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Contents

I. Special article

II. Review article

III. Original Articles

IV. Case Reports

V. Letter to Editor

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BJ

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Special article

Croatian Recommendations for Dialysis of HIV-Positive Patients

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Abstract

Human immunodeficiency virus (HIV) infection may be associated with renal impairment since about 0.4% of all HIV-positive patients develop end-stage renal disease. The share of patients with HIV infection in hemodialysis centers throughout the world ranges from 0.3% to as high as 38%. In Croatia, renal replacement therapy was needed by 1% of all the HIV-positive patients from 1985 until the end of 2014. Healthcare professionals (HP) should be aware of the risks of occupational exposure to blood-borne infections in their daily work. Performing dialysis in HIV-positive patients increases the risk of exposure to HIV during the extracorporeal circulation of the infected blood. However, post-exposure prophylaxis (PEP) with effective antiretroviral drugs significantly reduces the risk of infection after occupational exposure. On behalf of the Croatian Society of Nephrology, Dialysis and Transplantation, the authors of this paper have proposed recommendations for the management of HIV-positive patients on dialysis, which aim to prevent the transmission of HIV among patients and HPs. The important recommendations include the following:

1. when the need arises, it is necessary to provide HIV-positive patients with dialysis in the vicinity of their place of residence.
2. HIV-positive patients should be dialyzed with a separate hemodialysis machine in an isolated area. Alternatively, they can be dialyzed in an area for the hemodialysis of HCV-positive and/or HBV-positive patients.
3. Specialized and trained personnel should be provided during the hemodialysis procedure, together with strict compliance with the standard precautions for the prevention of blood-borne infections.
4. There should be a good and prompt cooperation with the National Referral Center for HIV infection.

Keywords: human immunodeficiency virus, HIV, dialysis, recommendations, blood transmitted infection, exposure, prevention

Introduction

When the disease caused by the human immunodeficiency virus (HIV) is left untreated, it generally progresses inexorably in all infected persons, from asymptomatic infection to the condition of complete destruction of the immune system, resulting in acquired immunodeficiency syndrome (AIDS) [1]. However, today, thanks to antiretroviral therapy (ART), HIV infection has become a chronic condition that can be successfully managed long-term [2-4]. Some observational studies have suggested that persons infected with HIV can live nearly as long as non-infected persons [5,6].

Owing to the prolonged life expectancy of persons infected with HIV, there has been an increase in the chronic diseases and complications associated with the treatment of HIV and the drugs used to manage HIV diseases, including acute and/or chronic renal disease [7]. In HIV-infected persons, kidney damage may occur as a result of the direct effects of the virus, such as HIV-associated nephropathy (HIVAN), as well as the indirect effects of HIV, including complications of immunodeficiency caused by HIV, secondary (opportunistic) infections and side effects from the treatment of these conditions, i.e., nephrotoxic drugs. Chronic renal failure is associated with common risk factors, such as age, hypertension and diabetes, but also with certain antiretroviral drugs (tenofovir, indinavir and others) [8].

Epidemiology of Renal Failure in Persons Infected with HIV

Croatia, with an annual rate of new HIV diagnoses of 10-20/1,000,000 inhabitants, is among the countries with the lowest prevalence rates. According to the HIV/ AIDS

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Registry of the Croatian National Institute of Public Health, from 1985, when the first cases of HIV infection were recorded in Croatia, to the end of 2014, a total of 1,194 HIV-positive individuals have been registered.
Possible factors responsible for an increased risk of developing acute/chronic renal failure (ARF/CRF) are advanced age, female sex, diabetes, hypertension, intravenous drug abuse, certain coinfections (hepatitis B virus, hepatitis C virus), low CD4 T-lymphocyte count, the use of some antiretroviral drugs, a history of renal impairment and high HIV viral load. Numerous studies have already demonstrated that the use of antiretroviral drugs and suppression of the viral load can improve kidney function and reduce proteinuria, thereby indicating that HIV has a nephrotoxic effect. This is particularly evident in Afro-Americans, for whom the risk for CRF is nearly three times higher than for Caucasians [9].
In a large study involving over 35,000 patients, 0.4% of them developed stage 4 or 5 renal failure (GFR <30 ml/min or dialysis or transplant), with an incidence rate of 0.67/1,000 person years of follow-up (PYFU) [8]. In a cross-sectional multicenter EuroSIDA survey, the prevalence of end-stage renal disease (ESRD) was 0.5% [10], and an observational cohort study conducted in Great Britain showed a 3.8-fold increase in ESRD among the black HIV-positive patients in the cohort during the 12-year study period [11].
The percentage of patients infected with HIV in dialysis centers around the world ranges from 0.3% to as high as 38% [12]. From 1985 to 1999 the percentage of dialysis centers providing care to HIV-positive patients in the United States increased from 11% to 39% [13].

Methods for Treating Chronic Renal Failure in HIV-infected Patients

For HIV-infected patients who develop severe renal impairment, whether acute or chronic, replacement of renal function is necessary. They can be treated with hemodialysis (HD), peritoneal dialysis (PD), and may be candidates for kidney transplantation [12-14]. In the aforementioned EuroSIDA survey, out of 122 patients with ESRD, 96 received dialysis and 26 renal transplant. The most frequent causes of ESRD were HIV-associated nephropathy and other glomerulonephritis [10]. The advantages and disadvantages of each form of dialysis in HIV-infected patients are presented in Table 1.

Table 1. Advantages and disadvantages of dialysis in patients with HIV-infection [adapted from 11,14,15]

METHOD	ADVANTAGES	DISADVANTAGES
HEMODIALYSIS	- Transmission of the virus by dialysis machines has not been confirmed* - Lowering of the viral load in the blood during the procedure	- Higher risk of HCV-infection for patients - Higher frequency of contacts with patients' blood, higher risk of infection transmission to personnel - Higher costs
PERITONEAL DIALYSIS	- Less risk of infection transmission to personnel - Lower costs	- Possibility of viral replication in the dialysate** - Higher incidence of peritonitis (due to opportunistic microorganisms)

*The size of the HIV virion is about 105 nm and the pores of the dialyzer are 1-7 nm. Viral RNA is not detectable in the dialysate.
**Peritoneal dialysate is less contagious than blood but the virus can replicate in the dialysate: up to 7 days at room temperature and up to 2 days in empty lines.

Additional shortcomings of PD are the loss of protein into the dialysate in already asthenic patients, cognitive motor dysfunction in advanced HIV diseases and reduced patient compliance [14,15]. Priority should be given to HD and transplantation when possible. The observational cohort study conducted in Great Britain showed that the 5-year survival of patients infected with HIV who had received transplants was similar to that of patients infected with HIV who were receiving dialysis and on the transplant list (85% and 89%, respectively). The good transplant results of this group of patients should be placed in the context of a young patient population, relatively short period of monitoring and, most importantly, the exclusion of patients with contraindications for transplantation, among whom survival is significantly limited. Patients infected with HIV have a markedly higher rate of kidney rejection in the first post-transplant year in comparison to transplant patients not infected with HIV: 31-48% vs. 12-24%, probably associated with HIV-modulated immune response and less exposure to immunosuppressants, together with highly active antiretroviral therapy [11].

Prevention of HIV Transmission in Dialysis Centers

Healthcare personnel should be aware of the risk of occupational exposure to blood-borne pathogens in their daily duties. Therefore, they should be expected to fully comply with the standard precautions to prevent exposure to blood,

other bodily fluids and tissues potentially containing HIV and other blood-borne pathogens [16,17].
Administration of dialysis to patients infected with HIV increases the risk of sharps injuries, particularly needlesticks. The risk of seroconversion after a needlestick involving exposure to the blood of a HIV-positive patient is 0.3%, while the risks for hepatitis B and C are considerably higher, 2% for HCV and 6-30% for HBV [16,18-20].
HIV, like HBV and HCV, does not pass through intact skin and the airborne transmission of this virus has not been confirmed. Contacts via broken skin, blood splashes on the mucous membranes and other forms of mucocutaneous incidents rarely result in seroconversion and infection [16]. In a retrospective study by Cardo *et al.* [19], the risk factors increasing the transmission of HIV infection after percutaneous exposure were deep injury, injury with a device that was visibly contaminated with blood, injury with a device that had previously been placed in the source patient's vein and the death of the source patient two months after the percutaneous incident. These factors are probably surrogate markers of viral inoculum. Although low titer viremia may mean lower inoculum, it does not entirely exclude the possibility of the transmission of HIV infection because the viral load does not include the intracellular HIV. Transmission of HIV infection from source patients with undetectable HIV levels in the blood has been documented [20].
The first case of the transmission of HIV infection from a patient to a healthcare worker occurred in 1984 [21]. In 1987, the US Centers for Disease Control and Prevention (CDC) issued Recommendations for Prevention of HIV Transmission in Healthcare Settings and for other blood-borne pathogens, in which the concept of universal precautions was introduced [22]. According to these recommendations, the blood and bodily fluids of every patient are potentially infectious and should be treated as such. The CDC recommends compliance with the recommendations for control and prevention of blood-borne infections issued by the United States Occupational Safety and Health Administration (OSHA). These recommendations are regularly updated and revised according to information from recent studies and are readily available in printed or electronic form via the CDC website [22, 23]. From 1984 to 1999, 57 healthcare workers in the United States acquired HIV infection occupationally, most often from needlestick incidents (84%). From 1999 to the end of 2013, owing to compliance with the CDC recommendations, only one healthcare worker acquired HIV infection occupationally (a laboratory technician from a needle puncture while working with a live HIV culture) [24]. In dialysis units, there have been no reported cases of the transmission of HIV among patients in the United States but cases were reported in Argentina (two dialysis centers), Columbia and Egypt [25]. Post-exposure prophylaxis (PEP) significantly reduces the risk of infection and is, therefore, justified whenever possible [19,20,26].

Experiences of Other Countries in the Management of Kidney Failure in Persons Infected with HIV

The international guidelines are largely based on the recommendations of the CDC, with certain particularities related to the dialysis centers, equipment and type of dialyzer.
The European Best Practice Guidelines for the Prevention and Management of HBV, HCV and HIV in Hemodialysis Patients recommend the suitable implementation of the standard precautions for protection from the transmission of infectious agents, which has achieved a very low risk of infection transmission. It is necessary to screen for the presence of individual pathogens (HBV, HCV and HIV) in all patients included in a dialysis program for the first time or when are transferred from other dialysis centers, having obtained the patients' prior informed consent. The isolation of patients infected with HIV in a separate area and the use of special dialysis machines for them are not recommended. The principles for the prevention of the transmission of HBV infection are also sufficient for the prevention of the transmission of HIV [27].
The most common errors in the protocol for infection control that can lead to the transmission of infection are the reuse of dialyzers, blood lines and the same needles for different patients; the use of contaminated multidose heparin vials and the use of ineffective disinfectant (benzalkonium chloride) [28].
The recommendations of the Infectious Diseases Society of America state that dialysis is safe for healthcare workers and patients if the recommendations of the CDC for the prevention and control of infection are strictly followed. Vascular access for dialysis (the placement of endovenous catheters and the creation of arteriovenous fistulae) should be provided for all patients, including those infected with HIV [29].
On the other hand, in some countries, such as the Republic of South Africa, in addition to the implementation of the standard precautions and annual screening for the causes of infectious diseases in all dialysis patients, it is recommended that patients infected with HIV should be dialyzed in separate areas or rooms, although it is not insisted on the use of dedicated machines [30].

Croatian Recommendations for the Dialysis of HIV-Positive Patients

At the meeting of the Board of the Croatian Society for Nephrology, Dialysis and Transplantation (HDNDT) on January 25, 2013, it was decided to prepare Recommendations for the Prevention of HIV Infection in Patients on Dialysis and Healthcare Workers, in cooperation with infectious disease specialists from the Dr. Fran Mihaljevic University Hospital for Infectious Diseases in Zagreb, the Croatian Referral Center for the Diagnosis and Treatment of HIV Infection. The first version of the

recommendations was published on the website of the Croatian Society for Nephrology, Dialysis and Transplantation in April 2014, for the purpose of public debate.

Until now, HIV-positive patients have been receiving acute dialysis at the Dr. Fran Mihaljevic University Hospital for Infectious Diseases, University Hospital Center in Zagreb, and the University Hospital Center in Split, while chronic hemodialysis, in addition to the Dr. Fran Mihaljevic University Hospital for Infectious Diseases and University Hospital Center in Zagreb (since 2003) is also provided at the Sibenik General Hospital (2013-2015). It may be expected that the need will arise to provide dialysis to patients with HIV in other centers. Therefore, the Croatian Society for Nephrology, Dialysis and Transplantation has proposed Recommendations for the Dialysis of HIV-Positive Patients, with the goal of preventing the transmission of HIV infection among patients and healthcare personnel.

Based on current knowledge, literature and the authors' experience, on behalf of the Croatian Society for Nephrology, Dialysis and Transplantation, recommendations have been made for the dialysis of HIV-positive patients, based on the level and degree of evidence in the guidelines presented/cited in Tables 2 and 3 [31].

Table 2. Level of Evidence in the Guidelines [adapted from 31]

LEVEL OF IMPACT	IMPACT OF THE GUIDELINES		
	ON PATIENTS	ON PHYSICIANS	ON DECISIONS
LEVEL 1 We recommend	The majority of patients would like to receive the recommended therapy.	The recommendations should be applied to the majority of patients.	The guidelines can be the basis for the recommended application.
LEVEL 2 We advise	A large number of patients would like to receive the recommended therapy.	Various options can be applied; an individualized approach is required.	The guidelines should be discussed before the recommendations are applied.

Table 3. Level of Evidence in the Guidelines [adapted from 31]

LEVEL OF IMPACT	QUALITY OF EVIDENCE	IMPACT OF THE GUIDELINES SIGNIFICANCE
A	High	We are convinced that the actual impact is very close to that of the estimated impact.
B	Medium	The actual impact is close to the estimated impact but there are possible discrepancies.
C	Low	The actual impact could be different from the estimated impact.
D	Very Low	The estimated impact is uncertain, probably far from the actual impact.

Recommendations

- When the need arises, it is necessary to provide HIV-positive patient with dialysis in the vicinity of his/her place of residence (1A).

Commentary

- *Renal function is impaired in over 30% of persons infected with HIV* [29].
- *HIV-positive persons who exhibit the following should be referred to a nephrologist:*
  - *a significant decrease in the glomerular filtration rate (GFR), >25%, compared to the previous value,*
  - *GFR <60 ml/min/1.73 m^2 with albuminuria >300 mg/24 hours, hematuria, elevated arterial pressure and*
  - *GFR <30 ml/min/1.73 m^2 (1C).*
- *This group of patients should be provided with vascular access for hemodialysis, optimally a native arteriovenous fistula* [32] *(1B).*
- It is necessary to determine the viral status of all patients included in a hemodialysis program and all patients transferred from other centers for hemodialysis, including HBsAg, anti-HBs, anti-HBc, HBeAg, anti-HBe, anti-HCV, anti-HIV, and HBV DNA screening for all anti-HBc total (IgG/IgM) and/or anti-HBe positive patients (1A).
- The viral status of all patients on hemodialysis should be checked every six months (1C).

Commentary on recommendations 2 and 3

- *It is necessary to diagnose persons infected with HIV early, in order to initiate antiretroviral therapy and reduce the incidence of opportunistic infections. Early ART would also lower the risk of HIV transmission and HIV-associated non-AIDS (HANA) conditions as it lowers the risk of opportunistic infections. However, when the CDC guidelines are strictly followed, the risk of HIV transmission is practically negligible* [27]. *Therefore, the recommendation of the European Renal Best Practice*

is to determine anti-HIV at the beginning of dialysis treatment and when patients are to be transferred from one to another dialysis center, although this is not necessary every six months [33,34]. *The Croatian Society for Nephrology, Dialysis and Transplantation considers that this opinion by the ERBP working group on Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for preventing infection transmission in hemodialysis units should be adapted to Croatian conditions. Since we believe that there is room for improvement in the implementation of CDC guidelines in dialysis centers and reduction of nosocomial transmission, and are prompted by our own experiences with a large proportion of HCV-positive patients 15 years ago, we recommend the monitoring of the viral status of hemodialysis patients every six months.*

- In HIV-positive patients, it is necessary to quantify the viral load (HIV RNA) every six months or more often, as needed (1C).

Commentary

- *HIV viremia should be determined once a year according to the infectious diseases recommendations (1A). However, due to the increased risk of nosocomial transmission of HIV owing to extracorporeal circulation during the hemodialysis procedure, we believe that it is necessary to determine the HIV viremia of HIV-positive patients on hemodialysis every six months. In cases of patient noncompliance and suspected irregular intake of therapy (that increases the possibility of developing antiretroviral-drug-resistant HIV), which can result in increased viremia and contagiousness, HIV viremia should be determined immediately.*
- HIV-positive patients should be dialyzed with a separate hemodialysis machine (in addition to providing a backup machine in the event of breakdown) in an isolated area. Alternatively, they can be dialyzed in an area for hemodialysis of HCV-positive and/or HBV-positive patients (1B).

Commentary

- *Although the KDIGO guidelines, opinion of the ERBP, and recommendations of the Infectious Disease Society of America do not endorse separate hemodialysis machines for HIV-positive patients (Level B of evidence for separate machines, Level C for an isolated area* [*27-29*])*, cases of the transmission of HIV among patients in the dialysis centers of developing countries have been recorded due to failure to comply with the CDC guidelines* [35,36]. *Therefore, our recommendation is that the dialysis of HIV-positive patients should be conducted using separate dialysis machines in isolated areas.*
- In the case of coinfection with HBV, hemodialysis should be performed in a HBV-positive area, and in the case of coinfection with HCV, in a HCV-positive area.
- HIV-positive patients should be vaccinated against HBV and HAV (1A).
- Trained personnel should be provided during the hemodialysis procedure (medical technician/nurse, cleaning staff), together with strict compliance with the general measures for the prevention of blood-borne infections (1A).

Commentary

- *The standard precautions for protection from pathogens are based on the principle that blood, bodily fluids, excretions* (*except perspiration*) *and mucous membranes can contain transmissible infectious agents. These precautions are designed to protect patients and healthcare personnel, and include hand hygiene, the use of adequate protection (gloves, masks, goggles and aseptic techniques in order to reduce patient exposure to microorganisms), procedures for sharps/infectious waste, spilled blood and bedding; routine cleaning of the hospital environment and the immunization of personnel. These measures should be especially carefully implemented in dialysis centers, owing to extracorporeal circulation during the HD procedure (1C).*
- *Nevertheless, we cannot be certain that all these measures will be implemented in their entirety* [37].
- Acute hemodialysis should be performed in separate areas of intensive care units on continuous dialysis/ hemofiltration machines (with the dialysis solution and dialysate in a closed system) or hemodialysis machines with a reservoir containing prepared solution for hemodialysis (Genius) (1B).
- Blood and other specimens from HIV-positive patients in institutions, the Department of Public Health or other public health institutions should be transported in leak-proof PVC containers with well fitted lids and labeled "B20". Specimens sent outside an institution should be conveyed by medical transport, not by public transportation or mail, in additional packaging (small wooden boxes).
- There should be good and prompt cooperation with the National Referral Center of the Ministry of Health for the Diagnosis and Treatment of HIV Infection (contact telephone 2826 227 or 2826 206, e-mail: bfm@bfm.hr) for rapid diagnosis and professional assistance in case PEP is needed. In the event of a needlestick involving the blood of a HIV-positive patient, PEP should begin as soon as possible, preferably within 24 hours, but no later than 72 hours after the incident, and continue for four weeks. Highly active antiretroviral therapy (HAART) should be adjusted according to the

therapy being received by the HIV-positive patient in consultation with the attending infectious disease specialist at the Dr. Fran Mihaljevic University Hospital for Infectious Diseases [17] (1A).

Conclusion

HIV is an important public health problem, which poses challenges to experts and healthcare personnel in cases of renal failure and the management of renal replacement therapy. The majority of these patients are on hemodialysis, while a significantly smaller number are on peritoneal dialysis or have received transplants. Healthcare personnel should be aware of the risk of occupational exposure to blood-borne infection in their daily work, and are expected to comply with all the measures that can prevent their exposure to blood, other bodily fluids and tissues that may contain potentially blood-borne infectious pathogens. The dialysis procedure for HIV-positive patients characterized by the extracorporeal circulation of blood presents a risk for inoculating the virus in the event of a needlestick incident, although the seroconversion risk after needlestick injuries is 0.3%, while the risks of seroconversion for hepatitis B and C are significantly higher: 2% for HCV and as high as 6-30% for HBV. Postexposure prophylaxis with antiretroviral therapy for four weeks significantly lowers the risk of seroconversion even further.

Conflict of interest statement. None declared.

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BANTAO Journal 2016; 14(1): 8-10

BJ

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Review article

MicroRNA in kidney disease

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Abstract

Clinical and laboratory findings of kidney disease in an adult may find an explanation in kidney functional and/or structural abnormalities that already existed during infancy and childhood, but that may have been missed or underdiagnosed.

All the cardiovascular abnormalities that occur in adults with chronic kidney disease are also present in children with chronic kidney disease. Complications in childhood chronic kidney disease will have consequences well beyond pediatric age and influence outcomes of affected young adults with disease. Kidney dysfunction appears early in the course of kidney disease and has been observed in children and adults with chronic kidney disease, condition characterised with kidney fibrosis. Transforming growth factor beta is recognized as a major mediator of kidney fibrosis. New evidence illustrates the relationship between transforming growth factor beta signaling and microRNAs expression during kidney diseases development.

MicroRNAs play important roles in kidney development and kidney diseases; they are naturally occurring, 22-nucleotide, noncoding RNAs that mediate posttranscriptional gene regulation. Dysregulation of miRNA expression is an indicator of several diseases including chronic kidney disease. Targeting microRNAs should be a therapeutic potential to ameliorate the disease related to fibrosis. The discovery that circulating miRNAs are detectable in serum and plasma, and that their expression varies as a result of disease, presents great potential to be used as biomarkers in kidney disease prevention and diagnosis.

Keywords: *kidney disease, microRNA*

Introduction

There are five important risk factors for chronic kidney disease (CKD): physical inactivity, high salt intake, smoking, diabetes and hypertension [1]. We have studies on prevention of CKD and its complications at the level of the general population, and at the level of those at high risk for CKD or CKD complications, but we have not enough information about impact of microRNA in CKD patients, both in pediatric and adult age. Some of the typical characteristics of pediatric CKD, such as the etiology or cardiovascular complications, do not only influence on the health of the pediatric patient, but also have an impact on the life of the adult age which is often under-recognized. All the cardiovascular abnormalities that occur in adults with CKD are also present in children with CKD. Despite similarities to the adult, CKD in children presents unique features, mostly preventable if recognized. In this review, we discuss the implications of microRNA in clinical diagnostics of early-onset CKD to prevent kidney fibrosis.

Chronic kidney disease in children

The most common etiologic categories of CKD in children are congenital anomalies of the kidneys and urinary tract (CAKUT), steroid-resistant nephrotic syndrome (SRNS), chronic glomerulonephritis and ciliopathies [2,3]. More than 200 genes are recognized as causative in children with CKD [3]. It is possible to address specific etiologic questions in 20% of children with early-onset CKD by selecting an appropriate panel of genes on the basis of the clinical phenotype of the patient and on a precise diagnostic suspicion [3]. The genetic background of patients with CKD is much more complex than we expected and besides disease-causing genes, a number of other genes are now recognized as playing an important role [3]. MicroRNAs are endogenous small noncoding single-stranded RNAs that regulate gene expression at the post-transcriptional level. MicroRNAs bind to the messenger RNAs of various genes and lead to their degradation. Some specific microRNAs called miR-193a inhibited the transcript for the Wilms tumor protein (WT1) in podocytes and therefore inhibited the expression of a variety of WT1-controlled genes that are important for podocyte function, such as nephrin.

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Premature children and impact on adult chronic kidney disease

Minor reductions in nephron numbers that are seen in low-birth weight and small for gestational age newborns are emerging as important predisposing factors to CKD [4]. It is very important that in humans all of the branches of the ureteric bud (UB) and the nephrons are formed by the 32nd to 36th week of gestation. The metanephros arises from the reciprocal interaction of two structures, UB and the metanephric mesenchyme (MM). These structures are not yet mature and will continue to grow and differentiate even after birth, during the perinatal period, as the generation of Henle's loop occurs [5]. While growing, UB generates the portion of the nephron from the renal papilla to the collecting ducts system of the mature kidneys. The capacity of generating new nephrons is lost at the time of birth so that human kidneys have an estimated number of nephrons of one million per kidney or more [6,7], proportional to body mass [5]. It is an important issue for all nephrologists as the number of premature children continues to grow [4,7]. Secondary sclerosis induced by the adaptive response to nephron loss occurs when there is a reduction in renal mass due to congenital absence or reflux nephropathy and ischemia [2]. Targeting microRNAs should be a therapeutic potential to ameliorate the disease related to fibrosis.

Pediatric obesity and chronic kidney disease in adults

Together with the exploding burden of pediatric obesity both are destined to significantly change the relative distribution of the causes of CKD in the early age [8,9]. An increase in the incidence of chronic kidney disease and hypertension has been parallel with the epidemic of obesity, and obesity and metabolic syndrome were independent predictors of renal injury. The pathophysiology of obesity related hypertension includes activation of sympathetic nervous system, renin angiotensin aldosterone system, hyperinsulinemia and inflammation. The body mass index (BMI) has been used to define obesity based on health risk factors in adult individuals. The National Institute of Health (NIH) determined an adult with a BMI of 25-29.9 as overweight and >30 as obese. The criteria used to define overweight or obese children have varied: based on the Centers for Disease Control and Prevention (CDC) growth charts defined children with >85th percentile BMI to be overweight and BMI >95th percentile to be obese with 10% of infants and <2 years old with a weight-for-height ≥95th percentile, 17% of children aged 2-19 years old ≥95th percentile, and 32% ≥85th percentile of BMI for age [10]. Excess weight gain appears to be a major risk factor for chronic kidney disease and hypertension in children (adults in future). Increased awareness is needed in children for early diagnosis of obesity and implementation of lifestyle modifications. Secondary focal segmental glomerulosclerosis (FSGS) usually results from an adaptive response to glomerular hypertrophy and hyperfiltration. Elevated microRNA-193a expression was found in glomeruli from patients with secondary FSGS, but not in glomeruli from healthy controls or patients with minimal change disease, IgA or membranous nephropathy [11].

MicroRNA and chronic kidney disease

Results from clinical and experimental animal studies demonstrate that miRNAs play essential roles in the pathogenesis of kidney diseases [11,12]. MicroRNAs (miRNAs) are naturally occurring, 22-nucleotide, noncoding RNAs that mediate posttranscriptional gene regulation. MiRNAs play an important role in many biological processes, including differentiation and development, cell signaling, and response to infection by regulating genes involved in these processes [12]. Patients with different types of CKD progressively lose their kidney functions and develop glomerular sclerosis and interstitial fibrosis, characterized by renal fibrosis. Transforming growth factor beta (TGF-β) is recognized as a major mediator of kidney fibrosis (stimulate the accumulation of extracellular matrix (ECM) proteins and impair normal kidney function). Evidence illustrates the relationship between TGF-β signaling and miRNAs expression during kidney diseases development [13]. The expressions of several miRNAs were up-regulated by TGF-β signaling pathway, such as miR-21, miR-29, miR-192, miR-200, and miR-433, in which miR-21, miR-192, and miR-433 are reported to be positively induced by TGF-β signaling, and they play a pathological role in kidney diseases [13]. Members of both miR-29 and miR-200 families that are inhibited by TGF-β signaling protect kidneys from renal fibrosis by suppressing the deposition of ECM and preventing epithelial-to-mesenchymal transition. The abundance of miR-21 is low in normal kidneys, and is greatly increased in both patient samples of kidney diseases and animal models of CKD and acute kidney injury and diabetic nephropathy, and it presents potential to be used as biomarkers in disease prevention and diagnosis [13].

Discussion

All the cardiovascular abnormalities that occur in adults with CKD are also present, to some extent, in children with CKD. As in adults, endothelial dysfunction and fibrosis appear early in the course of kidney disease and have been observed in children with CKD.

The primary causes of chronic kidney disease (CKD) in children differ from those of CKD in adults. In the USA the most common diagnostic groups of kidney disease before the age of 25 years are congenital anomalies of the kidneys and urinary tract, steroid-resistant nephrotic syndrome, chronic glomerulonephritis and renal cystic

ciliopathies, which together encompass >70% of early-onset CKD diagnoses. Findings from the last decade suggest that early-onset CKD is caused by mutations in any one of over 200 different monogenic genes. Use of genetic analyses in patients with early-onset CKD will provide patients a molecular genetic diagnosis, and might have consequences for personalized approaches to the prevention and treatment of CKD [14].

MicroRNAs could be useful as early biomarkers of kidney disease. Targeting miR-21 should be a therapeutic potential to ameliorate the disease related to fibrosis because inhibition of miR-21 is effective in decreasing fibrosis in animal models of heart, lung, and kidney diseases and new data show effect of antifibrotic microRNA in diabetes-related kidney fibrosis [15].

Conclusion

Conditions that alter nephron development or trigger nephron damage during neonatal, juvenile, or adult stages of life are important in development of CKD in early and adult age. Pediatric CKD share the basic pathophysiologic mechanisms with the same disease in the adult population. Kidney health depends on the complete integrity and functionality of the nephrons and their component parts developing in the early phases of life. There are new players like microRNA as biomarkers in diagnosis and prevention of chronic kidney disease in combating kidney fibrosis.

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Conflict of interest statement. None declared.

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Review article

Nephrin and Podocalyxin - New Podocyte Proteins for Early Detection of Secondary Nephropathies

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Abstract

In the last two decades a great progress was observed in understanding of podocytes, their specific structure and function identifying many specific podocyte proteins, such as nephrin and podocalyxin. Podocytes form the final barrier to plasma proteins leakage. Nephrin as a main component of the filtration diaphragm forms a physical barrier while podocalyxin as sialoglycoprotein forms an electrostatic barrier. Podocyte damage, i.e. podocytopathies and their loss through urine-podocyturia, are crucial in pathogenesis and progression of nephropathies with proteinuria as main clinical manifestation. In podocytopathies, nephrin and podocalyxin appear in the urine before proteinuria and microalbuminuria which were previously considered as earliest markers of nephropathies. Nephrinuria and podocalyxuria indicate damage of the podocytes on glomerular level and/or presence of apoptotic and necrotic podocytes in urine. These urinary markers are also important in early diagnosis of secondary nephropathies such as diabetic, lupus and hypertensive nephropathy as the most common causes of end-stage renal failure (ESRF). These markers are also important in the prediction of preeclampsia, which is the most common complication in pregnancy. In this review we elaborate in dept the main structural and functional features of podocytes and their specific proteins, nephrin and podocalyxin, summarizing the recent literature data on their importance in the early diagnosis of the most common secondary nephropathies.

Keywords: nephrin, podocalyxin, podocytes, podocytopathies, secondary nephropathies

Introduction

Nephrin and podocalyxin are specific podocyte proteins. Podocytes are terminally differentiated cells creating

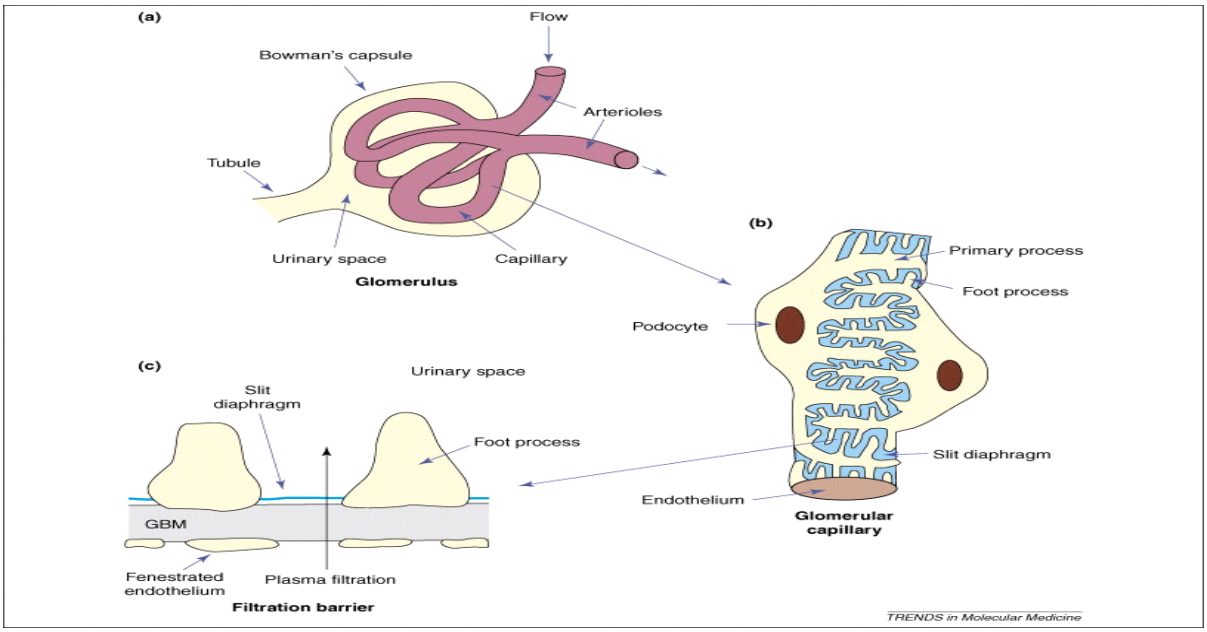

Fig. 1. a) Structure of the glomerulus b) structure of the glomerular filtration barrier c) structure of the slit diaphragm [3]

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the visceral epithelial layer of the glomerulus. The glomerulus is a network of capillary loops surrounded by the Bowman's capsule and performs the first step of blood filtering. As a selective filter, based on its size and charge, the glomerulus allows passage of materials that circulate through blood, creating primary ultrafiltrate. This selectivity is based on the structural integrity of the three main components of the glomerular filtration barrier: the fenestrated vascular endothelium, the glomerular basement membrane (GBM), and the visceral epithelium overlying the GBM. Podocytes as a part of glomerular filtration barrier have foot processes that encircle the GBM. The interdigitating foot process of podocytes is joined by a slit diaphragm. Slit diaphragm is described as a zipper-like interaction of membrane proteins such as nephrin molecules between neighboring podocyte foot processes. The slit diaphragm has an essential role in size selectivity of the glomerular filtration barrier [1,2]. Figure 1 illustrates the structure of the glomerulus, glomerular filtration barrier and filtration diaphragm also called slit diaphragm.

Nephrin - (NPH), structure and function

Nephrin was first discovered in 1998 as a mutant product of NPHS1 gene, which was first cloned by Kestila and colleagues in children with Finnish type of congenital nephrotic syndrome-(Congenital nephrotic syndrome of the Finnish type-CNF). CNF is an autosomal recessive disease characterized by massive proteinuria in utero and symptoms of nephrotic syndrome (hypoalbuminemia, hyperlipidemia and swelling) that occur in the first days after birth. Renal biopsy in these children shows obliteration of podocyte foot processes and lack of slit diaphragm [4]. In mice inactivation of NPHS1 gene causes massive proteinuria and death in the first 24 hours after birth [5]. This suggests the importance of nephrin in the process of glomerular filtration as a structural component of the slit diaphragm. Nephrin is exclusively expressed by podocytes but also may be expressed in brain, lymphoid tissue, heart, testis, placenta and β cells of the Langerhan's islets of the pancreas [6]. NPHS1 gene is located on chromosome 19 (19q13.1), organized in 29 exons [7]. Nephrin has 1241 amino acids with molecular weight of 180 kDa (135 kDa without posttranslational modification). It is a transmembrane glycoprotein belonging to the immunoglobulin superfamily of cell-adhesion receptors. It contains eight extracellular Ig like domains, followed by a fibronectin type III-like module, a short transmembrane domain and a cytoplasmic C-terminus. Cytoplasmic segment contains nine tyrosine residues which are phosphorilated in interaction with other nephrin molecules, a process which is very important in the intracellular signaling. Nephrin has three cysteines in the extracellular segment that are important in the podocyte foot process interaction, described as zipper interaction in the center of the slit diaphragm. As a major component of the slit diaphragm, nephrin forms the physical barrier to plasma proteins [8]. Nephrin is important in organization and maintainance of integrity of podocyte cytoskeleton and as a signal molecule, through several signaling pathways, regulates the shape and structure of the podocytes and slit diaphragm [9,10]. Nephrin is located laterally on the foot processes and it is a major component of the slit diaphragm (Figure 2).

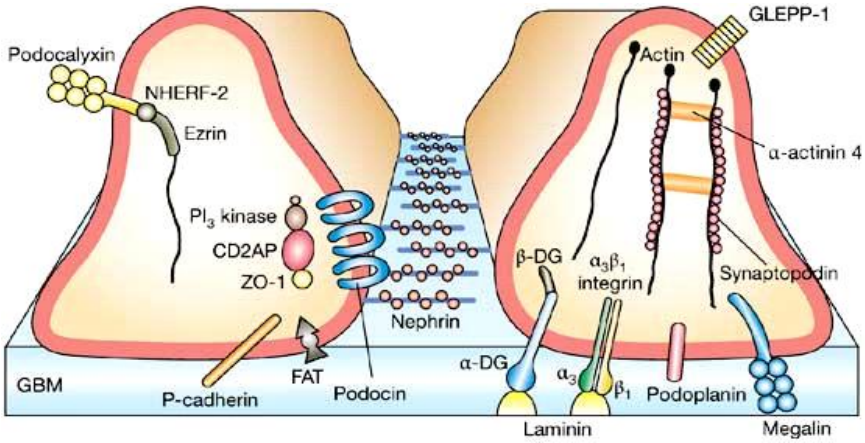

Fig. 2. Arrangement of the podocyte foot process and slit diaphragm proteins. Localization of nephrin and podocalyxin in podocytes [11]

Podocalyxin - (PODXL), structure and function

Podocalyxin is an anionic transmembrane protein localized at the apical surface of the podocytes (Figure 2); it may also be expressed on the surface of hematopoietic progenitor cells, vascular endothelial cells, neurons and numerous tumor cells [12]. Podocalyxin is a main sialoglycoprotein of the podocyte glycocalyx, which primarily has been identified in mice, and later in the humans. As sialoglycoprotein, podocalyxin forms the

electrostatic barrier to plasma proteins. Podocalyxin is a member of the CD34 (Cluster of Differentiation 34) family with a molecular weight of 140 kDa. The extracellular part of podocalyxin is rich in serine, threonine and proline, containing O-glycosylated, sialysed and N-glycosylated domain. The intracellular part has several phosphorylation sites along one protein interaction domain, through which domain, podocalyxin interacts with Na / H exchanger regulatory factor 1 and 2 (NHERF1 and NHERF2) [13-16]. Podocalyxin interacts with ezrin molecules that are part of the podocyte cytoskeleton [17]. Podocalyxin is important in the development of glomeruli and mice that do not express podocalyxin were found to have disrupted architecture of the podocytes and showed absence of foot processes and slit diaphragm [18]. Since sialomucin has cell-cell antiadhesive effect, which is important to keep the filtration pores open and prevent conglomeration of the parietal and visceral epithelial layer of Bowman's capsule. All these processes are important to keep the normal glomerular filtration [14]. Podocalyxin is a major hallmark of podocyte phenotype and preferred protein marker for the detection and identification of podocyte with immunofluorescence technique in bioptic material and urine.

Podocytopathies

In recent years the attention of scientists, especially nephrologists and pathologists, has been focused on the role of podocytes in the pathogenesis of glomerulopathies or nephrotic syndrome. Furthermore, a great progress has been achieved in the study of the biology of podocytes, their function and mechanisms of their impairment. The response to injury of podocytes as highly differentiated cells is not typical and once they are damaged, there is a progression towards glomerulosclerosis [19,20]. The etiology of podocytopathies may be different: immunological, mechanical, infectious, metabolic, toxic, genetic etc. Reaction of podocytes to etiological factors can be different:

1. foot process effacement without changes in the number of podocytes,
2. apoptosis and loss of podocytes,
3. changes in development of podocytes and their proliferation,
4. de-differentiation.

Hence, based on the histological changes there are four types of podocytopathies:

1. minimal change nephropathy with normal number of podocytes,
2. focal segmental glomerulosclerosis with podocytopenia,
3. diffuse mesangial sclerosis with low proliferative index,
4. collapsing glomerulopathy with high proliferative index [21].

Diagnosis of podocytopathies includes morpho-pathological examination by light and electron microscopy of bioptic kidney material, immunohistochemistry-identification of specific proteins of podocytes in the bioptic material, detection and quantification of circulating biomarkers, detection and quantification of urinary biomarkers (Enzyme-linked immunosorbent assay (ELISA), Western blot, immunoflorescence, flow cytometry, mass spectrometry and Reverse transcription polymerase chain reaction (RT-PCR) for detection of mRNA of specific podocyte proteins), genetic analyses in hereditary podocytopathies [2,22].

Diagnostic relevance of nephrin and podocalyxin in secondary nephropathies

Specific podocyte proteins, nephrin and podocalyxin are relatively new urinary markers for detection of nephropathies. The diagnostic advantages of these markers are: high specificity, non-invasive detection, monitoring of nephropathies, and they can be measured by relatively simple and sensitive methods such as ELISA. This is in agreement with the statement of Walter Piering, MD: "Urine is the liquid biopsy of the kidney". Relevance as an early diagnostic marker is reserved for secondary nephropathies such as diabetic, lupus, hypertensive and preeclampsia. Early nephropathy detection may allow timely treatment and prevention for the need of renal replacement therapy as well as significant reduction of complications and mortality in these patients.

Nephrinuria and podocalyxuria in diabetic nephropathy

The podocytopathies play a critical role in the early functional and structural changes of diabetic kidney disease [23]. In diabetic nephropathy (DN) there is a decreased podocyte number and/or density as a result of apoptosis or detachment, GBM thickening and a reduction in nephrin protein in the slit diaphragm with podocyte foot process effacement [24]. Pathohistologically, DN begins with hypertrophy and hyperactivity of podocytes which lead to damage of the slit diaphragm. In advanced stage there is an ensuing atrophy of podocytes, narrowing of the foot processes, fragmentation and detachment of podocytes from GBM. All these changes lead to proteinuria [24,25]. Thus, a significant increase of foot processes width is noted in histomorphological studies in diabetic patients with advanced nephropathy and proteinuria [26]. Diabetic Pima Indians with clinical nephropathy have fewer glomerular epithelial cells compared to those with less-advanced renal disease and also there is a correlation between the number of podocytes and the degree of proteinuria. In this study, it has been shown that the number of glomerular podocytes is the best predictor of glomerular damage in diabetics [27]. In another cohort study including patients with type 2 diabetes a significant reduction was found in the number of glomerular podocytes

even in the normoalbuminuric patients [28]. In one Japanese study podocytes were detected in the urine in 53% of microalbuminuric patients and 80% of macroalbuminuric patients with type 2 diabetes. In the same study, trandolapril reduced urinary albumin excretion, as well as urinary podocytes in patients with DN. This study showed that podocyturia can be a useful marker for disease activity and trandalopril can be useful drug in DN [29]. All these studies suggest that morphological changes in podocytes are present before appearence of proteinuria. In the study of Patari, nephrinuria was present in 30% of normoalbuminuric, 17% of microalbuminuric, 28% of macroalbuminuric, 28% of new-microalbuminuric patients and 0% in control subjects. This study reconfirmed that nephrinuria may have a prognostic value in DN [30]. It was also observed that the number of urinary podocalyxin-positive elements (PCX+EL) may be significantly increased in the early course of DN compared to health controls and correlated well with the clinical diagnosis of DN, especially in the stage of normoalbuminuria [31]. Hara *et al.* found that urinary podocalyxin was significantly higher in 53.8% of normoalbuminuric, 64.7% of microalbuminuric and 66.7% of macroalbuminuric patients with DN. Thus, podocalyxin measured in urine by the ELISA method can be used as a marker for early detection of diabetic nephropathy [32].

Nephrinuria and podocalyxuria in preeclampsia

Preeclampsia is a pregnancy-specific disorder associated with significant maternal-fetal morbidity and mortality. Hypertension (>140/90 mm Hg) and proteinuria (>300 mg in a 24-hour urine) are the main clinical manifestations of preeclampsia, which usually occurs after 20 weeks of gestation. Preeclampsia is a secondary nephropathy that includes damage to podocytes and their loss on glomerular level that leads to proteinuria. One study demonstrated that podocyturia was present in pregnant women who developed preeclampsia, at a time when hypertension and proteinuria were absent, suggesting that podocyturia may serve as a predictive marker in preeclampsia. In addition, there was a positive correlation between the number of podocytes and the degree of proteinuria, suggesting that podocyte loss may be related to the onset and severity of proteinuria [33]. In a study of Garovic *et al.* podocyturia exhibited 100% sensitivity and 100% specificity in the diagnosis of preeclampsia [34]. On the other hand, in the study of Wang urine nephrin and podocalyxin levels were found significantly higher in women with preeclampsia compared to those in normal pregnants [35]. Son *et al.* also found a positive correlation between urinary nephrin and proteinuria, creatinuria and diastolic blood pressure in preeclamptic women, which indicate the importance of nephrin in the pathogenesis of proteinuria in preeclampsia and the ability to be a reliable indicator of renal damage [36]. On the other hand, Jim *et al.* found that nephrinuria had 57% sensitivity and 58% specificity as a diagnostic tool in preeclampsia [37]. In pregnant women with preeclampsia and eclampsia in Paraguay elevated concentrations of podocalyxin in urine were found regardless of the presence of proteinuria. In fact, podocalyxin concentration in urine correlated with the degree of damage to podocytes [38]. In the same study the quantification of urinary podocalyxin was made by the ELISA method as a relatively inexpensive, simple and also a useful method for detecting damage of podocytes.

Nephrinuria and podocalyxuria in hypertensive nephropathy

Hypertensive nephropathy or hypertensive nephrosclerosis is a medical condition referring to damage to the kidney due to the high blood pressure. This is the second most common cause of ESRF [39]. Podocyte damage is important in the pathogenesis of hypertensive nephropathy, but human data on the mechanisms of damage to podocytes in hypertension are yet limited. However, it is supposed that mechanical damage of podocyte cytoskeleton is crucial in pathogenesis of the hypertensive podocytopathy [40]. Patohistological examination of bioptic material in hypertensive adult Africans showed that 13% of them presented with typical focal segmental glomerulosclerotic lesions [41]. The study of Wang demonstrated the presence of podocytopenia on glomerular level and reduced intrarenal gene expression of podocyte-associated molecules in patients with hypertensive nephropathy. These findings were in correlation with renal function and the degree of renal fibrosis, suggesting that podocyte loss may play an important role in the pathogenesis of hypertensive nephropathy [42].

Nephrinuria and podocalyxuria in lupus nephropathy

Systemic lupus erythematosus (SLE) is an inflammatory autoimmune disease characterized by the production of antinuclear antibodies. As a multi-organ disease SLE involves the kidney. Lupus nephritis (LN) patients present with proteinuria that has generally been associated with immune complex deposition in the glomerular capillary wall and endo-capillary proliferation and inflammation [43]. A decreased number of glomerular podocytes, an association between proteinuria and decreased podocyte numbers in lupus glomerulus and an increased excretion of urinary podocytes in patients with lupus nephritis have been recently found [44]. Interestingly, it has also been found that in patients with SLE there are increased urinary levels of podocyte proteins, nephrin and podocalyxin. Thus, urinary podocalyxin/creatinine ratio may be used as a non-invasive marker for pathological impact of SLE on the kidney [45].

Conclusion

Nephrin and podocalyxin are relatively new markers for detection of podocytopathies. They appear in urine before microalbuminuria and proteinuria and therefore may be useful in the early diagnosis of secondary nephropathies. They have a great importance as auxiliary tools in the diagnosis, differential diagnosis and prognosis in primary nephropathies, reducing the requirement of indications for renal biopsy. The meaning of early diagnostic markers is reserved for secondary nephropathies because in the primary nephropathies proteinuria is often the first clinical manifestation. Nephrin and podocalyxin are important as markers for early detection of secondary nephropathies such as diabetic, lupus, and hypertensive, which are the most common causes of end-stage renal disease. These markers are also important in the prediction of preeclampsia as a leading cause of complications during pregnancy. Early detection of these secondary nephropathies will allow timely treatment and reduce complications and mortality. The advantage of these urinary markers is high specificity and sensitivity for secondary nephropathies and ability to be measured by relatively inexpensive, simple and non-invasive methods. Nephrin and podocalyxin have a promising potential as diagnostic and prognostic markers for clinicians and researchers, but more extensive clinical research is required to assess their true diagnostic and prognostic value. These markers are also new potential therapeutic targets in renal diseases.

Conflict of interest statement. None declared.

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Original article

Lung Cancer in Renal Transplant Recipients

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Abstract

Introduction. Although the incidence of malignancy has increased after solid organ transplantation, data on lung cancer in this group of patients is scarce. The aim of this study was to determine clinical characteristics and outcome of patients who developed lung cancer after renal transplantation.
Methods. Among a cohort of 1658 patients who received a transplant at our institution and were followed-up between 1973 and 2014, five patients developed lung cancer. We analyzed risk factors, transplantation characteristics, treatment options and survival.
Results. Lung cancer was diagnosed in 5 patients (0.3%). Time to diagnosis after the transplant procedure ranged from 26 to 156 months (mean 115 months). All of them had a smoking history. Tumors were classified as IIB (20%), IIIA (40%), and IV (40%). Histological types included adenocarcinoma (80%) and there was one case of sarcomatoid carcinoma (20%). One patient had concomitant thyroid papillary carcinoma. Radiotherapy was applied in 2 patients, 2 underwent chemotherapy (erlotinib and combination of carboplatinum and etopozide in one patient each), and 2 died within one month after the diagnosis from disseminated malignant disease. Patients with stage IIIA survived 14 and 24 months after the diagnosis. The patient with sarcomatoid cancer underwent thoracotomy with a complete resection, lost his graft function and died 7 months after the diagnosis.
Conclusion. Lung cancer is relatively rare malignancy in renal transplant recipients, but associated with high mortality. Smoking is a significant risk factor, thus smoking cessation should be promoted among renal transplant recipients, as well as regular screening for lung cancer.

Keywords: lung cancer, kidney transplantation, smoking

Introduction

Renal transplantation is a life-prolonging treatment for end-stage kidney disease patients, but it increases risk for developing cancer, mostly because of medications administered to suppress the immune system and prevent rejection of the organ [1-4]. In developed countries most common posttransplant malignancies are skin cancer, Kaposi's sarcoma, renal and thyroid cancer and lymphoproliferative disorders [5,6]. Although the incidence of malignancy has increased after solid organ transplantation, data on lung cancer in this group of patients is scarce.
The aim of this study was to determine clinical characteristics and outcome of patients who developed lung cancer after renal transplantation.

Materials and methods

In this retrospective study, hospital files of 1658 renal transplant recipients who received renal allograft at the University hospital centre Zagreb between 1973 and 2014 were reviewed. We obtained data about smoking history, dialysis vintage, type of immunosuppression, time after transplantation until development of malignancy, tumor classification, histological type, treatment approach and outcome.
Descriptive statistical analysis was used. Data were compared with results from other countries.

Results

Patients' characteristics, treatment and outcome

Among a cohort of 1658 patients who received a transplant at our institution and were followed-up between 1973 and 2014, 5 patients developed lung cancer.
Time to diagnosis after the transplant procedure ranged from 26 to 156 months (mean 115 months). All patients who developed lung malignancy had a long-term (more than 20 years) smoking history.

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Immunosuppressive protocol included cyclosporine in 3 and tacrolimus in 2 patients, with mycophenolate mofetil and steroids. Three patients received basiliximab induction, two were transplanted without induction.
Tumors were classified as IIB (one patient), IIIA (two patients), and IV (two patients). Histological types included adenocarcinoma (n=4; 80%) and there was one case of sarcomatoid carcinoma (n=1; 20%). One patient had concomitant thyroid papillary carcinoma.
Treatment protocol varied depending on the severity of disease. Two patients were treated with radiotherapy, and two with chemotherapy (erlotinib in one patient, and a combination of carboplatinum and etopozide in the other). The patient with sarcomatoid carcinoma was treated with thoracotomy with complete resection.
The outcome was poor. Two patients died one month after the diagnosis. Patients with stage IIIA survived 14 and 24 months after the diagnosis. The patient with sarcomatoid cancer had lost his graft function and died 7 months after the diagnosis.
All patients refused to stop immunosuppressive treatment and undergo graphtectomy. They were switched from cyclosporine or tacrolimus to mTOR-based immunosuppressive protocol.

Lung cancer in national registries or studies

Few studies have focused on lung cancer in renal transplant recipients. In Table 1 we present the incidence in transplant population in Croatia and other countries.

Table 1. Incidence of lung cancer in transplant recipients in different countries [7-10]

Country	Our cohort	Turkey	China	England	Australia	New Zealand
Number of recipients	1 658	4 000	3 462	25 104	3 129 083	605 538
Time interval (years)	41	4,5	40	27	11	11
Incidence (%)	0.3	6	0.8	1.4	1.2	1.3

Discussion

The incidence of lung cancer has been particularly increased in recipients of heart and lung transplants, which may be related to the strong influence of cigarette smoking on the development of heart and lung diseases [11]. However, lung cancer may complicate posttransplant course after renal transplantation as well.
This study demonstrates that in our cohort of renal transplant recipients lung cancer is relatively rare malignancy, but has high mortality rate. Patients were diagnosed at advanced stage.
In the general population, non-small cell lung cancer accounts for about 85% of lung cancers and includes: adenocarcinoma which is the most common form of lung cancer among both genders; squamous cell carcinoma which accounts for approximately 25%, and large cell carcinoma which accounts for 10% of non-small cell lung malignancies. The remaining 15% of lung cancers are small lung cancer. Four patients from our cohort had non-small cell cancers and one was diagnosed with sarcomatoid carcinoma.
Significant differences may be noted among different countries. Based on data from the Croatian registry of malignant diseases in the general population, there were 2031 new cases of lung cancer in males and 722 in females in 2013. In the general public, lung cancer is the most common cancer in males, and third in females after breast and colorectal cancer, with the crude rate for males 98.3; for females 32.6, while total crude rate is 64.2 [12]. Thus, lung cancer that is frequent in the Croatian general population is rare in renal transplant population in our cohort of patients. Turkey has a very high prevalence of lung cancer among renal transplant recipients, while Croatia and China have low prevalence [7,8].

Conclusion

All patients who developed lung malignancy continued with smoking after transplantation despite the warnings from nephrologists. Since smoking represents the leading risk factor for development of lung malignancy we should encourage patients to quit smoking, and promote a screening program in this population for early discovery of lung cancer, with annual chest X-rays.

Conflict of interest statement. None declared.

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Original article

Prevalence and Causes of Proteinuria in Kidney Transplant Recipients: Data from a Single Center

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Abstract

Introduction. Proteinuria after renal transplantation increases the risk of graft failure and mortality. The aim of the study was to determine the prevalence and causes of proteinuria in kidney transplant recipients.

Methods. All kidney transplant recipients followed up in our clinic were included in the study. As a center protocol 24-hour urine collections were used to quantify protein excretion with 3-month intervals posttransplantation during the first year, and yearly thereafter. The etiology of chronic kidney disease and demographic characteristics of the study group were obtained from outpatient records. Data regarding the immunosuppressive regimens used, 24-hour proteinuria levels and creatinine clearences, new-onset hypertension, new-onset diabetes mellitus, rejection episodes, infections like cytomegalovirus (CMV) and polyoma (BK), and biopsy findings were noted.

Results. A total of 260 kidney transplant recipients (97 females, mean age 42.3±12.3 years) were evaluated. Median follow-up period was 36 months; 137 of all transplantations were from living donors. Mean age of donors was 42.7±15 years and 133 were female. Proteinuria with protein excretion ≥300 mg/d was present in 35.4% of patients. The most common cause of biopsy-proven proteinuria was transplant-specific conditions (acute rejection, and borderline changes).

Conclusion. The prevalence of proteinuria was 35.4%. The transplant-specific diagnoses were the most likely causes. Even in nonnephrotic ranges it was associated with decreased graft survival.

Keywords: renal transplantation, kidney graft survival, proteinuria

Introduction

Proteinuria is a well documented independent risk factor for progression of kidney disease, cardiovascular events, and increased mortality in both transplant and nontransplant populations [1,2]. Although the threshold to determine abnormal proteinuria in kidney transplant population is not clearly specified and although the low levels of proteinuria have been related to poor graft and patient survival, the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline on the care of the kidney transplant recipients suggested using the same values established for general population [1-4]. The prevalence of proteinuria varies from 7.5 to 45% in renal transplant patients, based on the threshold level to define proteinuria [1-5]. Recent reports have shown that posttransplantation proteinuria increases the risk of allograft failure by 2-to5-fold [3,5,6]. The origin of proteinuria in transplant patients primarily includes original renal disease that is associated with proteinuria (e.g. diabetic nephropathy or glomerulonephritis), recurrent or de novo glomerulonephritis, transplant-specific disorders such as rejections or transplant glomerulopathy, and drugs, especially mammalian target of rapamycin (m-TOR) inhibitors [1,3,7].

In this retrospective study we aimed to report the prevalence and etiology of proteinuria and its influence on graft function in kidney transplantation recipients in our center.

Materials and methods

In this retrospective study the records of 260 kidney transplant recipients were evaluated for the presence of proteinuria. Proteinuria was defined as ≥300 mg/d excretion which persisted for >6 months, and measured by 24-hour urine collection. The data regarding donor and the recipient demographic characteristics as well as clinical and laboratory variables were collected. The estimated glomerular filtration rate (eGFR) was determined by the modification of diet in renal disease [8].

Statistical analysis was performed using the SPSS for Windows, version 11.0 (SPSS, Chicago, IL). Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as percentage. Nonparametric variables were expressed as median (mini-

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mum-maximum). Categorical variables were analyzed by the chi-square and Fisher's exact tests. Comparisons between groups were analyzed by the Student's t-test, ANOVA; Mann-Whitney U, and Kruskal-Wallis tests, depending on the sample sizes and distribution of variables. Differences between matched groups were tested by the paired samples t-test, and Wilcoxon test. Bonferroni test was used for post-hoc analysis.

Results

Ninety-two (35.4%) kidney transplant recipients had proteinuria. The median value of proteinuria was 425 mg/d (300-1900). The median month of overt proteinuria was 24(3-204). The maintenance immunosuppressive protocol included calcineurin inhibitor (CNI) in majority of patients (82.6%). Sixteen out of 92 (17.4%) recipients used inhibitors of mammalian target of rapamycine (mTOR) in their immunosuppressive protocol. The demographic and clinical data of patients are given in Table 1.

Table 1. Demographic and clinical characteristics of the study group

Gender (F/M)	**42/50**
Recipient age (mean±SD)	43.5±12.1
Donor age (mean±SD)	43.8±15.1
Primary renal disease (%)	
Hypertension	26
Glomerular disease	25
Chronic pyelonephritis	12
Polycystic kidney disease	8
Other	29
Creatinine clearence at the time of overt proteinuria (mean ± SD, ml/min)	63±24.1
Immunosuppressive protocol	
CNI-based (%)	82.6
mTOR-based (%)	17.4

The distribution of causes of proteinuria on renal biopsies are shown in Figure 1.

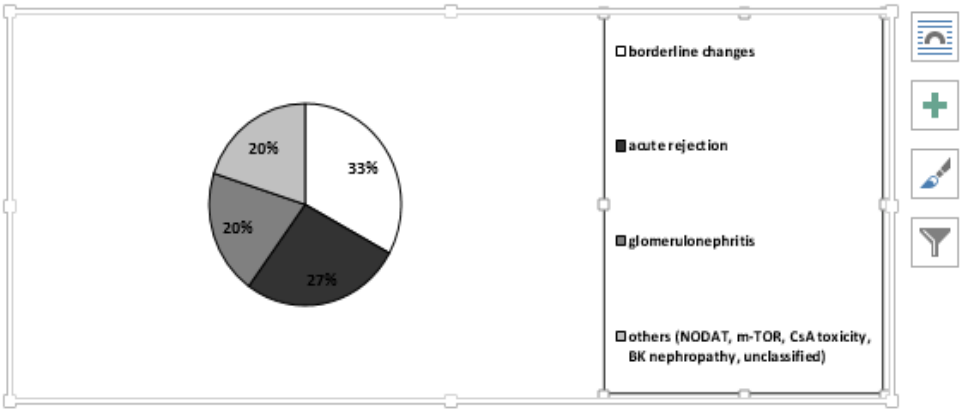

Fig. 1. Distribution of biopsy-proven etiology of proteinuria

The frequency of proteinuria in those under m-TOR inhibitor-based protocol was 39.4%, whereas in those under CNI-based protocol was 33.8%. Although the rate of proteinuria in m-TOR group was high, the difference was not statistically significant (p=0.35).

BK nephropathy (detected by serum viral load >4 log copies per ml) was diagnosed in 5.43% of patients (5 patients).

Mean e-GFR at the time of proteinuria was 63±24 ml/1.73m^2/min. Those without proteinuria had a significantly better mean e-GFR of 70±28 ml/1.73m^2/min (p=0.03).

The frequencies of new onset hypertension and diabetes in proteinuric patients were 44.2% and 42.3%, respectively.

Discussion

Proteinuria was implemented as an indicator of progression of kidney disease by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guideline on chronic kidney disease (CKD) [1-3]. Similarly, it is associated with progressive decrease in graft function, graft loss, and mortality in renal transplant recipients [1,5].

The prevalence of proteinuria varies from 7.5 to 45.0% depending on the criteria used to describe proteinuria in renal transplant patients, with the highest prevalence rates seen in thresholds just above the normal limit [1]. The amount of >150 mg/d at 1 year posttransplantation is detected in approximately 40% of patients [4]. Amer *et al*. [7] demonstrated that even at low levels (<500 mg/d) are significant prognostic factor at 1 year, independent of graft biopsy findings. In our study we demonstrated that over one-third of renal transplant patients (35.4%) had proteinuria, and transplant-specific causes were more commonly found on biopsies. Therefore, it can be accepted as a frequent complication of renal transplantation.

The pathological diagnoses varied between studies, depending primarily on the degree of proteinuria when biopsy was performed [1,3,9]. Overall, more common pathologies have been reported to be transplant-specific diseases, including transplant glomerulopathy, acute rejec-

tion, and borderline changes than glomerulonephritis (recurrent or *de novo*) [1-3,7]. However, in some studies but not in all, glomerular diseases have been shown to be more prevalent when the amount of proteinuria exceeds ≥1500 mg/d [7,10,11]. This finding has important implication when determining therapies to decrease proteinuria in kidney transplant recipients.

In our study glomerular diseases were found in 20% of biopsies. The most frequently detected type of glomerulonephritis was focal segmental glomerulosclerosis (62%). Graft survival is influenced by variable factors other than proteinuria, including donor type, donor and recipient age, and primary glomerular disease (e.g. hypertension, diabetes). Therefore, it is important to adjust such potential confounding variables before analyzing the association between graft survival and proteinuria. As a continuous variable proteinuria was proven to be associated with graft loss in several studies [3,5,7]. Amer *et al.* [7] showed that the risk of graft loss increased by 27% for each 1 g/d increase in protein excretion. The e-GFR values in the present study were found to be statistically lower in patients with proteinuria than in those without proteinuria. This finding was similar to the rates reported in other studies [1-3]. In a previous study from a different center in our country, Ibis *et al*. showed that patients with proteinuria had significantly lower graft survival rates than those without proteinuria (58.6% vs 80.4%, p=0.02), and proteinuria was significantly associated with cardiovascular diseases [5-7].

The use of mTOR inhibitors has been associated with proteinuria in kidney transplant patients. Although the prevalence rate was high in m-TOR group in our study population compared to CNI group, the difference was not significant (p=0.35). This can be attributed to the low number of patients in m-TOR group.

Major limitations to our study include: first, the study was a single-center design with a limited number of biopsy-proven diagnosis of proteinuric renal transplant recipients, which may restrain generalization, second, the data regarding pretransplantation presence of proteinuria from native kidneys could not be obtained, and third, we could not analyze the outcomes such as graft loss and death.

In conclusion, we demonstrated that proteinuria is a marker of poor prognosis in renal transplant patients. The goal of reduction of proteinuria by means of salt reduction and blood pressure control, diabetes regulation, use of renin-angiotensin-aldosterone blockers, and diagnosis-oriented therapies should be seriously taken into account during posttranplantation follow-up.

Conflict of interest statement. None declared.

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Original article

Factors that Influence Graft Function at 1-Year Posttransplantation and Correlation with Baseline Donated Kidney Function Measured with Radioisotopes

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Abstract

Introduction. Assessment of renal function is a crucial component of donor evaluation. The higher measured donor GFR is independently associated with a better allograft outcomes in living donor kidney transplantation (LDKT). Monitoring graft function and estimation of GFR is a recommended method for patients' follow-up in posttransplantation period. The aim of our study was to investigate the correlation of directly measured GFR of donated kidney with estimated GFR through creatinine-based formulas and to detect impact factors on the graft function at 12 months posttransplantation.

Methods. Fifty LDKT patients (related and non-related donors) with stable renal function in a period of 12 months after transplantation were included in our study. The mean recipient age was 30.7±9.6 years, and donor age 55.45±9.41 years. The mean directly measured donated kidney GFR was 47.61±5.72 ml/min. Graft function was estimated at 3, 6 and 12 months by 3 formulas: Cockcroft-Gault (C-G), MDRD 6 variables and Nankivell. Direct correlation of estimated with measured radiolabeled ^{99m}Tc DTPA GFR was performed. Various impact factors such as donor age, dialysis vintage and different calcineurin inhibitors as a part of immunosupression were evaluated.

Results. Estimated GFR at 12 months with MDRD, Cockroft Gault, and Nankivell formulas was 72.65±22.6, 94.25±36.42, and 81.78±17.89 ml/min, respectively. The highest estimated GFR was obtained with C-G formula at all three time points. The estimated allograft GFR did not correlate with directly measured GFR of donated kidney. Donor age well correlated with the graft function at 12 months. Allografts from standard criteria donors-SCD (<60 years) had better function than allografts form expanded criteria donors-ECD (>60 years). The highest GFR was estimated with C-G equation (106.08±39.26 ml/min), while GFR estimated with Nankivell was 86.86±15.30 ml/min, and with MDRD 79.67±20.28 ml/min, presenting patients in stage 2 of chronic kidney disease. Duration of hemodialysis treatment under 24 months showed better graft function estimated by C-G at 12 months (102.23±38.86 ml/min), compared to that above 24 months of HD (77.84±18.11 ml/min). Different type of calcineurin inhibitors did not influence on the graft function at any time point.

Conclusion. Creatinine-based formulas for estimation of the graft function did not correlate with directly measured function of the donated kidney with radiolabeled isotopes, nor between each other. Hence, the monitoring of the graft function should be done by a single formula in the posttransplantation period. Expectedly, a better graft function was observed in young donors (standard criteria) and in patients with shorter hemodialysis treatment.

Keywords: glomerular filtration rate, creatinine-based formulas, kidney transplantation

Introduction

Living donor kidney transplantation (LDKT) or cadaver transplantation is superior compared to keeping the patient on a dialysis treatment, and it represents a modality of choice for treatment of an end-stage kidney disease [1,2]. Superiority of a living donor transplantation compared to that from a deceased donor is visible though the shorter time of cold ischemia of the graft, better HLA matching, choice of a quality kidney and electivity during the surgery itself. At the same time, performing transplantation at the right time, that is to say the pre-emptive transplantation or shorter dialysis treatment is a precondition for long-term survival of both, the graft and the recipient. The patients who are kidney transplant

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candidates are well informed and aware of these advantages, and at the same time they represent a motive for kidney donation among closer and distant family members and spouses. Living donor transplantation is accompanied with very low short-term or long-term risk for the kidney donors themselves [3].
The assessment of the kidney function is the basic component when evaluating the potential kidney donors. Glomerular filtration rate (GFR) assessed through inulin clearance still remains to be the gold standard in the assessment of kidney function. At the same time, the other exogenous markers for direct measurement of GFR as the radiolabeled isotopes (^{99m} Tc DTPA or ^{125}I Iodthalamate) and non radioactive contrast agents (Iodthalamate or Iohexol) are considered to be the gold standard in the direct determination of GFR [4,5].
Transplantologists have dedicated much of their time and have made efforts to improve the renal transplant function. A lot of therapeutic interventions were developped in the last decades in order to improve or at least to preserve the graft function expressed through GFR [6]. The primary or secondary aim of many clinical studies, which include renal transplant patients, is the function of the graft [7]. The observations were conducted in terms of association between the levels of the graft function assessed with the serum concentration of creatinine or, the estimated GFR based on the serum creatinine formulas, and the survival of the graft [8].
The paradigm: The Higher GFR, the longer graft survival, remains to be a motto in the field of transplantation, especially in finding out new less nephrotoxic medications. Indeed, the process of survival of the transplantted kidney itself and the better function of the graft leads to longer survival of the kidney recipient [9,10].
The renal transplant patients by default are prone to develop chronic kidney disease (CKD) and related complications caused by the condition itself.
The recommendations of KDIGO (Kidney Disease: Improving Global Outcomes) include usage of mathematicc formulas based on creatinine, which are intended for routine clinical practice in the care of renal transplants patients [11].
The reduced graft function at a certain point of transplantation, especially after the first year is associated with a faster loss of graft as well as with a higher mortality of the renal transplant recipients [12].
The aim of our study was to compare the graft function through formulas based on creatinine as an estimated GFR with the basic function of the donated kidney determined with radioisotopes at 3, 6 and 12 months after transplantation. In addition, to determine the factors which directly influence on the improvement/worsening of the graft function during 12 months after transplantation.

Material and methods

Patients

A total number of 55 adult patients with LDKT from our transplant centre were included in the study. The transplantation was performed during the period from 2011 to 2014. The inclusion criteria were: first transplantation of one organ-kidney, use of living donor related or not related, emotionally related (spouses) donor; graft with a stable function during a 12-month-period after transplantation.

Methods

The data which are related to donor-sex, age of the donor, type of donation (related or not related donor).
Data which refer to the patient: sex, age, length of hemodialysis treatment prior to transplantation, basic disease, type of immunosuppressive therapy.
Clinical and biochemical variables, serum creatinine, serum urea, protein status, proteinuria 24 hours, body weight and height were analyzed at 3, 6 and 12 months after transplantation.
According to the immunosuppressive protocol, patients were divided into two groups-either on calcineurin inhibitor Cyclosporine or Tacrolimus.
The estimated GFR was calculated with three formulas.

1. **Cockcroft–Gault formula:**
$$[(140\text{-age}_{(\text{years})})\text{x}\text{weight}_{(\text{kg})}/(0.814\text{serum creatinine}_{(\mu\text{mol/l})}]\ (\text{x}0.85, \text{for females}).$$

2. **Nankivell equation:**
$$6.7/(\text{serum creatinine}_{(\text{mmol/l})})+0.25\text{x}\text{weight}_{(\text{kg})}\text{-}0.5\ \text{x urea(mmo/L)-}100/\text{height}_{(\text{m})}^{2}+35(25\ \text{for females})$$

3. **MDRD study equation:**
$$170\times(\text{serum creatinine}_{(\text{mg/dl})})^{-0.999}\times(\text{age}_{(\text{years})})^{-0.176}\times(0.762\ \text{if patient is female})\times(1.18\ \text{if patient is black})\times(\text{serum urea nitrogen concentration}_{(\text{mg/dl})})^{-0.170}\times(\text{serum albumin concentration}_{(\text{g/dl})})^{0.318}.$$

Statistical analysis was conducted by pair analysis and comparison of repetitive measurements with ANOVA. Further stratification of patients was conducted according to the improvement or worsening/stabilizing of the graft function and determination of the factors which influence them, with the multiple logistic regression analysis. P level <0.05 was considered significant.

Results

Characteristics of donors and recipients are listed in Table 1.

Table 1. Characteristics of donors and recipients

Age of recipient (years)	30.7±9.6
Age of donor (years)	55.48±9.41
Hemodialysis experience (months)	27.8±22.8
Creatinine (µcmol/L)	
3 months	116.9±58.9
6 months	114.1±57.4
12 months	109.5±41.7
Urea (mmo/l)	
3 months	6.9±2.6
6 months	6.9±2.5
12 months	6.9±1.9
Albumen (g/L)	
3 months	44±0,34
6 months	45±0.4
12 months	45±0.30
Scan of a donated kidney (^{99m}TcDTPA)	47.61±5,72

The mean age of the donors was 55.48±9.41. Out of these, 40 (78.4%) were related, and 11 (21.5%) donors were non-related, but emotionally related. From the performed radioisotope ^{99m} Tc DTPA kidney scans, the separated GFR of the donated kidney was analyzed. Prior to transplantation the mean value of the directly assessed GFR of donated kidney was 47.61±5.72 ml/min.

Characteristics of the recipients

The mean age of the recipients was 30.7± 9.6 years.
Forty-five (45) patients were included in a chronic hemodialysis program prior to actual transplantation and only one patient underwent peritoneal dialysis as a modality treatment of terminal kidney failure. A preemptive transplantation was conducted in five patients.
The average duration of hemodialysis treatment was 27.8±22.8 months. The average duration of peritoneal dialysis treatment was 24 months.
Based on the underlying disease patients were divided into four basic groups: chronic glomerulonephritis, polycystic kidney disease, diabetic nephropathy and non-differentiated CKD.

Biochemical variables

The mean value of s. creatinine at 3 months after transplantation was 116.9±58.9, at 6 months 114.1±57.4 and at 12 months 109.5±41.7 µcmol/L. The mean value of s. urea at three months was 6.9±2.6, at 6 months 6.8±2.5, and at 12 months 6.9±1.9 mmo/L.

Assessment of GFR with mathematical formulas (Cockcroft-Gault, MDRD 6 variables, Nankivell)

The monitoring of the GFR in graft recipients in the posttransplantation period was conducted with the three formulas at 3, 6 and 12 months after transplantation.
The results obtained with these estimated GFR values with the 3 formulas are given in Table 2.

Table 2. GFR at 3, 6 and 12 months

GFR (formulas)	ml/min
MDRD (6 variable)	71.26±23.75
3 months	71.26±23.75
6 months	73.87±24.74
12 months	72.65±22.6
Cockcroft-Gault (C-G)	
3 months	91.10±34.22
6 months	92.78±41.35
12 months	94.25±36.42
Nankivell	
3 months	80.04±18.39
6 months	80.44±19.91
12 months	81.78±17.89

The mean value of the calculated GFR with Cockroft - Gault at 3 months was 91.10±34.22 ml/min. At 6 months after transplantation, it was 92.78±41.35, and at 12 months 94.25± 36.42 ml/min.
The mean value of the calculated GFR with MDRD formula at 3 months after transplantation was 71.27±23.75 ml/min. At 6 months after transplantation it was 73.87±24.74, and at 12 months after transplantation 72.65±22.6 ml/min.
The mean value of the calculated GFR with Nankivell formula 3 months after transplantation was 80.04±18.39, and 6 months after transplantation 80.44±19.91 ml/min. At 12 months the mean value of GFR was 81.78±17.89 ml/min.
The results obtained showed that the largest number of patients at 12 months after transplantation were in the stage 2 of kidney failure.
The correlation of the directly assessed GFR of the donated kidney prior to transplantation with the estimated GFR with the three formulas at the three time points after transplantation is presented in Table 3.

Table 3. Correlation between the estimated GFR by formulas with the baseline GFR of the donated kidney

	Spearman	**p-level**
MRDR 3m& GFR graft	-0.005	0.973
MDRD 6m& GFR graft	-0.006	0.967
MDRD 12m& GFR graft	-0.060	0.705
C-G 3m& GFR graft	-0.042	0.781
C-G6m& GFR graft	0.108	0.484
C-G12m& GFR graft	0.006	0.964
Nankivell 3m	-0.036	0.811
Nankivell 6m	0.137	0.372
Nankivell 12 m	-0.043	0.778

Furthermore, we analyzed factors which may have had a direct influence on the function of the transplanted kidney.
According to the age of the donors, the patients were divided into two groups: donors with standard criteria - SCD (up to 60 years of age) and donors over the age of 60 (expanded criteria donors - ECD).
Of the total number of donors, 30 (58.8%) were under the age of 60, and 21 (41.1%) were over 60 years old.
In addition, the graft function was compared according to the age of the donors (<60 vs. >60 years or SCD vs. ECD).

Table 4. Comparison of estimated GFR with the age of donors

	Donor (≤60 years old) Mean ± SD	**Donor (≥60 years old) Mean** ± SD	**p**
MRDR 3m	75.03 ± 22.76	65.73 ± 17.58	0.188
MDRD 6m	79.91 ± 24.23	65.28± 17.08	0.058
MDRD 12m	**79.67 ± 20.28**	**60.72± 15.61**	**0.005**
C-G 3m	100.01± 37.53	80.38 ± 18.79	0.057
C-G 6m	103.23 ± 46.71	79.64 ± 18.86	0.068
C-G12m	**106.08 ±39.26**	**78.95 ± 18.87**	**0.012**
Nankivell3m	82.88 ±16.38	78.73 ± 14.98	0.406
Nankivell6m	84.62 ±16.73	77.34 ± 14.92	0.164
Nankivell12m	**86.86 ±15.30**	**76.76 ± 15.07**	**0.038**

Statistically significant difference was obtained for the estimated GFR with MDRD formula at 12 months in the group of allografts from ECD (older than 60), which was lower (60.72±15.61 ml/min), compared to the group of allografts from SCD (younger than 60) and it was 79.67±20.28 ml/min (p= 0.005) (Figure 1). Furthermore, statistically significant differences were found for the estimated GFR with C-G formula in patients from SCD 106±08 ml/min versus those from ECD 78.95±18.87 ml/min (p=0.012) (Figure 2). The results obtained with the Nankivell formula were 86.86±15.30 ml/min for the SCD group vs. 76.76±15.07 ml/min for the ECD (p=0.38) (Figure 3).

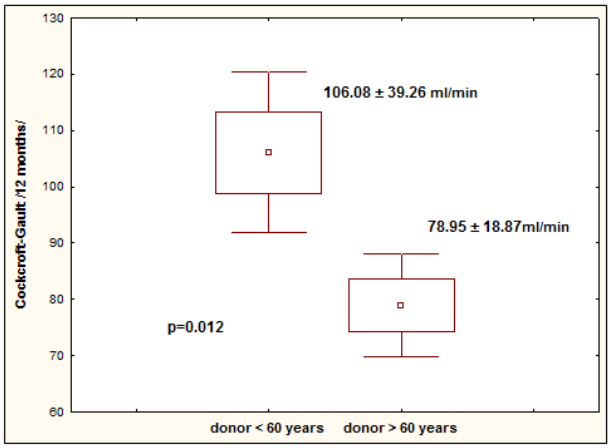

Fig. 2. Cockcroft-Gault at 12 months and donor age

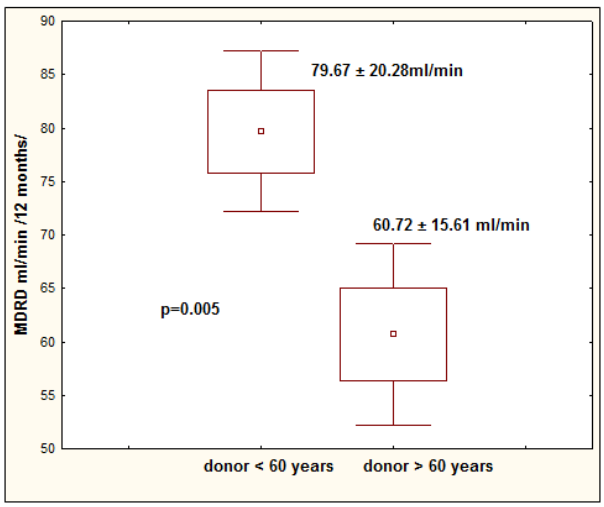

Fig. 1. MDRD at 12 months and donor age

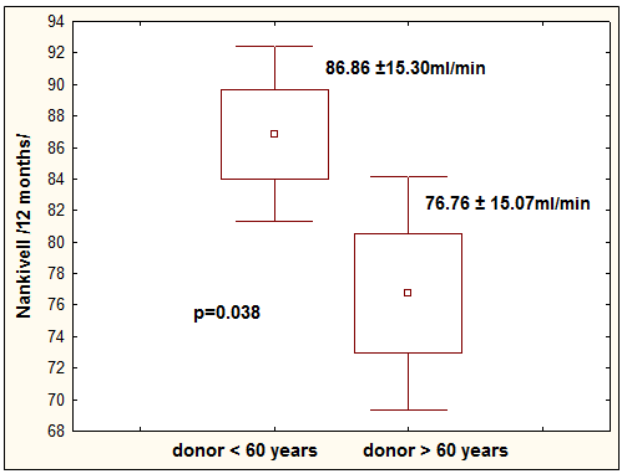

Fig. 3. Nankivell at 12 months and donor age

Table 5. Comparison of the estimated GFR compared to the duration of HD (<24 and >24 months)

	HD less than 24 months ± SD	**HD over 24 months** ± SD	**p**
MRDR 3m	75.45±24.58	64.38±15.93	0.159
MDRD 6m	80.46±25.71	64.99±13.23	0.057
MDRD 12m	77.52±23.04	64.77±13.92	0.084
C-G3m	96.89±36.37	78.70±21.09	0.111
C-G6m	100.69±45.82	78.27±19.14	0.110
C-G 12m	**102.23±38.86**	**77.84±18.11**	**0.043**
Nankivell 3m	82.80±16.81	75.61±14.23	0.196
Nankivell 6m	84.44±17.44	75.30±11.91	0.103
Nankivell 12m	**85.80**±16.09	**75.34**±13.59	**0.052**

The influence of the duration of hemodialysis treatment (more and less than 24 months) compared to the graft function estimated with the three formulas at 3 time points is given in Table 5.

A significantly higher estimated GFR was obtained with the C-G formula at 12 months after transplantation in patients undergoing hemodialysis treatment shorter than 24 months (102.23 ml/min±38.86 ml/min; p= 0.043), and it was at the borderline of significance with Nankivell formula at 12 months after transplanttation (85.80±16.09 ml/min; p= 0.052).

Table 6. Comparison of the type of calcineurin inhibitor (Cyclosporine/Tacrolimus) compared to the estimated GFR with three formulas

	Cyclosporine	Tacrolimus	P
MRDR 3m	70.57± 23.13	72.03±24.98	0.84
MDRD 6m	71.47±26.92	76.62±22.33	0.50
MDRD 12m	70.21±24.61	75.30±20.41	0.46
C-G3m	93.07±40.45	88.94±26.88	0.68
C-G6m	93.43±52.84	92.09±25.58	0.91
C-G12m	93.90±44.57	94.62±25.82	0.94
Nankivell 3m	78.38±19.00	81.84±17.95	0.52
Nankivell 6m	77.39±20.76	83.63±16.47	0.26
Nankivell 12m	78.80±18.69	85.03±16.79	0.23

The comparison of the estimated GFR with the three formulas related to the two groups of recipients treated with different calcineurin inhibitor (Cyclosporin or Tacrolimus) showed no statistical difference at any time point.

Discussion

Our study evaluated the association of the directly determined GFR of the donated kidney with the estimated GFR of the graft during the first year. Three mathematical formulas based on creatinine were used. These formulas have been extensively used in the clinical practice. According to the consulted studies, these formulas are with the best predictive performances or have been used for the longest period of time [13].

The Cockcroft-Gault (C-G) formula was initially presented in 1976. A study results were based on the 24 hours creatinine excretion/kg (creatinine clearance) in 236 adult patients, mostly men at the age of 18-92. Because most of them were men, a correction was made with the coefficient of 0.85 for women. A small number of studies have presented its application in transplant patients [14].

Nankivell formula is the only one which is derived from the group of transplant patients, as compared to the direct measurement of GFR of plasma clearance of ^{99m}TcDTPA. Thus, it was expected to be the most suitable for application in the transplant patients [15]. Nevertheless, this formula was integrated into methods of many clinical trials long time before the first studies trying to confirm the initial promising data were reported [13].

Levy *et al*. derived another predictive formula from a group of patients comprising 1628 subjects included in Modification of diet with renal diseases (MDRD) study, and derived clearance of ^{125}I Iothalamate. This study presented a new standard in the GFR prediction, and many studies which have been successively conducted confirmed this fact [16].

Our study evaluated the direct correlation of separate GFR of donated kidney with the estimated GFR of the graft with the three formulas. A direct correlation of the given time points was not registered. The superiority of the directly measured GFR with clearance of isotopes compared to the estimated GFR with formulas remains to be a topic for discussion and research. The awareness of the limits while conducting the methods for determining the GFR is important in the clinical application of the measurements and the need to understand their potential limits [17].

Our results demonstrated a slight decrease and stabilization of serum creatinine between the third and the twelfth month. This kind of stabilization of the graft function at 12 months has been confirmed in the literature. This trend is considered to be a result of the stable period between three to six months after transplantation with already determined concentrations of immunosuppressive therapy and lower level of acute rejections [12].

One of the important factors for long-term survival of the transplanted kidney is the quality of the transplantted kidney itself.

The literature data show better survival of kidneys received from living donors compared to kidneys from a cadaver. It may be partially explained with the careful pretransplantation evaluation, non-existing of the preagonal and agonal state which is present in cadaveric transplantations and short time of cold ischemia of the graft [18]. The kidneys received from donors of standard criteria (younger than 60 years) have a better function compared to the kidneys received from donors with extended features [19,20]. In our study the GFR values estimated with the three formulas in the group of allografts received from SCD were higher and statistically significantly different compared to the level of the estimated GFR of the grafts received from ECD (over 60 years of age).The highest estimated GFR was obtained with the C-G formula. These results were somewhat expected having in mind the already known fact that this formula overestimates GFR. The formula itself incorporates the body weight, but it does not express the muscle mass as a determinant for production of creatinine, but there are other factors which change the body weight, such as obesity, presence of edemas, the influence of long-term use of steroid therapy, etc. Although in the formula itself there is a correction related to sex, the creatinine itself is not exclusively filtrated through glomerulus and tubular excretion of creatinine remains to be an important factor [13,21,22].

From the other analyses, reduced estimated GFR was received for the recipients with hemodialysis duration longer than 24 months at 12 months after transplanttation compared to the patients who were with shorter hemodialysis treatment. In our study, there was a statistically significant difference between the two groups using the C-G formula. In the beginning of the 2000s Meier-Kriesche *et al.* showed that longer hemodialysis treatment induces shorter survival of the transplant kidney [23]. Long-term cardiovascular complications in the transplantation period are the second important factor for the graft survival. It is well known that patients with terminal kidney failure are at a higher risk of cardiovascular diseases and patients in chronic program of hemodialysis have 10 to 20 times higher risk of cardiovascular morbidity compared to the general population [24,25].

With reference to the used immunosuppressive therapy, standard protocols included calcineurin inhibitors for our research population. The comparison conducted between the two groups of patients who used Cyclosporine and Tacrolimus respectively in terms of the estimated GFR in the three time periods after transplantation did not show statistical difference. Both medications are in the same immunosuppression group (calcineurin inhibitors-CNI) and have the same immunosuppressive mechanism and both medications express nephrotoxicity. Certain studies show more rapid lowering of GFR in patients treated with Cyclosporine compared to Tacrolimus, in the long-term follow-up of the graft function [26]. Another study, which treated patients with Cyclosporine and Tacrolimus, registered a lower rate of acute rejections proved with biopsy at six months in the Tacrolimus group, but at 12 months there was no statistical difference. On the other hand, two and three year follow-up of patients showed lower rate of graft loss, lower serum creatinine and lower mortality in the Tacrolimus group. At the same time, the long term observation of the group treated with Tacrolimus showed usage of protocols with immunosuppressive monotherapy and less registered cardiovascular events [27,28].

Our study included only kidney transplant recipients from living donors, who were followed for 12 months, with short time of cold ischemia of the graft, good pretransplantation preparation and evaluation and with regards to the posttransplantation protocol with recommended lower levels of serum concentrations of immunosuppressive therapy. These parameters may reduce the nephrotoxicity of the calcineurin inhibitors.

The obtained difference in the GFR value with the different formulas and the decision which of them is most appropriate is a motive for another clinical study.

So far, there have been no comparisons with direct measurement of GFR with isotopes in transplant patients, which would probably confirm the value of the used formulas.

A question has been raised: which of the widely used formulas is a reference method for prediction of GFR in transplant patients. The analyses which have already been conducted pose the question whether it is time to create a new formula. We would like to point out several observations from studies which have been already conducted as also being a limitation of our study.

Most of these formulas are derived from the general population and do not include factors which refer exclusively to the transplant patients, and thus, it may have an impact on their predictive value. For instance, the number of acute rejections, or the cumulative steroid dosage which was received by recipients that could influence on the muscle mass should be probably incorporated in the mathematical formulas. The nephron mass itself transplanted to the recipient has never been taken into consideration in the mathematical formulas, and it directly influences the GFR after transplantation. Hence, the formula which is directly derived from the cohort of the transplant patients includes variables which are relevant only for the recipient. Relevant to the fact that the renal mass is in correlation with the body size itself, maybe it should raise an issue to create a formula which would include the donors' features [13].The studies so far do not give a conclusion which of the formulas would be superior for usage in transplant patients.

Conclusion

Formulas for assessment of the graft function based on creatinine were not in correlation with the assessed function of the donated kidney determined through radioisotopic measurement, nor were they in correlation with each other. Therefore, there is a need of monitoring of the transplanted kidney function through uniquely selected formula. In terms of the factors of influence, the better function of the graft was obtained in those from younger donors (SCD) and in patients with shorter dialysis treatment.

Conflict of interest statement. None declared.

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Original article

Changes in Health-Related Quality of Life in Greek Adult Patients Two Years after Successful Renal Transplantation

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Abstract

Introduction. This study was undertaken to compare and evaluate the heath-related quality of life (HRQOL) in Greek adult transplant recipients before and 2 years after successful renal transplantation (RT). The SF-36 survey score was used.

Methods. Eighty-five Greek hemodialysis patients underwent RT at the Transplant Unit of Evangelismos General Hospital of Athens, including 44 men and 41 women (mean age 43.8 years; range 21-59 years). The scale scores of a Greek version of the SF-36 survey were compared between the transplant and the hemodialysis patients. We also examined the relationships of the scale scores with the patients' age and the type of donor.

Results. According to the SF-36 health survey, transplant recipients had better results for general health perception ($p \leq 0.001$), role-physical functioning ($p \leq 0.01$), role-emotional functioning ($p \leq 0.01$), and vitality ($p \leq 0.01$). In addition, the scale score of physical functioning, general health and vitality of the patients who were younger than 30 years at the time of transplantation were significantly higher than those of the patients who were older than 30 years, while the scores of bodily pain, general health, and physical functioning were significantly lower in cadaveric graft recipients compared with living-related recipients.

Conclusions. The SF-36 health survey is a validated and comprehensive instrument for evaluating renal transplant patients' HRQOL. Our data demonstrated an improvement in HRQOL in renal transplant patients 2 years after successful renal transplantation. The data also confirmed that the recipients' age at transplantation and the type of donor were important factors affecting the HRQOL.

Keywords: end-stage renal disease, hemodialysis, immunosuppression, renal transplantation, quality of life, SF-36

Introduction

End-stage renal disease (ESRD) reduces the life-span of its victims, while renal transplantation (RT) has become the treatment of choice for all patients without contraindications for surgery and use of immunosuppressive drugs. The aim of RT is not only to restore renal function but also to enhance the patient's ability to enjoy as full a life as possible [1].

Health-related quality of life (HRQOL) has become a very important criterion in the evaluation of any type of medical treatment [2-4]. Especially in the field of RT, with the improvement of graft survival, HRQOL is well recognized as an important measure of outcome in transplant patients. Several determinations of HRQOL focus on physical status and symptoms, functional status, mental health, social functioning and general health perceptions [5].

The Short Form Health Survey (SF-36) is a generic instrument containing 8 multi-item scales to evaluate the subjective HRQOL [6]. This questionnaire has become a worldwide generic measure owing to its validation, reliability and conciseness [7]. A review of the literature shows many published studies reporting the results of its validation for different chronic conditions and healthy subjects, as well as its use in accessing the HRQOL in renal transplant patients [8-10].

The aim of this single-center study was to evaluate the changes in HRQOL in Greek adult hemodialysis patients who underwent successful RT and the elements that affect it using a standardized and validated Greek version of the SF-36 survey.

Materials and methods

This cross-sectional study was conducted from January 2009 to June 2011 at the Transplant Unit, Evangelismos General Hospital of Athens, Greece. Completed questionnaires from 85 patients were studied. Forty-four men

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and 41 women (mean age 43.8 years; range 21-59 years) were evaluated before RT and 24 months after successful RT. Thirty-nine patients (45.9%) received an allograft from a deceased donor, and 46(54.1%) received an allograft from a living-related donor. End-stage renal disease was caused by hypertensive nephropathy in 31 patients (36.5%), glomerulonephritis in 25 patients (29.4%), chronic pyelonephritis in 19 patients (22.3%), and in 10 patients (8%); the cause was unknown. Information about the patients' age, sex, medical history, hemodialysis, time of RT, and instances of rejection was abstracted from medical records.

All renal transplant patients received immunosuppressive therapy with cyclosporine, steroid, and mycophenolate-mofetil. Patients who had experienced an episode of graft rejection were excluded from the study. Only patients with serum creatinine $\leq$1.5 mg/dL (normal range 0.5-1.3 mg/dL) were included in investigation.

Multiple domains of objective and subjective data that may affect HRQOL were measured using the SF-36 survey, which contains 36 questions that assess 8 aspects of HRQOL: physical functioning, role-physical functioning, bodily pain, general health perception, vitality, social functioning, role-emotional functioning, and mental health.

These questionnaires were answered using a scale ranging from 1 to 100, with higher scores indicative of a better outcome. Both interview and questionnaire distributions were conducted by the same investigator who gave the same instructions and all data were collected anonymously.

Statistical analysis

All descriptive data of the SF-36 were reported as means $\pm$ standard deviation (SD). The data were analyzed by means of SPSS software. (Statistical Package for the Social Sciences version 12.01, SSPS Inc, Chicago, III, USA). The Mann-Whitney U and the chi-square tests were used for group comparison, and the Student's t-test was used to analyze normally distributed quantitative data. Values for P<0.5 were considered statistically significant.

Table 1. Results of SF-36 survey before and 2 years after renal transplantation

Generic scales of the SF - 36	Baseline- HP	2 years after RT	Baseline vs 2 years after RT
PF	55.8 ± 28.1	76.7±17	
RPF	10.2±44.7	61.7±36.0	p< 01
BP	45.5±23.1	90.2±15.1	
GH	34.4±22.7	84.0±23.2	P<001
VT	25.9±3.0	83±25.1	P<01
SF	30.9±19.1	78.1±29.6	
REF	39.6±18.5	83.0±13.2	P<01
MH	23.4±45.8	68.4±14.8	

RT, renal transplantation; HP, hemodialysis patients; PF, physical functioning; RPF, role-physical functioning; BP, bodily pain; GH, general health perception; VT, vitality; SF, social functioning; REF, role-emotional functioning; MH, mental health; values are presented as means ±SD

Results

The mean SF-36 score before RT was 55.8 versus 76.7 at 2 years after RT for physical functioning, 10.2 versus 61.7 for role-physical functioning, 45.5 versus 90.2 for bodily pain, 34.4 versus 84.0 for general health perception, 25.9 versus 83.0 for vitality, 30.9 versus 78.1 for social functioning, 39.6 versus 83.8 for role-emotional func-

Table 2. SF-36 scale scores in renal transplant patients classified according to their age at the time of transplantation and the type of the graft donor

Generic scales of the SF 36	Age at transplantation (years)		Donor	
	Age <30 (n= 28)	Age >30 (n=57)	Cadaveric (n=39)	Living-related (n=46)
PF	74.3±5.5*	68.9±13.2	46.8±8.57	80.2±15.4
RPF	56.31±34.8	51.7±36	51.9±17	60.2±5.5
BP	78.9±6.9	80.2±15.1	51.4±21.2*	89.4±17.9
GH	82.9±7.1*	64.0±23.2	6.0±17.67	85.1±16.8
VT	77.4±18.9*	63.0±25.1	70.8±18.4	76.8±23.1
SF	58.7±18.9	75.1±29.6	56.4±15.0	69.2±13.8
REF	63.6±11.5	77.0±13.2	69.3±11.7	74.3±19.6
MH	75.9±8.2	88.4±14.8	75.0±16.9	86.3±12.0

PF, physical functioning; RPF, role-physical functioning; BP, bodily pain; GH, general health perception; VT, vitality; SF, social functioning; REF, role-emotional functioning; MH, mental health. Values are presented as means ± SD*P<0.5, *P<0.1

tioning and 23.4 versus 68.4 for mental health (Table 1).
The SF-36 showed significant differences in 4 dimensions after RT. Better results were noticed in general health perception ($p \leq 0.001$), role-physical functioning ($p \leq 0.01$), role-emotional functioning ($p \leq 0.01$), and vitality ($p \leq 0.01$) (Table 1). Transplant patients also reported less bodily pain, better physical and social functioning and better mental health, but these differences were not significant ($p=0.065$, $p=0.06$, $p=0.062$ and $p=0.07$, respectively). No differences were found between men and women. Within the transplant group, the following observations were of considerable interest (Table 2): patients who were younger than 30 years at the time of transplantation showed significantly better levels of physical functioning ($p \leq 0.05$), general health ($p<0.05$), and vitality ($p<0.01$) two years after successful RT compared to those who were older than 30 years at the time of the procedure. In addition, recipients of allografts from deceased donors showed significantly worse levels of bodily pain ($p \leq 0.05$), general health ($p \leq 0.01$), and physical functioning ($p \leq 0.01$) compared to living-related allograft recipients (Table 2).

Discussion

Outcome measures after a procedure like RT have traditionally addressed only operative and long-term survival and complication rates. HRQOF is gaining importance as an outcome measure, especially because of the intense resource use demanded by transplantation. Improved technology and therapies have prolonged survival rates after RT, thus attention is shifting to the quality of those years.
Over the recent years, a considerable concern has been shown toward the HRQOL as an effective parameter in clinical investigations [9]. Many reports are available concerning the improvement of HRQOL in transplant patients [2,4,10]. Several methods for scoring the HRQOL have also been reported [2,11]. We used the SF-36 survey consisting of 36 questions because we believe that this instrument allowed us to assess RT's influence on patients' physical, social, and psychological status.
The results of the study showed that a higher HRQOL two years after RT was achieved especially in the dimensions of general health perception, role-physical functioning, role-emotional functioning, and vitality. These results are in accordance with the literature [2,9, 12,13]. Laupacis *et al*. [14] also reported improvement in almost all dimensions within 6 months of successful RT, according to the HRQOL of ESRD patients. However, the risk of graft rejection in patients with RT is highest within the first 6 postoperative months, hospital appointments are necessary every few days, and the patients are still adjusting to medication and its effects during this period [8].
Some scales of the SF-36 did not reveal a significant difference 2 years before and 2 years after RT, for example, physical functioning and mental health were not significantly improved after RT. This might be attributed to the fear of organ rejection that some recipients might have or to the fear of the effects on their appearance caused by surgery and immunosuppressive drugs. However, we must take into consideration that the transplant recipients were a select group with good clinical and demographic characteristics.
Waiser *et al*. [15] reported that the quality of life is dependent on the immunosuppressive regimen. However, in RT patients we found an association between HRQOL and immunosuppressive therapy. Unlike 2 other studies [16] we found that sex did not appear to have any significant effects on HRQOL.
We also analyzed which factors had the biggest effect on the SF-36 scale scores. The cross-sectional evaluation showed that age at the time of transplantation and the type of donor graft had a significant influence on the patients HRQOL. The lower the patient's age, the higher the scale scores, especially in relation to physical functioning, general health and vitality. Finally, the RT patients who received a living-related allograft had significantly better levels with regard to bodily pain, general health, and physical functioning compared to cadaveric graft recipients.

Conclusion

In conclusion, our results indicate that the overall HRQOL significantly improves after successful RT. General health perception, role-physical functioning, role-emotional functioning and vitality were demonstrated to have a profound positive influence on patients' HRQOL after RT. The lower the patients' age at the time of transplantation, the higher the SF-36 scale scores. The type of the donor was also an important factor affecting HRQOL in RT patients.

Conflict of interest statement. None declared.

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Original article

Knowledge and Attitude Regarding Organ Donation among Medical Students

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Abstract

Introduction. All over the world people on organ transplant waiting lists die due to shortage of donor organs. The success of organ donation program needs education of the population regarding organ donation for which healthcare professionals are most suitable. The present study was taken up to assess the knowledge and attitude of 1st, 2nd and 3rd year medical students about organ donation.
Methods. A specially designed self-administered questionnaire was distributed amongst all willing 1st, 2nd and 3rd year medical students at our Medical College and later analyzed statistically.
Results. A total of 157, 145 and 92 students from each year of medical education respectively gave their consent for participation in the study. Awareness regarding organ donation was found to be 98.7-100%, 69.4% claimed television as their source of information regarding organ donation and 46.7% stated that it is possible for patient to recover from brain death. The awareness regarding eye, liver, heart and kidney donations was found to be 92.4%, 87%, 87% and 97.8%, respectively. 87% of medical students were aware of need for legal supervision, and awareness regarding the existing laws was found to be 57.6%.
Conclusion. Medical students had a high level of awareness and a positive attitude towards organ donation. However, knowledge regarding "brain-death", organs and tissues donated, legislation and ethical issues was poor. A teaching intervention designed to specifically address these issues could help increase the confidence of the health-care professionals and may result finally in increased organ procurement rates.

Keywords: brain death, doctors, health-care professionals, organ donation

Introduction

Organ transplantation has been one of the greatest advances of modern science that has resulted in many patients getting a new lease of life. It is the most preferred treatment modality for end-stage organ disease and organ failures and is developing into a major treatment protocol all over the world [1]. However, implementation of organ donation program in India has been slow and there is an inadequate supply of donated organs.
While organs such as "part of liver" or "a kidney" can be donated by healthy living individuals, almost 30 or more organs can be donated by a person who is "brain dead". Fewer organs can be donated following cardiac death. There is awareness amongst the general public regarding eye and kidney donations. However, awareness regarding donation of liver, heart and many other transplantable organs and tissues is very low. While there is awareness regarding "live" organ donations and organ donation following "cardiac death", awareness regarding organ donation after "brain death" and its legality in India is very poor. Wig *et al.* stated that there is a need for education of people regarding various aspects of brain death and its immense importance for organ donation [2].
All over the world people on transplant waiting lists die due to shortage of donor organs. The success of organ donation program needs education of the population regarding organ donation. Healthcare professionals act as the critical link in the organ procurement process because they are the first individuals to establish relationship with the potential donors' family. Education of healthcare professionals in various aspects of organ donation is therefore a must as they in turn can propagate this knowledge at the community level [3].
Taimur *et al.* in 2009 carried out a knowledge, attitudes and practices survey on organ donation among urban population and stated that doctors can be used as efficient sources of information, to generate a favorable attitude towards organ donation amongst the population [4].
The medical students are the future doctors, and will one day take up the role of promoting organ donation. The present study was taken up to assess the knowledge and attitude of these future doctors i.e. 1st, 2nd and 3rd year medical students about organ donations i.e. at different stages in their undergraduate career.

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Materials and methods

The study was undertaken to ascertain the knowledge and attitude of medical students in Pune about organ donation. It was conducted after approval of the Ethics Review Committee during 2013-2015. All willing 1st, 2nd and 3rd year medical students at our Medical College were involved in the study. The methodology was explained to them in detail. The respondents were assured that their confidentiality would be maintained and ethical principles would be followed. The inclusion criteria for the study population were students enrolled in 1st, 2nd and 3rd year of medical education and exclued were students who were not present or refused to give consent. Only those consenting to participate were involved in the study.

A specially designed self-administered questionnaire covering demographic data, knowledge and attitude of medical students was prepared by the research team. It was a pilot testing of medical students who were given a time period of 15 minutes for completion of the questionnaire wherein the respondents would indicate their responses to the questions using the categories provided in the questionnaire in privacy without any discussion with peers. The questionnaire was thus tested for clarity of the questions as well as time period required for response. Suitable modifications were made in the questionnaire and time span provided.

The first four items in the final questionnaire collected demographic data, the item 5-16 focused on the knowledge and item 17-20 assessed the attitude of the medical students towards organ donation. Separate space was provided in the questionnaire for any comments by the respondents.

This final questionnaire was administered to the participating undergraduate medical students in paper format. All those students who filled in the questionnaire for the pilot testing were included in the study. The attitude of undergraduate medical students towards organ donation was studied by a 20-item questionnaire covering issues such as knowledge of possible donors, concept of brain death, the organs that can be donated, willingness to donate, religious beliefs and legislation related to organ donation and many others. The questions collected demographic data, assessed the knowledge as well as attitude of the medical students towards organ donation.

The data collected was analyzed using descriptive statistics on Microsoft Excel.

Results

The demographic data of the respondents from 1st, 2nd and 3rd MBBS was as shown in Table 1.

90% of the respondents in all 3 years were followers of Hinduism, 3-5% followers of Christianity and Islam respectively and about 4% were followers of other religions. All the participating medical students were

Table 1. Demographic data

	1st MBBS	2nd MBBS	3rd MBBS
Age	17-22	17-23	19-22
Mean age ± SD	18.60±0.77	19.72±0.88	20.39±0.63
Number of respondents (n)	157	145	92
Number of female respondents	92(58.5%)	105(72.4%)	53(57.6%)
Number of male respondents	65(41.4%)	40(27.5%)	39(42.3%)

Table 2. Knowledge of organ donation and different categories of donors with specific knowledge of brain death

	Item studied	1st MBBS	2nd MBBS	3rd MBBS
1	*Awareness of organ donation*	155(98.7%)	142(97.9%)	92(100.0%)
2	*Awareness of need for donation of organs?*	150(95.5%)	138(95.2%)	90(97.8%)
3	*Source of awareness of organ donation:*			
	Newspaper	87(55.4%)	77(53.1%)	47(51.1%)
	Television	109(69.4%)	91(62.8%)	53(57.6%)
	Internet	91(58.0%)	79(54.5%)	47(51.1%)
	Family members	42(26.8%)	19(13.1%)	8(8.7%)
	Discussed at Medical College	29(18.5%)	40(27.6%)	38(41.3%)
4	*Awareness of possible donors*			
	a) Living healthy person	78(49.7%)	75(51.7%)	41(44.6%)
	b) "Brain dead" person	52(33.1%)	63(43.4%)	45(48.9%)
	c) Naturally dead person	63(41.4%)	64(44.1%)	32(34.8%)
	d) Don't know	11(7.0%)	7(4.8%)	3(3.3%)
5	*Awareness about aspects of brain death*			
	a) Irreversible	36(22.9%)	36(24.8%)	24(26.1%)
	b) Loss of brain functioning	37(23.6%)	22(15.2%)	14(15.2%)
	c) Patient can recover from it	64(40.8%)	26(17.9%)	43(46.7%)
	d) Body may feel warm due to patient being on ventilator	18(11.5%)	22(15.2%)	19(20.7%)

Table 3. Knowledge about the different organs donated and contraindications to organ donation

	Item studied	1st MBBS	2nd MBBS	3rd MBBS
1	*Knowledge about when organ donation cannot be done:*			
	a) If donor is HIV, Hepatitis B or Hepatitis C positive	141(89.8%)	125(86.2%)	83(90.2%)
	b) If donor has active cancer	106(67.5%)	88(60.7%)	55(59.8%)
	c) Organ to be donated is badly injured	115(73.2%)	97(66.9%)	52(56.5%)
	d) There is an active legal case related to death of the donor	30(19.1%)	42(29.0%)	23(25.0%)
2	*Knowledge of organs that are donated*			
	a) Eye tissue	132(84.1%)	130(89.7%)	85(92.4%)
	b) Lungs	37(23.6%)	49(33.8%)	32(34.8%)
	c) Liver	114(72.6%)	116(80.0%)	80(87.0%)
	d) Intestine	16(10.2%)	24(16.6%)	10(10.9%)
	e) Ligament	10(6.4%)	12(8.3%)	12(13.0%)
	f) Heart	126(80.3%)	115(79.3%)	80(87.0%)
	g) Kidney	152(96.8%)	143(98.6%)	90(97.8%)
	h) Skin	63(40.1%)	73(50.3%)	38(41.3%)
	i) Bone	29(18.5%)	45(31.0%)	15(16.3%)
	j) Pancreas	19(12.1%)	23(15.9%)	16(17.4%)
3	*Knowledge that a single donor can donate to multiple recipients*			
	a) True	111(70.7%)	123(84.8%)	77(83.7%)
	b) False	75(28.7%)	61(10.3%)	34(13.0%)

Table 4. Knowledge of legalities related to organ donation

	Item studied	1st MBBS	2nd MBBS	3rd MBBS
1	*Is there need for laws to govern the process of organ donation?*			
	Yes	114(72.6%)	129(89.0%)	80(87.0%)
	No	12(7.6%)	9(6.2%)	5(5.4%)
	Don't know	31(19.7%)	8(4.1%)	7(7.6%)
2	*Are there laws regarding organ donation activity presently?*			
	Yes	73(46.5%)	80(55.2%)	53(57.6%)
	No	8(5.1%)	6(4.1%)	8(8.7%)
	Don't know	70(44.6%)	54(37.2%)	31(33.7%)
3	*Knowledge whether the family of a deceased person can pledge his organs even if the person had not signed a donor card during his lifetime*			
	a) True	71(45.2%)	79(54.5%)	53(57.6%)
	b) False	75(47.8%)	61(42.1%)	34(37.0%)
	c) Don't know	12(7.6%)	6(4.1%)	5(5.4%)

from higher socio-economic strata. The results have been grouped into two subgroups which are knowledge (Table 2, 3, 4) and attitude (Table 5). The knowledge of the respondents regarding organ donation, organ donors and brain death is summarized in Table 2 along with the study of sources from where the knowledge of organ donation was obtained. Table 3 depicts the level of knowledge of respondents about the different organs that can be donated, the related contraindications and ability of one donor to donate to mul-tiple recipients. Table 4 shows the respondent's knowledge of legalities of organ donation and whether the family of the deceased person could decide to donate organs in case the donor himself had not signed the donor card. The attitude of the respondents towards organ donation and aspects like willingness to be an organ donor and to motivate others for organ donation, who they were willing to donate to, and reasons for opting against organ donation in case of those unwilling to donate are depicted in Table 5.

Awareness of organ donation was seen to increase from 98.7% to 100% from 1st MBBS to 3rd MBBS years of education. Television was found to be the most effective source of awareness of organ donation for respondents in all 3 years. Internet and newspapers were also found to be effective sources. Even in the 3rd year of medical education, higher percentage of respondents got information about organ donation from television, internet and newspapers i.e 57.6%, 51.1% and 51.1%, respectively compared to education by discussion at the Medical College itself (41.3%).

Knowledge regarding possible organ donors ranged between 33.1% to 49.7%. 46.7% of the final year medical students believed that a patient can recover from "brain death".

Table 5. Attitude towards organ donation, willingness to donate organs and to promote organ donation and reasons for unwillingness to be an Organ donor

	Item studied	1st MBBS	2nd MBBS	3rd MBBS
1	*Would you like to be an organ donor?*			
	Yes	125(79.6%)	100(69.0%)	65(70.7%)
	No	21(13.4%)	12(8.3%)	11(12.0%)
	Don't know	27(17.2%)	34(23.4%)	14(15.2%)
2	*Whom would you like to donate to?*			
	Family member	128(81.5%)	113(77.9%)	70(76.1%)
	Friend	106(67.5%)	97(66.9%)	56(60.9%)
	Unknown individual	103(65.6%)	98(67.6%)	52(56.5%)
3	*What are your reasons for opting against organ donation?*			
	It is against your religious beliefs	2(1.3%)	3(2.1%)	
	I do not believe in organ donation	5(3.2%)	2(1.4%)	
	I do not wish to go through the disfigurement involved	4(2.5%)	5(3.4%)	4(4.3%)
	I do not believe in the ability of the system to support the donated organs till they reach a suitable donor	14(8.9%)	11(7.6%)	20(21.7%)
	I live very far away from closest center of organ donation	2(1.3%)	1(0.7%)	1(1.1%)
3	*Do you feel that organ donation is an individual's social commitment?*			
	Yes	118(75.2%)	90(62.1%)	60(65.2%)
	No	31(19.7%)	45(31.0%)	28(30.4%)
4	*Would you like to be part of Organ Donation Group in our city and motivate others for organ donation?*			
	Yes	133(84.7%)	115(79.3%)	74(80.4%)
	No	21(13.4%)	21(14.5%)	15(16.3%)

Discussion

Shortage of organs due to poor rate of organ donations is a major limiting factor in transplant programes all over the world. The waiting list for transplantation is therefore very long in many countries around the world and many patients die while on the waiting list due to lack of availability of donor organs [5].

This is especially true in India where the organ donation rate is about 0.16 donor per million population whereas in some countries such as Spain the rate is much higher i.e about 35 donors per million population [6]. A major reason for lack of availability of organs for transplant is refusal by the families of the potential donor, when approached to donate. Ageing population and increasing incidence of type 2 diabetes in India will further reduce the donor pool [7]. A favorable attitude of healthcare professionals to organ donation can positively influence the decision of the families of potential donors and hence educating them early in their careers to the need to encourage organ donation is crucial [8].

This study investigated the attitude of medical students towards organ donation. Undergraduate students from all 3 years of medical education participated in this study. While those in 1st year of MBBS (duration-1 year) had just started their medical education, those in 2nd year of MBBS (duration-1.5 years) were undergraduate students with some knowledge of pharmacology, microbiology, pathology and forensic medicine. The 3rd year (duration-2 years) students were the final year medical students in the process of studying medicine, surgery and gynecology and obstetrics.

It was observed that the awareness regarding organ donation was 98.7% in the 1st year increasing to 100% by the 3rd year. This is similar to the findings of 97% and 97.5% reported by Bapat *et al.* and Ali *et al.* in studies carried out at Medical College Hospitals in South India and Karachi, Pakistan, respectively [1,9]. Thus, it appears that medical students have high levels of awareness regarding organ donation.

69.4% of the 1st year students reported television, while 58% and 55.4% reported internet and newspaper as the sources of their knowledge regarding organ donation activity (Table 2). In a study carried out by Bapat *et al.* television, newspaper, radio and magazines were responsible for 61%, 60%, 31% and 51%, respectively of knowledge promotion regarding this issue [1]. The respondents in a similar study carried out by Bilgel *et al.* reported media and medical education as sources of knowledge in 72.1% and 22.7%, respectively [10]. Thus, it appears that television and newspaper are the most effective for knowledge promotion regarding organ donation. In the present study 18.5% of the 1st year students reported "discussion at medical college" as the source of their knowledge, and this percentage increased to 41.3% in case of final year students. Thus, knowledge of organ donation is being enhanced at the Medical College but it did not reach 100% of the students.

44.6% to 51.7% of medical students were aware of live organ donors and 34.8% to 44.1% were aware of organ donation after cardiac death (Table 2). 33.1% of the 1st year students were aware of organ donation following "brain-death". This percentage increased to 48.9% in case of the final year students. The primary sources of donor organs are patients who have been declared as

"brain-dead" i.e. have suffered from an irreversible loss of brain function but are being maintained temporarily on ventilators [11]. In the present study, though there is a rise in percentage of students having knowledge of "brain-death"-related organ donations, 51.1% still remain unaware of the important category of organ donors i.e. the "brain-dead" donor or "deceased organ donor". Furthermore, study of the knowledge regarding "brain death" revealed that 46.7% of the final year students believed that a person can recover from brain death. This is similar to findings reported by Bardell *et al.* in a study conducted in Canada, where 36% of the medical students did not know that "brain-death" is different from coma [12]. Chung *et al.* stated that insufficient knowledge and failure to identify possible donors are important contributing factors responsible for the shortage of available organs [13]. A future healthcare professional, who believes that it is possible for a patient to recover from "brain-death" would never discuss donation of organs with the relatives of the potential donor. Thus, inadequate knowledge of the concept of "brain-death" may lead to inability to identify the patient as a possible donor. Bapat *et al.* and Palanivelu *et al.* also reported a lack of adequate knowledge regarding "deceased organ donors" amongst medical students [1,14]. 3.3% to 7% of the respondents did not know anything about the different categories of possible organ donors.

The awareness regarding eye, liver, heart and kidney donations amongst the final year medical students was found to be 92.4%, 87%, 87% and 97.8%, respectively having consistently increased from the awareness levels reported by the 1st year medical students (Table 3). The awareness reported by the final year medical students regarding donation of other organs and tissues such as lungs, intestines, ligaments, skin, bones and pancreas was found to be in the range between 10.9% to 34.8% with a minimal rise in awareness levels over the years of medical education. These findings are similar to those reported by Ali et al. in a study carried out to assess the awareness levels of medical students in Karachi-Pakistan [9]. In our study high levels of awareness were also observed regarding donation of heart, kidneys, liver, cornea, but lower levels of awareness regarding all other organ and tissue donations. Study carried out by Edwin and Raja reported awareness regarding donation of eye to be 88%, of kidney 33% and of liver 27% amongst the study group [15]. This observation is similar to that reported by Annadurai *et al.* who studied the knowledge of college non-medical students regarding organs that can be donated and found that above 80% were aware of eye and kidney donations, and below 15% had knowledge regarding any other organ or tissue donations [16]. Thus, there are high levels of awareness regarding donation of eyes, kidney, heart and liver among medical students, and knowledge regarding donation of other organs and tissues is low. Also, it appears that medical students participating in the present study are not very much knowledgeable regarding organs that can be donated, compared to the non-medical students. A similar finding was reported by Bardell *et al.* where medical students were not shown to have any more knowledge of organ donation than their non-medical undergraduate counterparts [12].

While 72.6% of the 1st year medical students were aware of the need for legal supervision to govern organ donation activity, this percentage increased to 87% by the final year (Table 4). However, awareness regarding the existing laws related to organ donation was found to be between 46.5% and 57.6%. Only 25% of the final year medical students were aware that organ donation cannot be carried out if there is an active legal case regarding death of the donor. Tontus *et al.* state that probably the most important factor contributing to the shortage of donor organs today is the lack of information regarding the legal and procedural details among health care professionals themselves [17].

The Transplantation of Human Organs Act in India states that grandparents, mother, father, brothers, sisters, son, daughter, and spouse can be live donors without any legal formalities after providing proof of their relationship by genetic testing and/or by legal documents [18]. In case of any other live donor, the recipient and donor must seek special permission from the government appointed authorization committee to prove that the motive of donation is purely altruism or affection for the recipient. In case of "brain-death" if there is no reason to believe that the potential donor did not want to donate his/her organ(s) after his/her death, then a registered medical practitioner should make the patient's relatives aware of the option to authorize the donation of organs or tissues or both.

Many of the potential donors are cases that fall within the medicolegal case category. The act prohibits the recovery of organs in cases where inquest has to be conducted. In such a case the organ donation can be carried out by making a request to the SHO of the area to agree for recovery of organs from the donor. It has to be ensured that, by retrieving organs, the determination of the cause of death is not jeopardized. Dogra *et al.* have discussed certain guidelines to carry out organ recovery in medicolegal cases after observing the procedure prescribed under the law without interfering with the functioning of the investigating agencies, autopsy surgeons, the courts of law and serving the objective of Transplantation of human organs act [19].

Only 57.6% of the final year medical students were aware that close family members of the deceased person can pledge the donor's organs even if he/she died without signing the donor card. As most of the organ donations take place following sudden injury to the donor resulting in "brain-death", it occurs very often that the family members take the decision of organ donation on behalf of the donor. Awareness of this issue and the legalities involved is essential for all health care professionals if

they are to effectively promote organ donation following "brain-death" of patients.

70.7% to 79.6% of medical students were willing to be organ donors themselves. Table 6 illustrates the percentage of medical students willing to donate organs in the present study compared to reports by other authors. In a survey carried out by Tontus *et al.* in Turkey, 85.3% of medical students believed that organ donation is important and honorable for humanity [17]. In the present study 80.4% to 84.7% of the respondents were willing to participate in any organ donation promotional activity. Thus, above-mentioned observations suggest that medical students have a positive attitude towards organ donation. In the present study, the highest percentage of medical students (76.1%-81.5%) were willing to donate organs to family members, lower to friends (60.9% to 67.5%) and lowest percentage to unknown individuals (56.5% to 65.6%).

Table 6. Percentage of medical students willing to donate organs in the present study compared to reports by other authors.

	Percentage of medical students willing to donate organs
Present study	70.7%-79.6%
Bapat *et al.* (1)	89%
Bilgel *et al.* (10)	58.4%
Figueroa *et al.* (20)	80%
Burra P *et al.* (8)	88%

While 71-85% females showed willingness to donate organs, only 60-61% male respondents were willing to donate. Thus, in the present study higher percentage of female medical students showed willingness to donate organs compared to their male counterparts. This correlation was consistent throughout the 3 years of medical education. This finding is similar to that reported by Bilgel *et al* [10].

Percentage of medical students unwilling to donate organs for religious sentiments, non-belief in organ donation or fear of disfigurement was observed to be less than 5%. However, 21.7% of the final year medical students stated that they were opting against organ donation as they did not believe in the ability of the medical infrastructure to take care of the donated organs till they reach a suitable donor. A study by Chung *et al.* found that traditional cultural beliefs like the importance of preserving an intact body after death, unease thinking or talking about organ donation after death and objections from family members were factors significantly associated with "negative" attitudes of Chinese medical students towards organ donation [13]. 42.7% of respondents in a similar study by Tontus *et al.* stated that their religion restricts organ donation [17]. In the present study 90% of the respondents in all 3 years were followers of Hinduism, 3-5% were followers of Christianity and Islam, respectively and about 4% were followers of other faiths and less than 3% of all respondents stated religious beliefs as the reason for declining to donate organs. The present study did not enquire about the area of residence of the respondents and hence was unable to correlate the willingness to donate organs with the area of residence of the respondent. This could be a limitation of the present study. Studies taken up henceforth should enquire specifically into this aspect and its effect on organ donation activity.

A study carried out by Schaeffner *et al.* found that only 8% of the medical students felt sufficiently prepared to approach relatives of potential organ donors [3]. In a study carried out by Chung *et al.* only 23% of the medical students in the 5th year felt confident in organ donation counselling. Most students felt that medical curriculum was inadequate in providing transplant-related knowledge [13]. Physicians can play a very important role in solving the problem of shortage of organ donors but may miss opportunities because of lack of knowledge about organ donation [12]. The authors believe that a healthcare professional will only approach a family member of the potential donor if he/she is having adequate prior knowledge regarding organ donation, concept of brain death, related legalities and various organs that can be donated. Schaeffner found that knowledge about and attitude of the healthcare professional towards organ donation were highly associated with increasing levels of education [3].

Sawhney *et al*. state that good communication between the clinician and the family members of the potential donors is essential to improve number of organ donations [21]. In a study by Edwin and Raja the medical students who formed the study group themselves were of the opinion that the best persons to counsel the family of potential donors are the attending doctors [15].

Rykhoff *et al.* carried out a study that consisted of assessing the knowledge, attitude and beliefs of health sciences students towards organ donation before and after a related educational session. It was found that 86% were more aware of organ donation and the number of respondents willing to be organ donors themselves also increased [22]. Educational sessions in health sciences curriculum can increase awareness of organ and tissue donation and lead to better procurement rates for donor organs [12].

Although medical students are of the opinion that the best persons to counsel the family of potential donors are the attending doctors themselves, however most of them feel that medical curriculum is inadequate in providing transplant-related knowledge and very few feel sufficiently prepared to approach relatives of potential organ donors. Increasing levels of education have been proved to be associated with a positive attitude of the healthcare professional towards organ donation. Educational sessions in health sciences curriculum can increase awareness of organ and tissue donation. Thus, it appears that educational sessions on organ donation

can raise the knowledge and awareness levels of the medical professionals and make them confidant in approaching the family members of potential donors to raise the topic of organ donation. With this view in mind the medical curriculum does have hours specified for these educational sessions.

However, the present study has found that the present curriculum, knowledge of organ donation and related issues do not reach all medical students. It appears that while almost all medical students have high levels of awareness about organ donation, their level of knowledge regarding concepts of "brain-death" and other aspects such as legalities of organ donation is inadequate. Also, most medical students had good knowledge of transplantable organs such as eye, kidney, liver or heart, but there is a lack in knowledge of other transplantable tissues and organs. The fact that as high as 80% of students showed willingness to be organ donors themselves has to be appreciated and it speaks of their positive attitude towards organ donation.

Conclusion

A teaching intervention designed to specifically target certain topics such as anatomy and physiology of organ donation and transplant in the 1st year of medical education, its related pathology, immunology and pharmacology in the 2nd year and the relevant medical and surgical details and the social and ethical aspects of it in the final year along with separate sessions on related legalities may be beneficial. Also, a separate training on how and when to approach the family members of the potential donor (maybe in a form of problem-based learning) could help increase confidence of the healthcare professionals in this very delicate matter. Such teaching sessions could be the strategy needed to increase the organ procurement rates and resolve the problem of chronic shortage of donor organs for organ transplantation.

Conflict of interest statement. None declared.

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Case report

Bardet Biedel Syndrome: a Rare Cause of Chronic Kidney Disease

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Abstract

Bardet Biedl syndrome (BBS) is characterized by obesity, retinitis pigmentosa, hypogonadism, mental retardation and polydactyly. Additionally, renal, cardiac and neurological manifestations may be seen. We report a case of BBS with chronic kidney disease (CKD) at the age of 43.

Keywords: Bardet Biedl syndrome, chronic renal disease, retinitis pigmentosa

Introduction

Bardet Biedl syndrome (BBS) is an autosomal recessive condition characterized by obesity, retinitis pigmentosa, hypogonadism, mental retardation and polydactyly. It has prevalence of 1 in 1,40,000-1 in 1,60,000 worldwide [1]. Renal involvement in the form of various structural and functional abnormalities is common and renal insufficiency is noted in 5-25%, with progression to end-stage renal disease (ESRD) in 4-10% [2-4].
In our country a small number of cases with this syndrome has been reported. We report a case of BBS with chronic kidney disease (CKD) at the age of 43.

Case report

A 43-year-old female patient with swelling in the legs presented with nausea and a decrease in her oral intake for one-month-period. In the patient's medical history and the family tree blindness has occured at the age of 7 and she underwent a polydactyly surgery. From mother and father relatives, there is one brother with a loss of vision in the patient's family history (Figure 1).
On physical examination, she was with central obesity, her vital signs were: heart rate 80 per minute, respiratory rate 23/dk, blood pressure 150/90 mm/hg; weight 82 kg; height 148 cm; body mass index, 37.43.kg/m² and body temperature 36.5°C.
Positive findings of physical examination, bilateral +/+ pretibial edema, abdominal obesity, internal strabismus, common hyperpigmentation, left upper and lower extremity reconstruction polydactyly from the surgery with scar lesions are presented in Figure 2. The eye examination revealed severe retinitis pigmentosa.
Laboratory findings were: urea 135 mg/dL, creatinine 5.8 g/dL, Modification of Diet in Renal Disease (MDRD) Study glomerular filtration rate (GFR) value based on 4 variables (age, race, gender, plasma creatinine) was 8 ml/min/1.73 m2; calcium 8.6 mg/dL, phosphorus 5.2 mg/dL, sodium 140 mmol/L, potassium 4.7 mEq/L, chloride 115 mEq/L, ALT: 24 U/L, AST: 26 U/L, GGT 32 U/L, alkaline phosphatase 112 U/L, lactate dehydrogenase 421 U/L, total protein 7.8 g/dl, albumin 4.5 g/dl, triglycerides 226 mg/dl, total cholesterol 217mg/dL, serum iron levels of 58 mg/dL, serum iron binding capacity of 338 mg/dL, saturation index 17.2%, ferritin 47 ng/mL, vitamin B12

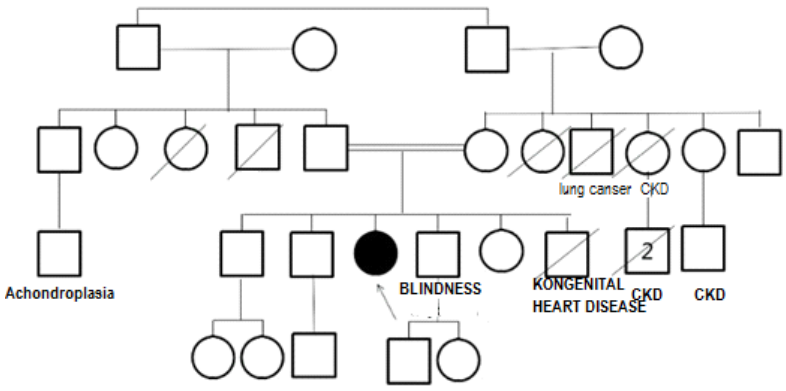

Fig. 1. The family three of the patient

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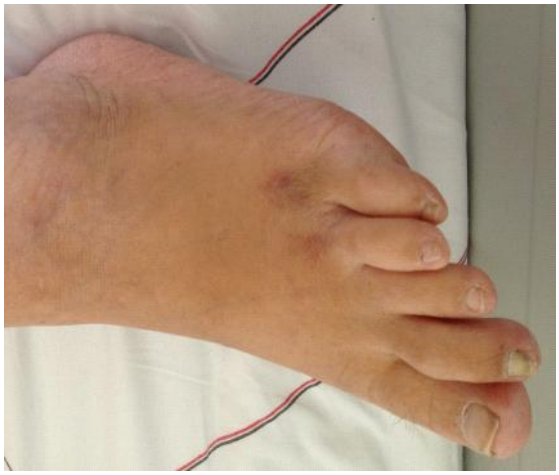

Fig. 2. Showing operation lesion of polydactyly in lower limb

was 275 pg/ml, and folate 5.9 ng/ml. Blood gas analysis were: pH 7.25, CO^2: 41 mm Hg, HCO_3 16.6 mmol/L. Evaluation of urine and the sediment: pH: 7,0 specific gravity: 1005, protein +, glucose +, and microscopic examination of the urine showed rare leukocytes.

The patient's initial diagnosis was Bardet Biedl. We sent a blood sample for the study of mutations in a genetic analysis center. Renal ultrasonography detected reduced kidney size and renal echogenicity increased bilaterally. The patient was considered as progressing towards ESRD, and renal replacement therapy was initiated.

Discussion

The diagnostic criteria for BBS as major features include retinal dystrophy (90%), post axialpolydactyly (21%), truncal obesity (72%), hypogonadism (more frequent in males), renal anomalies, hypertension (50-66%) and chronic renal failure (30-60%). Minor features include learning disabilities, speech delay, developmental delay, behavioral abnormalities, eye abnormalities, brachydactyly/syndactyly, ataxia, mild hypertonia, diabetes mellitus, orodental abnormalities, cardiovascular anomaly, and anosmia [1-4]. Four major or three major and two minor criteria are required for the diagnosis. BBS worldwide changes may be frequently found. Prevalence rates in North America and Europe is with 1:140000 - 1:160000 of live births.

ESRD in BBS patients has been reported at age range of 4-57 years [5-9]. We report a case of BBS with CKD in a 43-year-old female from Turkey. This diagnosis should be considered in patients with renal disease and the characteristic phenotype of retinitis pigmentosa, postaxial polydactyly and central obesity. Renal involvement is common and renal failure is most common cause of death in BBS. These patients should undergo regular monitoring of renal function test for an early diagnosis and treatment of CKD to prevent the progression and respective morbidity and mortality. Renal transplantation is a possible option of RRT in these patients. These findings are valuable for comparing phenotype of BBS patients with CKD from various national and international centers. Since our patient was diagnosed at a late stage once on hemodialysis, the patient and the relatives were informed about renal trasplantation, as well.

In conclusion, a patient presenting with uremia, polydactyly, obesity, mental retardation and if accompanied with retinitis pigmentosa, Bardet Biedl syndrome should be considered as most probable diagnosis.

Conflict of interest statement. None declared.

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Case report

Dialysis and Depression in the Light of Suicide Attempt with Fruits

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Abstract

Depression is a common morbidity seen in chronic renal failure patients but it is often underdiagnosed and undertreated. Here we present a 36-year-old male dialysis patient who had undiagnosed severe depression and attempted to commit suicide with overconsumption of fruits. Fortunately, he was saved with emergent dialysis treatment and was referred to a psychiatry clinic for treatment and observation. In the light of this case we want to point out that diagnosing and treating psychiatric problems of dialysis patients is of vital importance to prevent suicides and also to improve quality of life.

Keywords: Dialysis, depression, suicide

Introduction

Chronic renal failure is often seen with co-morbidities like diabetes, hypertension, cardiomyopathy, arthropathy and peripheral artery disease [1]. Depression is also a common morbidity seen in chronic renal failure patients but it is often underdiagnosed and undertreated [2]. Recognition of psychiatric problems and giving the necessary treatment on time is of vital importance in dialysis patients [3].

Case report

A 36-year-old male patient was brought to the Emergency Clinic with sudden onset of fatigue. He had been on dialysis treatment 3 times a week for the last 6 months. He also had hypertension and used 10 mg of amlodipine daily. He did not receive any other medications and his next dialysis was at the following day. He did not pay regular visits to a nephrologist, but attended his dialysis sessions on regular basis.

Physical examination revealed heart rate of 220/min and arterial blood pressure of 90/70 mmHg. The other findings were normal.

A venous catheter was introduced immediately, blood samples were taken for emergent routine tests and IV fluid was started. An electrocardiogram (ECG) was performed concurrently. It showed tachycardia with high T waves, broad QRS and P waves, prolonged PR distance (Figure 1). Considering his renal failure, these findings alarmed us on the possibility of serious hyperkalemia. He was given 10 mg of calcium gluconate in 10 cc of isotonic solution as IV push followed by 20 mg of furosemide. 5% of dextrose +16 units of regular insulin infusion was started. His potassium (K) level was found to be 9.55 mmol/L and received a 3-hour-emergency-hemodialysis. At the end of the session, ECG showed normal sinus rhythm and K: 4.86 mg/dl (Figure 2).

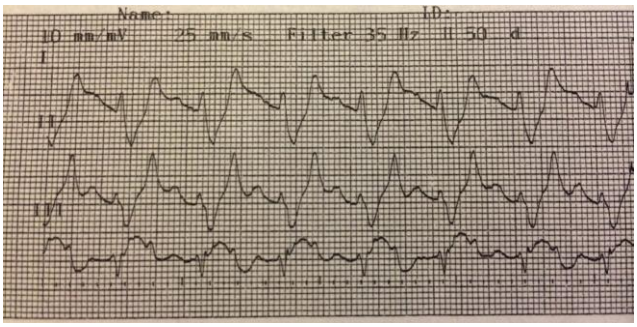

Fig. 1. ECG before dialysis

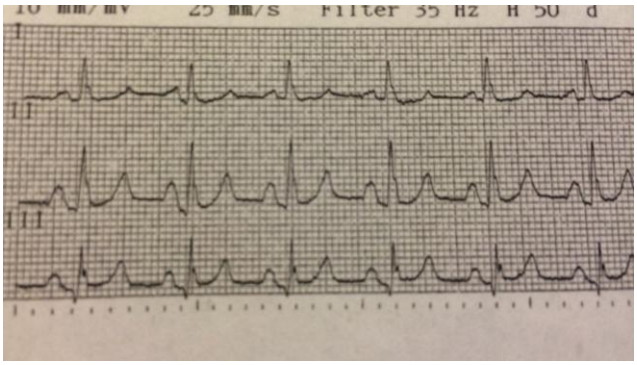

Fig. 2. ECG after dialysis

The patient told us that he had been eating apricots all day long although he was especially warned to avoid fruit consumption during his dialysis sessions. The importance of dietary compliance was repeated to him, and we emphasized to him that he could die by eating too much fruit.

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The following day, a dietician talked with the patient and gave him detailed educational brochures regarding his diet. The other day, he was seen by a nephrologist. His K level was 7.48 mg/dl and he received an emergent dialysis again. His wife declared that he had been eating a lot of grapes. She also stated that he fully understood the consequences of his behaviour; she tried to warn him every time he began to eat fruits but he didn't listen to her; it was his intentional act for the purpose of committing a suicide. Three months after his CRF diagnosis, he was on dialysis. He lost his job because of dialysis sessions and was still unemployed. He did not have health insurance and depended on government support. Having in mind these problems and his behaviour, the patient was considered to have major depression and to have suicidal ideas. Hence, he was referred to the Psychiatry Clinic for an observation and treatment.

Discussion

Depression is often comorbid with chronic diseases and can worsen their associated health outcomes [4]. Chronic kidney disease is a serious chronic disease with such psychological and physical outcomes. Dialysis is a stressful procedure on its own. Patients on dialysis have to depend on machines, invasive procedures and medical professionals for the rest of their lives. Also there is serious food and drink restriction for these patients. Most dialysis patients cannot sustain a full-time job. A serious percent of the patients are unemployed and as a consequence do not have medical insurance. Socioeconomic burdens often cause familial and marital problems [5-7].

According to various studies the prevalence of severe depression is 5-22% and mild/moderate depression 17.7-25% among CRF patients that receive dialysis treatment [8]. Also, dialysis patients have higher suicide rates than healthy population [9].

Presence of a chronic medical illness may decrease the possibility of recognition of accompanying depression by the physician because of overlapping symptoms. Our patient was not diagnosed with depression before attempting to commit suicide. Thus, attention must be paid to signs like depressed mood, loss of interest, slowed thought processes, pessimistic thoughts, lack of appetite, weight loss, fatigue, delay in falling asleep and loss of libido and patients should be questioned regularly about those signs to avoid undiagnosed depression [10]. Suicidal patients use methods like rejecting treatment, disconnecting shunt, overconsumption of K containing food and drugs [11-13].

Counselling and necessary interventions must be a priority of the general treatment when signs and symptoms of depression are present [14]. This would not only improve quality of life, but would also save lives preventing possible suicides among end-stage kidney disease patients [15,16].

Conflict of interest statement. None declared.

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Case report

A Rare Outcome Induced by Metformin Intoxication: Severe Lactic Acidosis and Hepatotoxicity

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Abstract

Metformin is a widely used oral anti-diabetic agent that decreases insulin resistance. Lactic acidosis rarely develops with this medication. Metformin-induced hepatotoxicity has been rarely reported in the literature. We describe a patient, who presented with lactic acidosis and hepatotoxicity after ingestion of 40 pills of metformin in order to commit suicide. The most important treatment step in patients with metformin-associated lactic acidosis (MALA) is high-volume hemodialysis and hemofiltration.

Keyword: metformin intoxication, dialysis, hemofiltration, lactic acidosis

Introduction

Metformin is a biguanide anti-diabetic drug that is widely used in the treatment of type 2 diabetes mellitus. Lactic acidosis is a rare but serious adverse effect of metformin especially in patients with renal failure. Advanced age, liver disease, alcoholism or cardiopulmonary disease can cause lactic acidosis or metformin accumulation. Metformin is absorbed quickly by the intestines and is not metabolized. About 90% of the drug is eliminated by glomerular filtration and tubular secretion [1,2]. The mechanism by which metformin causes acidosis and hepatotoxicity is not entirely understood. In this report we describe a 19-year-old female patient who presented with lactic acidosis, elevated liver enzymes and alterations in the coagulation tests after metformin overdose.

Case Report

A 19-year-old female patient presented to the emergency department with complaints of nausea and vomiting after ingestion of 40 pills of metformin (850 miligram), 4 pills atorvastatin and 4 pills dexsketoprofen in order to commit suicide. Nasogastric tube was inserted and gastric lavage was performed with activated charcoal. She was

Table. 1. Laboratory values of the patient

Initial tests		7^{th} day		14^{th} day	
Glucose	73 mg/dl	Glucose		Glucose	87 mg/dl
Urea	25 mg/dl	Urea	24 mg/dl	Urea	20 mg/dl
Creatinine	1.1 mg/dl	Creatinine	0.8 mg/dl	Creatinine	0.8 mg/dl
Sodium	139 mEq/L	Sodium	141 mEq/L	Sodium	140 mEq/L
Potassium	4.0 mEq/L	Potassium	4.3 mEq/L	Potassium	4.3 mEq/L
Aspartate aminotransferase (AST)	19 IU/L	Aspartate aminotransferase (AST)	82 IU/L	Aspartate aminotransferase (AST)	17 IU/L
Alanine aminotransferase (ALT)	12 IU/L	Alanine aminotransferase (ALT)	91 IU/L	Alanine aminotransferase (ALT)	24 IU/L
Total bilirubin	1.23 mg/dl	Total bilirubin		Total bilirubin	0.9 mg/dl
Direct bilirubin	0.21 mg/dl	Ddirect bilirubin		Ddirect bilirubin	0.15 mg/dl
Amylase	131 IU/L	Amylase		Amylase	70 IU/L
White blood cell	16800 /UL	White blood cell	7300 /UL	White blood cell	
aPTT	19.9 sc	aPTT	21 sc	aPTT	21 sc
PT	18 sc	PT	13 sc	PT	15 sc
INR	1.6	INR	1.1	INR	1.3 sc
pH	7.33 mmHg	pH	7.44 mmHg	pH	
pCO2	32 mmHg	pCO2	36 mmHg	pCO2	
HCO3	9.6 mmol/L	HCO3	25 mmHg	HCO3	
Lactate	4.7 mmol/L	Lactate	0.9 mmHg	Lactate	

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conscious and alert, with blood pressure 100/60 mm Hg, pulse rate 80 beats per minute and body temperature 36°C. There was no significant finding in the physical examination. Initial blood tests revealed glucose 73 mg/dl, urea 25 mg/dl, creatinine 1.1 mg/dl, sodium 139 mEq/L, potassium 4.0 mEq/L, chloride 110 mEq/L, aspartate aminotransferase 19 IU/L, alanine aminotransferase 12 IU/L, total bilirubin 1.23 mg/dl, direct bilirubin 0.21 mg/dl, amylase 131 IU/L, white blood cell 16.800/UL. Arterial blood gas showed acidosis (pH: 7.3 mmHg, pCO2: 32 mmHg, pO2: 70 mmHg, HCO3: 9.6 mmol/L, SatO2: 78, lactate: 4.7 mmol/L, anion gap: 23.4 mmol/L). Initial serum coagulation profile revealed an INR of 1.6 and a PT of 18 seconds. Her acidosis was tried to be controlled with NaHCO3. She was admitted to the hemodialysis (HD) unit where she was treated with 2 hours of HD. Then she was transferred to the intensive care unit due to her depressed alertness. She was treated with hemodiafiltration (HDF) for 24 hours. The patient's level of consciousness returned to normal, lactic acidosis was improved and then she was transferred to the general medical ward.

On the fifth hospital day, elevation of liver enzymes were noticed-AST: 91 IU/L and ALT: 82 IU/L (Table 1). The patient was found clinically to have metformin intoxication with mild hepatoxicity and prolongation in INR and PT on the initial presentation. Markers of autoimmune and viral hepatitis were all negative. The patient underwent abdominal ultrasound that revealed normal findings. N-acetylsysteine and ursodooxycholic acid were started. The symptoms and abnormal laboratory tests of the patient gradually normalized with supportive treatment. Seven days after her admission, the patient was discharged with mild elevations in liver enzymes levels.

Discussion

Metformin is a biguanide commonly used in type 2 diabetics and is considered to be a safe drug with minimal side effects. The anti-hyperglycemic effect of metformin is caused by a decrease in hepatic glucose production, a reduction in intestinal glucose absorption, an increase in insulin sensitivity and an elevation in peripheral glucose uptake and utilization [1].

Lactic acidosis is one of deadly side effects of metformin intoxication [3]. Pathogenesis of metformin-associated lactic acidosis (MALA) is considered to increase intestinal lactate production after accumulation of metformin in the gastrointestinal system associated with using these drugs [3]. In intensive care patients mortality rates have been demonstrated to be as high as 80% [4].

There is no effective antidote in the treatment of MALA. For this purpose parenteral NaHCO3, continuous veno-venous hemodiafiltration (CVVHF) and intermittent hemodialysis are frequently applied methods [5]. Hemodialysis corrects acidosis and also removes metformin from plasma reducing lactate production rate [2].We applied these methods in our patient and received positive results; lactic acidosis improved. Although metformin-associated gastrointestinal discomfort and lactic acidosis is a widely recognized side effect of this drug, metformin-induced liver injury has been rarely reported [1,6,7]. Although pathophysiology of hepatotoxicity is unclear, Zheng suggested that metformin-induced liver injury was associated with concomitant intake of other hepatotoxic drugs, in most of the reported cases as in our case. Although rare, metformin can be responsible for inducing liver damage [7]. Nammour reported a case with metformin-induced cholestatic hepatitis, treated with discontinuation of the drug, and liver enzymes normalized except for a persistently increased level of alkaline phosphatase, most likely related to a prolonged cholestatic effect of metformin [7]. Hashmi suggested that in published cases with metformin-induced hepatotoxicity the number of reported cases on this subject was underestimated, probably due to the lack of a consistent terminology [8]. Because metformin is not metabolized in the liver, it has been considered safe from a hepatic standpoint; however, metformin hepatotoxicity has rarely been reported [9,10]. Possible mechanisms of injury are direct, idiosyncratic, or a drug-drug interaction leading to acute hepatocellular and/or cholestatic jaundice [9,11].

Akinci *et al.* showed a temporary decrease in proteins of the coagulation system synthesized by the liver with no effect on the coagulation factors produced by the endothelium [12]. Probably, prolongation in our patient's coagulation parameters might reflect a temporary defect in hepatic function.

The most important treatment step in patients with MALA is high-volume hemodialysis and hemodiafiltration [5]. A few case reports related with hepatotoxicity have been associated with metformin usage.

Packer *et al.* reported a case with fulminant and fatal hemolysis that occurred shortly after metformin was started for treatment of type 2 diabetes mellitus [13]. Boyd *et al.* suggested that diabetic heart failure patients with elevated systolic blood pressure are at an increased risk of developing acute decompensated heart failure, which is often associated with decreased kidney function [14]. It is well known that patients with concurrent conditions, including advanced age, liver disease, alcoholism, cardiopulmonary disease or renal failure, which in themselves can cause lactic acidosis or metformin accumulation [15]. Since renal function can appear to be normal when measured by serum-creatinine concentration in older patients with reduced muscle mass, calculation of GFR often reveals impairment, and metformin is contraindicated in these patients with poor renal function [16]. MALA should also be considered in the acutely unwell diabetic patients on metformin [17].

The initial presentation of this patient would suggest a picture of MALA. Classically metformin overdose has

been found to produce lactic acidosis. This case illustrated that we should also be aware of the potential rare side effects of metformin as hepatotoxicity, cholestatic hepatitis and hemolytic anemia. Routine workup of metformin overdose should include liver enzymes and tests for coagulation and hemolysis.

Conflict of interest statement. None declared.

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Case report

Different Outcome of Goodpasture Syndrome

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Abstract

Goodpasture syndrome is a rare autoimmune disease, with significant morbidity and mortality in young people and otherwise healthy population. Complete disease remission is possible with prompt diagnosis and treatment. We report 3 cases with Goodpasture syndrome treated at the Department of Nephrology, University Clinic of Nephrology, with different outcome. All of the patients were with similar clinical feature, with renal failure that needed treatment with hemodialysis. But results of the treatment with plasmapheresis indicate that this procedure reduces morbidity in patients with Goodpasture syndrome. The clinical course and the outcome of the disease were different. The disease is unpredictable, and the early diagnosis and start with the treatment is important for the remission.

Keywords: goodpasture syndrome, kidney function, plasmapheresis, treatment

Introduction

Goodpasture syndrome is a rare, but serious autoimmune disease, that attacks the lungs and kidneys. The disease occurs when the body's immune system, mistakenly produces antibodies against collagen in the lungs and kidneys. It is almost always fatal; if it is not quickly diagnosed and treated [1-3].

Researchers do not fully understand why immune system attacks collagen in the lungs and kidneys. Goodpasture syndrome usually affects young people, between 20-30 years old and sometimes older than 60 years. The first signs of the disease may include fatigue, nausea and vomiting, difficult breathing and pale skin. Because the disease may rapidly involve the lungs, initial symptoms like shortness of breath and cough may occur sometimes with blood. When the kidneys are affected, symptoms include high blood pressure, hematuria, dysuria, swelling and back pain [4,5]. Although Goodpasture syndrome may cause life-threatening bleeding in the lungs, it usually does not cause long-term lung damage, but the most serious consequence is kidney failure, which may require either dialysis or kidney transplantation [6,7].

We report 3 cases with Goodpasture syndrome, treated at the Department of Nephrology, University Clinic of Nephrology in Skopje. The different outcome of the 3 cases shows that the disease is unpredictable.

Case 1

A 61-year-old woman was admitted to our Department with a history of coughing and mild hemoptysis, associated with fatigue, febrility and inappetence. She was treated as virosis several months ago, with temporary stabilizing, but after that, the malaise and coughing were repeated again, and she was hospitalized at our Department, with similar clinical symptoms. Before admission a computerized tomography of the lungs was done and after that a transthoracic biopsy of a nodular formation in the lungs was performed. The result of the lung biopsy showed granulomatous inflammation. The control chest-x rays disclosed a few scattered pulmonary infiltrates and a small exudative pleuritis.

Laboratory findings were as follows: hemoglobin 85 g/l, erythrocytes $3{,}5x10^9$/l, leukocytes $24{,}6x10^3$/l, CRP 329. Serum protein was 75 g/l, albumin 29, globulin 46, and proteinuria 1.7 g/24h. Renal function was diminished with urea 21.2 mmol/l and creatinine levels 670 micromol/l, and creatinine clearance 12.5 ml/min. Serum immunogobulins were within the normal range, and c-ANCA was negative. There was an evidence of circulating anti-GBM antibodies in patient's serum, 6-times higher than reference values. The antibodies were against the glomerular basal membrane, affecting the alfa-3 chains of type IV collagen.

As the renal function was impaired, anuria appeared, and treatment with hemodialysis was started. Renal biopsy was performed, with immunofluorescence estimation that showed massive infiltration of the interstitium with crescent formations, over 90%, anti IGA negative, anti IgG diffuse deposition along the GBM +3. Histopathological analysis showed extracapillary glomerulonephritis, which was in conjunction with Goodpasture syndrome.

The treatment included corticosteroids as pulse therapy, and plasmapheresis was done every day for a period of

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one week. This treatment was combined with hemodialysis, because of the renal failure and the high levels of urea and serum creatinine. After 3 weeks the clinical signs were stabilized with the restitution of the pulmonary damage, but the necessity of dialysis treatment was evident. The patient continues with chronic hemodialysis program for the next period.

Case 2

A 28-year-old male, with intensive coughing with hemoptysis and fatigue was hospitalized at the Department of Pulmonology, University Clinic of Pulmonology in Skopje, as pneumonia. The 24-hour proteinuria was 5 g/l, with oliguria. The values of urea were 15.5mmol/l and creatinine 318 micromol/l; chest radiography detected alveolar infiltrates. Renal biopsy was performed with immunofluorescence estimation for focal necrotizing glomerulonephritis with linear IgG deposits along the GBM and histopathological diagnosis for glomerulonephritis extracappilaris proliferative, rapidly progressive-Goodpasture syndrome. Because of the renal failure the patient was admitted to the Department of Nephrology for further treatment. Plasmapheresis, 15 sessions against 2000-2400 ml fresh frozen plasma within 20 days, was done. Because of of the renal function deterioration, treatment with hemodialysis was started every second day. Treatment with corticosteroids was also performed 2 times/3 day course of methylprednisolone (500 mg/day) with tapering the dose of orally steroids in the following days. Three courses i.v. cyclophosphamide 500 mg were given for 8 days, followed by oral cyclophosphamide 100 mg/day/7days, proceeding with 50 mg/day afterwards. At first, antibodies against GBM were positive with high positive titer 1:320, but after the treatment the titer was 1:20. Laboratory findings were as follows: Hb 80, Er 3.1, Htc 0.30, Le 22.2…6.2, Tr 397…176, urea 42.8 mmol/l, creatinine 912 micromol/l, proteinuria up to 12.6 g/l. Immunoglobulins: IgA 1.78, IgG 7.13, IgM 0.64, C3=0.50, C4=0.11, circulating immunocomplexes 0.20.
The patient's condition improved, the last h-ray control was completely normal. However, the patient became dependent on hemodialysis. Re-biopsy revealed still active extracapillary glomerulonephritis in 10/14 glomeruli with extensive tubule-interstitial changes that can explain anuria.
After several months of chronic hemodialysis treatment, kidney transplantation was performed, with good effect and further improved condition.

Case 3

An 18-year-old female had breathing problems, coughing with hemoptysis and fatigue for 3 months. The lung biopsy revealed Goodpasture syndrome. After the biopsy and worsening of the condition, with hypoxia, the patient was treated at the Department of Pulmonology, and the respiratory symptoms were improved. Because renal function impairment with urea 22.8 mmol/l, creatinine 400 micromol/l, oligoanuria, hospitalization at the Department of Nephrology was indicated. The other laboratory findings were as follows: Hb 98, Er 3.2, Htc 0.29, Le 12.4, Tr 124, creatinine clearance 17.8 ml/min, total protein 46, albumin 27, globulin 19, proteinuria /24h: 1.57 g. Anti-GBM antibodies were 5 times higher than normal reference values.
Renal biopsy was performed with immunoflorescence estimation without signs for definitive sclerosis, but the presence of crescent formations is 100% with different expansion. Anti IgG intensive linear deposit along GBM +3. Histopathological analysis showed extracapillary glomerulonephritis-Goodpasture syndrome.
Treatment with plasmapheresis was started and 6 plasmapheresis were performed in the following period of 10 days. A therapy with corticosteroid was also performed, with pulse methylprednisolone therapy 500mg/3 days, followed by steroids per os. Amp. cyclophosphamide was given once, and after that improvement of the symptoms was registered. There was no need of hemodialysis. The renal function slowly improved. During the period of several months after hospitalization the therapy with corticosteroids continued. Proteinuria/24; 0.78-1.6 g/l, persisted, the values for urea and creatinine were normalized (urea 3.6, creatinine 73). One year later complete improvement was noticed and the patient had no need of therapy. At the last control all the results were normal and the patient was clinically stable.

Discussion

Substantial variation exists in the clinical manifestations of patients with anti-glomerular basement membrane (anti-GBM) disease [1,3,8]. From 60-80% of patients have clinically apparent manifestations of pulmonary and renal disease, 20-40% have renal disease alone, and less than 10% have disease that is limited to the lungs. Environmental factors are thought to play a role in triggering the disease. All age groups are affected, but the peak incidence is in the third decade in young men. The second peak may occur in the sixth and seventh decade, affecting men and women equally. Lung hemorrhage is more common in younger men, while isolated renal disease is more frequent in the elderly, with near equal gender distribution [4,5].
In the past, Goodpasture syndrome was usually fatal. Aggressive therapy with plasmapheresis, corticosteroids, and immunosuppressive agents has dramatically improved prognosis [9,10]. With this approach, the 5-year survival rate exceeds 80% and fewer than 30% of patients require long-term dialysis.
We presented 3 cases of Goodpasture syndrome, with similar presentation at onset: severe pulmonary involvement, more than 90% crescents at renal biopsy, with

linear IgG diffuse deposition along the GBM+3 and high titer of antibodies against GBM.

All of the patients were with similar clinical features, with renal failure that needed treatment with hemodialysis. But results of the treatment with plasmapheresis have indicated that this procedure reduces morbidity in patients with Goodpasture syndrome. Although all patients were treated with cytotoxic therapy, it can be used only as an adjunct to plasmapheresis. In one of the cases we used this therapy only once, and the clinical feature was improved after several sessions.

Conclusions

We can conclude that Goodpasture syndrome has different outcome and the course of the disease is unpredictable. The early diagnosis and initiation of plasmapheresis treatment may be important for remission of the disease.

Early diagnosis and treatment lead to improved prognosis. The combination of cytotoxic agents and steroids with plasmapheresis is effective if instituted early in the course of the disease.

Conflict of interest statement. None declared.

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Letter to the Editor

Unexpected Extremely High Level of Creatinine in Non-dialysed Female Patient

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Dear Sir,

There are only a few published studies confirming the ability of either urea or creatinine to induce adverse biochemical and physiological effects and there is not a defined level of serum creatinine that is lethal itself. Given the fact that by consulting the literature we did not find the highest level of creatinine in a surviving patient published in Croatia, we want to present the highest recorded level in our practice and probably in Croatia.

A sixty-two year old woman presented to the Merkur Clinical Hospital Emergency Department in Zagreb with the serum creatinine 2316 µmol/L (26.2 mg/dl) and a one week history of uremic symptoms. Her previous medical history was negative; she has not been taking any medications. Renal failure in this patient occurred due to bilateral hydronephrosis developed as the result of advanced cervical malignancy and was accompanied by severe microcytic anemia (hemoglobin 35 g/l, hematocrit 0.120, MCV 71.4 fL), compensated metabolic acidosis (arterial pH 7.230) and hyperkalemia (serum potassium 6.4 mmol/l). An acute hemodialysis was made on the day of admission. About one month later at the time of the discharge the serum creatinine was 490 µmol/L. During hospitalization the patient was conscious, oriented and cardiorespiratory compensated.

Creatinine is the endogenous marker most commonly used to measure kidney function [1]. The proximal tubules secrete creatinine, which accounts for 10-20% of the excreted load [2]. The normal reference range for serum creatinine is 0.7 to 1.3 mg/dL (62-115 umol/L) for men and 0.6 to 1.1 mg/dL (53-97 umol/L) for women [3]. Progressive obstructive uropathy may lead to uremia, electrolyte imbalances and persistent urinary tract infections, if obstruction is not bypassed [4], as we report in this case. Although it is a marker of uremic toxicity, the actual effect of creatinine on homeostasis in humans is unresolved [3]. One of the most disabling features of kidney failure is encephalopathy that is caused by the accumulation of uremic toxins [5]. The patient we report on presented the highest creatinine level (2316 µmol/L) we experienced in our twenty-eight years long practice and presented with symptoms of uremia including nausea, vomiting, fatigue and slowed cognitive functions. Searching through literature and available data we could not find written evidence on the highest creatinine level in practice in Croatia in non-dialysed patients. A literature search indicates that the surviving uremic male patient (BMI 28) with creatinine 53 mg/dl (4685.2µmol/L) reported by A.C. Storm *et al.* in Open Journal of Nephrology (2013) could be the highest creatinine in the literature [3].

A renal failure and increased creatinine level in the patient we reported occurred due to bilateral hydronephrosis that had been developed due to advanced stage of cervical carcinoma. The finding of ureteral obstruction due to malignancy carries a poor prognosis with a resulting median survival of 3 to 7 months, and confers a worse overall prognosis [4,6]. Relief of obstruction is usually achieved by placement of a percutaneous nephrostomy tube, an internalized double J nephroureteral stent, or an internal/external nephroureteral stent (NUS) [7]. Our patient had rejected suggested bilateral percutaneous nephrostomy as modality of decompression and accepted life saving dialysis. This patient with the highest recorded serum creatinine in our practice and according to available data in Croatia has survived uremic symptoms and has been discharged with a program of hemodialysis three times per week.

The highest level of creatinine (2316 µmol/L) we registered manifested through early symptoms of uremia and minimal changes in mental status suggest that creatinine as a potential uremic toxin has a minor pathophysiologic role in causing uremic syndrome and encephalopathy.

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Conflict of interest statement. None declared.

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