is concluded that much larger patient group and a longer period of observation are needed in order to reach a significant relationship, but also a lot of other local factors remains to be investigated.

Conflict of interest statement. None declared.

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tance of residual renal function in continuous ambulatory peri-
toneal dialysis: is influence on different parameters of renreplace-
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Impact of the endothelial factors following ischemia/reperfusion injury on the allograft function and histology at 1 and 6 months after renal transplantation

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¹Department of Nephrology, ²Department of Physiology, ³Department of Pathology, ⁴Department of Urology, Medical Faculty, University “SS. Cyril and Methodius” of Skopje, R. Macedonia

Abstract

Background. Ischaemia-reperfusion injury (IRI) continues to be one of the leading causes of renal failure following renal transplantation (Tx). Post IRI results in acute endothelial injury. The aim of our study was to evaluate the levels of vasoactive endothelial factors following IRI and to assess the possible impact of the post-IRI effects on the allograft function and histology at 1 and 6 months after Tx.

Methods. Forty consecutive living related kidney transplant recipients were included. Endothelial factors followed before, immediately after Tx and at day 1, and week 1, 2, 3 and 4 after Tx were: endothelin (ET₁), nitric oxide (NO) and free oxygen radicals (FOR). The protocol biopsies performed at 1 and 6 months after Tx were blindly reviewed using Banff’ 97 criteria. Patients were divided in two groups according to the occurrence of delayed graft function (DGF) and acute rejection (AR) during the first posttransplant week: Group 1 (G1 - without DGF and AR, n=28) and Group 2 (G2 - with DGF and/or AR, n=12).

Results. The two groups were similar regarding donor and recipient age, gender and body weight, glomerular filtration rate of donated kidney, and HLA matching. However, the groups differed significantly in the mean cold ischemic time (CIT) and previous time on dialysis (3.2±1.1 vs. 4.2±0.6 hours; p<0.006 and 22.2±32.2 vs. 37.2±44.7, months; p<0.05) for G1 vs. G2, respectively. When the groups were compared according to the changes of endothelial factors of IRI, G2 had a significantly higher ET₁ levels after Tx and at day 1 post Tx [102.7±37.1 vs. 44.9±22.4 pg/ml (p<0.001); 76.5±43.7 vs. 40.5±12.8 (p<0.01)], with a significantly lower NO levels at the same time points, [80.8±12.8 vs. 100.6±38.6 µmol (p<0.05); 35.8±19.9 vs. 86.7±20.3 (p<0.001)], respectively. Moreover, a significantly higher levels of FOR were found in Group 2 when compared with Group 1, after Tx, at day 1, and at 1 and 2 weeks post-Tx: [306.3±48.2 vs. 266.6±58.3 CARR units (p<0.001); 420.3±112.8 vs. 319.8±61.6 (p<0.001); 449.3±90.3 vs. 354.6±92.8 (p<0.001), and 345.8±133.3 vs. 256.9±67.5 (p<0.05)], respectively. At 1-month biopsy a higher percentage of acute histological changes was found in G2 compared with G1 (83% vs. 75%). Importantly, the groups differed significantly in the mean HI score (sum of scores for acute and chronic histological changes) at 6 months biopsy [9.1±4.9 (G2) vs. 7.2±2.9 (G1); (p<0.001)]. Thereby, a significantly higher percentage of chronic allograft nephropathy (CAN) progression was found in G2 (75% vs. 57%). However, there was no significant difference in the graft function, i.e. calculated creatinine clearance at 1 and 6 months after Tx, in both groups.

Conclusion. Post IRI is mediated by endothelial release of vasoactive factors such as endothelin, nitric oxide and free oxygen radicals, potentially key molecules in the link of IRI and AR. In fact, the group with DGF and AR early after Tx showed higher percentage of acute histological lesions at 1-month biopsy, and a greater susceptibility for histological deterioration on the 6-month biopsy, accelerating the process of CAN. Endothelial activation may facilitate enhanced graft immunogenecity and induce development of AR, which in turn results in development of chronic allograft nephropathy.

Keywords: kidney transplantation; ischaemia-reperfusion injury; endothelin, nitric oxide; free oxygen radicals; protocol biopsy; delayed graft function; acute rejection
**Introduction**

Chronic allograft nephropathy (CAN) has become the leading cause of late kidney transplant failure [1]. Its histological hallmarks are tubular atrophy, interstitial fibrosis, microvascular changes and glomerulosclerosis [2]. CAN is driven by a number of immunological and non-immunological factors such as pre-existing donor pathology, ischaemia-reperfusion injury, delayed graft function and/or acute tubular necrosis, acute rejection, ineffectively and/or un/treated clinical and subclinical rejection, hypertension and calcineurin inhibitor toxicity [3,4].

Ischaemia-reperfusion injury (IRI) following kidney transplantation, can result in delayed graft function (DGF), and according to large scale clinical analyses there is consensus that DGF has a significant impact on short and long-term graft survival [5]. Ischaemia and reperfusion induce the development of inflammation and adhesion molecules are essential intermediates between activated endothelial cells and circulating leukocytes. Reperfusion injury represents a cascade of events, initiated by tissue ischaemia and production of free oxygen radicals during the reperfusion process, leading to the development of inflammation, through activation of endothelial cells in the transplant and recruitment of circulating leukocytes [6]. Although the precise mechanisms of IRI have not been clarified, some chemical mediators, such as oxygen radicals and platelet activating factor accompanied by vasculo-endothelial dysfunction, have been suggested to play a role [7]. It is well known that cell damage following ischaemia is a biphasic process: ischaemia initiates injury by depriving cells of the energy needed to maintain ionic gradients and homeostasis, while the reperfusion exacerbates this damage by triggering an inflammatory reaction involving oxygen-free radicals, endothelial factors, and leukocytes [8].

The aim of our study was to evaluate the levels of vasoactive endothelial factors following IRI: endothelin (ET-1), nitric oxide (NO) and free oxygen radicals (FOR), and to estimate the post-IRI effects on allograft function and history at 1 and 6 months after transplantation (Tx).

**Patients and methods**

Forty consecutive living related (LR) transplant patients were studied. All patients received their first transplant. Methylprednisolone (500 mg) and Daclizumab (Zenapax; 1 mg/kg BW at implantation and thereafter every 2 weeks x five doses) were administered as induction therapy. Maintenance immunosuppression consisted of: cyclosporine (Neoral; 6 to 8 mg/kg/day) to reach target C2 levels (blood concentration 2 hours after administration of the drug), prednisolone (1 mg/kg/day tapered to 0.1 mg/kg/day after 4 weeks) and mycophenolate mofetil (Cell Cept 1 g/bid).

During the first postoperative month patients with delayed graft function who suffered post-transplant acute tubular necrosis or experienced a clinical episode of acute rejection (AR) were treated with hemodialysis or pulse corticosteroids, respectively. Protocol biopsies were performed using ultrasound-guided automated biopsy "gun". The formalin fixed biopsies were embedded in paraffin, serially sectioned at 3 to 5 µm thickness and stained with hematoxylin-eosin (HE), periodic acid-Schiff (PAS), Masson's trichrome as well as methenamine silver. Biopsies were considered adequate when they contained ≥7 glomeruli and at least one artery. Renal histology was reviewed according to the Banff '97 scoring schema [2]. CAN score was calculated as a sum of scores for the individual histological markers for chronicity: interstitial fibrosis, tubular atrophy, vascular fibrous intimal thickening, arterial hyalinosis, and chronic glomerulopathy. The histological index (HI) was calculated as a total sum of scores for acute and chronic changes.

Patients with histology at 1-month biopsy of borderline changes (BC) or AR type I or IIA, and an increase in serum creatinine (sCr) between 10 and 20% from the baseline (sCr 2 weeks prior to the biopsy) were assessed as subclinical acute rejection (SAR) and consequently treated with pulse corticoid therapy. The patients with histology of BC or AR followed by a rise in sCr < 10% from baseline were not treated.

<table>
<thead>
<tr>
<th>Table 1. Clinical data and post-transplant events of all patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor age (yr)</td>
</tr>
<tr>
<td>Female/male</td>
</tr>
<tr>
<td>Recipient age (yr)</td>
</tr>
<tr>
<td>Female/male</td>
</tr>
<tr>
<td>Cause of and-stage renal disease</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Hypertensive renal disease</td>
</tr>
<tr>
<td>Polycystic renal disease</td>
</tr>
<tr>
<td>Reflux nephropathy</td>
</tr>
<tr>
<td>Lupus nephropathy</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Time on dialysis (mo)</td>
</tr>
<tr>
<td>Total HLA mismatch score</td>
</tr>
<tr>
<td>Mean CIT (h)</td>
</tr>
<tr>
<td>DGF (%)</td>
</tr>
<tr>
<td>AR (%)</td>
</tr>
<tr>
<td>DGF and AR (%)</td>
</tr>
</tbody>
</table>

In order to determine the possible impact of IRI on graft function and histology at 1 and 6 months after Tx, we have divided our patients in two groups according to the occurrence of DGF and AR during the first posttransplant week: Group 1 (G1 - without DGF and AR, n=28); Group 2 (G2 - with DGF and AR, n=12).

Endothelial factors (ET1, NO and FOR) were assessed before, immediately after Tx and at day 1 and week 1, 2, 3 and 4 after Tx. The high sensitivity 125Iodine-endothelin 1 assay system with Amerlex-M (Amersham, UK) magnetic separation was used to determinate plasma ET1 levels. NO was measured by a microplate enzymatic method based on assay kit from OXIS, USA. Colorimetric determination of reactive oxygen metabolites, with...
d-ROMs test, (Diacron International S.a.S. Grosseto, Italy) was used for measurement of FOR.

The patient’s clinical and biochemical data were recorded at the time of transplantation as well as at 1 and 6 months after Tx. Results were expressed as mean values±SD. For numeric data, an unpaired two-tailed Student’s t test was used, and Chi-square analysis for categorical variables. A difference was considered significant if \( P \) value was <0.05.

**Results**

The mean age of the entire cohort of donors and recipients were 59.3±13.1 and 34.3±9.8 years, respectively.

| Table 2. Biochemical, clinical data and histological findings and scores at 1 and 6 months posttransplantation of all transplant recipients (n=40) |
|------------------|------------------|------------------|------------------|
|                   | 1 month          | 6 month          | P value         |
| parameter         | Mean ± St Dev    | Mean ± St Dev    |                 |
| BMI recipient     | 22.5 ± 4.0       | 23.6 ± 4.2       | <0.01           |
| sCr               | 125.0 ± 33.9     | 144.7 ± 44.5     | <0.01           |
| cCrCl             | 64.7 ± 16.7      | 60.0 ± 19.1      | n.s.            |
| proteinuria       | 0.72 ± 0.4       | 0.60 ± 0.6       | n.s.            |
| No lesions        | 3/40 (7.5%)      | 3/40 (7.5%)      | n.s.            |
| AR                | 2/40 (5%)        | 2/40 (2%)        | n.s.            |
| BC                | 13/40 (32.5%)    | 12/40 (30%)      | n.s.            |
| SAR               | 16/40 (40%)      | 19/40 (47.5%)    | n.s.            |
| BC/SAR treated    | 9/29 (31%)       | 7/31 (22.6%)     | n.s.            |
| CAN score         | 2.1 ± 1.5        | 4.6 ± 2.3        | <0.01           |
| HI                | 5.3 ± 2.9        | 7.8 ± 3.6        | <0.01           |

n.s. not significant

From the cohort of forty patients with acute histopathological lesions (13 BC + 16 SAR) at 1-month biopsy, an increase in sCr between 10 and 20 % from baseline was observed in 2 and 7 patients, respectively, and therefore pulse corticoid therapy was administered. In 27 patients (33.8%) no CAN lesions were present in both biopsies, 27 (67.5%) showed progression of CAN and 13 (32.5%) presented with stable CAN changes, at 6-month biopsy.

There was no difference between G1 and G2 group in the following parameters: donor age and BMI, recipient age, BMI and time on dialysis, number of HLA matching, GFR of donated kidney, cyclosporine (CyA) levels (C2), sCr, cCrCl, and proteinuria, between the groups neither at 1 nor at 6 months after transplantation. However, the mean cold ischaemic time (CIT) and warm ischaemic time (WIT) were much shorter in the G1 group (Table 3).

**Table 3. Comparison of clinical and biochemical data between the groups**

<table>
<thead>
<tr>
<th>parameter</th>
<th>G1-without DGF and AR (n= 28)</th>
<th>G2-with DGF and AR (n=12)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor age</td>
<td>Mean ± St Dev</td>
<td>Mean ± St Dev</td>
<td></td>
</tr>
<tr>
<td>Recipient age</td>
<td>59.8 ± 12.4</td>
<td>57.6 ± 16.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>BMI donor</td>
<td>35.1 ± 9.8</td>
<td>32.3 ± 10.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>BMI recipient</td>
<td>25.7 ± 4.1</td>
<td>26.9 ± 3.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>GFR don. kidney</td>
<td>22.4 ± 4.0</td>
<td>22.8 ± 3.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>HLA mismatch</td>
<td>54.6 ± 16.7</td>
<td>46.7 ± 15.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>HD duration</td>
<td>2.1 ± 1.2</td>
<td>2.1 ± 1.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>CIT (b)</td>
<td>22.2 ± 32.2</td>
<td>37.2 ± 44.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>WIT(min)</td>
<td>3.2 ± 1.1</td>
<td>4.1 ± 0.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>sCr 1 month</td>
<td>121.3 ± 33.2</td>
<td>133.8 ± 35.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>sCr 6 months</td>
<td>144.6 ± 46.2</td>
<td>144.9 ± 42.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>cCrCl / 1 mo</td>
<td>67.3 ± 17.7</td>
<td>58.6 ± 13.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>cCrCl / 6 mo</td>
<td>60.7 ± 19.0</td>
<td>58.5 ± 20.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>CyA / 1 mo (ng/mL)</td>
<td>724.7 ± 175.2</td>
<td>798.1 ± 265.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>CyA / 6 mo (ng/mL)</td>
<td>689.8 ± 248.2</td>
<td>632.8 ± 210.2</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

At 1-month biopsy a higher percentage of acute histological changes (AR, BC and SAR) was found in G2 when compared with G1 (83 vs. 75%). As expected, the G2 group had a significantly higher score of acute histologic lesions found at 1- and 6-month biopsy, compared with G1. Importantly, the groups differed significantly in the mean HI score (Table 4).
Table 4. Comparison of histological findings and scores at 1 and 6 month posttransplantation between the groups

<table>
<thead>
<tr>
<th>parameter</th>
<th>G1-without DGF and AR (n= 28)</th>
<th>G2-with DGF and AR (n=12)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR /1 mo</td>
<td>1/28</td>
<td>1/12</td>
<td>3.6%</td>
</tr>
<tr>
<td>BC+ SAR/ 1 mo</td>
<td>20/28</td>
<td>9/12</td>
<td>71.4%</td>
</tr>
<tr>
<td>ac.les.score / 1mo</td>
<td>0.71</td>
<td>0.98</td>
<td>0.78</td>
</tr>
<tr>
<td>AR / 6 mo</td>
<td>1/28</td>
<td>1/12</td>
<td>3.6%</td>
</tr>
<tr>
<td>BC+ SAR / 6 mo</td>
<td>23/28</td>
<td>8/12</td>
<td>82.1%</td>
</tr>
<tr>
<td>ac.les.score / 6mo</td>
<td>0.69</td>
<td>1.02</td>
<td>0.79</td>
</tr>
<tr>
<td>CAN score / 1mo</td>
<td>2.2</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>CAN score/ 6 mo</td>
<td>4.5</td>
<td>2.0</td>
<td>5.0</td>
</tr>
<tr>
<td>HI / 1mo</td>
<td>5.1</td>
<td>2.9</td>
<td>5.7</td>
</tr>
<tr>
<td>HI / 6 mo</td>
<td>7.2</td>
<td>2.9</td>
<td>9.1</td>
</tr>
</tbody>
</table>

Following the evolution of histological lesions and scores at 1- and 6-month biopsy of each group separately, a significant increase of CAN score and HI was found in both groups at 6 months after transplantation (Table 5). A higher percentage and intensity of acute rejection grade and chronic lesions was observed in patients who experienced DGF and AR at first month posttransplantation (G2).

Table 5. Comparison of histological findings and scores at 1 and 6 month posttransplantation within the groups

<table>
<thead>
<tr>
<th>parameter</th>
<th>G1-without DGF and AR (n= 28)</th>
<th>G2-with DGF and AR (n=12)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAN score</td>
<td>2.2 ± 1.5</td>
<td>4.5 ± 2.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HI</td>
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<td>7.2 ± 2.9</td>
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<td>0.69 ± 0.79</td>
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</tr>
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<tr>
<td>ac.les. score</td>
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<td>9/12 (75%)</td>
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Fig. 1. Comparison of changes of ET1 between the groups

Fig. 2. Comparison of changes of NO between the groups

When the groups were compared according to the changes of endothelial factors of IRI, G2 had a significantly higher ET1 levels after Tx and at day 1 post Tx [102.7±37.1 vs. 44.9±22.4 pg/ml (p<0.001); 76.5±43.7 vs. 40.5±12.8 (p<0.01)], with a significantly lower NO levels at the same time points, [80.8±12.8 vs. 100.6±38.6 µmol (p<0.05); 35.8±19.9 vs. 86.7±20.3 (p<0.001)], respectively, (Figure 1 and 2). Moreover, a significantly higher levels of FOR were found in Group 2 when compared with Group 1, after Tx, at day 1, and at 1 and 2 weeks post-Tx: [306.3±48.2 vs. 266.6±58.3 CARR units (p<0.001); 420.3±112.8 vs. 319.8±61.6 (p<0.001); 449.3±90.3 vs. 354.6±92.8 (p<0.001), and 345.8±133.3 vs. 256.9±67.5 (p<0.05)], respectively, (Figure 3).
Discussion

The full significance of IRI after organ transplantation is still debatable, but is clearly established as major determinant of early graft dysfunction. In renal transplantation clinical practice, it is most commonly recognised as DGF, being largely reversible process with many features in common with the acute tubular necrosis. It is uncertain yet whether IRI manifesting as DGF has long-term sequel following renal transplantation, but there is increasing evidence that it may compromise long-term graft survival [9-11] and contribute to the increased incidence of graft rejection [12,13]. It has been confirmed that ischaemic damage during kidney transplantation is responsible for 20-30% of the worldwide incidence of DGF increasing the incidence of acute rejection, and favoring development of CAN [14,15].

The principal finding in our study was the evidence of DGF in 30% of the patients, whereby 50% of them were associated with an early episode of AR. Furthermore, the group with DGF/AR (i.e. clinical manifestation of IRI) had a significantly longer cold ischemic time in comparison with the group without DGF/AR. These results confirmed the association between the CIT with a higher probability of IRI and the increased risk for DGF [9,12,16]. Moreover, our results have also confirmed the strong correlation between duration of dialysis and the incidence of DGF [17], i.e. the group with DGF/AR had significantly longer dialysis duration.

It has been reported that ischemia not only damages parenchymatous cells but also has a prolonged effect on the function and reactivity of the vasculature of the kidney [18]. Vascular endothelin-1 (ET-1) levels have been reported as elevated during IRI and in patients with acute and chronic renal allograft rejection. Namely, ischemia, hypoxia and vessel wall mechanical stress are the main stimuli to ET-1 production [18]. On the other hand, nitric oxide (NO) produced by the nitric oxide synthase (NOS) enzymes, is a potentially key molecule in the link between IRI and kidney rejection. Decreased NO production following graft reperfusion leads to microvascular constriction and localized reduction in blood flow. In addition, oxidative stress associated with IRI leads to increased production of FOR. Thus, IRI is considered a systemic event resulting in endothelial dysfunction, FOR production, NO depletion, and release of cytokines, leading to the development of an inflammatory response [6,9,19]. In this regard, it is relevant to compare our results of significantly higher ET-1 and FOR levels, and significantly lower NO levels early after transplantation, in the group with DGF/AR, with those of the group without DGF/AR. As expected, the group with DGF/AR showed higher percentage and grade of acute histological lesions at 1- and 6-month biopsy, followed by a greater histological deterioration at 6-month biopsy. The group with DGF/AR was characterized with higher percentage of histological progression of CAN from 1 to 6 months. However, there was no difference in the graft function between and within the groups at 1 and 6 months. A possible hypothesis explaining these findings might be that IRI-mediated tissue injury enhances alloantigen presentation and/or increases graft immunogenesity, predisposing it to a later chronic rejection, especially when a vigorous alloimmune response has been exerted by the occurrence of an acute rejection episode. Other compelling evidence of long term importance of IRI is provided by a randomised study of superoxide dismutase (SOD) administrated intravenously at the time of cadaveric renal transplantation [20]. The hypothesis proposed by Land et al., was that early non-specific reactive oxygen intermediate (ROI) - mediated injury to the graft predisposed to later chronic rejection and that SOD was effective at blocking the early allograft injury [21].

Finally, accruing clinical and experimental evidence suggests that an initial insult to organ allografts may influence both early and late functional survival. This injury may be either immunologic (acute rejection) or antigen independent (ischaemia/reperfusion) [22]. There seems to be a clear association between early (within 6 months of engraftment) acute rejections episodes and late graft loss from chronic rejection [23].

Whether delayed graft function, the principal manifestation of initial IRI, alone affects ultimate graft behavior is under debate, particularly because the authors of many reported series have controlled their studies for the presence of rejection, most studies were retrospective, and some of them required inclusion of grafts surviving >1 year [14,24]. On the other hand, many analyses have reported clear differences. In one such study, the 5-year functional survival rate of renal allografts that had early dysfunction was 69% vs. 79% among those that functioned immediately [23]. In another, the 1-year graft survival was 84% vs. 61% in kidneys with satisfactory and unsatisfactory initial function, respectively [25]. In addition, much of the effect of this early immune-independent event seems to occur during the first year after transplantation.

It is not unreasonable to accept the hypothesis that IRI initiates an inflammatory response that provokes an increased level of acute host immunological reactivity. This would explain the apparent synergy between DGF and episodes of acute rejection, whereby, these two types of events following IRI lead to less favorable graft outcome. Several explanations have been offered for these observations: DGF increases the immunogenesity of the transplanted organ, making it more prone to host alloreactivity, and an acute rejection episode occurring in the functioning graft is difficult to diagnose and may be missed. However, it is possible that increased number of biopsies often performed in grafts with initial poor or absent function may show a higher rate of rejection than appreciated when a biopsy is not undertaken. The early injuries may also affect later events: DGF may initiate a programmed inflammatory process within the graft, which leads to chronic changes, while initial acute rejection injury predisposes to chronic graft dysfunction [23-25].

Our data support this view [26]. Immunological inflammation presented with a higher percentage of acute
histological changes: AR, BC and SAR (83% vs. 75%), with a significantly higher percentage of untreated BC and SAR (22.2% vs. 35%; p<0.05) at 1-month biopsy, and an evolution towards acute histological deterioration at 6-month biopsy in the Group 2 (with DGF and/or AR), might be an additional explanation for significantly higher percentage of CAN progression in this group (75% vs. 57%). This finding goes in line with the reports from recent studies that corticosteroid treatment of early subclinical rejection is associated with better outcomes in renal transplant patients [26-30].

With regard to the possible link between vasoconstriction, ischaemia, and chronic allograft nephropathy development in CyA-treated renal transplant recipients, our study could not confirm any difference in CyA levels at 1 and 6 months after transplantation between the groups.

Conclusions

Post IRI is mediated by endothelial release of vasoactive factors such as endothelin, nitric oxide and free oxygen radicals, potentially key molecules in the link of IRI, DGF and AR. Endothelial activation may facilitate enhanced graft immunogenicity and development of AR, with a greater susceptibility for acute histological deterioration on the 1 and 6-month biopsy, accelerating the process of CAN. This observation may have important implications in the design of clinical trials aimed to promote therapeutic strategies to prevent IRI, and thereby the progression of CAN.

Conflict of interest statement. None declared.

References

Case report

Primary renal vein thrombosis: a case report

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\(^1\)Department of Nephrology and \(^2\)Department of Radiology, Haseki Training and Research Hospital, Istanbul, Turkey

Abstract

Renal vein thrombosis is an uncommon condition with variable etiology and clinical presentation. The most common reasons are nephrotic syndrome, malignancies especially those of the kidneys. Hypercoagulability states, estrogen-containing pills, pregnancy, trauma and surgery of kidneys and its vessels, systemic inflammatory states and renal transplantation are other possible reasons. Here we present a 39-year-old female patient who was hospitalized with the complaints of fever, right flank pain, nausea, vomiting and blood in her urine for about 15 days. Hematuria, elevated CRP and erythrocyte sedimentation rate, anemia due to iron and vitamin B12 deficiency, mildly elevated transaminase levels and mild proteinuria were remarkable in her laboratory results. Ultrasonography showed increased dimensions and echogenicity of the right kidney. Doppler ultrasonography showed thrombus in the right renal vein; and CT angiography confirmed the diagnosis. She was found to be negative for hypercoagulability with normal prothrombin time, activated partial thromboplastin time, protein C and S, homocysteine levels and negative antiphospholipid antibodies, factor V Leiden and prothrombin gene mutations. Antinuclear and anti-double stranded antibodies were negative. There was no clinical and radiological sign of malignancy and tumor markers were negative. We started anticoagulant therapy immediately; but during follow-up the thrombus sustained with a nonfunctioning and shrunken right kidney demonstrated with CT and scintigraphy.

This case is rare in that she has no nephrotic syndrome, no malignancy, hypercoagulability and other etiologies except the use of oral contraceptive agent. It also reminds us the importance of early diagnosis and treatment to preserve renal functions.

Keywords: primary; renal; thrombosis; vein

Introduction

Renal vein thrombosis (RVT) is an uncommon condition with variable presentations. The causes are also variable; the most common ones being nephrotic syndrome and, malignancies, mainly renal cell carcinoma [1]. Other less common etiologies include primary hypercoagulability, trauma, estrogen containing preparations, pregnancy, infections, sepsis, systemic inflammatory diseases like inflammatory bowel disease [2], interventions to or surgery of renal veins, extrinsic compression and renal transplantation [3]. Idiopathic cases have been reported rarely [4].

The most common symptoms are flank pain and hematuria, which may be mistaken for renal colic or pyelonephritis [5]. Nausea and vomiting, fever, a palpable flank mass, edema often accompany other symptoms. Leukocytosis is a frequent finding [6]. Moreover; unexpected worsening of proteinuria and renal functions may be observed in nephrotic syndrome patients. When chronic, it may be totally asymptomatic as collateral veins develop and allow preservation of renal function, but still with risk of pulmonary embolism. Waldemer et al [1] studied the clinical characteristics and long-term follow-up of 218 patients with RVT and reported the occurrence rate of signs and symptoms as follows: Flank pain (73%), gross hematuria (36%), nausea/vomiting (13%), anorexia (21%), fever (12%), dyspnea (2%), edema (2%), anemia (38%), palpable flank mass (9%), splenomegaly (6%), ascites (6%), peritoneal signs (4%), encephalopathy (2%), and asymptomatic (15%).

Diagnosis is based on clinical, laboratory and radiologic findings. Computerized tomography (CT) angiography is the investigation of choice. Magnetic Resonance Imaging and venography in highly selected patients are other alternatives [7].

The treatment options include anticoagulation, thrombolytic therapy and surgery [8]. The prognosis is variable; the main prognostic factors are the acuteness of the disease, involvement of one or two veins, underlying etiology (membranous glomerulopathy having a better prognosis) and presence of initial renal insufficiency (a bad prognostic factor) [9].

Here we present a case of renal vein thrombosis with a delayed diagnosis and no response to anticoagulation.
Case report

A 39-year-old woman presented with right flank pain, nausea, vomiting and blood in urine that started 15 days ago. Three months earlier she was admitted to another hospital with right pleural pain, cough, fever and hemoptysis: where lobar pneumonia and parapneumonic effusion were diagnosed. Her symptoms completely resolved without any sequel with antibiotherapy. Fifteen days ago a sudden onset right flank pain, nausea and vomiting began; followed by hematuria. When she presented to the emergency unit, nephrolithiasis was suspected; but urinary ultrasonography (US) and abdominal CT did not verify this diagnosis; ultrasonography showed increased echogenicity of the kidneys while CT was reported to be totally normal. Her past medical history consisted of a uterine myomectomy performed six months ago. She gave birth to a healthy girl 6 years ago. She had no abortus or stillbirths. She smoked 10 pack-years.

On admission her blood pressure was 100/70 mmHg, pulse was 88/minute and rhythmic, the temperature was 37.2°C. Skin was pale without jaundice, cyanosis and edema. Examination of the respiratory and cardiovascular systems revealed no pathological findings. Abdominal examination revealed right upper quadrant tenderness without distension and rebound. There was tenderness of the right costovertebral junction.

<table>
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<tr>
<th>Parameter</th>
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<td>Hemoglobin</td>
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<tr>
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Laboratory investigations were as follows: Urine sediment was active with many erythrocytes and leukocytes at each high power field. Blood tests included white blood cells 14.5x10^3/microliters, hemoglobin 8.4 g/dl with mean corpuscular volume of 61.5 fl, platelets 661x10^3/microliter, erythrocyte sedimentation rate 124 mm/hour, C-reactive protein 149 mg/L, urea 23 mg/dl, creatinine 1.03 mg/dl, sodium 134 mmol/L, potassium 4.83 mmol/L, AST 74 U/L, ALT 54 U/L, GGT 316 U/L, alkaline phosphatase 280 U/L and lactate dehydrogenase 864 mg/dl. Coagulation parameters included international normalized ratio of 0.94, partial thromboplastin time of 22.7 seconds and fibrinogen level of 1214 mg/dl. Iron (16 µg/dl) and vitamin B12 levels (142 pg/ml) were below the normal limits. Creatinin clearance rate was 52 ml/min and there was a microalbuminuria of 283 mg/day. Her hypercoagulopathy panel was negative for antiphospholipid antibodies, hyperhomocysteinemia, factor V Leiden mutation and prothrombin gene mutation. Protein C and S levels were within normal limits. Antinuclear antibodies and Anti double stranded DNA antibodies were negative.

Fig. 1. CT and CT angiography of the kidneys

Fig. 2. CT scan two months after the onset of treatment

Urinary system US and CT was repeated that showed an enlarged right kidney (124x61 mm) with increased echogenicity. Doppler ultrasonography of renal vasculature was consistent with right renal vein thrombosis. CT angiography demonstrated that there was a thrombus in the right renal vein with extension into the inferior vena cava and the nephrogramme phase at the right kidney could not be demonstrated (Figure 1). With DTPA/DMSA
renal scintigraphy, a nonfunctioning right kidney was reported. Low molecular weight heparin was started followed by warfarin. During follow-up, she had no symptoms, renal functions were well preserved, no hematuria reoccurred, but control renal Doppler ultrasonography performed two months after the onset of anticoagulant therapy revealed that the thrombus occluding the right renal vein remained with no sign of flow. Control CT showed that the right kidney was shrunken (Figure 2), with no function as assessed by scintigraphic study. She still uses warfarin for the risk of embolism.

Discussion

Diagnosis of renal vein thrombosis requires a high index of suspicion. Since the clinical presentation is so variable, the diagnosis is often delayed. The pain it causes may easily be confused with nephrolithiasis, pleurisy; and inquiry to these diagnoses may lead to waste of time and loss of renal parenchyma. Our case presented with right flank pain, fever and hematuria and there was a history of pneumonia. Nephrolithiasis, pyelonephritis, pulmonary embolism and renal infarct were within the list of differential diagnosis. Macroscopic hematuria and right loin pain supported the diagnosis of nephrolithiasis; but urinary US and CT revealed no stones. Pyuria, fever and high CRP levels suggested pyelonephritis, but urine culture remained sterile. The CT scan demonstrated that the right kidney was larger than normal. A unilateral large kidney may be due to renal cysts, tumors, hydronephrosis, abscess formation or edema due to vascular obstruction. Our case did not have signs consistent with tumor, hydronephrosis or abscess in the CT scans. So the possible diagnosis was renal vascular disease which was proved with Doppler ultrasonography and CT angiography.

Experimentally acute RVT is associated with immediate enlargement of the kidney with marked increase in renal vein pressure, leading to a marked decrease in renal arterial flow. In dogs the kidney enlarges over a period of one week, then fibrosis gradually ensues [10] which suggests that the practitioner must carry the suspicion to prevent delay in diagnosis and loss of renal tissue. In our patient there was a delay of at least 15 days. The left renal vein is in communication with ureteric, gonadal, adrenal and phrenic veins; whereas the right renal vein has not this much communication. This network of venous complexes provides some protection of suspicion to diagnose. The diagnosis of RVT is not a single but necessitates investigation of a probable underlying disease, although it may be rarely primary. It is always important to pay attention to flank pain and hematuria not to lose time and renal parenchyma.

Conclusions

RVT is a disease, which requires a high index of suspicion to diagnose. The diagnosis of RVT is not a single one but necessitates investigation of a probable underlying disease, although it may be rarely primary. It is always important to pay attention to flank pain and hematuria not to lose time and renal parenchyma.

Conflict of interest statement. None declared.

References


Case report

A case of retroperitoneal fibrosis presenting with uremic encephalopathy

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Abstract

Retroperitoneal fibrosis (RPF) is characterized by the development of dense fibrous tissue that may cause obstruction of retroperitoneal organs, especially the ureters. It is usually primary; but may be secondary to malignancies, collagen vascular diseases, some drugs, radiation and trauma. Clinical presentation is variable. Here we discuss a case presenting with uremic encephalopathy. A sixty-one years old male was brought to the emergency clinic due to nausea, vomiting, fatigue, decreased urine volume and insensible speech. He was confused with distorted orientation for time and place. Skin was pale and there was flapping tremor. Other physical findings were unremarkable. Uremia, uremic encephalopathy and metabolic acidosis with increased anion gap lead to urgent hemodialysis. Ultrasonography showed bilateral grade 2-3 hydronephrosis without stones and other intraluminal obstructing lesion. Both abdominal computerized tomography and magnetic resonance imaging revealed a retroperitoneal soft tissue mass surrounding the aorta and inferior vena cava. Further investigations provided no further information about the etiology. He had bilateral laparoscopic ureterolysis operation and tissue samples were taken for pathological examination which was consistent with RPF with no findings of malignancy. He is under follow-up with no symptoms and with normal renal functions.

RPF may have highly variable etiology and clinical presentation. Our case represented with uremic encephalopathy. The diagnosis of RPF should lead to a thorough evaluation for a possible underlying disease. Primary cases relapse frequently, so these patients must be followed regularly.

Post renal causes of renal failure especially RPF must always be kept in mind when there is no obvious intraluminal obstructive lesion and diagnostic phase must be as short as possible to prevent loss of renal parenchyma.

Key words: encephalopathy; fibrosis; primary; retroperitoneal

Introduction

The French urologist Albarran first described retroperitoneal fibrosis (RPF) in 1905, but with Ormond's publication in 1948, the disease became an established clinical entity [1]. Retroperitoneal fibrosis is characterized by the development of dense fibrous tissue all through the retroperitoneum especially in front of the fourth and fifth lumbar vertebrae, surrounding abdominal aorta and iliac vessels. This fibrous tissue may cause obstruction of retroperitoneal organs, especially the ureters [2]. Annual incidence is 1/200000 with peak at 40-60 years of age [3]. It is two times more commonly seen in males. 70% of cases are idiopathic. 8% of cases were associated with malignancies (lymphoma, sarcoma, carcinoma of breast, stomach, lung, colon, bladder, prostate and cervix). Other possible etiologic factors are retroperitoneal inflammation, trauma, some drugs (methysergide, methyldopa, and beta blockers), collagen vascular diseases and radiation [2].

Clinical presentation varies from constitutional symptoms like fever, fatigue and weight loss to symptoms due to venous obstruction, or varying degrees of renal failure, abdominal pain, nausea and vomiting due to ureteric obstruction. Absolute diagnosis depends on pathological examination. Intravenous urography, computerized tomography (CT) and magnetic resonance imaging (MRI) helps to determine the extent of the disease and to follow-up. The primary aim of any treatment is to preserve the renal functions. Stent application to the ureters, surgical ureterolysis, corticosteroids, cytotoxic agents and tamoxifen are main modalities of treatment [4,5]. There are studies reporting 100% five year survival among idiopathic cases with these treatment strategies [6].

Case report

A sixty-one year old male presented with with fatigue, nausea, vomiting, decreased urine volume and confusion. He was without any symptoms until the last two weeks during which progressive fatigue, loss of appetite, nausea
and vomiting developed and followed by decreased urine volume, insensible speech and tremor of the hands for the last few days. His past medical and family histories were unremarkable. He had smoked twenty pack-years. He was confused when seen in the emergency room with distorted orientation for time and place. Skin was pale and there was flapping tremor. Other physical findings were unremarkable. Abnormal laboratory findings were as follows: blood urea: 74.97 mmol/L, creatinine: 845.72 µmol/L, sodium: 138 mmol/L, potassium: 6.51 mmol/L, calcium: 2.27 mmol/L, phosphorus: 1.94 mmol/L, intact parathyroid hormone: 130 ng/L, hemoglobin: 113 g/L, hematocrite: 0.31, MCV: 77 fl, sedimentation rate: 55 mm/hour and C-reactive protein: 454000 µg/L. Urine sediment had 10-15 erythrocytes and 4-5 leukocytes per high power field; creatinine clearance was 8.9 ml/minute and he had 586 ng/day proteinuria. Arterial blood gas analysis revealed metabolic acidosis with respiratory compensation (pH: 7.25, HCO$_3$- 13 mmol/l, pCO$_2$: 26.4 mmHg, pO$_2$: 106 mmHg). Hemodialysis therapy was initiated due to uremic encephalopathy and immediately afterwards laboratory and radiological examinations for evaluating the etiology of renal failure were commenced. Bilateral grade 2-3 hydronephrosis was reported after the urinary system ultrasonography; which also demonstrated normal echogenity and parenchymal thicknesses of the kidneys. The abdominal CT was showed an enlarged liver (180 mm) and spleen (144 mm) and bilateral grade 3 hydronephrosis. Ureters could be followed as dilated to the aortic bifurcation level. A retroperitoneal soft tissue mass surrounding the aorta and inferior vena cava at the aorto-iliac bifurcation, and descending caudally as long as the main vasculature was seen during abdominal MRI (Figure 1). Ureters were ending within this soft tissue density.

Autoantibodies were studied and anti-nuclear antibody, anti-double stranded DNA antibody, and antineutrophil cytoplasmic antibody were found to be negative. For definitive diagnosis of RPF and treatment, he had bilateral laparoscopic ureterolysis during which tissue samples were taken for pathological examination. Pathology report was consistent with RPF with no findings of malignancy. Currently he is under follow-up with no symptoms and with normal renal functions.

**Discussion**

Retroperitoneal fibrosis is most common in people aged 40 - 60, and men are twice as likely to develop them as women [3]. It may have highly variable clinical presentation ranging from constitutional symptoms such as severe pain in the lower back, abdominal, and flank areas, swelling in one or both legs to different degrees of renal failure (three quarters of patients) [6]. Our male case had presented with uremic encephalopathy without any prior constitutional symptoms.

Post-renal causes of renal failure must always be kept in mind and diagnostic phase must be as short as possible to prevent loss of renal parenchyma. Since bilateral grade 2-3 hydronephrosis was reported after the urinary system ultrasonography in our case, a post-renal etiology was sought. Although rare, RPF is a treatable cause and must be remembered when there is no obvious reason for obstruction.

The diagnosis of RPF should lead to a thorough evaluation for a possible malignancy, collagen vascular disease, autoimmune disease; and history of trauma and drug use should be asked insistently [4]. Our patient had no history of trauma or any drug use. Moreover, he did not have any significant laboratory result regarding the etiology of RPF; so he was regarded as primary.

Primary RPF cases relapse frequently, so these patients must be followed regularly for relapse and for an underlying disease which may be detected years after the diagnosis of RPF.

**Conclusions**

We wanted to share this case to remind approach to the etiology of renal failure, especially of post-renal causes. RPF must be kept in mind in cases without obvious reason for obstruction.

**Conflict of interest statement.** None declared.

**References**


Case report

Recurrent focal segmental glomerular sclerosis after kidney transplantation

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²Department of Nephrology, University of Skopje, R. Macedonia

Abstract

Renal transplantation is the optimal mode of treatment for end-stage renal disease in the pediatric population. Compared with dialysis, transplantation is offered to the children with chronic renal failure as best chance for obtaining normal growth and neurophysiologic development. We present a case of 13 years old girl who had clinical and laboratory symptoms of nephrotic syndrome since her 1 year of age. She underwent renal biopsy which showed histopathology of focal segmental glomerular sclerosis (FSGS). The therapy with steroids, cyclosporin and cyclophosphamide did not show any result of remission of the disease. At her 6-year of age she progressed to terminal renal insufficiency and commenced with peritoneal dialysis treatment for the next 2.5 years. In her 9 year of age she obtained her first living donor kidney transplantation in Thessalonica (Greece). One year after transplantation a high proteinuria with an increased serum creatinine and hypertension was observed. She underwent graft biopsy and the recurrence of the primary disease (FSGS) was confirmed. The treatment of these progressive recurrent FSGS has included pulse corticosteroid therapy and immunoadsorption. The severe course of the disease ended up with a rapid loss of graft function and development of chronic transplant nephropathy and end stage renal disease at 3 years after transplantation. A treatment with an automatic peritoneal dialysis was instituted and a look into the future and possible second transplantation is considered. Recurrence of the FSGS in renal transplant recipients is an important cause of allograft dysfunction. Dilemma, which might be raised in this case is the time of treatment with renal replacement therapy and pretransplant work, as well as pretransplant work up in order to possibly improve the graft survival.

Key words: live donor transplantation; FSGS recurrence; treatment

Introduction

Focal segmental glomerulosclerosis (FSGS) is the most frequent cause of intractable proteinuria in children and is a major cause of progressive chronic kidney disease [1]. Approximately 30% of patients with idiopathic FSGS recur after renal transplantation and in very young pediatric recipients and in patients with a rapid course of the disease from Caucasian origin there is a higher risk of recurrence. It is worrisome complication for pediatric nephrologist because of its high rate of incidence, the subsequent graft loss and inability to predict its occurrence. Hence, an early diagnosis and adequate treatment are considered as crucial issue. Plasmapheresis and immunoadsorption with protein A columns have been used successfully in induction of the remission of proteinuria and the disease itself.

In addition, patients having recurrence of FSGS in the first year after transplantation with rapid loss of their graft are at very high risk (>80%) of having recurrences in the subsequent grafts. Recurrence of FSGS with proteinuria can occur within hours of transplantation and is associated with diffuse effacement of the foot processes [1]. Recent advances in molecular genetics of FSGS led to the identification of several genes responsible for coding proteins of the podocyte and are localized in the glomerular diaphragm where they play role in the control of glomerular permeability.

Living-related donors are not recommended for renal transplantation in children with FSGS in many centers because of the high incidence of recurrence. However, the dilemma is arisen in the societies where there is no other choice than living-related transplantation.
Case report

We present a case of a 13 years old girl with clinical and laboratory symptoms of nephrotic syndrome since her 1 year of age. She underwent renal biopsy which showed hystopathology of focal segmental glomerulosclerosis. The therapy with steroids, cyclosporin and cyclophosphamid did not achieve any substantial degree of remission of the disease.

At her 6 of age she progressed to terminal renal insufficiency and started her treatment with peritoneal dialysis for the next 2.5 years. In 2002 (at her 9 years of age), living donor kidney transplantation has been performed in Thessalonica (Greece). However, she did not receive preoperative immunoadsorption or other preconditioning regimen. The maintenance therapy consisted of cyclosporin, mycophenolat mofetil and steroids. Early recurrence of the nephrotic syndrome was clinically defined as a development of massive proteinuria (>40 mg/m²/day) and hypoalbuminemia (<2.5 g/l). She underwent graft biopsy and the recurrence of the primary disease (FSGS) was confirmed with a diffuse foot process effacement and/or glomerulosclerosis in the graft histology. The recurrence of the primary disease (FSGS) started at one year after transplantation with a high proteinuria (up to 4 g/l), elevated serum creatinine and urea levels and a therapy resistant hypertension.

The treatment of these progressive recurrent FSGS has included pulse corticosteroid therapy (methylprednisolone 250 mg/m²/day) for the first 3 days and then the dose was tapered at the level of the previous one. Immunoadsorption sessions (n=10) were conducted over the next 4 weeks.

Discussion

We present a case report of a 13 years old girl with an as extremely early onset of the original nephrotic syndrome as 1.5 years of age. The histology of the first renal biopsy showed initial focal segmental glomerulosclerosis. The therapy with steroids and cyclophosphamid did not show any improvement in the disease progression. The patient developed edema and hypertension, under a condition of overt proteinuria of 1.5-2g/l. In parallel there was manifestation of a classical nephrotic syndrome with hyperlipidemia (triglicerides 14.4 mmol/l), while serum creatinine and urea were still maintained within the normal range. At her 2 years of age a therapy with Cyclosporine (150 mg/m²) and steroids 30 mg/m² according to the internationally adopted protocols for FSGS in pediatric patients was administered.

The duration of the original nephrotic syndrome prior to development of ESRD was in a course of 4 years. We started peritoneal dialysis for 2.5 years (1 year CAPD and 1.5 year APD). She had four peritonitis episodes with staphylococcus aureus. She underwent living related kidney transplantation from her mother at 9 years of age with an excellent graft function of 90 µmol/l. However, recurrent proteinuria developed 8 months posttransplantation. Kidney graft biopsy was performed and didn't show any significant changes apart from mild interstitial inflammation. The therapy was switched to Prograf instead of Cyclosporine A. One year after transplantation we had already established severe persistent nephrotic syndrome and a deterioration of the graft function, with serum creatinine level 350 µmol/l. A new graft biopsy confirmed recurrent FSGS of the renal allograft. A bolus methylprednisolon therapy for 3 days and immunoabsorption sessions for two weeks were started. Only a partial remission was obtained within the next six months. There was persistent nephrotic proteinuria and elevated degradation products. Moreover, the patient had an episode of graft rejection and shortly thereafter, she lost her graft function and was put on automated peritoneal dialysis.

Steroid-resistant nephrotic syndrome with FSGS is one of the most frequent lesions leading to renal transplantation in children. The recurrence of the disease is 20-40% in renal allografts and graft failure in 40-50% of patients with recurrence occur early after transplantation [2,3].

Living-related transplants are not recommended for children with FSGS in many centers, because of the high rate 20-30% of recurrence that is hard to predict, and the 30-50% rate of graft loss [4]. Unfortunately, in our country there is no possible choice of cadaveric transplantation yet. Hence, in cases when recurrent nephrotic syndrome is suspected clinically, an immediate graft biopsy is essential to confirm the recurrence and to differentiate a possible acute rejection.

An aggressive anti-rejection therapy should be started for patients experiencing graft rejection. On the other hand, an additional difficulty in managing recurrent FSGS is that it is hard to predict and hard to prevent [5]. The duration of the disease, the interval on dialysis and many peritonitis episodes made very hard decision for timing of the kidney transplantation [5]. It might have been better if we could have waited some more years on peritoneal dialysis, because of a possible acute rejection that could not have been excluded. The patient had cyclosporine nephrotoxicity early in the beginning, and we had to change the therapy switching it to tacrolimus. The serum creatinin and urea reached high levels several months after Prograf® was commenced. Aggressive anti-rejection therapy should be initialised for patients experiencing graft rejection. Recently, rituximab, primarily indicated for treatment of lymphoma, has been successfully used in cases of immediate post transplant recurrence of FSGS [6]. Rituximab is a high-affinity-specific antibody against the CD20+ antigen. It is a chimeric monoclonal antibody composed of human immunoglobulin IgG1 heavy chain and kappa light chain constant regions and variable light and heavy chain murine regions. By targeting CD20 on precursor B cell we can decrease the production of activated B cell and limit antibody production. Rituximab directly inhibits B-cell proliferation and induces cellular apoptosis through the binding of complement. On the other hand, complement mediates cytotoxicity and antibody-dependent cell-mediated cytotoxicity.
The doses may vary between 375 mg/m\(^2\) per dose at weekly intervals for 6 weeks and a single dose of 375 mg/m\(^2\) which might result in a rapid clearing of circulating CD 20-positive B cells. Intermittent immunoabsorption combined with B cell depletion by rituximab treatment induced prolonged reduction of proteinuria in a high-risk patient for recurrence of FSGS in the graft [6].

Conclusions

Recurrence or onset of de novo disease in the renal allograft is an important cause of allograft dysfunction. Recurrence in patients who develop ESRD secondary to FSGS can occur early, within days or weeks after transplantation (as it was in the present case). Treatment of recurrent FSGS has included high doses methylprednisolon, in combination with plasmapheresis and eventually combined with rituximab. However, randomized studies are required to establish new therapy for improvement and establishing therapy for graft rejection in patients with FGSG. The recurrence of the FGSG in renal transplant recipients is not only an important cause of allograft dysfunction but also a dilemma, as raised in our case on when the time of treatment with renal replacement therapy and pretransplant work should be initialised, as well as the pre/posttransplant work up in order to possibly maintain the graft function and a survival.

Conflict of interest statement. None declared.

References

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Contacts: Milan Radovic: milan.r@EUnet.yu; www.kidney-belgrade.org

V International Symposium - Advances in Bone and Mineral Disorders in CKD
March 19-20, 2009 - Oviedo, Spain
Contacts: Jorge Cannata: bmd-ckd.oviedo2009@hca.es

Diagnostic and Treatment Options in CKD in the New Millennium
April 25, 2009 - Skopje, R. Macedonia
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WCN 2009 Satellite - Symposium on IgA on Nephropathy
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Contacts: Rosanna Coppo, John Feehally: igan2009@euromeetings.it

7th Renal Failure Academy
June 11-13, 2009 - Timisoara, Roma
Adrian Covic, Paul Gusbeth: adrianccovic@gmail.com; paulgusbeth@yahoo.com

Chronic Renal Failure in Elderly
June 13, 2009 - Zagreb, Croatia
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16th Budapest School of Nephrology
August 26-31, 2009 - Budapest, Hungary

International Society of Blood Purification (ISBP 2009)
September 17-19, 2009 - Stockholm, Sweden
Contacts: Peter Stenvinkel: peter.stenvinkel@ki.se

DiaTransplant 2009
October 16-18, Opatija, Croatia

National Nephrology Congress of Bosnia and Herzegovina
May 5-8, 2010, Sarajevo, Bosnia and Herzegovina
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