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Contents

Dear readership

The Hellenic College for Nephrology and Hypertension (HCNH) was founded in 2004. The aims of HCNC are as follows:

a. The continuous and by program education of Greek doctors and especially the Nephrologists of recent medical data and research activity in relation with:

1. Physiology of kidneys
2. Epidemiology, pathophysiology and pathogenesis of primary renal disease
3. Secondary renal disease after systemic, metabolic and other diseases
4. Control of electrolyte and acid-base disorders
5. Treatment of hypertension
6. Study of acute renal failure in the Hospital and especially in Intensive Care Units
7. Prognosis, prevention and treatment of end - stage renal failure
8. Renal transplantation

b. The constant communication with the common people in order to teach simple meanings concerning the prevention of renal diseases, especially for hypertension, diabetes and food conditions

In the time past the College has organised a significant number of meetings in various areas of Greek territory. The first Congress of HCNH was held in Patras on Jan 2011. In this supplement we publish, after peer review, selected papers from the 1st Congress of HCNH.

Georgios Vergoulas

Editor in chief of Hippokratia

REVIEW ARTICLE

Drug abuse and kidney

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Abstract

Over the past 30 years, the number of drugs' dependents has increased. Drugs cause psychosomatic changes and ultimately death. The rapid increasing of illicit drug use is an important social health problem. Their use may be therapeutic under medical supervision or illegal by users in dependency. The majority of these substances or their metabolites are excreted through the kidneys and renal complications of drug abuse are frequently encountered. They include a wide range of glomerular, interstitial and vascular diseases. The damage may be acute and reversible or chronic and may lead to end stage renal failure. The involvement of the kidney in drug use is either attributed to their elimination through it, to a direct nephrotoxic effect, or through other mechanisms. Acute renal failure (ARF) can be caused by rhabdomyolysis, hypotension and dehydration or by the direct toxic effect of heroin, cocaine abuse, MDMA or volatile solutes use. Glomerulonephritis and nephrotic syndrome can be presented as focal glomerulosclerosis in heroin nephropathy and cocaine abuse, post infectious or associated to HBV, HIV or HCV infection nephropathy. Chronic parenteral drug users may develop secondary amyloidosis. Finally, drug abuse can lead to ESRD mainly by causing deterioration of pre-existing renal disease at a higher rate. In conclusion, significant alterations have been observed in the kidneys' structure since they participate in drug metabolism. There is lack of retrospective studies and information has been given from case reports. The continuation of substance abuse after the appearance of renal damage increases the risk of permanent renal disease and consequently may lead to end stage renal failure. Hippokratia 2011; 15 (Suppl 2): 4-8

Key words: drug abuse, heroin nephropathy, glomerulonephritis, acute renal failure, review

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Knowledge of drug abuse dates back to ancient times. In the 3rd century BC, Arab traders of opium as well as the Aztecs were using hallucinogenic substances, particularly mushrooms around the same time[1]. Over the past 30 years, the number of drugs' dependents appears increased[2]. By 1997, 25% of the population reported use of drugs at least once in their life time. Drug abuse appears to be more common in middle social-economic class and in young men 25 to 29 years of age[3]. There are available data on drug use in the general population in Greece from the study conducted by the University of Mental Health (UMHRI), in 2004 (European Monitoring Centre for Drugs and Addiction). It seems that drug use in Greece rose significantly from 1984 to 2004. According to this study, 8.6% of the Greek population, aged 12 to 24 years, indicate to have experienced drug use, mainly cannabis. A study in 2006 indicates a rate of 17.4% having used drugs at least once (24% men and 14% women). The ESPAD study in 2007 involved high school students aged 14 to 16 years showed that 6% had tried marijuana or hashish, and 9% of the students reported use of inhalants[4]. The efforts of researchers to highlight addicted personalities of special predisposition have not yielded positive results, but in Strang J's report, a genetic predisposition on drug abuse seems to exist[2]. Drugs cause psychosomatic changes and ultimately death. Among Europeans aged 15-39 years, drug overdoses accounted 4% of all deaths[5]. The rapid increasing of illicit drug use is clearly an important social health problem.

Characteristics of drugs

Drugs are defined as natural or synthetic substances that are used for medical or recreational purposes and the repeated use leads to transient or chronic dependency. This behaviour of mental and physical dependence is described as "toxic addiction" or the recently used term "substance addiction". Drugs have toxic effects on human central nervous system; therefore, more correct is the term "toxic substances"[6]. According to the U.S. Justice Department, 33 pharmaceutical substances are classified in the group of drugs (Table 1). Their use may be therapeutic under medical supervision or illegal by users in dependency[7].

a) Heroin (diacetylmorphine, diamorphine) is the most commonly used drug of the opioids group. The intake may be through the nasal, gastrointestinal, respiratory, subcutaneous («skin popping»), or intravenous («mainlining») route. It is often injected in combination with cocaine («speed balling»)[8]. Heroin's half life is 3 minutes and is rapidly metabolized into morphine, which is mainly responsible for the pharmacological actions of heroin. Heroin is excreted in urine as free and unconjugated morphine. There are multiple renal complications from its abuse [9].

b) Cocaine is an alkaloid derived from a shrub (Erythroxylon) that grows in the Andes. It can be absorbed through

Amphetamines	Hydromorphone	Narcotics
Barbiturates	Inhalants	Opium
Benzodiazepines	K2	Oxycodone
Cannabis	Ketamine	Painkillers
Cocaine	Khat	PCP
Depressants	LSD	Peyote and Mescaline
Dextromethorphan (DXM)	Marijuana	Psilocybin
GHB	MDMA or Ecstasy	Rohypnol
Hallucinogens	Methadone	Salvia Divinorum
Heroin	Methamphetamine	Steroids (anabolic)
Hydrocodone	Morphine	Stimulants

Table 1: Pharmaceutical substances which are classified in the group of drugs according to the U.S. Justice Department (http://www.justice.gov/dea/concern/concern.htm)

any mucous membrane, smoked or injected, intravenous or intramuscular. It is estimated that it has a half-life of 30 to 90 minutes. A rate of 80 to 90% of cocaine is metabolized and the rest is excreted unchanged in urine, where metabolites can be detected for 36 to 48 hours[10]. c) Ecstasy (MDMA: 3, 4 - methylenedioxymethamphetamine), originally patented in 1914 as appetite suppressant, is a widely used recreational drug in the nightclubs of Europe during the so-called "rave" parties. It is generally taken orally. In the U.S.A., MDMA has not been taken as a dance drug and consequentially the spectrum of side effects is different with cardiac arrhythmias being more common[11]. The MDMA is rapidly absorbed, reaching maximum plasma concentration within approximately 2 hours[12]. It is metabolized by the liver and excreted by the kidneys. d) Temazepam and diazepam abuse is usually attributed to legitimate prescriptions or theft from pharmacies. Temazepam is now a controlled drug and can be taken individually or as part of a substances "cocktail". About 70% of injecting drug users has used temazepam at some time[13]. e) The mushroom species of Panaeolus muscaria and Psilocybe (including Psilocybe Semilanceata - «liberty cap», «magic mushrooms») are hallucinogenic if eaten[14]. They are not nephrotoxic themselves, however, proper identification of the mushroom is difficult and eating poisonous species is not uncommon. The Cortinarius mushrooms which contain the nephrotoxic agents of orellanine are not easily identifiable and can lead to kidney damage[15]. f) Deliberate inhalation of volatile solvents ("glue sniffing") was first appeared as a form of substance abuse in the early 1960's by inhaling glue used in model planes. The practice is diversified and includes the use of cement glue, aerosol paints, lacquers, solvents, typewriter correction fluid and fuel[16]. These products contain some volatile substances, including toluene, n-hexane, methyl ketones, chlorohydrocarbons and benzene. The euphoria induced by inhaling solvents is similar to alcohol intoxication. In addition, solvents can cause hallucinations, of short-term duration (15 to 30 minutes)[17] and may develop serious heart, lung, liver, neurological and renal complications, as well as sudden death[18].

Renal complications

Key property of drugs is their analgesic effect via the central nervous system. Consequently, this action has an impact on other functions, such as heart rate, breathing rate and blood pressure. The majority of these substances or their metabolites are excreted through the kidneys and renal complications of drug abuse are common. They include a wide range of glomerular, interstitial and vascular diseases. The damage may be acute and reversible or chronic and can leads to end stage renal failure. The involvement of the kidney in the use of drugs is either attributed to their elimination through the kidney, or a direct nephrotoxic effect, or through other mechanisms.

Acute renal failure

Coma caused by heroin overdose leads to muscle damage and rhabdomyolysis. Hypotension, hypoxia, acidosis and dehydration cause deterioration of renal function and development of acute renal failure. Grossman RA et al. indicate rhabdomyolysis in heroin users without the presence of coma, or evidence of muscle compression. They refer that this may be due to a direct toxic effect or an allergic reaction to heroin, or heroin additives flawed[19]. Also, acute or chronic cocaine use seems to be involved in acute renal failure which may occur as a result of rhabdomyolysis[20, 21]. Approximately 24% of patients examined in the emergency department with complaints related to cocaine, showed concentrations of creatine kinase over 1000 U / l[22]. A rate of almost one third of these patients developed acute renal failure[20, 23]. Cocaine can cause rhabdomyolysis through muscle ischemia caused by prolonged vasoconstriction of intramuscular arteries, by generalized convulsions and coma which leads to secondary compression of the muscles, or by direct damage to muscle fibres. Cocaine may be contaminated with arsenic, strychnine, amphetamines and phencyclidine. These substances could be responsible for convulsions and rhabdomyolysis. Acute renal failure due to massive infarction in both kidneys and accelerated atherosclerosis in kidney has been reported in drug users[24-27]. Acute renal failure may occur also to users of MDMA or other amphetamines and the main mechanism is rhabdomyolysis.

The patients usually present muscle pain and tenderness. Laboratory tests find an increase of creatinine and urea, potassium, phosphorus and creatine kinase. Myoglobin and granular casts are also detected in urine. Because of the frequency of acute renal failure, users are aware of the risk when dehydration coexists and often consume large quantities of water, so they may present hyponatremia and / or cerebral edema[28]. Hyponatremia on dilution due to excessive fluid intake can coexist with inappropriate antidiuretic hormone[29]. Moreover, there are reported cases of MDMA users with malignant hypertension and acute renal failure which is associated with intense sympathomimetic effects of MDMA[30]. Acute renal failure has been also described after intra-arterial injection of temazepam. Ischemia of the extremities is induced as a result of embolization particles and subsequent rhabdomyolysis and myoglobinuria[31]. Severe, but temporally dialysis depended, renal failure was present in 20% of temazepam users[32]. Oliguric acute renal failure may develop after ingestion of the mushroom Cortinarius within 5 to 12 days. In some patients, renal failure is transient[33], but in others may be permanent[34]. Acute kidney failure can also occur in users of volatile solutes due to acute tubular necrosis[35] or acute interstitial nephropathy[36] possibly due to toluene. Although there is no unanimity of opinion about the risk of health effects of smoking marijuana, there have been reported cases of patients with multisystemic involvement after intravenous administration of marijuana. The severity appears to be dose dependent. It includes fulminant toxic hepatitis, gastroenteritis, hypoalbuminemia, acute renal failure, electrolyte disturbances, leukocytosis, anemia, and relative thrombocytopenia[37].

Glomerulonephritis and nephrotic syndrome

The focal glomerulosclerosis is the predominant glomerular lesion in heroin nephropathy and increased mesangial matrix is considered a precursor of glomerulosclerosis, which seems to depend on the time of exposure to morphine[38]. Heroin can cause glomerulonephritis with many indirect mechanisms, such as immune-mediated in bacterial and fungal endocarditis caused mainly in intravenous use[39, 40]. There is a high rate of viral, bacterial and fungal infections associated with intravenous drug use, including heroin[41]. Thus, the occurring glomerulonephritis (GN) can be post-infectious. Local pyogenic abscesses by Staphylococcus aureus, have been associated with GN and this is due to deposition of immune complexes. Membranous glomerulonephritis due to HBV infection and mesangiocapillary glomerulonephritis due to cryoglobulinemia accompanying the HCV infection have also been described. Secondary (AA) amyloidosis has increased in frequency as a cause of renal disease in chronic drug users by parenteral route, especially among those who inject drugs subcutaneously («skin poppers»)[42,43]. Chronic use can lead to end stage renal failure. Nephrotic syndrome has been reported due to secondary amyloidosis in chronic drug users by parenteral route. Terminating the usage is the most effective therapy[44, 45]. Unfortunately, there is no experimental model that relates heroin with renal failure, but the heterogeneity of the response indicates different pathogenetic mechanisms. Also, there are no well-designed epidemiological studies providing information about heroin nephropathy[39]. In the 1970s and 1980s, nephropathy associated with heroin (HAN) was described. It is clinically shown as nephrotic syndrome and progresses rapidly to end stage renal failure. The process can be reversed with discontinuation of use[9]. The findings of renal biopsy usually present focal segmental glomerulosclerosis[46]. The pathogenesis is unclear. Heroin or any addition to its manipulation is considered to act as an antigen, leading to renal deposition of immune complexes[9]. Studies in animals have shown that morphine may have a direct effect on the glomerulus, causing proliferation of fibroblasts and reducing the degradation of collagen type IV. In North America, a reduction in the incidence of heroin nephropathy (HAN) among intravenous users has been described[47]. This is explained by the improvement of the quality of heroin supplied to addicts, thus exposed to lower doses of potentially nephrotoxic additional substances. Nowadays, nephropathy associated with the virus HIV (HIVAN) is diagnosed more frequently in heroin addicts[48]. The HIVAN is also presented with nephrotic syndrome and rapidly progressive renal failure and in some urban communities in the U.S., can cause up to 38% of end stage renal failure[49]. Renal biopsy usually reveals characteristically focal glomerulosclerosis of a glomerular collapse type (collapsing glomerular) with protrusion of epithelial cells. A recent publication incident with clinical and histological outcome of HIVAN after treatment with triple antiretroviral treatment and reduction of viral load supports the hypothesis that the virus has a direct cytotoxic action in the kidney [50]. Purpura glomerulonephritis with Henoch-Shonlein has also been described after using acetaminophen and codeine[51]. Severe renal failure has been reported in users of oxycodone while biopsy revealed by the electron microscopy, fiber depositions between the glomeruli and between the tubular basement membrane[52]. Immunologically, cocaine has been proved to increase the mesangial through the release of interleukin-6 by macrophages and evolves focal segmental glomerulosclerosis[53]. Administration of cocaine in experimental models has both non-specific lesions in the glomerulus and the interstitial tissue[39].Cases of renal scleroderma[54] Henoch-Schoenlain purpura[55], necrotizing vasculitis with multiorgan failure[56] and Goodpasture's syndrome[57] have been reported in cocaine users. Marijuana and cannabis do not seem to be implicated in glomerular injury but a de- novo posttransplant membranous GN in a chronic marijuana user after cadaveric kidney transplantation has been described[58]. The nephrotoxic action of volatile adhesives seems to be attributed to toluene[59]. Various renal lesions have been associated with its abuse. Microhematuria, pyuria and proteinuria[60], distal renal tubular acidosis and Fanconi syndrome, urinary stones[61], glomerulonephri-

tis[62], Goodpasture syndrome[63] have been described . The use of anabolic steroids can cause focal segmental glomerulosclerosis with proteinuria, either by hyperplasia or by mesangial direct nephrotoxic effect[64].

Chronic Renal Failure and Hypertension

Increasing numbers of African-Americans in urban centers, developing hypertensive end stage renal failure has been observed in recent years[65]. Forty-four per cent of these patients have a history of substance abuse, compared to a 5% of diabetics and 11% of patients with other causes of renal disease. However, a study of 301 chronic cocaine users showed no correlation with chronic hypertension or development of microalbuminuria[66]. It also seems that cocaine may cause deterioration of preexisting renal disease at a higher rate, rather than cause a de novo disease[67].

Conclusion:

Drug abuse is a major social problem of the modern world. The impact on the psychological and the organic sphere causes severe burden on social behavior and physical health in this population. Significant alterations have been observed in the kidneys' structure since they participate in drug metabolism. Glomerulus and interstitial injury has been found in case reports. Unfortunately there is a lack of an experimental model as well as an efficiently designed research plan for the drug users. The continuation of substance abuse after the appearance of renal damage increases the risk of permanent renal disease and consequently leads to end stage renal failure. Decreasing the number of users seems to be the best way in order to avoid renal complications.

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REVIEW ARTICLE

Cardiorenal-anemia syndrome - definition, epidemiology and management: The Cardiologist's view

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Abstract

The term "cardiorenal anemia syndrome" (CRAS) was introduced to describe the frequent coexistence of heart failure (HF), renal dysfunction and anemia as well as the close pathogenetic relationship between them. Up to two thirds of patients with acute heart failure (HF) and nearly one third of those with chronic HF have at least moderate renal dysfunction. Anemia, on the other hand, is detected in 10-60% of HF patients, depending on definitions and HF severity. Data on the coexistence of anemia and kidney disease in HF is quite variable and a prevalence of 3-22% is reported by various studies. Both renal dysfunction and anemia are independent predictors of adverse prognosis in HF and seem to have an additive effect on patients' survival. Anemia pathogenesis in CRAS is multifactorial and among other factors includes reduced synthesis of and/or resistance to erythropoietin and iron deficiency. As a result, erythropoiesis stimulating agents (ESA) and iron supplementation have both emerged as potential therapeutic modalities for CRAS. Although the first small clinical trials on ESA were promising, the subsequent large-scale testing of those agents resulted in controversial findings. Recent studies on the use of iron therapy in HF patients with iron deficiency have shown beneficial effects regarding patients' symptoms, functional status and quality of life, which seem to occur irrespectively of the presence of anemia. However, there are several issues that need to be clarified, including whether the correction of iron deficiency is followed by better long-term prognosis, what patients benefit the most and therefore need to be treated or what therapeutic targets should be pursued. Hippokratia 2011; 15 (Suppl 2): 9-14

Key-words: cardiorenal syndrome, anemia, iron deficiency, iron replacement therapy, review

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Definition

Cardiorenal syndrome is defined as the coexistence of cardiac and renal dysfunction, in which an acute or chronic deterioration of one of the two organs leads to an acute or chronic worsening of the other[1]. As a result, cardiorenal syndrome represents a wide range of conditions in acute or chronic setting, in which the primarily affected organ may be either the heart or the kidney. Other terms that have been used in this population but are not identical to cardiorenal syndrome include "diuretic resistance", defined as congestion persistence despite treatment with intravenous furosemide in high dose or combination of loop, thiazides and/or aldosterone inhibitors and "worsening renal function" (WRF) defined as an increase in serum creatinine ≥0.3 mg/dL or ≥25% from baseline during hospitalization for acute heart failure (HF)[2].

As both HF and chronic kidney disease (CKD) cause anemia, which in turn leads to both cardiac and renal deterioration, Silverberg expanded the term "cardiorenal syndrome" to also include anemia and therefore the term "cardiorenal anemia syndrome" (CRAS) was born in 2002[3,4]. As a result, CRAS may be defined as the combination of HF, kidney disease and anemia, in which each one of the three conditions causes worsening of the other two, establishing a vicious circle of progressive deterioration.

Although questioned, the use of the term CRAS stresses on one hand the close epidemiologic and pathogenetic relationship of its three components and on the other the need for a comprehensive approach for their prevention and treatment.

Epidemiology

The epidemiology of CRAS is complicated as it depends on the prevalence of each one of its components, which in turn is largely dependent upon the applied definitions and the disease severity of the population studied. As a result, the reported data is considerably variable. Seen from the Cardiologist's view, the majority of clinical trials in HF exclude patients with clinically important co-morbidities, such as moderate to severe renal dysfunction or significant anemia. HF registries in contrast provide a better picture of the prevalence of renal dysfunction and anemia in the real-world HF populations. In the Acute Decompensated Heart Failure National Registry (ADHERE), the largest registry on

acute HF including nearly 120,000 patients in U.S.A., normal renal function [estimated glomelural filtration rate (eGFR) ≥90 ml/min/1.73m^2) was present in only 9% of patients; two thirds of patients (64%) had at least moderate renal dysfunction (eGFR <60 ml/min/1.73m^2), while 20% of them had severe renal dysfunction (eGFR <30 ml/min/1.73m^2)[5]. In the recent European Society of Cardiology – Heart Failure (ESC-HF) Pilot registry including more than 5000 patients, either hospitalized for acute HF or ambulatory ones with chronic HF, chronic renal dysfunction was present in 26% and 19% of acute and chronic HF patients, respectively, while severe renal dysfunction (eGFR <30 ml/min/1.73m^2) was detected in 10% and 5% of patients, respectively[6]. Moreover, nearly one fourth of patients hospitalized for acute HF develop WRF during their hospital stay, with an occurrence reported by different studies between 21 and 29%[7-9].

On the other hand, anemia is detected in 10-60% of HF patients, depending on the applied definition of anemia and the severity of heart failure[10]. A meta-analysis of 34 trials including 150,000 patients reported a prevalence of 37%[11]. In HF registries, anemia, defined as a hemoglobin level <12 g/dL, was encountered in 40% of patients in ADHERE, 33% in EuroHeart Failure Survey program, 31% and 19% of hospitalized and ambulatory patients, respectively, in the ESC-HF Pilot registry[6,12,13].

Data on the coexistence of anemia and CKD in HF patients is quite variable. In a population-based cohort of 12,065 patients with new-onset HF in Canada, 3% had both anemia and chronic kidney disease[14], while in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) trial on 2653 HF patients the coexistence of both conditions was present in 14% of patients[15]. Finally, in a single-center study on 955 HF patients, 22% had both anemia and chronic kidney disease[16].

Renal dysfunction leading to fluid retention and congestion is one of the mechanisms implicated in HF worsening and progression and represent a strong and independent predictor of adverse prognosis in those patients. A GFR <60 mL/min has been associated with a two fold increase in the risk of mortality in HF, while patients in the lowest GFR quartile (<44 mL/min) had almost a three fold increase (relative risk, 2.85)[17]. Moreover, WRF is

Table 1: Measures for the prevention and treatment of cardiorenal syndrome.

General measures
Early and correct optimization of heart failure medication
Close monitoring of hemodynamics and renal function (clinical/biomarkers)
Correct usage of diuretics
• Diuretic combinations of different categories for sequential nephron blockade
• Avoidance of diuretic combinations of the same category
• Avoidance of thiazides when GFR <15-20 ml/min
• Avoidance of extremely high doses
Avoidance of hypovolemia
Avoidance of excess salt and fluid intake
Avoidance of nephrotoxic agents
Specific measures in acute conditions
Inotropes (dopamine, dobutamine, levosimendan)
Renal replacement therapy (ultrafiltration)
Mechanical circulatory support
Novel/investigational agents
Nesiritide
Vasopressin antagonists
Adenosine antagonists

Table 2: Treatment options for anemia that have been used in cardiorenal-anemia syndrome.

Intervention	Comments
Blood transfusions	In severe anemia or urgent conditions
Iron supplementation	In iron deficiency
• Iron sucrose - intravenous	Amelioration of functional status and
• Ferric carboxymaltose - intravenous	quality of life
• Ferrous sulfate - per os	
Vitamin B12 and /or folic acid supplementation	In B12 and /or folic acid deficiency
Erythropoiesis stimulating agents (with or without iron supplementation)	Inconclusive/conflicting evidence
• Epoetin alpha - subcutaneous	
• Epoetin beta - subcutaneous	
• Darbepoetin alfa – subcutaneous	

Table 3: Causes and pathogenetic mechanisms of iron deficiency in cardiorenal-anemia syndrome.

Cause	Mechanism
Intestinal ischemia and/or edema	Reduced iron absorption
Gastrointestinal bleeding due to antiplatelets or anticoagulants	Increased iron loss
Increased hepcidin release due to inflammatory activation	Reduced iron release from enterocytes and macrophages
Malnutrition	Reduced iron intake
Erythropoietin therapy without iron supplementation	Increased iron usage

also independently associated with worse prognosis in acute HF[7-9]. Finally, markers of renal function such as BUN are independent predictors of adverse prognosis in HF[18]. Anemia is also an independent predictor of survival and prognosis in HF as shown by several studies, registries and meta-analyses[11,19,20]. The combination of anemia and kidney disease seem to have an additive effect on the prognosis of HF patients; according to data from a population of 1,136,201 individuals, the 2-year mortality risk rose from 27% in patients with HF alone to 35% in those with HF and anemia, 38% in those with HF and kidney disease and finally to 46% in those with all three conditions[21].

Prevention and treatment

Worsening renal function and diuretic resistance

Table 1 summarizes the strategies for the prevention and/or management of renal dysfunction in HF patients. The careful introduction and up-titration of HF medications, and especially of RAAS inhibitors and diuretics, and the close clinical and laboratory monitoring of patients is essential[22,23]. The education of patients to avoid excess fluid and salt intake and nephrotoxic agents such as non-steroid anti-inflammatory drugs is also important. In acute settings, the proper use of inotropes and mechanical circulatory support may be beneficial while renal replacement therapy and particularly continuous venous-venous ultrafiltration, although not yet widely used, should be early considered in those patients[24,25]. Some recently developed agents that are currently under investigation, including nesiritide, arginine-vasopressin antagonists and adenosine antagonists, as well as statins may also play a role in renal protection and management of diuretic resistance, but solid evidence on those agents is still missing

and most trials failed to show any benefit[26-30].

Anemia

Anemia in the context of the CRAS is multifactorial and several mechanisms have been implicated. These mechanisms include decreased erythropoietin synthesis due to renal dysfunction and renin-angiotensin-aldosterone system (RAAS) inhibitors, further inhibition of red cell production by RAAS inhibitors, bone marrow hypoperfusion due to low cardiac output, gastrointestinal blood losses due to antiplatelets and anticoagulants, iron deficiency, erythropoietin resistance and deregulation of iron metabolism due to inflammatory activation in the context of chronic disease and finally hemodilution, although this latter mechanism has recently been questioned[31-35]. As erythropoietin and iron metabolism are believed to play an important role in the pathogenesis of anemia in CRAS, erythropoiesis stimulating agents (ESAs) and iron supplementation have emerged as potential therapeutic interventions in anemic patients with CKD and/or HF (Table 2).

The findings on the use of ESAs both in HF and CKD remain controversial. In chronic HF, several small trials showed improvement in functional status and/or quality of life or cardiac performance[36-40]. However, evidence on patients' prognosis remains inconclusive as large-scale testing of ESAs in HF is generally missing[41,42]. The ongoing Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF) trial designed to recruit 2600 HF patients may shed some new light on this issue[43].

In CKD, on the other hand, a series of large randomized trials showed that the aggressive correction of the generally mild anemia occurring in those patients has either neutral results or even negative effects on patients' prognosis. More specifically, the CREATE trial in 603 CKD patients with mild anemia (hemoglobin 11.0-12.5 g/dL) showed neutral effects on the occurrence of cardiovascular events at 3 years[44]. In the CHOIR trial in 1432 patients with CKD and mild to moderate anemia (hemoglobin <11.0 g/dL), erythropoietin increased the occurrence of death and cardiovascular events at 3 years, without having a significantly beneficial effect on quality of life[45]. Finally, the TREAT trial in 4038 patients with CKD, diabetes mellitus and mild to moderate anemia (hemoglobin <11.0 g/dL) demonstrated an increase in the rate of stroke at 3 years in the darbepoetin arm[46].

Iron deficiency

Iron deficiency is frequently encountered in HF patients, both with and without anemia, especially in those with advanced disease[32,33]. In a group of 546 patients with chronic HF of varying severity, the prevalence of iron deficiency was 37% in the whole cohort, 57% in anemic patients and 32% in non-anemic ones.[33]. Moreover, in a group of 37 patients with advanced chronic HF, iron deficiency, as indicated by the absence of iron stores in bone marrow, was present in 73% of cases[32]. It has been shown that iron deficiency is independently associated with reduced exercise performance and worse prognosis in HF patients, irrespectively of the presence of anemia[33].

The etiology of iron deficiency in CRAS is also multifactorial (Table 3). Gastrointestinal losses, malabsorption, reduced iron intake, inflammatory activation and ESA therapy without iron supplementation may all be implicated[47-49]. Iron deficiency is generally indicated by a serum ferritin concentration <100 ng/mL or a serum ferritin <300 ng/mL with transferrin saturation <20%[50].

A number of clinical trials on the use of iron regimens in chronic HF patients with iron deficiency, with or without anemia, have shown beneficial effects mainly in terms of functional capacity and quality of life. Intravenous iron sucrose (200 mg once/week for 5 weeks) was compared with placebo in 40 chronic HF patients with mild anemia, iron deficiency and at least mild renal insufficiency (creatinine clearance <90 ml/min); iron repletion was followed by significant decrease in natriuretic peptides and C-reactive protein, increase in 6-min walked distance and left ventricular ejection fraction (LVEF) and amelioration of quality of life at 6 months[51]. In the subsequent FERRIC-HF trial, 35 chronic HF patients with iron deficiency were randomized to intravenous ferric carboxymaltose (at 200 mg/week until to iron repletion and then at 200 mg/month for a total of 4 months) or placebo[52]. Iron supplementation was followed by a significant increase in peak VO_2 (primary end point) as well as a significant amelioration of patients' self-reported symptoms (Patient Global Assessment, PGA) and New York Heart Association (NYHA) class. However, those beneficial effects were mostly observed in patients with anemia at baseline. The most recent FAIR-HF trial, the largest study concerning iron repletion therapy in HF, randomized 459 NYHA II-III patients with impaired LVEF and iron deficiency to intravenous ferric carboxymaltose (at 200 mg/week till iron repletion followed by 200 mg/month) or placebo[50]. The primary end point, PGA and NYHA class at week 24, was met and in addition 6-min walked distance and quality of life questionnaires were significantly improved by iron therapy at weeks 4, 12 and 24. Interestingly and in contrast to FERRIC-HF trial, the positive effects on primary end points were observed both in patients with and without anemia at baseline, defined as hemoglobin ≤12 g/dL. Finally, iron therapy was safe.

There are still several issues that require clarification regarding the management of anemia or iron deficiency in HF patients, with or without CKD. First, as previously stressed, the evidence on the role of ESAs is still inconclusive. Given the adverse effects caused by those agents in CKD patients, the safety issues regarding their use are the first that need to be properly addressed. Moreover, it is not yet known whether correction of either anemia or iron deficiency prevents the development of CRAS or affects beneficially patients' prognosis. Other open issues include the profile of HF of CRAS patient who benefits the most of those therapies and therefore needs to be treated as well as the therapeutic targets that should be pursued (e.g., hemoglobin, serum ferritin) as well as its desirable target levels or rate of achieving these levels. Finally, confirmation of the promising results by large study populations will also be required.

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REVIEW ARTICLE

The present and the future of Peritoneal Dialysis

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Abstract

Peritoneal Dialysis (PD) has been established as an effective renal replacement therapy complementary to hemodialysis (HD) for End-Stage Renal Disease (ESRD) patients. However, its prevalence has been decreasing during the last decades in Western Europe and USA, whereas in some regions such as Hong Kong or Mexico its penetration remains higher than 70%. These dramatic differences around the world can not be explained only by medical reasons. There are also many "hidden" factors such as financial issues (for profit HD), completely unproven dogmatic beliefs about the superiority of HD over PD, or more recently a fear about "the epidemic" of encapsulating peritoneal sclerosis in long standing PD. During the last two decades, there has been a significant progress in many fields of PD, such as reduced PD related peritonitis rates by new connectology systems, prevention of exit site infections by mupirocin or gentamycin ointments, wide application of automated PD by reliable cyclers, use of icodextrin for the long exchanges, better preservation of residual renal function, newer and more biocompatible PD solutions and timely placement of PD catheters by nephrologists. In addition, basic and clinical research is focusing on future improvements such as the use of two icodextrin exchanges per day, the application of new PD solutions with low sodium concentration, the wider use of "assisted" PD, and a better understanding of the pathogenetic mechanisms that may lead to peritoneal sclerosis with new therapies that may prevent it. The dilemma regarding the best modality for ESRD (HD or PD?) should be abandoned and the modern nephrologist should be wise enough to recognize the possible advantages and contraindications of each modality and confident enough to offer both of them to the ESRD patients as appropriate. Hippokratia 2011; 15 (Suppl 2): 15-20

Key words: hemodialysis, icodextrin, peritoneal dialysis, peritonitis, exit site infection, review

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Currently about 200,000 patients are treated with Peritoneal Dialysis (PD) around the world, whereas more than 1.5 million patients are undergoing hemodialysis (HD) for End-Stage Renal Disease (ESRD)[1]. However there are countries such as Mexico or Hong Kong where PD dominates by far (70-80%). In Europe the prevalence of PD varies with Sweden, Norway, UK and the Netherlands to dialyze almost 20% of their ESRD patients with PD and Southern Europe countries to have a mean PD prevalence of about 8-10%. In Canada almost 18% of the ESRD patients are undergoing PD and in US the PD rates are about 7-8%. These dramatic differences around the world are not so easy to be explained [1-4]. It is well known that non medical reasons (financial) always drive heath-care practices but we should not neglect the medical reasons as well.

If we look carefully back to the past, the trend for the fall of PD penetration started in the late nineties. In 1995 Bloembergen et al reported dramatically higher mortality rates for patients who started PD in the late eighties compared with HD patients during the same time period [5]. In 1996 the CANUSA study reported that the targets for PD adequacy should include a Kt/V urea of > 2.1 and a weekly creatinine clearance of more than 70L[6]. Soon, these targets were adopted by the first KDOQI guidelines, although there were many voices against these recommendations. So then, the well informed nephrologist would be quite reluctant to offer to his patients a renal replacement modality with proven inferiority compared with the gold standard of HD and should strive to achieve these high targets of adequacy for the poor patients which would select to undergo this "second line" modality. Wise PD authorities argued these data and provided scientific evidence that the initial assumptions were completely false[7]. During the next years the ADEMEX study showed that the adequacy targets should be revised [8] and finally the new KDOQI guidelines adopted these results. Recently Mehrotra et al reported that PD and HD can achieve similar survival rates for the US patients which have started renal replacement therapy after 1996 [9]. During the last years, PD was accused once again as a fatal and short term only modality that eventually leads to encapsulating peritoneal sclerosis and death, even after successful renal transplantation[10].

All these data show that PD has not only dedicated "supporters" but also devoted "enemies". The open

Table 1: "Hot issues" for the present and the future of PD.

- Infectious Complications
- PD catheters
- Residual Renal Function
- Automated PD
- Assisted PD
- PD solutions
- Encapsulating Peritoneal Sclerosis

minded nephrologist should consider PD and HD not as competitors but collaborators in order to fight ESRD. If we omit the financial issues (that are the most important) we should try to examine the scientific evidence about PD. Is it a second line treatment for second line nephrologists, is it inferior to HD, patients like it or hate it, or has its own place in the treatment of ESRD? We strongly believe that any effort to speculate PD will impact the holistic approach regarding ESRD treatment.

Hard scientific data show that there are some barriers about PD, if we consider it as a self-therapy. However as we will see, there are also alternatives in order to overcome them if we wish to do so [2,11,12]. In the next lines we will try to provide data about the "hot issues" that may impact the present and the future of PD (Table 1).

Infectious Complications

PD related peritonitis rates have improved substantially during the last decades mainly due to the introduction of the double bag system and the improvements in the various connectologies with many PD units reporting peritonitis rates of one episode every more than 30 months [12-14]. However this progress is mainly due to the decrease of the milder forms of PD related peritonitis due to skin contamination by Staph. epidermitis strains, whereas the serious episodes due to organisms such as Pseudomonas, Staph aureus of fungi still remain a significant problem and a frequent cause of (temporary or even permanent) transfer to HD.

During the last years there were significant improvements regarding the prevention of the infectious complications of PD mainly by the daily application of mupirocin (for Staph aureus) or gentamycin ointment (for Staph aureus and Pseudomonas infections) to the exit-site of the PD catheter[12]. Two studies also provide evidence about the prophylactic use of antifungal agents (oral nystatin of fluconazole) for the prevention of fungal infections in PD patients receiving antibiotics for various reasons, especially in PD units with high rates of fungal peritonitis[15,16].

However, optimal and frequent training of the PD patient by the nursing staff with a detailed educational protocol, early identification of patients at risk and frequent data collection and evaluation remain the cornerstone of a successful PD program in order to prevent and minimize infectious complications.

PD catheter: The lifeline of the PD patient

Among the several reasons that may contribute to the decline of PD, a key factor remains the permanent access to the peritoneal cavity. The PD catheter has been characterized a0s the "lifeline" of the PD patient and catheter related problems remain a cause of permanent transfer to HD in up to 20% of patients needing a therapy change[17].

Although traditionally the vast majority of PD catheters has been inserted by surgeons under local or general anaesthesia with the open dissection or the laparoscopic technique, many nephrologists have started getting involved in catheter insertion, by percutaneous methods using the Seldinger technique[18,19] or more recently by the peritoneoscopic method [20,21].

PD catheter implantation by nephrologists has been reported to improve PD utilization and expansion of the PD programs in US[22], or Asia [23], mainly due to timely placement of the PD catheter, avoiding unnecessary delays that may drive patients to permanent HD.

As the European Best Practice Guidelines for Peritoneal Dialysis state, the most important element of success for PD catheter implantation does not rely on the technique used (surgical, percutaneous, or laparoscopic) but the experience of the people getting involved [24]. Li and Chow[25] also underline that "practice makes perfect", and all nephrologists dealing with PD and facing problems should be encouraged to start putting PD catheters by themselves regardless of the preferred technique.

The International Society of Peritoneal Dialysis[26] and the European Best Practice Guidelines for Peritoneal Dialysis[24] guidelines suggest that regardless of the technique used, one years' PD catheter survival should exceed 80% and all PD units should strive to increase their PD catheter survival rates.

Residual Renal Function

Preservation of Residual Renal Function (RRF) is one of the main clinical benefits of PD compared with HD. The initial hypotheses was that PD offers better stability of the volume status avoiding the excessive and rapid ultrafiltration of a HD session, where a large volume of ultrafiltrate is removed during a short time period (4 hours) with frequent hypotensive episodes[27] . This was also the explanation regarding a more rapid loss of RRF in patients undergoing APD compared with CAPD in some studies. However, some authorities claim that this happens just because PD patients tend to be more volume overloaded compared with HD patients[28].

The CANUSA study was the first which underlined the close association of RRF (and not peritoneal solute clearances) with better patient survival rates and this was also confirmed by others[6,29]. So, every PD program should strive to maintain RRF as long as possible by prescribing loop diuretics and angiotensin converting enzyme inhibitors or angiotensin receptor blockers and avoiding any nephrotoxic agents such as non-steroidal anti-inflammatory agents, unnecessary radio contrast media or aminoglycosides[28].

There is also growing experience from HD, that ultrapure HD dialysate preserves RRF compared with regular HD implying that biocompatibility may have a significant impact on RRF preservation[27]. The new more biocompatible PD solutions may also preserve RRF in PD patients as shown in small retrospective studies but further and better designed prospective studies are needed before definite conclusions. Fan et al in randomized prospective study with 93 PD patients failed to show any benefit of a more biocompatible bicarbonate/lactate PD solution regarding RRF[30].

Automated Peritoneal Dialysis

Automated PD is growing fast as a PD modality around the world. Although in USA the majority of the PD patients (almost 60%) are undergoing APD, its penetration is also increasing in Europe and Australia, expect Asia probably due to financial restrictions[31].

The European best practice guidelines for PD suggest that APD should be used according to patients' preference, problems with increased intraperitoneal pressure and problems with adequate ultrafiltration and solute removal[24]. However, there are multiple prescriptions of APD such as nocturnal APD with a dry daytime or with a wet abdomen during daytime with or without a daily exchange (CCPD). All these modifications of APD make comparisons with classical CAPD rather difficult[32]. Its main advantage is that the patient is undergoing his/her therapy during the night and remains free for his daily activities. So, it is preferable for the younger who want to work fulltime, the children and the students. It is also recommended for the elderly which are treated by "assisted" PD at home as the nurse has to visit them only twice per day in order to connect and disconnect them from the cycler.

Regarding medical issues it is definitely offering an advantage for the high/fast transporters as the short dwell time allows them to have increased ultrafiltrate per exchange. Although theoretically APD should be associated with lower peritonitis rates due to the positive effect of the dry abdomen on the immune function of the peritoneal cavity and the fewer connections per day, the clinical results are rather conflicting. Piraino and Sheth[33] have suggested that this may be due to the different connectologies used in these studies (luer-lock versus spiking) and the different prescriptions of APD (none versus one day time exchange). Regarding residual renal function (RRF), there are many studies reporting a more rapid loss with APD. Mehrotra[32] suggests that the effect of cycler use on native renal clearances, if any, is small and probably not clinically significant but a recent study[34] from the Netherlands is not in favour of his suggestions. Finally there are concerns about the nature of the modality as the main advantages of classic CAPD were its simplicity (no machines) and its continuous nature (24 hours per day). Although these concerns are of value (especially for the solute clearances) patients' preferences and quality of life issues are of paramount importance when we are dealing with a chronic and devastating disease [35].

"Assisted" Peritoneal Dialysis

The dialysis population is aging and carries a significant burden of co-morbidities. The number and extend of co-morbid illnesses in the average patient initiating dialysis have increased over the past two decades highlighting the need for more attention not only for prognostic reasons, but mainly for the day-to-day care of these patients. So, many patients are incapable for self therapies such as PD at home, or have no family members/partners to help[37].

The recently introduced concept of "assisted" PD, where patients can be assisted in performing their PD exchanges at home by private nurses is a real solution for these patients, provided that the local health systems are reimbursing this modality[38-41]. Most programs are choosing to offer "assisted" PD with cyclers (APD) than with CAPD due to fewer connections per day. The results regarding patient survival rates and infectious complications are improving but better results are reported when the "assistants" are well trained or registered PD nurses. Unfortunately, at the moment in Greece and many other European countries except Denmark, France, Belgium and one region in Spain, assisted PD is not reimbursed[41]. Intermittent PD (IPD) in the hospital three times per week with high dialysate volumes (15-20L) for 8-10 hours per session might be an option for this special ESRD population with acceptable survival rates [42].

Peritoneal Dialysis solutions

Icodextrin containing PD solutions

Icodextrin containing PD solutions have been introduced in PD for more than 10 years and have undergone extensive clinical studies[43]. Although icodextrin was firstly indicated only for PD patients with ultrafiltration failure and a high transport status, it has some extra advantages as it is not containing glucose and has been shown to result to higher ultrafiltration rates and sodium removal compared with hypertonic glucose containing solutions during the long exchange[44,45]. However there is an inter- and intra- variation of the amount of ultrafiltrate produced by icodextrin that has not been fully explained and diabetics and males seem to produce more ultrafiltrate[46]. There were some experimental studies about a possible detrimental effect of icodextrin in mesothelial cell cultures [45] questioning its biocompatibility mainly due to its acidic nature (pH 5.2), but its glucose-sparing effect with minimal concentrations of the harmful glucose degradation products (GDPs) and/or Advanced Glycosylation End-products (AGEs) is overcoming these experimental concerns. Gobin et al[48] were the first to explore the use of two daytime icodextrin exchanges for 6 months in 9 patients undergoing APD, as a glucose-sparing regimen, reporting also a slight increase of blood icodextrin levels at 3 months which remained stable at the 6 months of the study. Sav et al[39] have prospectively studied 40 CAPD patients with ultrafiltration failure with two icodextrin exchanges for 3 months and reported higher daily ultrafiltration rates and a decrease in left ventricular mass index (LVMI), with a mild but not statistically signifi-

cant increase of blood icodextrin and maltose levels at 3 months[49]. Dousdampanis et al[50] have recently reported reduced body weight in 6 out of 9 PD patients during a 6 months study with two icodextrin exchanges per day. Although hyponatremia remains a theoretical side effect of icodextrin therapy there were no reports of such side effects in these 3 studies. However, the possible accumulation of maltose in the blood during more extensive (> 6 months) therapy should be examined in future studies, whereas the application of 2 icodextrin exchanges will increase the daily cost of therapy[50].

New more biocompatible PD solutions

Long-term systemic exposure of the peritoneal cavity to glucose results into peritoneal membrane structural and functional alterations over time and eventually to technique failure expressed clinically as ultrafiltration failure and reduced solute clearance. In addition glucose and its degradation products have been implicated into various undesirable systemic metabolic and cardiovascular side effects. The new more biocompatible PD solutions have been designed in order to reduce the concentration of GDPs by separating the PD solution into two (Balance®, Fresenius) or three (Gambrosol Trio®, Gambro) chambers and by approaching to a more physiological pH (7.4), by a combination of bicarbonate/lactate (Physioneal®, Baxter) or pure bicarbonate (Bicavera®, Fresenius) as a buffer[12,13,51,52].

Most of the studies regarding these new PD solutions have shown reduced infusion pain and better correction of metabolic acidosis, although some times they may induce even alkalosis in patients with significant RRF[53]. The first reports with these new solutions have given rather enthusiastic results regarding better preservation of RRF, reduced rates of peritonitis and better preservation of the peritoneal membrane function,as expressed by several peritoneal biomarkers . Nevertheless, a randomized study from UK failed to maintain this enthusiasm[30]. In addition two studies from Korea have claimed a survival benefit for patients treated with these solutions [54,55]. Both studies were criticized for their design (retrospective and observational) and until now it is premature to conclude that the new PD solutions provide a clear survival benefit despite their significant cost. However, their theoretical superiority has created a great enthusiasm and in Europe there is trend to use them in the younger and healthier PD patients.

Low sodium PD solutions

Many patients undergoing PD are frequently overloaded. A low sodium diet and adequate sodium removal by PD are equally important in order to avoid overhydration. There are only a few studies examining sodium removal rates in PD patients and it has been argued that APD may be less effective than CAPD in sodium removal due its frequently lower capacity for ultrafiltration and also due to the short dwell schedule that may result in significant Na sieving and less efficient Na removal[56,57].

During the last years there was an attempt to develop new low sodium solutions in order to increase sodium removal by PD. Nakayama et al[58] from Japan have studied two different PD solutions with low sodium (126 and 118 mmol/L) in 41 CAPD patients. Although sodium removal was increased, there were concerns about hyponatremia and the need for increased concentrations of glucose in order to compensate the low osmolality of these solutions. Davies et al[59] in a short multicentre prospective study used two different low sodium PD solutions (115 mmol/l with 2.0% glucose and 102 mmol/L with 2.5% glucose) for one exchange per day in 25 patients for two months. He reported increased sodium removal but the ultrafiltrate was reduced in the 102 mmol/L solution. In patients with adequate ultrafiltrate, he reported improvement of blood pressure, thirst and fluid status but no hyponatremia during the study period. Both studies have shown a rather positive impact of the low sodium PD solutions on sodium removal, but the risk of hyponatremia and the need to use higher glucose concentrations should be further studied [59].

Encapsulating Peritoneal Sclerosis

The concerns regarding Encapsulating Peritoneal Sclerosis (EPS) have increased during the last years in the literature. There are many suggestions that PD duration should not exceed 5 years or it should be terminated when there are indications of ultrafiltration failure, as long-term PD is associated with increased rates of EPS[12,60]. Although EPS is a severe condition with significant mortality its pathogenesis remains rather obscure. The “two hit” hypothesis, where there is a first hit by the chronic exposure to PD that leads to simple sclerosis and in a few patients a second hit that eventually leads to EPS seems the most rationale according to the current knowledge[10]. In addition most cases of EPS in the literature are not associated with PD (spontaneous EPS) and there is indirect evidence that there is also a genetic background in patients with EPS. Epidemiological data from large centers have shown that the incidence of EPS is not so high (average 1.5%, range 0.5-2.8%), but is usually accompanied with a fatal outcome[61,62]. Treatment of EPS includes preventive measures, transfer to HD with prophylactic periodic peritoneal lavage and tamoxifen. For the most severe cases, patients should receive total parenteral nutrition and surgical exploration by experienced surgeons[61]. For the PD patients which are candidates for renal transplantation after a long period in the modality, it seems prudent to avoid steroid avoiding or sparing protocols and perhaps to aim towards mTOR inhibitors based immunosuppressive protocols and avoid calcineurin inhibitors which may induce or aggravate fibrosis[10].

Conclusions

Since its introduction by Moncrief and Popovich and its expansion after the application of the plastic bags by Oreopoulos, PD remains a field of continuous improvements and innovations. Although its prevalence and penetration decreased during the last years, this was mainly due to non medical reasons[1,2,4]. The new change of policy

regarding reimbursement of ESRD therapies (the "bundling") will overcome many of the financial issues that favored HD for a long time in USA[63]. All the unbiased scientific data provide evidence that PD is at least as effective as HD for the treatment of ESRD, if applied correctly. This is the main issue that should be our focus for the future. Local and international nephrology societies should strive to offer more education, training and exposure to PD, in order to equip the young nephologists with the appropriate knowledge, regarding the best therapeutic options for the individualized ESRD patient.

Conflict of Interest: None to declare

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ORIGINAL ARTICLE

Magnesium levels and magnesium containing phosphate binders in haemodialysis patients

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Abstract

Background and aim: Sufficient evidence suggests that serum magnesium exerts beneficial effect upon cardiovascular status and arterial calcification among dialysis patients. Magnesium containing salts are as effective as the usual phosphate binders in lowering serum phosphorus in haemodialysis patients and posses the advantage of increasing serum magnesium levels which may play an important role in cardiovascular outcome. The aim of this study was To investigate serum magnesium levels among dialysis patients before and after administration of magnesium containing phosphate binders and its clinical significance. Hippokratia 2011; 15 (Suppl 2): 21-26

Patients and Methods: In this prospective cohort we investigated 70 patients (45 men, 25 women) undergoing standard bicarbonate dialysis, thrice weekly (3-4 hours) for longer that 6 months. Age 66.1±13.2 (33-88) years, dialysis duration 62.6±57.9 (7-267) months. Presence of coronary artery disease (CAD) was established by previous history of acute myocardial infarction or coronary angiography. Chronic use (>1 year) of proton pump inhibitors (PPIs) was sought from previous history of the patients. Patients with serum magnesium levels lower than 3 mg/dl were eligible to be administered calcium acetate-magnesium carbonate (CalMag) as phosphate binder. We estimated serum calcium, phosphorus, magnesium and calcium-phosphate product monthly and iPTH every three months. In order to avoid hypermagnesaemia after two months patients receiving CalMag underwent dialysis with low magnesium dialysate (0.75 mEq/L) while the rest continued dialysis with usual magnesium dialysate (1 mEq/L).

Results: Lower magnesium levels were identified among patients with coronary artery disease (p=0.01) as well as among patients chronically receiving proton pump inhibitors (p=0.03). Administration of CalMag showed a considerable increase in the magnesium level (p=0.0004) and a significant decrease of phosphate level (p=0.01). Substitution with low magnesium dialysate (0.75 mEq/L) showed a considerable decrease of serum magnesium level (p=0.005). Variations in the levels of calcium, phosphate and calcium-phosphate product between the individual phosphate binders (PBND) showed no statistically significant difference. The estimated three month cost for the individual phosphate binders was lower for calcium carbonate and CalMag compared to the other phosphate binders.

Conclusions: The results of this study suggest that presence of coronary artery disease and chronic use of PPIs is related to lower serum magnesium levels. Administration of CalMag in haemodialysis patients is related to lower phosphorus levels and increased magnesium levels. Low dialysate magnesium concentration reduces effectively serum magnesium levels. The efficacy of CalMag in lowering serum phosphorus level is comparable with the usual phosphate binders. The lower cost of CalMag suggests its more frequent use in clinical practice among selected patients.

Key words: magnesium, haemodialysis, coronary artery disease, proton pump inhibitors, magnesium containing phosphate binders

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Serum magnesium levels among patients undergoing haemodialysis has been neglected for a long time because of minor effect upon bone mineral disorders and because of very rare clinical syndromes related to hyper or hypo-magnesaemia. In early sixties it has been evident that magnesium absorption is normal among dialysis patients and diminished excretion from the kidneys produce hypermagnesaemia which may be dangerous especially in cases that magnesium containing drugs administered. This notion has led to the elimination of magnesium containing drugs such as antioxidants, laxatives and phosphate binders from the regimens of end stage renal disease (ESRD) patients as well as use of low magnesium dialysate concentration (0.5-0.7 mmol/L)[1]. One decade later it became evident that increased magnesium levels suppress parathyroid hormone (PTH) production and arterial calcification. There after increased evidence in literature pointed to the possible beneficial effect of

magnesium upon bone metabolism, arterial calcification and atherosclerosis not only among ESRD patients as well as among healthy individuals[2-4]. The advent of aluminum intoxication among patients receiving aluminum hydroxide as phosphate binder prompted the necessity to use other less toxic but effective drugs and so magnesium salts, mainly magnesium carbonate, was used in order to control hyperphosphataemia among ESRD patients and proved effective and safe[5-7]. In order to avoid hypermagnesaemia, either among dialysis or peritoneal dialysis patients who receive magnesium containing phosphate binders, it was necessary to lower the dialysate or peritoneal fluid content of magnesium[8,9]. Accumulating evidence suggest that magnesium apart from its efficacy as phosphate binder may exert pleiotropic actions upon intradialytic blood pressure stability, cardiac arrhythmias and heart ischemic attacks but it has to be proved[10,11]. The aim of this study was to investigate serum magnesium levels among dialysis patients before and after calcium-magnesium salts administration its clinical significance and the efficacy of these salts as phosphate binders among a limited number of patients.

Subjects and methods.

Study design

In this prospective cohort we investigated 70 patients (45 men, 25 women) suffering from ESRD and undergoing standard bicarbonate dialysis for longer than six months. Dialysis schedule was thrice weekly (3-4 hours) with magnesium dialysate concentration of 1 mEq/L. The mean age of the patients was 66.1±13.2 (33-88) years and the mean dialysis duration 62.6±57.9 (7-267) months. Presence of coronary artery disease (CAD) was established by previous history of acute myocardial infarction or coronary angiography. Presence of calcification in the hand interosseous arteries was established by x-rays. Chronic use (greater than one year) of proton pump inhibitors (PPIs) was sought from medical records of the patients and by personal communication with each one of them (Table 1).

Table 1: Demographic characteristics of the patients (n=70).

Age: 66.1±13.2 (33-88) years.
Gender: 45 men, 25 women.
Haemodialysis duration: 62.6±57.9 (7-267) months.
Dialysis schedule: Standard bicarbonate, thrice weekly.
Coronary artery disease: 15/70 (21.4 %).
Chronic use of PPIs: 41/70 (58.7 %).
Arterial calcification (hands): 23/68 (33.8 %).
Phosphate binders:
Calcium acetate (435 mg)/Magnesium carbonate (235 mg): n=12 (17.1 %).
Calcium carbonate (420 mg)/Glycine (180 mg): n=4 (5.7 %).
Lanthanum carbonate (750 mg): n=16 (22.8 %).
Sevelamer hydrochloride (800 mg): n=38 (54.**2 %).**

Patients with serum magnesium level lower than 3 mg/dl were eligible to administer calcium acetate/magnesium carbonate (CalMag) phosphate binders. After a two weeks washout period CalMag was administered in 12 patients (seven men and five women), 1-2 tablets per meal according to phosphate levels. After two months patients receiving CalMag underwent dialysis with low magnesium dialysate (0.75 mEq/L) instead of 1 mEq/L for all the others. We used the following phosphate binders: Calcium acetate (435 mg)/Magnesium carbonate (235 mg) (OsvaRen, Fresenius Medical Care Nephrologica, Deutschland GmbH, Homburg v.d.H. Germany) 12 patients (17.1 %), Calcium carbonate (420 mg)/Glycine (180 mg) (Titralac, Meda Pharmaceuticals SA, Chalandri Attikis, Greece) 4 patients (5.7 %), Lanthanum carbonate (750 mg) (Fosrenol, Shire Pharmaceuticals Ltd, Hampshire, United Kingdom)) 16 patients (22.8 %) and Sevelamer hydrochloride (800 mg) (Renagel, Genzyme Europe B.V., Naarden, Netherlands) 38 patients (54.2 %). We estimated pre-dialysis serum calcium, phosphorus, magnesium and calcium-phosphate product monthly and iPTH every three months. Pre-dialysis serum magnesium level with usual dialysate magnesium concentration before and after CalMag administration was estimated as well as after substitution of low dialysate magnesium concentration. Serum magnesium (mg/dl) was estimated by using the xylidyl blue method, serum phosphorous (mg/dl) by molybdate UV method, serum calcium (mg/dl) by arsenazo III pigment method all the above calculations were performed by AU 600/OLYMPUS equipment. Intact iPTH (pg/ml) was estimated by two site sandwich type chemiluminescence immunoassay (CLIA, DiaSorin Inc, Stillwater, MN 55082, USA).

Statistical analysis

One-way ANOVA was used in order to test the rela-

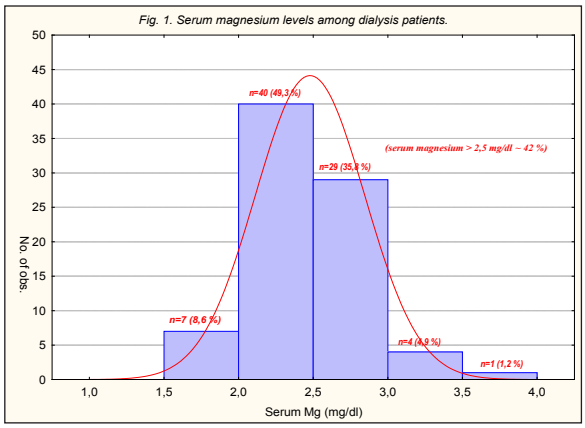

Figure 1: Pre-dialysis serum magnesium levels among ESRD patients. About 42 % of them exhibited magnesium levels greater than 2,5 mg/dl.

tionship between serum magnesium and coronary artery disease, the effect of PPIs upon magnesium level as well as the effect of magnesium upon interosseous arteries calcification. No post-hoc analysis was conducted because categorical predictors were binary and ANOVA converts to independent sample t-test. One-way ANOVA was also used with Bonferroni correction in order to compare the variation of calcium, phosphorus and calcium/phosphorus product between patients receiving various phosphate binders. Student's t-test for dependent samples was used in order to test the variation of magnesium level before and after CalMag administration as well as with high and low dialysate magnesium concentration. Multiple regression analysis was used in order to test the effect of magnesium (Mg) and calcium (Ca) levels as well as CaXP product upon iPTH. All calculations are expressed as means ± 1 standard deviation, all analysis have been conducted on the level p=0.05 of statistical significance.

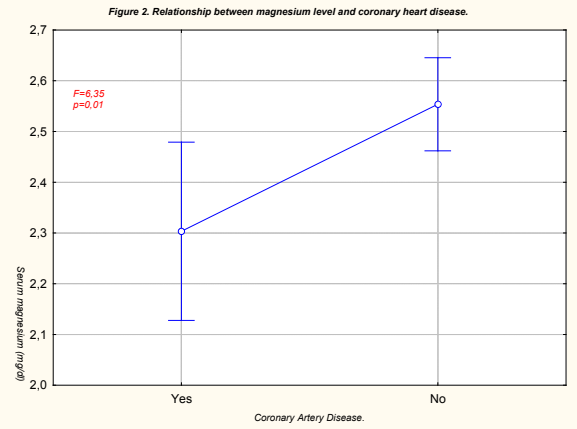

Figure 2: Patients suffering from coronary artery disease exhibited lower levels of serum magnesium than the remainders.

Results

Laboratory determinations before and after CalMag administration, with dialysate magnesium concentration at 1 mEq/L and 0.75 mEq/L are shown in table 2. Dialysate composition with high (=1 mEq/L) and low (=0.75 mEq/L) magnesium concentration is shown in table 3. Detailed analysis of magnesium levels showed that seven patients (8.6 %) exhibited magnesium level between 1.5 and 2.0 mg/dl and thirty two patients (42 %) exhibited magnesium level greater than 2.5 mg/dl (Figure 1).

Fifteen out of seventy patients (21.4 %) suffered from CAD, analysis of variance between magnesium level and CAD (F=6.35, p=0.01) showed that patients suffering from CAD exhibited the lower magnesium level (Figure 2). Forty one patients (58.7 %) received PPIs for longer than one year, analysis of variance between magnesium level and PPIs (F=4.5, p=0.03) showed that patients receiving PPIs exhibited the lower level of serum magnesium (Figure 3). Twenty three patients, out of sixty eight with radiographic data (33.8 %), exhibited interosseous arteries calcification (CALC) of the hands, analysis of variance showed no significant effect of age, haemodialysis duration (HDUR), Mg, Ca, P, CaXP product and iPTH levels upon vascular calcification but the most pronounced effect, although not statistically significant, was exhibited by iPTH, haemodialysis duration and Mg (iPTH vs CALC: F=3.53, p=0.06 NS, HDUR vs CALC: F=2.19, p=0.1 NS and Mg vs CALC: F=1.09, p=0.2 NS). Correlation between magnesium level and iPTH showed no relationship of these two variables (n=70, r=0.006, p=0.9 NS). Twenty two patients received cinacalcet and four additional patients underwent parathyroidectomy by excluding these patients from the model showed again no relationship (n=44, r=0.08, p=0.5 NS). Moreover multiple regression analysis between iPTH as depended variable and Mg, Ca, P and CaXP product as independent variables showed no significant effect (n=70, F=0.94, p<0.44 NS).

CalMag administration under basal conditions (dialysate magnesium concentration 1 mEq/L) was coupled with a significant increase of serum magnesium level (n=12, t= -4.9, p=0.0004), substitution of dialysate with low magnesium concentration (0.75 mEq/L) produced a

Table 2: Laboratory determinations before and after CalMag administration.

Parameters	All patients (n=70)	No CalMag + dialysate Mg=1 mEq/L (n=12)	CalMag + dialysate Mg=1 mEq/L (n=12)	CalMag + dialysate Mg=0,75 mEq/L (n=12)	p
Magnesium (mg/dl)	*2.5 ± 0.35*	*2.25 ± 0.29*	*2.52 ± 0.34 (p=0.0004)*	*2.25 ± 0.27*	*0.005*
Calcium (mg/dl)	*9.6 ± 0.8*		*9.51 ± 1.09*	*9.8 ± 0.8*	*0.1*
Phosphate (mg/dl)	*5.3 ± 1.4*		*5.7 ± 1.9*	*4.7 ± 1.4*	*0.01*
CaXP product (mg^2/dl^2)	*51.7 ± 14.1*		*53.6 ±17.7*	*46.2 ±12.7*	*0.06*
iPTH (pg/ml)	*277.3 ± 246.1*		*131.8 ± 83.6*	155.3 ± *123.5*	*0.3*

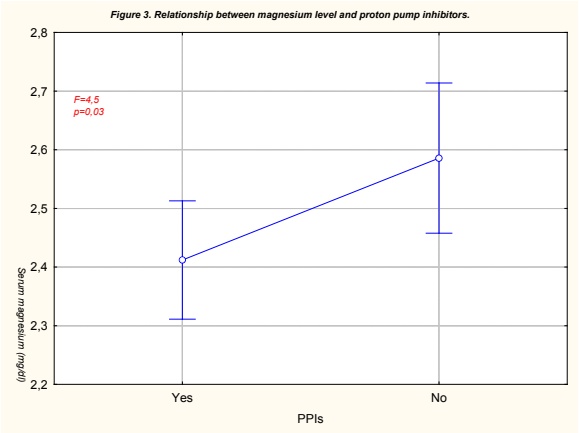

Figure 3: Patients receiving chronically (more than one year) proton pump inhibitors (PPIs) exhibited lower levels of serum magnesium.

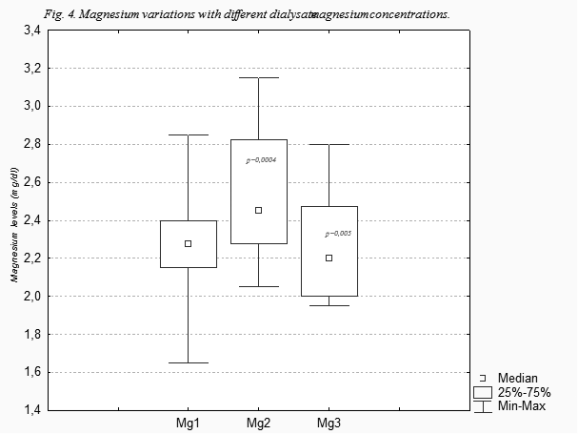

Figure 4: Variations of serum magnesium levels before and after CalMag administration and with various dialysate magnesium concentrations. (Mg1 = Dialysate magnesium concentration 1 mEq/L before Cal/Mag administration. Mg2 = Dialysate magnesium concentration 1 mEq/L + CalMag. Mg3 = Dialysate magnesium concentration 0,75 mEq/L + CalMag).

Table 3: Dialysate composition.

High Magnesium dialysate (1 mEq/L)		Low Magnesium dialysate (0,75 mEq/L)	
Na^+	138	Na^+	138
K^+	2	K^+	2
Ca^{++}	3.5 (=1.75 mmol/L)	Ca^{++}	3.5 (=1.75 mmol/L)
Mg^{++}	1 (=0.5 mmol/L)	Mg^{++}	0.75 (=0.375 mmol/L)
Cl^-	109.5	Cl^-	109.5
$CH3COO^-$	3	$CH3COO^-$	3
$HCO3^-$	35	$HCO3^-$	35

Table 4: Effect of individual phosphate binders upon Ca, P and CaXP product.

	OsvaRen (n=12)	Titralac (n=4)	Fosrenol (n=16)	Renagel (n=38)
Ca1 (mg/dl)	9.5 ± 1.09 (95 % CI=8.8-10.2)	9.6 ± 0.5 (95 % CI=8.6-10.5)	9.8 ± 0.7 (95 % CI=9.4-10.1)	9.5 ± 0.7 (95 % CI=9.3-9.8)
Ca2 (mg/dl)	9.8 ± 0.88 (95 % CI=9.2-10.3)	9.3 ± 0.7 (95 % CI=81-10.4) ***‡: (F=1.0, p=0.2 NS)***	9.5 ± 0.7 (95 % CI=9.1-9.9)	9.5 ± 0.5 (95 % CI=9.3-9.7) ***†(F=1.21, p=0.3 NS)***
P1 (mg/dl)	5.7 ± 1.9 (95 % CI=4.4-6.9)	5,2 ± 0,5 (95 % CI=4,2-6,2)	5,9 ± 1,4 (95 % CI=5,1-6,7)	5,0 ± 1,3 (95 % CI=4,6-5,5)
P2 (mg/dl)	4.7 ± 1.4 (95 % CI=3.8-5.6)	4.8 ± 0.8 (95 % CI=3.4-6.2)	5.7 ± 1.7 (95 % CI=4.8-6.7)	5.0 ± 1.2 (95 % CI=4.6-5.4) ***††: (F=1.8, p=0.08 NS)***
CaXP1 (mg^2/dl^2)	53.6 ± 17.7 (95 % CI=42.3-64.9)	50.2 ± 5.5 (95 % CI=41.4-59.0)	58.1 ± 15.0 (95 % CI=50.0-66.1)	48.5 ± 12.5 (95 % CI=44,.4-52.6)
CaXP2 (mg^2/dl^2)	46.2 ± 12.7 (95 % CI=38.0-54.3)	45.1 ± 7.4 (95 % CI=33.2-56.9)	55.4 ± 17.0 (95 % CI=46.3-64.4)	48.1 ± 11.5 (95 % CI=44.3-51.9) ***†††: (F=1.5, p=0.1 NS)***

†: Variation of calcium level between individual phosphate binders.
††: Variation of phosphate level between individual phosphate binders.
†††: Variation of calcium X phosphate product between individual phosphate binders.
‡: Comparison of calcium level between OsvaRen and Titralac.

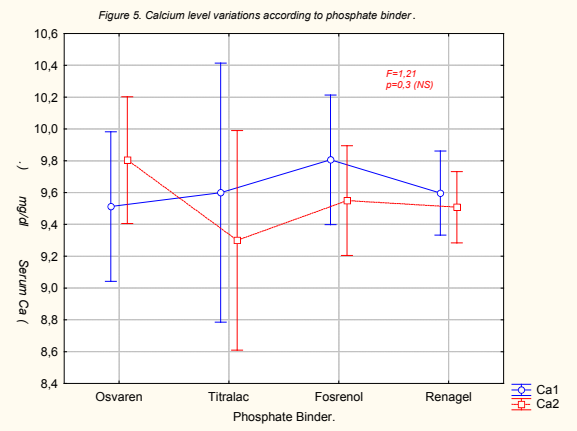

Figure 5: Calcium level variation with various phosphate binders showed no statistically significant difference between individual medications. Although it is noted a slightly increased calcium level among patients receiving Cal/Mag (Ca2) it has not reached statistical significance.

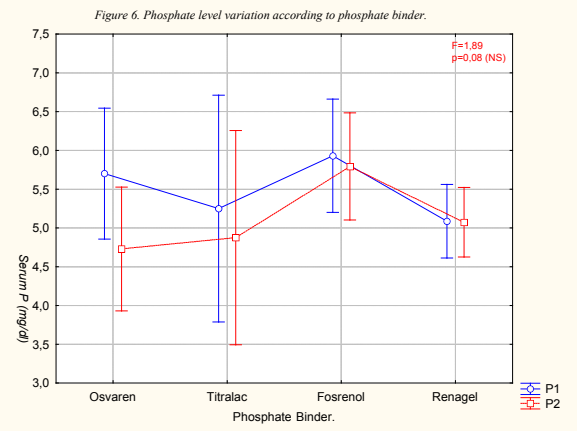

Figure 6: Phosphate level variation between individual phosphate binders showed no statistically significant difference suggesting that all phosphate binders used are equally effective.

significant decrease of serum magnesium level (n=12, t=3.45, p=0.005, Figure 4). Calcium level showed a slight, but not statistically significant, increase (n=12, t= -1.47, p=0.1 NS). On the other hand a considerable decrease of phosphate level was noted (n=12, t=2.8, p=0.01). Calcium-phosphate product showed a marginally significant decrease mainly due to phosphate decrease (n=12, t=2.0, p=0.06), iPTH level showed no significant alteration (n=12, t= -1.25, p=0.23, Table 2).

The effect of individual phosphate binders (PBND) upon the levels of calcium, phosphate and calcium-phosphate product, among the total cohort of patients, was tested by one way ANOVA (Table 4). The results showed no significant difference between the individual variables especially calcium (F=1.21, p=0.3 NS, Figure 5) and phosphate levels (F=1.8, p=0.08 NS, Figure 6). Moreover we tested the variation of calcium levels between Cal-Mag and Titralac and we found no statistically significant results (F=1.0, p=0.2 NS).

Finally we estimated the three-month cost for the individual phosphate binders which was as follow: OsvaRen=89.37 €, Titralac=17.1 €, Fosrenol=860.7 €, Renagel=678.24 €.

Discussion

Although our patients were dialyzed with a relatively low dialysate magnesium concentration (1 mEq/l = 0.5 mmol/dl) they exhibited a considerable increase in their serum magnesium. About 42 % of them exhibited serum magnesium level greater than 2.5 mg/dl. This finding suggests that ESRD patients are prone to hypermagnesaemia because of increased dietary magnesium intake and decreased magnesium excretion by diseased kidneys. The lower serum magnesium levels among patients with coronary artery disease is an interesting finding because there are very few reports addressing this issue among dialysis patients[12] and because it is of great importance taking into consideration the increased incidence of CAD among these patients. We do not say that there is a causative relationship between serum magnesium level and CAD but special attention should be paid under the light of previous findings among general population which showed that magnesium content of myocardium among persons dying from myocardial infarction is significantly lower than among persons dying from accidents and that magnesium content of myocardium was closely related with drinking water hardness[13]. The negative effect of chronic use of PPIs upon serum magnesium level is a recently recognized harm of these drugs and according to a recent review only 23 cases of documented hypomagnesaemia attributable to PPIs have been reported in literature[14]. According to our knowledge no report concerning the effect of PPIs upon serum magnesium level in haemodialysis patients published in literature until now. Although there is strong evidence that serum magnesium affects vascular calcification in haemodialysis patients[3,11,12] our data doesn't support this hypothesis but it is worthy to emphasize that, as mentioned above, no one of known variables which affect vascular calcification showed any significant effect upon this hazardous complication although iPTH, haemodialysis duration and magnesium level found to exhibit a weak relationship but not statistically significant. Although our study is underpowered this finding may suggest that vascular calcification is genetically determined and acquired disturbances of internal milieu simply accelerates the emergence of this phenomenon which is absolutely truth in ESRD patients with known derangement of calcium, phosphate and magnesium metabolism as well as PTH secretion. Recently an original article published by Hilaire CS et al suggest that certain mutations of NT5E gene encoding the production of CD73 protein which converts ATP to adenosine are responsible for the familial occurrence of extensive vascular calcifications of the lower extremities and joint calcifications among members of studied families[15]. Another topic which is controversial in literature is

the effect of serum magnesium upon PTH level[12]. Our data support a neutral effect of magnesium level upon iPTH level it is worthy to emphasize that multiple regression analysis between iPTH level and magnesium, calcium, phosphate and CaXP product revealed again a neutral effect of all tested variables upon iPTH level. We have to note that 22 of our patients received cinacalcet, because of increased iPTH levels, for more than six months and additional four patients underwent previous parathyroidectomy because of severe hyperparathyroidism but by excluding these patients from the statistical model we obtained again comparable results.

Administration of magnesium containing phosphate binders (CalMag) in twelve patients proved efficient in lowering serum phosphorus level but in expense of a significant increase in pre-dialysis serum magnesium level although no hazardous hypermagnesaemia was observed in our patients probably because we selected patients with low serum magnesium (<3.0 mg/dl). Substitution of dialysate with a lower magnesium concentration (0.75 mEq/L) achieved a significant decrease of pre-dialysis magnesium level comparable to that before CalMag administration. These findings suggest that magnesium containing phosphate binders are effective and safe in lowering phosphorus level in selected haemodialysis patients and that serum magnesium concentration is easily manipulated by dialysate magnesium concentration. Until large scale randomized controlled trials become available, using low magnesium concentration dialysate in order to avoid hypermagnesaemia and bone magnesium accumulation in haemodialysis patients seems reasonable but not definite answer can be given.

Comparing the efficacy of individual phosphate binders upon calcium, phosphate and CaXP product we did not find any significant difference upon serum level of phosphorus and calcium as well as upon CaXP product. A comparison of calcium levels between patients on CalMag or calcium carbonate did not reveal any significant result. These findings suggest that CalMag possesses similar efficacy compared to the usual phosphate binders in lowering phosphate levels without producing significant disturbances in calcium and calcium-phosphate product. More over calcium levels were comparable between CalMag and calcium carbonate phosphate binders. The three-month cost favours firstly the use of Titralac and secondly OsvaRen but we have to account more concern in choosing the proper phosphate binder among individual patients. Our findings support the use of CalMag in selected haemodialysis patients by taking into consideration a possibly beneficial effect of mildly increased serum magnesium level among these patients.

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ORIGINAL ARTICLE

Peritoneoscopic insertion of peritoneal dialysis catheters by nephrologists. A single centre preliminary experience

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Abstract

Background: Peritoneal Dialysis (PD) catheter has been characterized as the "lifeline" of PD patients. Timely and effective insertion of the PD catheter is essential for the success of a PD program. We describe our initial experience with peritoneoscopic implantation of PD catheters by nephrologists.

Patients and Methods: Twenty-one patients underwent peritoneoscopic PD catheter implantation in our centre during 2007 – 2009. Their mean age was 57.3±14.7 years, 8 patients (38%) were transferred from hemodialysis and 12 patients (57%) had a previous history of uncomplicated abdominal surgery for various reasons.

Results: All PD catheters were inserted under local anaesthesia in a nephrology ward. There were no major complications during, or immediately after catheter implantation. There were 4 cases of eosinophilic peritonitis following air entrapment in the peritoneal cavity. PD fluid leak was observed in two cases and an abdominal hernia in one case. The PD catheter did not work properly in 3 cases and in two of them the catheter was removed and replaced by a new one by surgeons. During the follow up period a total of 5 catheters were removed: three of them after successful renal transplantation and two due to poor functioning.

Conclusions: PD catheter insertion by nephrologists with peritoneoscopy is a rather simple, safe and efficient method. It offers the opportunity for timely initiation of PD and a relative independence from surgeons, reducing the waiting times and therefore enhancing PD uptake. Hippokratia 2011; 15 (Suppl 2): 27-29

Key words: catheter, peritoneal dialysis, peritoneoscopy

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Peritoneal Dialysis (PD) has been established as an effective therapy for End Stage Renal Disease (ESRD). However, PD is constantly declining as a dialysis modality in Europe and US, whereas its prevalence remains high in Asia[1]. Among the several reasons that may contribute to its decline[1,2], a key factor remains the permanent access to the peritoneal cavity. The PD catheter has been characterized as the "lifeline" of the PD patient and catheter related problems remain a cause of permanent transfer to hemodialysis (HD) in up to 20% of patients needing a therapy change[3].

PD catheters should provide rapid dialysate flow rates without leaks or infections and should be placed by an experienced operator. Although traditionally the vast majority of PD catheters has been inserted by surgeons[3,4], many nephrologists have started getting involved in catheter insertion, by percutaneous methods using the Seldinger technique[5,6], or more recently by the peritoneoscopic method[7-10].

PD catheter implantation by nephrologists has been reported to improve PD utilization and expansion of the PD programs in US[10,11], or Asia[12,13], mainly due to timely placement of the PD catheter, avoiding unnecessary delays that may drive patients to permanent HD.

Our PD program was started in 1996 and the PD catheters were inserted by surgeons using the open dissection technique under local or general anaesthesia in an operating room. However, during the last years we have observed a big delay in PD catheter insertions (more than months) due tight operating theatre schedules that made many patients to select HD and started to jeopardize our PD program. So, we decided to start a PD catheter implantation program by using the peritoneoscopic technique operated by ourselves. This technique is minimally invasive, rather simple to learn and quick and offers the opportunities to have a visual inspection of the peritoneal cavity and stabilize the deep cuff into the rectus sheath.

Materials and Methods

We prospectively collected data from all patients which underwent peritoneoscopic insertion of PD catheters in our unit from 2007 to 2009. Patient demographics are shown in table 1. Twelve (12) patients (pts) had a history of previous uncomplicated abdominal operations such as appendectomy (3 pts), cholecystectomy (5 pts), caesarian section (2 pts) and renal transplantation (2 pts). Eight patients (38%) were transferred from HD due to vascular access problems

We used a modified peritoneoscopic technique,

Number of Patients	21
Age	57.3±14.7 (30-83)
Males	13 (61%)
Causes of ESRD	
Glomerulonephritis	5
Diabetic Nephropathy	4
Unknown Etiology	8
Chronic Allograft Nephropathy	2
Polycystic Kidney Disease	1
Malignant Hypertension	1

Table 1: Demographics of the patient population.

applying an initial step with a laparoscopic Veress needle, as introduced by Asif et al, in order to reduce the risk of bowel perforation[8]. All patients were admitted one day before the procedure receiving laxatives and enemas for bowel preparation and antibiotic prophylaxis with vancomycin i.v. one hour before catheter implantation. Catheter break-in for initiation of PD was usually performed after 2 weeks post implantation.

Results

All PD catheters (coiled double cuff Tenckhoff catheters) were placed in a nephrology ward under local anaesthesia. Most catheters (19) were placed on the left lateral border of the rectus sheath 2-3 cm below umbilicus and two (2) on the right side due to the presence of a renal allograft on the left side.

There were no major complications during and immediately after catheter implantation. Mild tingeing of dialysate with blood was noted in five (5) cases that were cleared with subsequent exchanges the next day after implantation.

In four cases a cloudy effluent was observed during the first week after catheter implantation due to eosinophilic peritonitis, after air entrapment in the peritoneal cavity.

PD fluid leak was observed in two cases. In one case, as PD was immediately introduced in an old lady, whereas in the second case, leaking was observed after one month of in hospital intermitted PD.

PD catheter migration was seen in four (4) patients: in three of them, after at least 3 months post catheter implantation due to constipation and was treated successfully by laxatives and in one case during the first days after catheter placement. That catheter was repositioned under direct fluoroscopic control.

There was only one case of incisional hernia observed in a thin female patient after 4 months of CAPD therapy probably due to increased intra-abdominal pressure.

In three patients the PD catheter could not work properly. One case was due to PD catheter occlusion by a large intraluminal fibrin clot, repaired by laparoscopic surgery, whereas two catheters had to be removed and replaced in one time by our surgical team.

During the follow-up period a total of 5 PD catheters were removed: three during operations for renal transplantation and two due to poor functioning leading to a total primary catheter failure of 10%.

Discussion

Here, we describe our initial experience with peritoneoscopic PD catheter implantation in twenty-one (21) patients. This technique is minimally invasive, rather simple to learn and quick, leading to independence from surgeons or anaesthesiologists and operating theatres.

We decided to use it as the delay in PD catheter implantation in our hospital (more than months) had started to jeopardize our PD program. By using this technique there was no more waiting time for catheter implantation, as the PD catheters were placed in a nephrology ward.

Our total primary catheter failure was almost 10% (2/21) and rather low compared with the recommendations of the International Society of Peritoneal Dialysis[3,14] and the European Best Practice Guidelines for Peritoneal Dialysis[15] guidelines, which suggest that regardless of the technique used, one years' PD catheter survival should exceed 80%.

All except one, cases were primary PD catheter implantations. In one case the PD catheter was reinserted after an episode of fungal peritonitis and peritoneoscopy offered the advantage of visual information about the status of the peritoneal cavity[16].

With the modification of the technique[8] by applying an initial step with a laparoscopic Veress needle, we have avoided major complications such as bowel or bladder perforation, or major bleeding.

Eosinophilic peritonitis was seen in 4 cases due to air entrapment in the peritoneal cavity. This is a rather benign condition not needing antibiotic therapy or catheter removal. Reabsorption of entrapped air and/or treatment with ketotifen might be all that is required [17]. This complication was avoided during future procedures by placing the patients in the Trendelenburg position and manually compressing the abdomen gently toward the quill. In this way air can escaped through the quill inserted at the catheter insertion site.

Catheter migration is rather frequent in PD patients. It is mainly due to constipation and resolves easily by administration of laxatives or enemas. Only one PD catheter in our series needed to be corrected under direct fluoroscopy with relative ease.

Incisional hernias are more frequent after surgical placement of PD catheters due to larger incisions[3,14]. However, we observed one case of incisional hernia in a thin female patient, probably as an adverse effect of increased intra-abdominal pressure during CAPD therapy. The patient was treated by switching to Automated PD with a dry daytime.

Our experience is supporting previous studies indicating that placement of PD catheters by nephrologists is a feasible option in order to maintain and expand a PD

program[10-13]. As the European Best Practice Guidelines for Peritoneal Dialysis state, the most important element of success for PD catheter implantation does not rely on the technique used (surgical, percutaneous, or laparoscopic) but the experience of the people getting involved[15]. As Li and Chow also underline "practice makes perfect"[13], and all nephrologists dealing with PD and facing similar problems should be encouraged to start putting PD catheters by themselves regardless of the preferred technique.

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ORIGINAL ARTICLE

Evolution of secondary hyperparathyroidism one year after successful renal transplantation

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Abstract

Background: The natural history of parathyroid function after successful renal transplantation (Tx) as well as the factors predisposing to persistent secondary hyperpathyroidism (sHPT) are not well established, whereas regression of sHPT is not always observed and depends on renal graft function. The aim of the present study was to evaluate the post-Tx natural history of parathyroid function in patients with a well functioning renal graft.

Patients and Methods: One hundred and five (105) patients, which underwent successful renal transplantation, were studied. Sixteen (16) patients had a history of previous parathyroidectomy for severe HPT.

Results: Parathyroid hormone (PTH) mean value presented a significant fall from 373.2±418 to 128±121 pg/ml ($p<0.001$) at 12 months post-Tx. Pre-Tx PTH levels were significantly correlated with 12 months post-Tx levels ($r= 0.46$, $p< 0.001$). Serum calcium did not present significant alterations, whereas serum phosphorus decreased significantly, since the third month post-Tx from 5.9±1.67 mg/dl to 3.2±0.75 mg/dl ($p<0.001$). Renal graft function remained well preserved and mean serum creatinine was 1.59±0.44 mg/dl at the 12th month post-Tx. Eighteen (18) patients presented severe HPT (PTH > 800 pg/ml) at the time of transplantation. In this group of patients, PTH was also significantly decreased, but remained in abnormal levels (PTH > 100 pg/ml) after 12 months post-Tx in 6 cases.

Conclusions: These results suggest an improvement of parathyroid function as measured by PTH levels, during the first year after successful renal transplantation in patients with mild or moderate sHPT. Twelve months' PTH levels depend on pre-Tx levels. However severe pre-existing sHPT may persist even after one year post-Tx in a significant number of patients. Hippokratia 2011; 15 (Suppl 2): 30-32

Key words: calcium, phosphorus, PTH, renal transplantation

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Secondary hyperparathyroidism (sHPT) is a frequent complication of uremia. Ideally, successful renal transplantation (Tx) corrects the endocrine and metabolic imbalances and the main abnormalities responsible for sHPT during the first months[1].

The natural history of parathyroid function after successful renal transplantation, as well as the factors predisposing to persistent hyperparathyroidism is not well established and only a few data are available in the literature on this subject. Renal transplant recipients may present signs of disturbed calcium homeostasis, such as hypercalcemia or bone loss[2-7], whereas regression of sHPT is not always observed and also depends on renal graft function [2,4,8,9] .

The aim of the present study was to evaluate the post-Tx natural history of parathyroid function in patients with well functioning renal grafts one year post-Tx and to identify any possible risk factors for persistent sHPT.

Materials and Methods

One hundred and five (105) patients aged 43.8±12.3 (13-67) years, which were on renal replacement therapy for 64.2±41.3 (8-204) months and underwent successful renal transplantation in our centre from 1998 until 2005 were retrospectively studied. Their original renal diseases included chronic glomerulonephritis (n=40), unknown aetiology (n=31), polycystic kidney disease (n=13), diabetic nephropathy (n=12) and other aetiologies (n=9). Ninety-four patients had undergone cadaveric renal transplantation and 11 patients living related transplantation. All patients received induction therapy with basiliximab and were on triple immunosuppressive regimens with calcineurin inhibitors, mycophenolate mofetil and steroids. Sixteen (16) patients had a history of previous parathyroidectomy for severe sHPT.

Parathyroid hormone (PTH) was measured before renal transplantation and every three months during the first year post-Tx by a RIA technique. Serum creatinine, calcium and phosphorus were measured at least monthly by standard techniques and estimated Glomerular Filtration Rate (eGFR) was calculated by the MDRD formula.

All values are expressed as mean± SD. Analysis of

Months post-Tx	0	3	6	12
PTH* (pg/ml)	373.2±418	206.2±197	138.9±126*	128±121*
Calcium (mg/dl)	9.7±1	10±0.72	10.1±0.7	10.1±0.8
Phosphorus* (mg/dl)	5.9±1.7	2.88±0.75*	3.3±0.7*	3.2±0.75*
Creatinine* (mg/dl)	10.3±2.8	1.56±0.48*	1.63±0.48*	1.59±0.44*

Table 1: Evolution of serum parathyroid hormone (PTH), calcium, phosphorus and creatinine levels during the first 12 months post renal transplantation. (*p< 0.001).

variance (ANOVA) test and correlation analysis by Pearson coefficient were used as appropriate. A p value < 0.05 was considered as statistically significant.

Results

Evolution of serum PTH, calcium, phosphorus and creatinine during the first 12 months post renal transplantation is shown in table 1. Renal graft function remained well preserved with a mean serum creatinine of 1.59±0.44 mg/dl and a GFR of 57±12 ml/min/1.73m^2 at the 12th month post-Tx .

Mean value of PTH decreased significantly from 373.2±418 to 128±121 pg/ml (p<0.001) at 12 months post-Tx (Table 1). Serum calcium did not present significant alterations, whereas serum phosphorus decreased significantly, since the third month post-Tx from 5.9±1.7 mg/dl to 3.2 ± 0.75 mg/dl at 12 months post-Tx (p<0.001) (Table 1).

Pre-Tx PTH levels were significantly correlated with 12 months post-Tx levels (r= 0.46, p< 0.001). Post-Tx PTH levels were positively correlated with serum calcium levels (r= 0.278, p< 0.05) and negatively with serum phosphorus levels (r= - 0.283, p< 0.05) at 12 months post-Tx. There was no significant correlation of PTH levels with serum creatinine, or GFR at 12 months post-Tx.

Patients with severe pre-existing hyperparathyroidism.

Eighteen (18) patients presented severe sHPT (PTH > 800 pg/ml) at the time of transplantation (1074±365 pg/ml). In this group of patients, PTH was also significantly decreased (186±125 pg/ml, p<0.001), but remained in abnormal levels (> 100 pg/ml) after 12 months post-Tx in 6 cases. Only one patient underwent parathyroidectomy due to severe hypercalcemia and graft dysfunction four months post-Tx.

Discussion

Successful renal transplantation restores, at least partially, the main abnormalities responsible for sHPT (vitamin D deficiency, phosphorus retention, hypocalcemia and metabolic acidosis), but information is scarce about the natural course of parathyroid function post-Tx[1,2,5,9,10].

In the present study we retrospectively evaluated data from 105 renal transplant recipients with stable renal function, as reflected by their serum creatinine and calculated GFR. According to our results, there is an improvement of parathyroid function, as measured by PTH levels, during the first year after successful renal transplantation in patients with mild or moderate sHPT. Although our patients' allograft function can generally be considered optimal with a mean eGFR of about 57 ml/min/1.73m^2, this rate is rather insufficient to suppress all of the PTH stimulatory signals and normalize totally parathyroid glands function.

Bonarek et al reported a reduction of parathyroid mass 6 months post-Tx with both static and dynamic tests in 11 renal transplant recipients with good renal function. However normalization of parathyroid function was not complete, possibly due to a slow regression and low parathyroid cell turnover[7].

Bravo et al have prospectively studied 36 patients before and one year post-Tx by ultrasound examination of the parathyroid glands[6]. The authors reported a clinical reduction in gland volume of about 58% in patients with detectable parathyroid glands at the time of Tx that was also accompanied with better allograft function.

Reinhardt et al studied prospectively 129 renal transplant recipients for 2 years dividing the study population in two groups according to optimal or suboptimal renal function with a serum creatinine cut-off of about 1.5 mg/dl[5]. Post-Tx serum PTH levels were significantly higher in the group with impaired allograft function, implicating that the better the graft function, the more complete the reversal of HPT.

Evenepoel et al have retrospectively reviewed the charts from 1165 renal transplant recipients and found that sHPT persisted in 17% of the patients even after 4 years post-Tx[2]. Possible risk factors for persistent sHPT included a long dialysis vintage and elevated serum levels of PTH, calcium and phosphorus at the time of transplantation. Post-Tx PTH serum levels correlated significantly with pre-Tx levels (r=0.52), serum calcium (r=0.30) and serum creatinine (r=0.24). We have also found a rather similar correlation between post-Tx and pre-Tx PTH levels (r=0.46) as well as with serum calcium (r=0.278) but not with serum creatinine, or GFR at 12 months post-Tx. This may be probably due to the smaller sample in our study. However, we found a significantly negative correlation between PTH levels and serum phosphorus that was not examined in the study of Evenepoel et al[2].

In our study, phosphorus levels decreased significantly after 3 months post-Tx. Hypophosphatemia is a

common complication of renal transplantation. Recently, fibroblast growth factor 23 (FGF 23) emerged as its most important mediator, as increased FGF 23 levels, but not PTH levels are independently associated with low serum phosphorus in renal transplant recipients[11]. However, increased PTH may act synergistically to increase phosphaturia in these patients[11].

In the literature the prevalence rates of parathyroidectomy post-Tx range from 0.6 to 5.6%. However there are no evidence-based guidelines for the absolute indications for parathyroidectomy post-Tx, except in cases of calciphylaxis. Although laboratory data, clinical symptoms and imaging data should all taken into account, for most clinicians persistent HPT with hypercalcemia represents the main indication. Besides these, increased alkaline phosphatase activity, unexplained deterioration of allograft function and clinical symptoms such as bone pain and pruritus may serve as additional indications. Evenepoel et al in a retrospective study reported a parathyroidectomy rate of 8.89% per 1000 person-years and female gender, high pre-Tx PTH levels and high pre-Tx calcium as significant risk factors[9]. These authors also reported a deterioration of allograft function after parathyroidectomy, without any alterations in graft survival rates. In our study, only one female patient with high PTH levels pre-Tx underwent parathyroidectomy for persistent hypercalcemia and sHPT, but renal function presented a rapid improvement after the procedure.

The advent of the calcimimetic drugs such as cinacalcet, that has been already been used successfully for the treatment of hypercalcemia and sHPT in the renal transplant recipients[12] will probably reduce parathyroidectomy rates in the near future. However, cinacalcet is a rather expensive therapy and oral pulse calcitriol may result in successful regression sHPT post-Tx with less cost[13].

In conclusion, the majority of renal allograft recipients present a rapid but incomplete decrease of serum PTH levels after successful Tx and renal Tx remains the best option for the treatment of sHPT. Somewhat higher level of PTH should not be regarded as suboptimal, as they may secure a better turnover of the bone and prevent osteopenia after renal Tx. Treatment with vitamin D is preferable, but cinacalcet can be used in selected cases of no other option, such as hypercalcemia or contraindications for parathyroidectomy. However, cinacalcet remains extremely expensive, if applied for a long time and its use has not been justified so far by any large and prospective study in renal Tx.

Conflicts of Interest: None to declare

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