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BANTAO Journal

Official Publication of the BANTAO Association

Incorporating Proceedings of the BANTAO Association

Published by: Balkan Cities Association of Nephrology, Dialysis, Transplantation and Artificial Organs

Printing: BANTAO, 2014

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Special feature

Clinical Practice Guideline on Diagnosis and Treatment of Hyponatraemia

Goce Spasovski[1], Raymond Vanholder[2], Bruno Allolio[3], Djillali Annane[4], Steve Ball[5], Daniel Bichet[6], Guy Decaux[7], Wiebke Fenske[8], Ewout Hoorn[9], Carole Ichai[10], Michael Joannidis[11], Alain Soupart[12], Robert Zietse[13], Maria Haller[14], Evi Nagler[15], Wim Van Biesen[16] and Sabine van der Veer[17]

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Abstract

Hyponatraemia, defined as a serum sodium concentration <135 mmol/l, is the most common disorder of body fuid and electrolyte balance encountered in clinical practice. It can lead to a wide spectrum of clinical symptoms, from subtle to severe or even life threatening, and is associated with increased mortality, morbidity and length of hospital stay in patients presenting with a range of conditions. Despite this, the management of patients remains problematic. The prevalence of hyponatraemia in widely different conditions and the fact that hyponatraemia is managed by clinicians with a broad variety of backgrounds have fostered diverse institution-and speciality-based approaches to diagnosis and treatment. To obtain a common and holistic view, the European Society of Intensive Care Medicine (ESICM), the European Society of Endocrinology (ESE) and the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA), represented by European Renal Best Practice (ERBP), have developed the Clinical Practice Guideline on the diagnostic approach and treatment of hyponatraemia as a joint venture of three societies representing specialists with a natural interest in hyponatraemia. In addition to a rigorous approach to methodology and evaluation, we were keen to ensure that the document focused on patient-important outcomes and included utility for clinicians involved in everyday practice.

Key words: hyponatremia, mild, moderate, severe, acute, chronic

Chapter 1. Introduction and Methodology

Hyponatraemia, defined as a serum sodium concentration <135 mmol/L, is the most common disorder of body fluid and electrolyte balance encountered in clinical practice. Hyponatraemia is present in 15-20% of emergency admissions to hospital and occurs in up to 20% of critically ill patients. It can lead to a wide spectrum of clinical symptoms, from subtle to severe or even life threatening and is associated with increased mortality, morbidity and length of hospital stay in patients presenting with a range of conditions. Despite this, the management of patients remains problematic. The prevalence of hyponatraemia in widely different conditions and the fact that hyponatraemia is managed by clinicians with a broad variety of backgrounds, has fostered diverse institution- and speciality-based approaches to diagnosis and treatment.
Against this background, the European Society of Intensive Care Medicine (ESICM), the European Society of Endocrinology (ESE) and the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA), represented by European Renal Best Practice (ERBP) have developed this Clinical Practice Guideline on the diagnostic approach and treatment of hyponatraemia as a joint venture of three societies representing specialists with a natural interest in hyponatraemia. In addition to a rigorous approach to methodology and evaluation, we

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were keen to ensure the document focused on patient-important outcomes and had utility for clinicians involved in every-day practice.

This condensed and translated version of the Clinical Practice Guideline on Diagnosis and Treatment of Hyponatraemia focuses on recommendations on diagnosis and treatment of hyponatraemia. For aspects of conflict of interest, purpose and scope, methods of guideline development and pathophysiology of hyponatraemia, we refer to the full version of the guideline, which is free available on http://ndt.oxfordiournals.ore/content/29/suppl 2/i1.full.pdf+html.

Disclaimer: this guideline was translated with approval of ERBP, the official guideline body of ERA-EDTA. However, ERBP only takes full responsibility for the original full guideline in English as published in Nephrol. Dial. Transplant. (2014) 29 (suppl 2): i1-i39. doi: 10.1093/ndt/gfu 040-First published online: February 25, 2014: http://ndt. oxfordiournals.org/content/29/suppl2/i1.full.pdf+html; http://european-renal-best-practice.org [1].

Chapter 2. Diagnosis of Hyponatraemia

2.1. Classification of hyponatraemia

2.1.1. Definition of hyponatraemia based on biochemical severity

We define "mild" hyponatraemia as a biochemical finding of a serum sodium concentration between 130 and 135 mmol/L as measured by ion specific electrode.

We define "moderate" hyponatraemia as a biochemical finding of a serum sodium concentration between 125 and 129 mmol/L as measured by ion specific electrode.

We define "profound" hyponatraemia as a biochemical finding of a serum sodium concentration <125 mmol/L as measured by ion specific electrode.

2.1.2. Definition of hyponatraemia based on time of development

We define "acute" hyponatraemia as hyponatraemia that is documented to exist <48 hours. We define "chronic" hyponatraemia as hyponatraemia that is documented to exist for at least 48 hours.

Table 1. (Table 5 of the online full document): Classification of symptoms of hyponatraemia

Severity	Symptom
Moderately severe	Nausea without vomiting
	Confusion
	Headache
Severe	Vomiting
	Cardio-respiratory distress
	Abnormal and deep somnolence
	Seizures
	Coma (Glazgow Coma Scale ≤8)

If the hyponatraemia cannot be classified, we consider it being chronic, unless there is clinical or anamnestic evidence of the contrary (Table 1, 2).

2.1.3. Definition of hyponatraemia based on symptoms

We define "moderately symptomatic" hyponatraemia as any biochemical degree of hyponatraemia in the presence of moderately severe symptoms of hyponatraemia (Table 1).

We define "severely symptomatic" hyponatraemia as any biochemical degree of hyponatraemia in the presence of severe symptoms of hyponatraemia (Table 1).

Table 2. (Table 8 of the online full document): Drugs and conditions associated with acute hyponatraemia (< 48 hours)

hyponatraemia (< 48 hours)
Postoperative phase
Post-resection of the prostate, post-resection of endoscopic uterine surgery
Polydipsia
Exercise
Recent thiazides prescription
3,4-methyleendioxymethamfetamine (MDMA, XTC)
Colonoscopy preparation
Cyclophosphamide (intravenous)
Oxytocin
Recently started desmopressin therapy
Recently started terlipressin, vasopressin

Hyponatraemia can be classified based on different parameters, such as serum sodium concentration, rate of development, symptom severity, serum osmolality, and volume status. We intended to make the classification directly relevant for patient management. However, treatment strategies cannot be adequately classified with reference to a single criterion. Hence, treatment strategies have been classified according to combinations of these criteria.

Published research suggests using a threshold of 48 hours to distinguish "acute" from "chronic" hyponatraemia, as brain oedema seems to occur more frequently when hyponatraemia develops in less than 48 hours. Experimental studies also suggest that the brain needs approximately 48 hours to adapt to a hypotonic environment. Before adaptation, there is a risk of brain oedema, because the lower extracellular osmolality promotes a shift of water into the cells. However, once adaptation is completed, brain cells can again sustain damage if the serum sodium concentration increases too rapidly. Breakdown of the myelin sheath insulating individual neurons can result in what is called the osmotic demyelination syndrome. It is thus important to distinguish between acute and chronic hyponatraemia to assess whether someone is at greater risk of immediate brain oedema than of osmotic demyelination. In clinical practice, the distinction between acute and chronic hyponatraemia is often unclear, particularly for patients presenting to the emergency room. If classification as acute or chronic

is not possible or when there is doubt, it should be considered chronic, unless there are reasons to assume it is acute (see Table 10 of original document).
The classification based on symptoms aims to reflect the degree of brain oedema and the extent of immediate danger. It allows matching treatment to the immediate risk, with more aggressive treatment for symptoms that are more severe. Nevertheless, a classification based only on symptom severity has several shortcomings, as patients may porgress from moderately severe to severe symptoms within hours. In addition, symptoms of hyponatraemia are nonspecific and clinicians need to assess the possibility that symptoms can be caused by conditions other than hyponatraemia on itself. In general, one should be particularly careful when attributing moderately severe to severe symptoms to hyponatraemia when the biochemical degree of hyponatraemia is only mild.
Patients with hyponatraemia may be hypovolaemic, euvolaemic, or hypervolaemic, and many traditional diagnostic algorithms start with a clinical assessment of volume status [2] .The sensitivity and specificity of clinical assessments of volume status are low, potentially leading to misclassification early in the diagnostic tree. In addition, there might be confusion regarding the compartment the fluid is in (circulating or extracellular). Therefore, we have used the terms "effective circulating volume" and "extracellular fluid volume" throughout the text to reduce ambiguity.

2.2. Confirming hypotonic and excluding non-hypotonic hyponatraemia

We recommend excluding hyperglycaemic hyponatraemia by measuring the serum glucose concentration and correcting the measured serum sodium concentration for the serum glucose concentration if the latter is increased (1D).
Hyponatraemia with a measured osmolality <275 mOsm/kg always reflects hypotonic hyponatraemia (Not Graded).
Accept as "hypotonic hyponatraemia" a hyponatraemia without evidence for causes of non-hypotonic hyponatraemia as listed in table 3 (Not Graded). Estimates of the serum sodium concentration corrected for the presence of hyperglycaemia can be obtained from the following equations:

Table 3. (Table 10 of the online full document): Causes of nonhypotonic hyponatraemia

Setting	Serum osmolality	Examples
Presence of "effective" osmoles that raise serum osmolality and can cause hyponatraemia	Isotonic or hypertonic	Glucose Mannitol Glycine Histidine-tryptophane-ketoglutarate Hyperosmolar radiocontrast media Maltose
Presence of "ineffective" osmoles that raise serum osmolality but do not cause hyponatraemia	Isotonic or hyperosmolar	Urea Alcohols Ethylene-glycol
Presence of endogenous solutes that cause pseudohyponatraemia (laboratory artifact)	Isotonic	Triglycerides, cholesterol, protein Intravenous immunoglobulins Monoclonal gammapathies

$$\text{Corrected serum } (Na^+) = \text{measured } (Na^+) + 2.4 \times \frac{\text{glucose (mmol/l)} - 100 \text{ (mmol/l)}}{100 \text{ mmol/l}}$$

$$\text{Corrected } (Na^+) = \text{measured } (Na^+) + 2.4 \times \frac{\text{glucose (mmol/l)} - 5.5 \text{ (mmol/l)}}{5.5 \text{ mmol/l}}$$

† [Na+], serum sodium concentration; [Glucose], serum glucose concentration.

This translates into adding 2.4 mmol/L to the measured serum sodium concentration for every 5.5 mmol/L (100 mg/dL) incremental rise in serum glucose concentration above a standard serum glucose concentration of 5.5 mmol/L (100 mg/dL).

2.3. Which parameters to use for differentiating causes of hypotonic hyponatraemia? (Figure 1.)

We recommend interpreting urine osmolality of a spot urine sample as a first step (1D).

If urine osmolality ≤100 mOsm/kg, we recommend accepting relative *excess* water intake as a cause of the hypotonic hyponatraemia (1D).
If urine osmolality >100 mOsm/kg, we recommend interpreting the urine sodium concentration on a spot urine sample taken simultaneously with a blood sample (1D).
If urine sodium concentration ≤30 mmol/L, we suggest accepting low effective arterial volume as a cause of the hypotonic hyponatraemia (2D).
If urine sodium concentration >30 mmol/L, we suggest assessing extracellular fluid status and use of diuretics to further differentiate likely causes of the hyponatraemia (2D).
We suggest against measuring vasopressin for confirming the diagnosis of SIADH (2D).

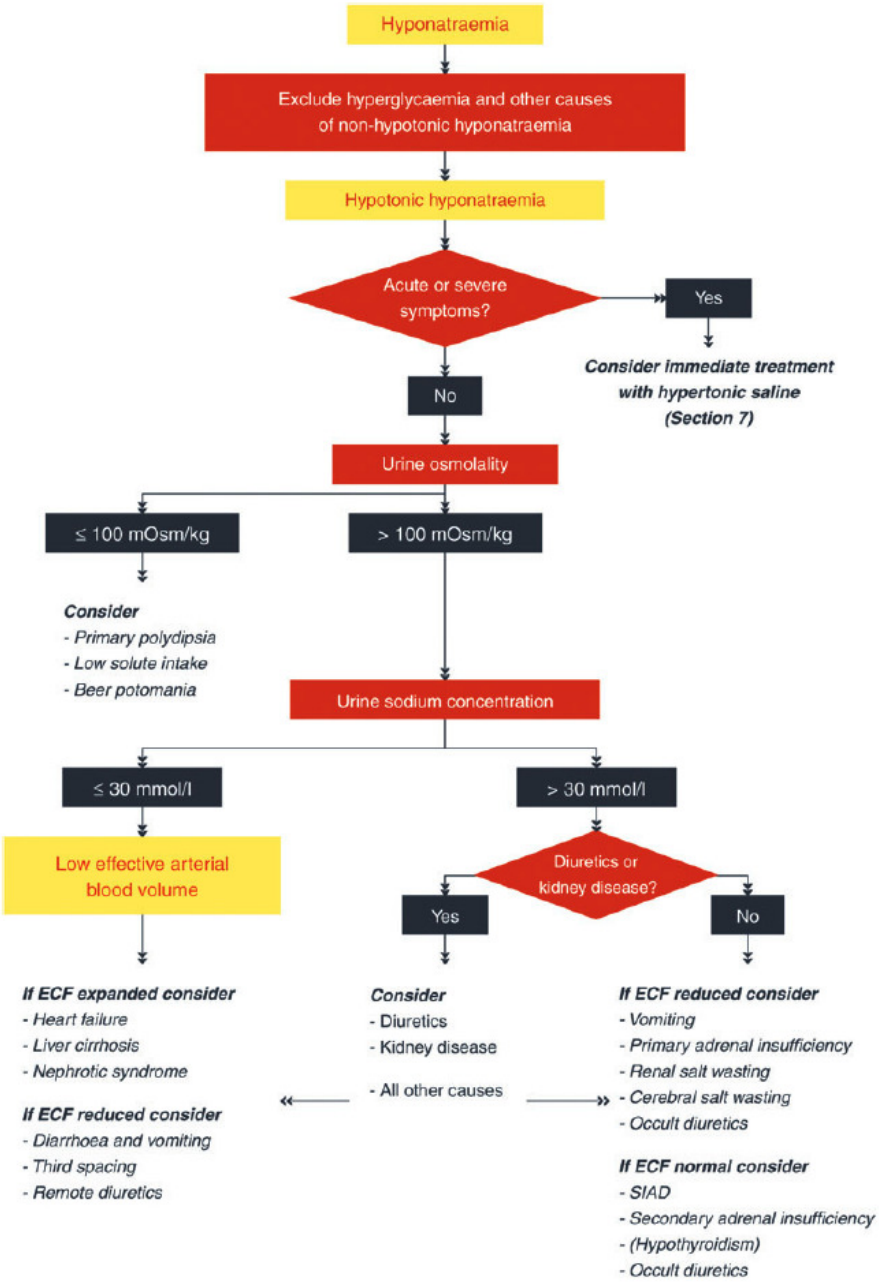

Fig. 1. (Figure 6 of the online full document): Algorithm for the diagnosis of hyponatraemia

Advice for clinical practice

Correct interpretation of laboratory measurements requires contemporaneous collection of blood and urine specimens. For practical reasons, urine osmolality and sodium concentration are best determined in the same urine sample.
If clinical assessment indicates the volume of extracellular fluid is not overly increased and the urine sodium concentration >30 mmol/L, exclude other causes of hypotonic hyponatraemia before implicating SIAD.

Table 4. (Table 6 of the full online document): Diagnostic criteria for the syndrome of inappropriate antidiuresis

Essential criteria
Effective serum osmolality < 275 mOsm/kg
Urine osmolality > 100 mOsm/kg at some level of decreased effective osmolality
Clinical euvolaemia
Urine sodium concentration > 30 mmol/L with normal dietary salt and water intake
Absence of adrenal, thyroid, pituitary or renal insufficiency
No recent use of diuretic agents
Supplemental criteria
Serum uric acid < 0.24 mmol/L (< 4 mg/dL)
Serum urea < 3.6 mmol/L (< 21.6 mg/dL)
Failure to correct hyponatraemia after 0.9% saline infusion
Fractional sodium excretion > 0.5%
Fractional urea excretion > 55%
Fractional uric acid excretion > 12%
Correction of hyponatraemia through fluid restriction___

Adapted from Schwartz WB *et al.* Am J Med 1957; 23: 529-543. and Janicic N *et al.* Endocrinol Metab Clin North Am 2003; 32: 459-481 [3].

Consider using the diagnostic criteria listed in Table 4 and looking for known causes of SIAD (Table 5 and 6).
Consider primary or secondary adrenal insufficiency as an underlying cause of the hypotonic hyponatraemia.
Kidney disease complicates differential diagnosis of hyponatraemia. Besides possibly contributing to thehyponatraemia, the ability of the kidneys to regulate urine osmolality and urine sodium is often diminished, much like with the use of diuretics.
As urine osmolality and sodium may no longer reflect the effects of the regular hormonal axes regulating water and sodium homeostasis, any diagnostic algorithm for hyponatraemia must be used with caution in patients with kidney disease.
The water-loading test is generally not helpful for differential diagnosis of hypotonic hyponatraemia and may be dangerous in this setting.

Table 5. (Table 7 of the online full document): Differences between SIADH and cerebral salt wasting

Malignant diseases	**Pulmonary disorders**	**Disorders of the nervous system**
Carcinoma	Infections	Infection
Lung	Bacterial pneumonia	Encephalitis
Oropharynx	Viral pneumonia	Meningitis
Gastrointestinal tract	Pulmonary abscess	Brain abscess
Stomach	Tuberculosis	Rocky Mountain spotted fever
Duodenum	Aspergillosis	AIDS
Pancreas	Asthma	Malaria
Genitourinary tract	Cystic fibrosis	Vascular and masses
Ureter	Respiratory failure associated with positive - pressure breathing	Subdural hematoma
Bladder		Subarachnoid haemorrhage
Prostate		Stroke
Endometrium		Brain tumors
Endocrine thymoma		Head trauma
Lymphomas		Other
Sarsomas		Hydrocephalus
Ewing's sarcoma		Cavernous sinus thrombosis
Olfactory neuroblastoma		Multiple sclerosis
		Guillain-Barre' syndrome
		Shy-Drager syndrome
		Delirium tremens
		Acute intermittent porphyria

AIDS, acquired immunodeficiency syndrome; MOAI, monoamine oxidase inhibitors; MDMA, 3,4-methylenedioxymethamphetamine; NSAIDs, non-steroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors

Drugs	**Other causes**
Vasopressin release or action stimulants	Hereditary
Antidepressants	Gain-of-function mutation of the vasopressin V2 receptor
SSRIs	Idiopathic
Tricyclic	Transient
MAOI	Exercise-associated hyponatraemia
Venlafaxine	General anaesthesia
Anticonvulsants	Nausea
Carbamazepine	Pain
Oxcarbazepine	Stress

Sodium valproate
Lamotrigine
Antipsychotics
Phenothiazides
Butyrophenones
Anticancer drugs
Vinca alkaloids
Platinum compounds
Ifosfamide
Melphalan
Cyclophosphamide
Methotrexate
Pentostatin
Antidiabetic drugs
Chlorpropamide
Tolbutamine
Miscellaneous
Opiates
MDMA (XTC)
Levamisole
Interferon
NSAIDs
Clofibrate
Nicotine
Amiodarone
Proton pump inhibitors
MABs
Vasopressin analogues
Desmopressin
Oxytocin
Terlipressin
Vasopressin

Table 6. (table 11 of the online full document): Differences between SIADH and cerebral salt wasting

	SIADH	Cerebral salt wasting
Serum urea concetration	Normal-low	Normal-high
Serum uric acid concentration	Low	Low
Urine volume	Normal-low	High
Urine sodium concentration	>30 mmol/L	>>30 mmol/L
Blood pressure	Normal	Normal-orthostatic hypotension
Central venous pressure	Normal	Low

Adapted from Sherlock M *et al*. *Clin Endocrinol* 2006; 64: 250*2S4 and Brimioulle S *et al*. Intensive Care Med 2008; 34: 125-31 [5].

Chapter 3. Treatment of Hypotonic Hyponatraemia

How to use the treatment recommendations?

Individual recommendations and statements on management of hyponatraemia can only be correctly interpreted and implemented if considered within the structure illustrated in figure 2.

The guideline development group felt that with severe or moderately severe symptoms, the acute risk of brain oedema outweighs the risk of osmotic de- myelination syndrome. They felt it justifies urgent treatment in these conditions, irrespective of biochemical degree or timing (acute versus chronic) of hyponatraemia. Conversely, the guideline development group believed that in the absence of severe or moderately severe symptoms, there is time for diagnostic assessment, and cause-specific treatment is the most reasonable approach.

It is crucial to understand that for correctly classifying symptoms as "severe" or "moderately severe", there must be sufficient confidence that the symptoms are caused by hyponatraemia itself. If hyponatraemia is mild and symptoms are severe or moderately severe, the guideline development group advises to only accept causality in exceptional cases. Consequently, generally, chapters 3.1, 3.2, and 3.3 are not applicable when hyponatraemia is mild (see chapters 7.1, 7.2 and 7.3 full guideline publication). It is also essential to understand that the guideline development group distinguishes between targets and limits. A target is a goal one is aiming for; it is the change in serum sodium concentration that one wishes and expects to achieve with a particular treatment. In contrast, a limit is a change in serum sodium concentration one does not want to exceed and if surpassed, requires prompt counter-regulating intervention. In addition, the reader should bear in mind that the absolute numbers provided as "targets" or "limits" should always be interpreted in the clinical context of the individual patient.

3.1. Hyponatraemia with severe symptoms

3.1.1. First hour management, regardless of whether hyponatraemia is acute or chronic

We recommend prompt intravenous infusion of 150 mL 3% hypertonic saline or equivalent over 20 minutes (1D).
We suggest checking the serum sodium concentration after 20 minutes while repeating an infusion of 150 mL 3% hypertonic saline or equivalent over the next 20 minutes (2D).
We suggest repeating the two therapeutic recommendations above twice or until a target of 5 mmol/L increase in serum sodium concentration is achieved (2D).
Manage patients with severely symptomatic hyponatraemia in an environment where close biochemical and clinical monitoring can be provided (Not Graded).

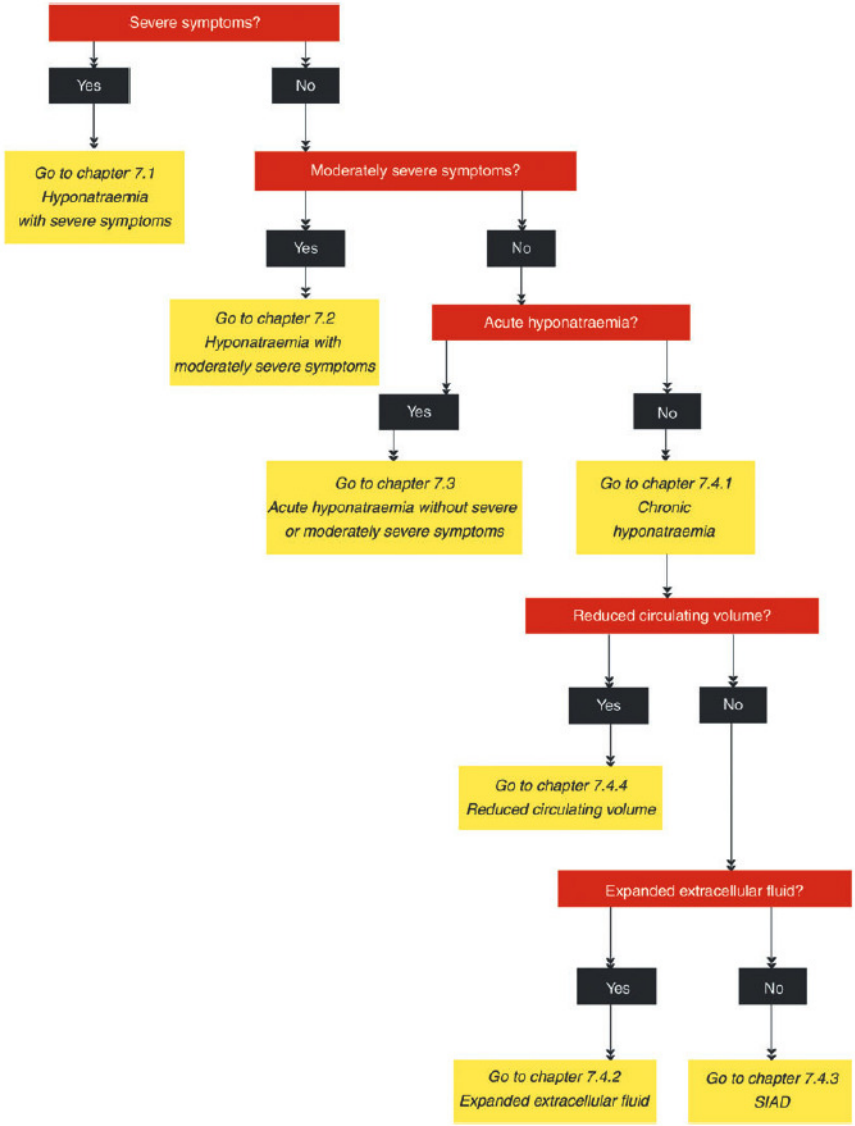

Fig. 2. (Figure 7 of the online full document): Algorithm for the management of hypotonic hyponatraemia*

3.1.2. Follow up management in case of improvement of symptoms after a 5 mmol/L increase in serum sodium concentration in the first hour, regardless of whether hypo-natraemia is acute or chronic

We recommend stopping the infusion of hypertonic saline (1D).
We recommend keeping the intravenous line open by infusing the smallest feasible volume of 0.9% saline until cause-specific treatment is started (1D).
We recommend starting a diagnosis specific treatment if available, aiming at least to stabilize sodium concentration (1D).
We recommend limiting the increase in serum sodium concentration to a total of 10 mmol/L during the first 24 hours and an additional 8 mmol/L during every 24

hours thereafter until the serum sodium concentration reaches 130 mmol/L (1D).
We suggest checking the serum sodium concentration after 6 and 12 hours, and daily afterwards until the serum sodium concentration has stabilised under stable treatment (2D).

3.1.3 Follow up management in case of no improvement of symptoms after a 5 mmol/L increase in serum sodium concentration in the first hour, regardless of whether the hyponatraemia is acute or chronic

We recommend continuing an intravenous infusion of 3% hypertonic saline or equivalent aiming for an additional 1 mmol/L/h increase in serum sodium concentration (1D).
We recommend stopping the infusion of 3% hypertonic saline or equivalent when the symptoms improve, the serum sodium concentration increases 10 mmol/L in total or the serum sodium concentration reaches 130 mmol/L, whichever occurs first (1D).
We recommend additional diagnostic exploration for other causes of the symptoms than hyponatraemia (1D).
We suggest checking the serum sodium concentration every 4 hours as long as an intravenous infusion of 3% hypertonic saline or equivalent is continued (2D).

Advice for clinical practice

Prompt infusion of hypertonic saline may save lives. However, preparing a 3% hypertonic saline infusion takes time and errors may occur in calculating the required amount of sodium chloride. Therefore, it may be wise for the pharmacy to store pre-prepared 150 mL bags of 3% hypertonic saline. It ensures that solutions are prepared under sterile conditions, by either the pharmacist or the manufacturer, and are available for immediate infusion without having to prepare them on the spot.
Consider using weight based (2mL/kg) rather than the fixed 150 mL infusion volumes of 3% hypertonic saline in case of obviously deviant body composition.
Do not expect patients with severe symptoms to completely recover immediately, as it may take some time for the brain to fully recover. Be aware that sometimes it may not be possible to assess an improvement in symptoms, e.g. because the patient is intubated and sedated. In these cases, we advise to follow guidance as described under 3.1.2. (see chapter (7.1.2. full guideline publication).
Keep in mind that if hypokalaemia is present, correction of the hypokalaemia will contribute to an increase in serum sodium concentration.
To achieve the 1 mmol/L/h increase advised in 3.1.3. (see chapter 7.1.3. full guideline publication)., the formula of Adrogue-Madias may be used, but keep in mind that the actual increase may exceed the calculated increase [7]:

$$\text{Change in serum } [Na^+] = \frac{\text{infusate } [Na+] - \text{serum } [Na+]}{\text{total body water} + 1}$$

$$\text{Change in serum } [Na+] = \frac{(\text{infusate } [Na+] + \text{infusate } [K+]) - \text{serum } [Na+]}{\text{total body water} + 1}$$

+ [Na+], sodium concentration in mmol/L; [K+], potassium concentration in mmol/L

§ The numerator in formula 1 is a simplification of the expression in formula 2, with the value yielded by the equation in mmol/L. The estimated total body water (in litres) is calculated as a fraction of body weight. The fraction is 0.6 in nonelderly men and 0.5 in nonelderly women; and 0.5 and 0.45 in elderly men and women respectively. Normally, extracellular and intracellular fluids account for 40% and 60% of total body water respectively.

3.2. Hyponatraemia with moderately severe symptoms

We recommend starting prompt diagnostic assessment (1D).
Stop, if possible, medications and other factors that can contribute to or provoke the hyponatraemia (Not Graded).
We recommend cause-specific treatment (1D).
We suggest immediate treatment with a single intravenous infusion of 150 mL 3% hypertonic saline or equivalent over 20 minutes (2D).
We suggest aiming for a 5 mmol/L/24 h increase in serum sodium concentration (2D).
We suggest limiting the increase in serum sodium concentration to 10 mmol/L in the first 24 hours and 8 mmol/L during every 24 hours thereafter, until a serum sodium concentration of 130 mmol/L is reached (2D).
We suggest checking the serum sodium concentration after one, 6 and 12 hours (2D).
We suggest additional diagnostic exploration for other causes of the symptoms if the symptoms do not improve with an increase in serum sodium concentration (2D).
We suggest considering to manage the patient as in severely symptomatic hyponatraemia if the serum sodium concentration further decreases despite treating the underlying diagnosis (2D).

3.3. Acute hyponatraemia without severe or moderately severe symptoms

Make sure that the serum sodium concentration has been measured using the same technique as used for the previous measurement and that no administrative errors in sample handling have occurred (Not Graded).
If possible, stop fluids, medications and other factors that can contribute to or provoke the hyponatraemia (Not Graded).
We recommend starting prompt diagnostic assessment (1D).
We recommend cause-specific treatment (1D).
If the acute decrease in serum sodium concentration exceeds 10 mmol/L, we suggest a single intravenous infusion of 150 mL 3% hypertonic saline or equivalent over 20 minutes (2D).
We suggest checking the serum sodium concentration after four hours, using the same technique as used for the previous measurement (2D).

3.4. Chronic hyponatraemia without severe or moderately severe symptoms

3.4.1. General management

Stop non-essential fluids, medications and other factors that can contribute to or provoke the hyponatraemia (Not Graded).
We recommend cause-specific treatment (1D).
In mild hyponatraemia, we suggest against treatment with the sole aim of increasing the serum sodium concentration (2C).
In moderate or profound hyponatraemia, we recommend avoiding an increase in serum sodium concentration of >10 mmol/L during the first 24 hours and >8 mmol/L during every 24 hours thereafter (1D).
In moderate or profound hyponatraemia, we suggest checking the serum sodium concentration every six hours until the serum sodium concentration has stabilised under stable treatment (2D).
In case of unresolved hyponatraemia, reconsider the diagnostic algorithm and ask for expert advice (Not Graded).

3.4.2. Patients with expanded extracellular fluid

We recommend against a treatment with the sole aim of increasing the serum sodium concentration in mild or moderate hyponatraemia (1C).
We suggest fluid restriction to prevent further fluid overload (2D).
We recommend against vasopressin receptor antagonists (1C).
We recommend against demeclocycline (1D).

3.4.3. Patients with syndrome of inappropriate antidiuresis

In moderate or profound hyponatraemia, we suggest restricting fluid intake as first- line treatment (2D).
In moderate or profound hyponatraemia, we suggest the following can be considered equal second line treatments: increasing solute intake with 0.25 to 0.50 g/kg/day of urea or a combination of low dose loop diuretics and oral sodium chloride (2D).
In moderate or profound hyponatraemia, we recommend against lithium or demeclocycline (1D).
In moderate hyponatraemia, we do not recommend vasopressin receptor antagonists (1C).
In profound hyponatraemia, we recommend against vasopressin receptor antagonists (1C).

3.4.4. Patients with contracted circulating volume

We recommend restoring extracellular volume with intravenous infusion of 0.9 % saline or a balanced crystalloid solution at 0.5 to 1.0 mL/kg/h (1B).
Manage patients with haemodynamic instability in an environment where close biochemical and clinical monitoring can be provided (Not Graded).
In case of haemodynamic instability, the need for rapid fluid resuscitation overrides the risk of an overly rapid increase in serum sodium concentration (Not Graded).

Advice for clinical practice

A sudden increase in urine output to >100 mL/h signals increased risk of overly rapid rise in serum sodium concentration. If vasopressin activity is suddenly suppressed, as happens when intravascular volume is restored in hypovolaemia, free water clearance can dramatically increase, resulting in serum sodium concentrations rising more rapidly than expected. If urine output suddenly increases, we would advise measuring the serum sodium concentration every two hours until it has stabilised under stable treatment. The implicit advice to monitor urine output does not imply we advise a bladder catheter solely for this purpose. Most patients will be able to void spontaneously and collect urine for output monitoring.
As a means of increasing solute intake, we suggest daily intake of 0.25 to 0.50 g/kg urea can be used. The bitter taste can be reduced by combining it with sweet tasting substances. The pharmacist may be asked to prepare the following as sachets: urea 10 g+NaHCO3 2 g+citric acid 1.5 g+sucrose 200 mg, to be dissolved in 50 to 100 mL water. This will result in a more palatable, slightly sparkling solution.

3.5. What to do in case hyponatraemia is corrected too rapidly?

We recommend prompt intervention for relowering the serum sodium concentration if it increases >10 mmol/L during the first 24 hours or >8 mmol/L in any 24 hours thereafter (1D).
We recommend discontinuing the ongoing active treatment (1D).
We recommend consulting an expert to discuss if it is appropriate to start an infusion of 10 mL/kg body weight of electrolyte-free water (e.g. glucose solutions) over one hour under strict monitoring of urine output and fluid balance (1D).
We recommend consulting an expert to discuss if it is appropriate to add intravenous desmopressin 2 µg, with the understanding that this should not be repeated more frequently than every 8 hours (1D).
The guideline development group wants to underscore that these symptoms can also be induced by other conditions. Clinical and anamnestic data should be taken into account when assessing the causal relation between the hyponatraemia and a certain symptom (i.e. to assess whether the symptom has been caused by the hyponatraemia or the hyponatraemia by the underlying condition/symptom). The less pronounced (e.g. mild) the biochemical degree of hyponatraemia, the more caution should be taken when considering that the hyponatraemia is the cause of the symptoms. This list is not exhaustive, and all symptoms that can be signs of cerebral oedema should be considered as severe or moderate symptoms that can be caused by hyponatraemia.

Conflict of interest statement. None declared.

References

1. Spasovski G, Vanholder R, Allolio B, *et al.* Hyponatraemia Guideline Development Group. Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Nephrol Dial Transplant* 2014; 29: Suppl 2:i1-i39.
2. Hoorn EJ, Halperin ML, Zietse R. Diagnostic approach to a patient with hyponatraemia: traditional versus physiology-based options. *QJM: Monthly Journal of the Association of Physicians* 2005; 98: 529-540.
3. Schwartz WB, Bennett W, Curelop S, Bartter FC. A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. *Am J Me* 1957; 23(4): 529-542.
4. Janicic N, Verbalis JG. Evaluation and management of hypo-osmolality in hospitalized patients. E*ndocrinol Metab Clin North Am* 2003; 32(2): 459-481, vii.
5. Sherlock M, O'Sullivan E, Agha A, *et al*. The incidence and pathophysiology of hyponatraemia after subarachnoid haemorrhage. *Clin Endocrinol (Oxf)* 2006; 64(3): 250-254.
6. Brimioulle S, Orellana-Jimenez C, Aminian A, Vincent JL. Hyponatremia in neurological patients: cerebral salt wasting versus inappropriate antidiuretic hormone secretion. *Intensive Care Med* 2008; 34(1): 125-131.
7. Adrogue HJ, Madias NE. Hyponatremia. *New England Journal of Medicine* 2000; 342: 1581-1589.

BANTAO Journal 2014; 12(1): 75-76

BJ
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Editorial

Another Reached Milestone with Bantao Journal - First Issue Associated Under De Gruyter Open Platform

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We are proud to announce that BANTAO Journal (BJ) as an official journal of the BANTAO association has reached another milestone joining De Gruyter Open publisher group.

Nowadays, it's not an easy task to run the journal as Editor in chief for at least two reasons. Scientifically, the associated editors (Mustafa Arici, Ankara, Turkey; Nada Dimkovic, Belgrade, Serbia; Dimitrious Goumenos, Patra, Greece; and Nikolina Basic-Jukic, Zagreb, Croatia) are doing a great deal of work, but there is tough competition among journals in the academic world and scientists reasonably seek for journal with as high as possible impact factor where they could publish their work. Second, the funds for running small journals without a subscription fee do not allow secretarial assistance and thus the workload is overwhelming. Finally, the reviewers for small journals are not seriously taking this task when invited, so, considerable efforts and engagement was and still is to be shared with the associate editors.

However, BJ has succeeded to be included in the EBSCO, DOAJ and SCOPUS/SCIMAGO databases. This great progress was made thanks to the contributors to the Journal, as well as Veselin Nenov as responsible for the maintenance of the Journal web page over the years as an important milestone for the improvement and worldwide recognition of the Journal. Reaching certain level of BJ within all above mentioned circumstances we considered further progress of the journal may not be achieved without a professional help of a publisher. Hence, at the last few Bantao Board meetings this question was discussed and agreed among the members, but the establishment of such contract was difficult primarily because of the problems with the registration of the BANTAO association and related taxation numbers.

So, the process of joining De Gruyter Open (DGO) as the leading publisher of Open Access academic content for further improvement and promotion of the journal and Medline application was initiated [4] somewhere at the beginning of 2014 when the current President of BANTAO, Adalbert Schiller, Timisoara, Romania signed the contract. Then, many files had to be completed and special technical criteria were to be fulfilled in addition to the improving scientific content of the journal from issue to issue. Finally, IT professionals were communicated to get submitted to the advanced DGO web established platform for easier promotion of the journal. Finally, we have already got BJ published under the DGO platform and we are proud of that as the first step towards our aim for Medline application.

In the meanwhile, BJ was further applied to the largest number of abstracting and indexing services that cover the scope of our journal either entirely or to some extent (such as ProQuest, CAB Abstracts etc). In addition, the data of BJ has been already promoted by the services which index all titles from the DGO platform: Celdes, CNPIEC, CNKI Scholar (China National Knowledge Infrastructure), EBSCO Discovery Service, Google Scholar, J-Gate, Naviga (Softweco), Primo Central (ExLibris), ReadCube, Summon (Serials Solutions/ProQuest), TDOne (TDNet) and WorldCat (OCLC).

We are proud to announce that we have our own web site www.bantao.org, but now BJ could also be found at http://www.degruyter.com/view/j/bj. We have already received certain DGO evaluation that BANTAO Journal has got the potential to apply for inclusion in the Master Journal List and to be indexed in other products of

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Thomson Reuters. However, we have been also warned that Thomson Reuters' requirements for inclusion of journals are very high. In this regard, further journal preparations are to be undertaken before the application to Thomson Reuters is possible. Among the other issues it is advisable to get as many as possible citation of BJ manuscripts and further careful selection of the submitted papers.

We are at the edge of reaching our goal and do hope we'll have your support!

Goce Spasovski
Editor in Chief BJ

Adalbert Schiller
Bantao President

Conflict of interest statement. None declared.

References:

1. Dimkovic N, Arici M, Goumenos D, *et al.* BANTAO Journal: A Story of Ten Years. *BANTAO Journal* 2014; 12(1): 8-9.
2. Dimkovic N, Kes P, Basic-Jukic N, *et al.* Editors' Observation: Scientific Research and Publication Opus of the Balkans' Nephrologists is Worth Mentioning. *BANTAO Journal* 2013; 11 (1): 4-6.
3. Polenakovic M, Nenov D, Basci A, *et al.* 20 years since the establishment of the BANTAO association (Balkan Cities Association of Nephrology, Dialysis, Transplantation and Artificial Organs). *Prilozi* 2013; 34(2): 189-214.
4. Spasovski G. Editorial policies and background in editing Macedonian Medical Review and BANTAO journal. *Prilozi* 2014; 35(3): 81-84.

BANTAO Journal 2014; 12(1): 77-83

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Review

Automated Peritoneal Dialysis: An alternative to Continuous Ambulatory or a First Choice Treatment?

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Abstract

The use of the various forms of Automated Peritoneal Dialysis (APD) has considerably increased in the past few years. This increase is driven by improved cycler design, apparent lifestyle advantages, and the increased ability to achieve adequacy and ultrafiltration targets. It is therefore reasonable to raise the question whether APD is superior to Continuous Ambulatory Peritoneal Dialysis (CAPD). APD is considered the most suitable Peritoneal Dialysis (PD) modality for high transporters as well as for assisted PD. It has also been associated with improved compliance, lower intraperitoneal pressure and possibly lower incidence of peritonitis. On the other hand, there are concerns regarding increased cost, a more rapid decline in residual renal function, inadequate sodium removal and disturbed sleep. Besides its beneficial results in high transporters, other medical advantages of APD still remain unclear. Individual patient's choice remains the most important indication for applying APD, which should be made available to all patients starting PD.

Key words: automated peritoneal dialysis (APD), continuous ambulatory peritoneal dialysis (CAPD), high transporters, patient selection

Introduction

The utilization of the various modalities of Automated Peritoneal Dialysis (APD) has increased considerably during the past few years. This upward trend could be mainly attributed to the improved cycler design as well as better adjustment of APD to patient's lifestyle. According to the ERA/EDTA Registry Annual Report for the year 2010, a significant increase in the utilization of APD has been noted in Europe. In Greece, 40% of patients who initiated peritoneal dialysis (PD) in 2010 were switched to APD (annual incidence). Fifty-eight percent (58%) of all PD patients utilized APD. This proportion varied between 40 to 50% in France, UK, Italy and the Netherlands. Moreover, in countries such as Belgium, Finland and Denmark, more than 60% of PD patients used APD [1]. In USA, the preference of APD as the modality of choice for patients being treated with PD was evident from the late 90s'. This fact together with the decline in the overall PD utilization, suggests that the development of APD was rather accomplished at the expense of CAPD. Thus according to the USRDS, the proportion of patients on APD in the USA increased from 47% in 2000 to 66% in 2009, while the overall proportion of patients undergoing PD (APD and CAPD) decreased from 8.9% to 6.9% during the same time period [2]. Accordingly, the percentages of APD in Canada were 43% in 2001 and 62% in 2010 [3]. In 2010, 61% and 43% of patients on PD underwent APD in Australia and New Zealand, respectively [4]. A recent epidemiological study [5] showed that the proportion of patients on APD is significantly smaller in the developing countries compared to the developed ones (15.8% in developing countries versus 42.4% in developed countries, of all patients on PD). It appears that the increase in APD utilization in the developed world is attributed mainly to patient's personal choice [6]. The predominance of APD over CAPD could not be supported by robust clinical evidence, but by the improved cycler design as well as the improvement of patient's quality of life [7].

Patient and technique survival

Whether APD is superior to CAPD regarding patient and technique survival remains to be elucidated. This question is hard to answer considering that the accomplishment of randomized controlled clinical trials is apparently difficult and moreover it is impossible to conduct blinded randomized controlled clinical trials. The results of the already available trials are controversial. The study of Guo and Mujais from the USA, which was based on the Baxter Healthcare Corporation On-Call TM system, including approximately 30.000 patients,

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showed improved patient and technique survival during the first year in patients on APD [8]. In a more recent trial, including approximately 40.000 patients, Mujais and Storey reported that APD has a dominant effect on technique success, with a relative risk of 0.845 compared to CAPD [9]. According to Australia and New Zealand Registry Report (ANZDATA), the ***application*** of ***APD*** had ***similar*** technique and ***patient survival*** with ***CAPD*** in ***4128 patients [4]***. A meta-analysis of 3 randomized controlled trials which compared CAPD to APD, including a total of 139 patients, did not show any benefit of either technique over the other regarding patient mortality or technique survival [10]. In particular, APD seems to be superior to CAPD regarding patient and technique survival in patients less than 65 years old [11]. A prospective trial, with 5-year follow-up (NECOSAD) showed similar results with respect to patient and technique survival [12]. The superiority of APD, with regards to technique survival, was shown by a trial based on a database of 620 patients from the USA [13], while a similar superiority of APD reported in a UK trial was lost after adjusting for comorbidities [14]. A recent trial from Thailand, in which 121 patients were retrospectively evaluated, showed that APD was associated with a lower risk of technique failure. Specifically, although there was no difference shown in the mortality risk, technique survival during the first 2 years was better in patients on APD compared to those on CAPD [15]. In conclusion, both methods do not seem to differ substantially regarding technique and patient survival, except a possible comparable advantage of APD in the subpopulation of high transporters.

APD and high transporters

The European Best Practice Guidelines-EBPG, acknowledge three main indications for APD application: patient's preference, the necessity to avoid increased intraperitoneal pressure and inability to achieve the targets of ultrafiltration and substance clearance, especially in high transporters [16]. Towards the same direction, the International Society of Peritoneal Dialysis ad hoc Committee on Ultrafiltration Management in Peritoneal Dialysis recommends the application of APD in cases of ultrafiltration loss in high transporters [17].

The status of high or more precisely rapid transport of substances across the peritoneal membrane is most probably the ideal circumstance when APD is indicated. The association between high peritoneal permeability with poor patient and technique survival in PD is already recognized [18-20]. Still, several clinical trials have shown that high transporters might benefit from the utilization of APD. The EAPOS trial showed that the baseline peritoneal membrane transport status does not correlate with the ultrafiltration rate achieved during the first year and it does not affect technique survival [21]. In a publication ensuing from the Oceania Registry (ANZDATA), an association between high peritoneal transport and worse outcomes was shown only in patients on CAPD and not in those on APD [20]. A more recent trial from Toronto has shown that a high peritoneal transport status does not constitute a risk predicttive factor of worse patient survival or technique failure in patients on APD, with or without icodextrin use [22]. Another trial including 4128 patients managed to show that APD is associated with a significant survival advantage in high transporters compared with CAPD. However, APD treatment was associated with inferior survival in low transporters. There was no difference observed between APD and CAPD in the same trial regarding technique survival [23]. Thus, the initial concern regarding clinical outcomes of high transporters undergoing PD seems to be how to overcome APD utilization in this subgroup of patients, regardless of the icodextrin use.

Peritonitis-exit site infections

Over a 24-hour period, APD involves one connection and one disconnection. On the other hand, CAPD involves on average four connections and four disconnections. It is obvious that the smaller number of manipulations required from patients on APD could probably result in a substantial reduction in the incidence of peritonitis [24]. Moreover, it has been demonstrated that white blood cell function is improved with prolonged dwell times of fluid in PD [25], such as the daily dwell in continuous cycling PD (CCPD). The peritoneal mesothelial cells show improved function after several hours of peritoneal membrane rest [26], as occurs during daytime with nocturnal intermittent PD (NIPD). Nevertheless, the delay in the diagnosis of peritonitis in APD raises several concerns. The evidence with respect to the effect of APD on peritonitis when compared to CAPD is controversial. A number of retrospective studies favor APD [27], some other favor CAPD [28,29], while other publications have shown that both methods are equivalent regarding the overall rate of peritonitis [30]. A large prospective non-randomized trial including 328 patients demonstrated similar rates of peritonitis and exit site infections for both modalities [31]. Nevertheless, a smaller trial (n=20) showed lower rates of peritonitis in patients on APD [32]. A more recent publication from Mexico including 237 patients, has reported a significantly lower peritonitis rate, in favor of APD [33]. In this trial, the relative risk for suffering the first peritonitis event was 0.68 in patients on APD compared to patients on CAPD. The above-mentioned meta-analysis of 2007 did not detect any differences between APD and CAPD in respect to relative risk, although APD was found to have significantly lower peritonitis rates compared to CAPD [10]. This meta-analysis was based on three randomized controlled trials, from which only two dealt with the issue of peritonitis and just one reported only three peritonitis episodes. Moreover, the results of this study

were virtually based on a clinical trial which included patients employing a cycler that had been abandoned [34] and thus should be interpreted cautiously [35]. Another prospective clinical trial from USA, from the late 80s', included 82 young patients and managed to demonstrate superiority of APD, with an approximately double risk for peritonitis events with CAPD, but still a similar incidence of exit site infections between both modalities [36].
A clinical trial including 132 pediatric patients in Turkey revealed a similar rate of peritonitis events between the two submodalities, but an increased peritonitis events rate caused by Gram-negative bacteria in children on APD [37]. In another study which analyzed data from 4247 patients from Canada, who had undergone PD from 1996 until 2005, a similar risk for peritonitis events was found between the two submodalities [38]. Another noteworthy recent clinical trial, including 508 cases of peritonitis in 205 patients, showed that APD was associated with prolonged duration of elevated leukocyte count in peritoneal dialysis fluid as well as longer duration of antibiotic treatment [39]**.** A prospective, multicenter clinical trial including 10 nephrological centers in Scotland, with follow-up period of 8 years, showed lower rates of peritonitis in patients on APD [40]. The authors commented that their results warrant cautious interpretation, considering the fact that patients on CAPD were older and that there were significant differences between the participating centers, such as the different peritonitis rates reported from the different centers, the small patient sample as well as the short follow-up period after the first peritonitis event. Finally, the utilization of the spike system for dialysis bag connection to the cycler in the USA instead of the safer Luer-lock connector used in Europe might play the most important role [41,42].

Intraperitoneal pressure-Patient compliance

The increased intraperitoneal pressure observed during the application of PD might lead to hernia formation and leakage of peritoneal fluid, causing discomfort in some patients. Performing the exchanges in the supine position, as occurs in APD, reduces the intraperitoneal pressure for more than 50% compared to the upright "full abdomen" position. The incidence of hernias is reported to be lower in patients on APD [16]; still this has not been confirmed by all trials [10]. Nevertheless, increased nighttime volumes and decreased daytime volumes (or even the preservation of an empty abdominal cavity during the day), might prove to be beneficial for patients unable to tolerate increased intra-abdominal pressure [43]. Thus, APD might be a satisfactory alternative solution to the surgical treatment of such hernias [6].
Patient compliance to the prescribed regimen is an important issue, since a considerable proportion of patients on PD do not comply with the treatment, with detrimental consequences to patient and technique survival [44]. The risk of inadequate compliance seems to be higher in patients on CAPD compared to those on APD, most probably due to the higher number of connections and disconnections needed in CAPD [45], as well as the discomfort associated with the increased intraabdominal pressure during CAPD [46].

Arterial blood pressure-Ultrafiltration and sodium clearance-Residual renal function

It is well-known that it is more difficult to achieve the ultrafiltration targets when the residual renal function declines. Existing data is not clear whether APD aids in achieving these targets. In a prospective study, including 53 patients on CAPD and 51 patients on APD, with a 10 month follow-up, ultrafiltration and sodium removal were lower in patients on APD than in their counterparts undergoing CAPD. Moreover, patients on CAPD demonstrated a better control of systolic blood pressure [47]. On the other hand, the EAPOS trial (European APD Outcome Study) enrolling 177 anuric patients undergoing APD demonstrated that more than 75% of patients achieved the ultrafiltration target of more than 750 mL/24h [48]. In a Canadian study including 56 patients on APD, with liberal icodextrin use during daytime dwells, blood pressure control was achieved in 93% of patients while volume control was independent of sodium removal [49]. Furthermore, recent data showed that fluid state and blood pressure control were not different between APD and CAPD, despite a higher daily sodium removal in CAPD patients [50]. A study from Korea, where 24-hour ambulatory blood pressure monitoring was performed in 26 patients on CAPD and 18 patients on APD, did not show any significant differences in blood pressure control and left ventricular hypertrophy in APD compared to CAPD [51]. A recent study from a Greek nephrological center enrolling 46 patients did not show any significant differences in sodium removal between patients on APD and CAPD, assuming appropriate utilization of icodextrin in both groups [52]. In conclusion, it appears that APD could be effective in achieving the targets of ultrafiltration and euvolemia despite the declining residual renal function, provided that prescribed clearance dose is adjusted accordingly [53].
The probability of a faster decline of residual renal function in patients on APD remains a subject of concern, especially regarding patients on NIPD. Although the results of the existing studies might be controversial, Marron *et al.* in their review report showed no statistically significant reduction of residual renal function in patients on APD [54]. Data from the NECOSAD trial demonstrated a higher risk of losing residual renal function in patients starting dialysis on APD compared to those starting on CAPD, especially during the first year [55]. Still this fact has not been confirmed in other recent publications [13,14] and both modalities appear to be equivalent.

Quality of life and sleep quality

APD appears to be superior compared to CAPD with respect to patient's quality of life; still all related published evidence is not definitive. In a multicenter study from the Netherlands investigators showed that patients on APD demonstrated better mental health, with lower levels of anxiety or depression compared to patients on CAPD during the same period of treatment. On the other hand, the physical aspects of quality of life were similar in both groups [56]. Another study from Denmark showed that patients on APD had significantly more time available for work, family, and social activities compared to those on CAPD. There was a tendency for less physical and emotional discomfort in the APD group, yet the difference was not significant [57]. In another interesting, although small study with regards to sample size, patients were allocated to CAPD treatment for 6 months and then they were shifted to APD therapy for the next 6 months. Patients showed improvement in parameters such as vitality, social functioning and mental health scores while being on APD; however this tendency was not significant [58]. More recent studies have not demonstrated any difference regarding the quality of life between the two methods [59-61]. A recent meta-analysis of 190 trials, all of them evaluating quality of life in end-stage CKD patients in relation to treatment modality, showed superiority of APD compared to CAPD, though not significant [62].
The issue of sleep disorders in patients on APD was studied in a randomized trial of Bro and associates, who showed that patients on APD demonstrated more sleep problems as compared to those on CAPD [57]. APD was also associated with a higher incidence of excessive daytime sleepiness [61]. Yet in another study, sleep quality was estimated as similar in both methods [59], whilst in another one, in which overnight polysomnography was performed in the patients enrolled, APD was associated with improved sleep quality and lower sleep apnea incidence, most probably due to better control of the hydration status during sleep [63].

APD in children and the elderly-assisted PD

In the United States approximately 95% of children with end-stage CKD, younger than 19 years old, undergo APD [2]. The same applies in Europe as well, for example in Italy [64]. Regarding the elderly patients on PD, APD is the prevalent modality of renal replacement treatment. In the USA more than 60% of PD patients over 65 years old, receive APD [2]. In this patient-group there is a greater need of assistance by a caregiver in order to perform the exchanges [65], a fact which might explain the increased use of APD, as it requires fewer connections.
Moreover APD has proved to be a reliable method of renal replacement treatment in patients older than 65 years. According to a study from the USA, technique failure and peritonitis rates in the elderly (>65 years old) patients on APD were not different compared to the younger patients. Additionally, quality of life measures were similar between all age groups [66].
APD plays a central role in the treatment of pediatric patients with end-stage CKD, especially infants. APD due to accurate determination of fill volume allows appropriate treatment individualization according to age, body size and growth- related metabolic needs [67]. Moreover, children on APD and their parents have more free time available during the day, as no exchanges are required during school time [68]. Compared to children on CAPD, children on APD showed lower peritonitis rates [68]. In another trial, enrolling more than 300 pediatric patients who were switched from CAPD to APD, results showed improved ultrafiltration, less edema, lower mean arterial blood pressure, improved peritonitis rates and fewer hospitalizations [69]. Another study from Hong-Kong reported impressing results with respect to quality of life of patients included. In this study, both children on APD (as well as their parents) and children who underwent renal transplantation and their parents seemed to experience similar quality of life [70].
A significant number of patients on PD need the assistance of a companion, nurse or caregiver in order to perform the exchanges. APD might be the modality of choice in these cases. APD requires only two connections and disconnections daily, which is an important advantage with regard to time saving. This diminishes the daily workload of the assistant and also might prove to be useful for patients who reside in nursing care institutions [25,71]. In another study from Denmark, 65 patients underwent assisted APD with satisfying results (54% two year survival and one episode of peritonitis in 26 patient-months), confirming the aforementioned results [72]. A recent observational trial from Brazil, enrolling elderly patients with physical or cognitive disabilities and lack of assistance as well as patients with lack of vascular access or hemodynamic instability during hemodialysis, showed that assisted APD is a reliable and effective homecare alternative for patients without other renal replacement therapy options [73].

When to apply APD

APD remains an alternative option for patients who are unable to achieve adequate clearance and ultrafiltration targets with CAPD. In such cases, an increased number of exchanges with CAPD leads to an impaired quality of life and might cause switching of dialysis modality to hemodialysis. Thus the application of APD with larger dwell volumes and longer nocturnal sessions, especially in combination with the use of icodextrin for the long dwell, or the addition of one daytime exchange (CCPD plus), could probably prolong technique survival. In slow transporters, a regimen with less frequent

exchanges during the night and probably the addition of one manual exchange during the day could be an alternative option.

Additionally, APD has been tried as a dialysis modality in patients who require urgent renal replacement therapy. The association of APD with lower intraperitoneal pressure might render the best option for immediate initiation of PD. In a retrospective study from Denmark, patients who initiated PD in less than 24 hours after peritoneal catheter insertion had a technique survival that was similar to that of patients who initiated APD on a scheduled basis [74]. In a prospective study from France, acute initiation of APD was an effective dialysis method [75], whilst it has been performed as a first-line emergent dialysis therapy as well, with satisfactory results [76].

APD and patient's employment and financial cost

In a study from Finland [77], similar employment rates were observed between patients on APD, those on home hemodialysis and transplanted patients, which ranged from 39-44%. Another study from Hong-Kong showed a statistically significant difference in the employment status of patients on APD compared to those on CAPD [78]. Thus, patients on APD had higher rates of full-time employment compared to those on CAPD (62.2% versus 15%). Moreover, a Spanish study concluded that APD, and to a lesser extent renal transplantation are the modalities of renal replacement treatment with the lowest impact on indirect costs due to morbidity, showing higher rates of employment than hemodialysis and requiring less disability benefits [79]. Another trial from the same research group demonstrated that the most active patients prefer APD as the initial modality of renal replacement therapy. Thus, approximately half of patients on APD are working, while approximately only one in five patients on hemodialysis are working [80]. Finally, according to a study from Mexico the annual direct medical cost per patient on PD increased from 15072 dollars in 2008 to 16452 dollars in 2010. The cost was higher for patients on APD compared to those on CAPD, although the difference was not statistically significant [81].

Conclusions

Automated PD is the most promising PD modality, with undoubtable advantages in patient's lifestyle. The possible clinical benefits of the method are still controversial and currently high peritoneal permeability remains the only strong indication for APD application. APD offers the advantage of choice and it can be more easily performed by employed patients, while offering more time for personal or family activities. It is suitable for children, elderly patients and patients who need assisted PD. APD should always be offered with respect to the patient's choice, which should not be overlooked during initiation of therapy [82]. Accepting (and application of) the patient's preference, regarding the modality of renal replacement therapy, has positive effects on quality of life [83], which is probably the most important criterion in the treatment of end-stage kidney disease.

Conflict of interest statement. None declared.

References

1. ERA-EDTA Registry: ERA-EDTA Registry 2011 Annual Report. Academic Medical Center, Department of Medical Informatics, Amsterdam, The Netherlands, 2013.
2. U.S. Renal data system, USRDS 2012 Annual Data Report: Atlas of chronic kidney disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of diabetes and Digestive and Kidney diseases, Bethesda, MD, 2012.
3. Canadian Institute for Health Information, Canadian Organ Replacement Register annual report: Treatment of End Stage Organ Failure in Canada, 2001 to 2010, (Ottawa, Ont.: CIHI, 2011).
4. ANZDATA registry report 2011. Australia and New Zealand Dialysis and Transplant Registry. Adelaide, South Australia.
5. Jain AK, Blake P, Cordy P, Garg AX. Global trends in rates of peritoneal dialysis. *J Am Soc Nephrol* 2012; 23: 533-544.
6. Tang SCW, Lai KN. Does automated peritoneal dialysis provide better outcomes than continuous ambulatory peritoneal dialysis? *Nat Clin Pract Nephrol* 2007; 3 (11): 596-597.
7. Blake PG. Cycling forward. *Perit Dial Int* 2006; 26: 306-308.
8. Guo A, Mujais S. Patient and technique survival on peritoneal dialysis in the United States: evaluation in large incident cohorts. *Kidney Int* 2003; Suppl 88: S3-S12.
9. Mujais S, Story K. Peritoneal dialysis in the US: evaluation of outcomes in contemporary cohorts. *Kidney Int* 2006; 70: S21-S26.
10. Rabindranath KS, Adams J, Ali TZ, *et al*. Automated vs. continuous ambulatory peritoneal dialysis: a systematic review of randomized controlled trials. *Nephrol Dial Transplant* 2007; 22: 2991-2998.
11. Sun CY, Lee CC, Lin YY, Wu MS. In younger dialysis patients automated peritoneal dialysis is associated with better long-term patient and technique survival than is continuous ambulatory peritoneal dialysis. *Perit Dial Int* 2011; 31: 301-307.
12. Michels WM, Verduijn M, Boeschoten EW, *et al*. Similar survival on automated peritoneal dialysis and continuous ambulatory peritoneal dialysis in a large prospective cohort. *Clin J Am Soc Nephrol* 2009; 4: 943-949.
13. Cnossen TT, Usvyat L, Kotanko P, *et al*. Comparison of outcomes on continuous ambulatory peritoneal dialysis: results from a USA database. *Perit Dial Int* 2011; 31: 679-684.
14. Balasubramanian G, McKitty K, Fan SLS. Comparing automated peritoneal dialysis with continuous ambulatory peritoneal dialysis: survival and quality of life differences. *Nephrol Dial Transplant* 2011; 26: 1702-1708.
15. Katavetin P, Theerasin Y, Treamtrakanpon W, *et al.* Treatment failure in automated peritoneal dialysis and double-bag continuous ambulatory peritoneal dialysis. *Nephrology* 2013; 18: 545-548.
16. Dombros NV, Dratwa M, Feriani M, *et al*. European best practice guidelines for peritoneal dialysis. 6 Automated peritoneal dialysis. *Nephrol Dial Transplant* 2005; 20 (Suppl 9): ix21-23.

17. Mujais S, Nolph K, Gokal R, *et al*. Evaluation and management of ultrafiltration problems in peritoneal dialysis. International Society for Peritoneal Dialysis Ad Hoc Committee on Ultrafiltration Management in Peritoneal Dialysis. *Perit Dial Int* 2000; 20 (Suppl 4): S5-S21.
18. Churchill DN, Thorpe KE, Nolph KD, *et al*. Increased peritoneal membrane transport is associated with decreased patient and technique survival for continuous peritoneal dialysis patients. The Canada-USA (CANUSA) Peritoneal Dialysis Study Group. *J Am Soc Nephrol* 1998; 9 (7): 1285-1292.
19. Davies SJ, Phillips L, Russell GI. Peritoneal solute transport predicts survival on CAPD independently of residual renal function. *Nephrol Dial Transplant* 1998; 13 (4): 962-968.
20. Rumpsfeld M, McDonald SP, Johnson DW. Higher peritoneal transport status is associated with higher mortality and technique failure in the Australian and New Zealand peritoneal dialysis patient populations. *J Am Soc Nephrol* 2006; 17 (1): 271-278.
21. Brown EA, Davies SJ, Rutherford P, *et al*. Survival of functionally anuric patients on automated peritoneal dialysis: The European APD outcome study. *J Am Soc Nephrol* 2003; 14: 2948-2957.
22. Yang X, Fang W, Bargman JM, Oreopoulos DG. High peritoneal permeability is not associated with higher mortality or technique failure in patients on automated peritoneal dialysis. *Perit Dial Int* 2008; 28: 82-92.
23. Johnson DW, Hawley CM, McDonald SP, *et al*. Superior survival of high transporters treated with automated versus continuous ambulatory peritoneal dialysis. *Nephrol Dial Transplant* 2010; 25: 1973-1979.
24. Chung SH, Heimburger O, Lindholm B. Poor outcomes for fast transporters on PD: the rise and fall of a clinical concern. *Semin Dial* 2007; 21 (1): 7-10.
25. Wilson J, Nissenson AR. Determinants in APD selection. *Semin Dial* 2002; 15 (6): 388-392.
26. Tomo T, Okabe E, Matsuyama K, *et al*. The effect of peritoneal rest in combination therapy of peritoneal dialysis and hemodialysis: using the cultured human peritoneal mesothelial cell model. *Artif Organs* 2005; 8: 125-129.
27. Huang JW, Hung KY, Yen CJ, *et al*. Comparison of infectious complications in peritoneal dialysis patients using either a twin-bag system or automated peritoneal dialysis. *Nephrol Dial Transplant* 2001; 16 (3): 604-607.
28. Gahrmani N, Gorban-Brennan N, Kliger AS, Finkelstein FO. Infection rates in end-stage renal disease patients treated with CCPD and CAPD using the UltraBag system. *Adv Perit Dial* 1995; 11: 164-167.
29. Basile C, De Padova F. Comparison of peritonitis incidence in CAPD and automated peritoneal dialysis. *Nephrol Dial Transplant* 2001; 16 (9): 1957-1958.
30. Troidle LK, Gorban-Brennan N, Kliger AS, Finkelstein FO. Continuous cycler therapy, manual peritoneal dialysis therapy, and peritonitis. *Adv Perit Dial* 1998; 14: 137-141.
31. Rodriguez-Carmona A, Perez Fontan M, Garcia Falcon T, *et al*. A comparative analysis on the incidence of peritonitis and exit-site infection in CAPD and automated peritoneal dialysis. *Perit Dial Int* 1999; 19 (3): 253-258.
32. Locatelli AJ, Marcos GM, Gomez MG, *et al*. Comparing peritonitis in continuous ambulatory peritoneal dialysis patients versus automated peritoneal dialysis patients. *Adv Perit Dial* 1999; 15: 193-196.
33. Ramos Sanchez A, Madonia C, Rascon-pacheco RA. Improved patient/technique survival and peritonitis rates in patients treated with automated peritoneal dialysis when compared to continuous ambulatory peritoneal dialysis in a Mexican PD center. *Kidney Int* 2008; 73 (Suppl 108): S76-S80.
34. de Fijter CW, Oe LP, Nauta JJ, *et al*. Clinical efficacy and morbidity associated with continuous cyclic compared with continuous ambulatory peritoneal dialysis. *Ann Intern Med* 1994; 120 (4): 264-271.
35. Nessim SJ, Bargman JM. Occurrence of peritonitis in APD versus CAPD: methodologic problems. *Nephrol Dial Transplant* 2008; 23: 1769-1770.
36. Holley JL, Bernardini J, Piraino B. Continuous cycling peritoneal dialysis is associated with lower rates of catheter infections than continuous ambulatory peritoneal dialysis. *Am J Kidney Dis* 1990; 16: 133-136.
37. Akman S, Bakkaloglu SA, Ekim M, *et al*. Peritonitis rates and common microorganisms in continuous ambulatory peritoneal dialysis and automated peritoneal dialysis. *Pediatr Int* 2009; 51: 246-249.
38. Nessim SJ, Bargman JM, Austin PC, *et al*. Predictors of peritonitis in patients on peritoneal dialysis: results of a large, prospective Canadian database. *Clin J Am Soc Nephrol* 2009; 4: 1195-1200.
39. Ruger W, van Ittersum FJ, Comazzetto LF, *et al*. Similar peritonitis outcome in CAPD and APD patients with dialysis modality continuation during peritonitis. *Perit Dial Int* 2011; 31: 39-47.
40. Brown MC, Simpson K, Kersens JJ, Mactier RA. Peritoneal dialysis-associated peritonitis rates and outcomes in a national cohort are not improving in the post-millenium (2000-2007). *Perit Dial Int* 2011; 31(6): 639-650.
41. Piraino B, Sheth H. Peritonitis-Does peritoneal dialysis modality make a difference? *Blood Purif* 2010; 29: 145-149.
42. Liakopoulos V, Stefanidis I, Dombros NV. Peritoneal dialysis glossary 2009. *Int Urol Nephrol* 2010; 42: 417-423.
43. Anonymous. Clinical practice recommendations for peritoneal dialysis adequacy. *Am J Kidney Dis* 2006; 48 (Suppl 1): S130-S158.
44. Raj DSC. Role of APD in compliance with therapy. *Semin Dial* 2002; 15 (6): 434-436.
45. Bernardini J, Nagy M, Piraino B. Pattern of noncompliance with dialysis exchanges in peritoneal dialysis patients. *Am J Kidney Dis* 2000; 35 (6): 1104-1110.
46. Caruana RJ, Smith KL, Hess CP, *et al*. Dialysate dumping: a novel cause of inadequate dialysis in continuous ambulatory peritoneal dialysis (CAPD) patients. *Perit Dial Int* 1989; 9 (4): 319-320.
47. Rodriguez-Carmona A, Perez-Fontan M, Garca-Naveiro R, *et al*. Compared time profiles of ultrafiltration, sodium removal, and renal function in incident CAPD and automated peritoneal dialysis patients. *Am J Kidney Dis* 2004; 44 (1): 132-145.
48. Brown EA, Davies SJ, Heimburger O, *et al*. Adequacy targets can be met in anuric patients by automated peritoneal dialysis: baseline data from EAPOS. *Perit Dial Int* 2001; 21 (Suppl 3): S133-S137.
49. Boudville NC, Cordy P, Millman K, *et al*. Blood pressure, volume, and sodium control in an automated peritoneal dialysis population. *Perit Dial Int* 2007; 27 (5): 537-543.
50. Cnossen TT, Konnings CJAM, Fagel WJ, *et al*. Fluid state and blood pressure control: no differences between APD and CAPD. *ASAIO J* 2012; 58: 132-136.
51. Jang JS, Kwon SK, Kim HY. Comparison of blood pressure control and left ventricular hypertrophy in patients on continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD). *Electrolyte Blood Press* 2011; 9: 16-22.
52. Fourtounas C, Dousdampanis P, Hardalias A, Vlachogiannis J. Sodium removal and peritoneal dialysis modalities: no difference with optimal prescription of icodextrin. *Artif Organs* 2013; 37(7): E107-E113.

53. Brunkhorst RR. Individualized PD prescription: APD versus CAPD. *Perit Dial Int* 2005; 25 (Suppl 3): S92-S94.
54. Marron B, Remon C, Perez-Fontan M, Quiros P, Ortiz A. Benefits of preserving residual renal function in peritoneal dialysis. *Kidney Int* 2008; Suppl 108: S42-S51.
55. Michels WM, Verduijn M, Grototendorst DC, *et al*. Decline in renal function in automated compared with continuous ambulatory peritoneal dialysis. *Clin J Am Soc Nephrol* 2011; 6: 537-542.
56. de Wit GA, Merkus MP, Krediet RT, de Charro FT. A comparison of quality of life of patients on automated and continuous ambulatory peritoneal dialysis. *Perit Dial Int* 2001; 21: 306-312.
57. Bro S, Bjorner JB, Tofte-Jensen P, *et al*. A prospective, randomized multicenter study comparing APD and CAPD treatment. *Perit Dial Int* 1999; 19: 526-533.
58. Sunder S, Kalra OP, Nashine S, *et al*. Comparative Study of Adequacy of Dialysis and Health-Related Quality of Life in Patients on CAPD and APD. *Perit Dial Int* 2008; 28 (5): 542-544.
59. Guney I, Solak Y, Atalay H, *et al*. Comparison of effects of automated peritoneal dialysis and continuous ambulatory peritoneal dialysis on health-related quality of life, sleep quality and depression. *Hemodial Int* 2010; 14: 515-522.
60. Michels WM, van Dijk S, Verduijn M, *et al*. Quality of life in automated and continuous ambulatory peritoneal dialysis. *Perit Dial Int* 2011; 31: 138-147.
61. Bilgic A, Akman B, Sezer S, *et al.* Daytime sleepiness and quality of life in peritoneal dialysis patients. *Ther Apher Dial* 2011; 15: 565-571.
62. Wyld M, Morton RL, Hayen A, *et al*. A systematic review and meta-analysis of utility-based quality of life in chronic kidney disease treatments. *PLoS Med* 2012; 9(9): e1001307.
63. Tang SC, Lam B, Ku PP, *et al.* Alleviation of sleep apnea in patients with chronic renal failure by nocturnal cycler-assisted peritoneal dialysis compared with conventional continuous ambulatory peritoneal dialysis. *J Am Soc Nephrol* 2006; 17: 2607-2616.
64. Verrina E, Edefonti A, Gianoglio B, *et al*. A multicenter experience on patient and technique survival in children on chronic dialysis. *Pediatr Nephrol* 2004; 19 (1): 82-90.
65. Oreopoulos D, Thodis E, Paraskevas KI. The promising future of long-term peritoneal dialysis. *Int Urol Nephrol* 2008; 40 (2): 405-410.
66. Kadambi P, Troidle L, Gorban-Brennan N, Kliger AS, Finkelstein FO, *et al*. APD in the elderly. *Semin Dial* 2002; 15 (6): 430-433.
67. Verrina E, Cappelli V, Perfumo F. Selection of modalities, prescription, and technical issues in children on peritoneal dialysis. *Pediatr Nephrol* 2009; 24: 1453-1464.
68. Fine RN, Ho M. The role of APD in the management of pediatric patients: a report of the North American Pediatric Renal Transplant Cooperative Study. *Semin Dial* 2002; 15 (6): 427-429.
69. Fabian Velasco R, Lagunas Munoz J, Sanchez Saavedra V, *et al*. Automated peritoneal dialysis as the modality of choice: a single-center, 3-year experience with 458 children in Mexico. *Pediatr Nephrol* 2008; 23 (3): 465-71.
70. Chiu MC, Ng CF, Lee LP, *et al*. Automated peritoneal dialysis in children and adolescents-benefits: a survey of patients and parents on health-related quality of life. *Perit Dial Int* 2007; 27 (Suppl 2): S138-S142.
71. Blake PG. Advantages and disadvantages of automated peritoneal dialysis compared to continuous ambulatory peritoneal dialysis. *Perit Dial Int* 1999; 19 (Suppl 2): S121-S124.
72. Povlsen JV, Ivarsen P. Assisted automated peritoneal dialysis (AAPD) for the functionally dependent and elderly patient. *Perit Dial Int* 2005; 25 (Suppl 3): S60-S63.
73. Gianotti-Franco MR, Fernandes N, Ribeiro CA, *et al*. A Brazilian experience in assisted automated peritoneal dialysis: a reliable and effective home care approach. *Perit Dial Int* 2013; 33(3): 252-258.
74. Povlsen JV, Ivarsen P. How to start the late referred ESRD patient urgently on chronic APD. *Nephrol Dial Transplant* 2006; 21 (Suppl 2): ii56-59.
75. Lobbedez T, Lecouf A, Ficheux M, *et al.* Is rapid initiation of peritoneal dialysis feasible in unplanned dialysis patients? A single-centre experience. *Nephrol Dial Transplant* 2008; 23(10): 3290-3294.
76. Ilabaca-Avendano MB, Yarza-Solorzano G, Rodriguez-Valenzuela J, *et al*. Automated peritoneal dialysis as a lifesaving therapy in an emergency room: report of four cases. *Kidney Int* 2008; Suppl 108; S173-S176.
77. Helantera I, Haapio M, KoskinenP, *et al*. Employment of patients receiving maintenance hemodialysis and after kidney transplant: a cross-sectional study from Finland. *Am J Kidney Dis* 2012; 59(5): 700-706.
78. Kwan BC, Ma TK, Yu V, *et al*. Automated peritoneal dialysis in Hong-Kong: there are two distinct group of patients. *Nephrology* 2013; 18: 356-364.
79. Julian-Mauro JC, Cuervo J, Rebollo P, Callejo D. Employment status and indirect costs in patients with renal failure: differences between different modalities of renal replacement therpy. *Nefrologia* 2013; 33(3): 333-341.
80. Julian-Mauro JC, Molinuero-Tobalina JA, Sanchez-Gonalez JC. Employment in the patient with chronic kidney disease related to renal replacement therapy. *Nefrologia* 2012; 32 (4): 439-445.
81. Cortes-Sanabria L, Rodriguez-Arreola BE, Ortiz-Suarez VR, *et al.* Comparison of direct medical costs between automated and continuous ambulatory peritoneal dialysis. *Perit Dial Int* 2013; 33 (6): 679-686.
82. Liakopoulos V, Dombros NV. Patient selection for automated peritoneal dialysis: for whom, when? *Perit Dial Int* 2009; 29 (suppl. 2): S102-S107.
83. Szabo E, Moody H, Hamilton T, *et al*. Choice of treatment improves quality of life. A study on patients undergoing dialysis. *Arch Intern Med* 1997; 157 (12): 1352-1356.

BANTAO Journal 2014; 12(1): 84-89

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Review

Vascular Access for Hemodialysis: When and how?

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Abstract

As chronic kidney disease (CKD) progresses to the terminal stage, proper actions must be taken to prepare the patient for the initiation of the renal replacement therapy (RRT). If hemodialysis is an option for RRT, decisions should be made about the right vascular access for each individual patient. The available options for vascular access include the use of native arteriovenous fistulas (AVF), synthetic arteriovenous grafts (AVG) and double lumen dialysis catheters. With the help of ultrasound mapping, chances for choosing a right access are today very high. For hemodialysis patients the selection of the proper vascular access is of vital issue in regard of preventing complications and unnecessary procedures. Planning, creation and monitoring of the vascular access in dialysis patients should involve not only the nephrologist, but also the vascular surgeon and the interventional radiologist. Thus, multidisciplinary approach should be taken, in order to choose the way that has the most advantages and the least damage for the patient. That is the proper mode for hemodialysis patients to have longer and better quality of life.

Key words: vascular access, hemodialysis, arteriovenous fistula, graft, catheter, ultrasound

Introduction

As chronic kidney disease (CKD) progresses to the terminal stage, proper actions must be taken to prepare the patient for the initiation of the renal replacement therapy (RRT). If hemodialysis is an option for RRT, decisions should be made about the right vascular access for each individual patient. The available options for vascular access include the use of native arteriovenous fistulas (AVF), synthetic arteriovenous grafts (AVG) and double lumen dialysis catheters. In the following text, the proper approach to each patient in the creation of vascular access will be discussed.

Arteriovenous fistulas

Arteriovenous fistula (AVF) is a surgically created direct juncture between an artery and a vein resulting in dilatation and maintenance of arterial blood flow rates in the adjacent vein. This groundbreaking type of access was first introduced by Brescia and Cimino in 1966 and enabled hemodialysis to be widely applied around the world [1]. In their publication, the authors described the creation of side-to-side anastomosis between the cephalic vein and the radial artery in the wrist. This originally described type of anastomosis is still created for almost 50 years now without major modifications.

According to the 2006 published KDOQI Guidelines, in patients with CKD stage 4 or 5, arm veins should be spared from venipuncture allowing them to be used in the future for creation of AV fistulas. Also, the use of jugular vein catheters should be prefered over subclavian vein catheters because of the smaller propability of stenosis and vein occlusion. An AVF should be created at least 6 months before the planned start of hemodialysis, and when glomerular filtration rate (GFR) is less than 25 ml/min and the serum creatinine level is above 350 μmol/l. European Best Practice Guidelines (EBPG) suggest that patients should be referred to the surgeon for preparing a vascular access in stage 4 of CKD (GFR<30 ml/min/ 1.73 m^2) or earlier in case of rapidly progressive nephropathy or specific clinical conditions (e.g. diabetes, severe peripheral vascular disease) [2]. Similarly, UK Renal Association advises that planning for access should be started in stage 4 of CKD, and the exact time will be determined by the rate of decline of renal function, comorbidities and by the surgical pathway [3]. Canadian Society of Nephrology recommends that vascular access should be provided when GFR is about 15-20 ml/min [4]. Arteriovenous fistulas are the preferred type of vascular access because of their better long-term patency rates, the lower frequency of infection and the lesser need for interventions to maintain patency and functionality compared to the other types of access [5,6].

The American Vascular Surgery Society recommends

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that the first created native fistula should be located in the non-dominant arm and as far distally as possible in order to preserve proximal sites if needed for future access creation [7]. The order for creating AV fistula, according to KDOQI Guidelines is: radio-cephalic or distal AV fistula, brachio-cephalic or proximal AV fistula, brachial-basilic AV fistula with transposition or proximal AV fistula [8].
When an AVF is surgically created, maturation process is the next important issue that determines its future use and long-term patency. Therefore, besides an adequate surgical technique, the quality of the veins is an important factor that allows a sufficient maturation process. It is known that the fistula failure is more common among women, older patients, and patients that have vascular disease or diabetes [9-11].
The percentage of patients who are using a native arteriovenous fistula as a vascular access varies remarkably between Europe and the United States (US). It is interesting to note, that the use of AV fistulas is much more common in Europe than in the US, while patients on hemodialysis have lower comorbidity in Europe than in the US as it was shown in the DOPPS study [12]. More than half of the US dialysis patients receive a synthetic arteriovenous graft. Meta-analysis done by Murad *et al.* on 83 studies, has shown that AVF for chronic hemodialysis is superior to the AVG (significant reduction of death and access infection, non-significant reduction in the risk of postoperative complications-hematoma, bleeding pseudoaneurysm, steal syndrome, and also shorter lenght of hospitalization and primary and secondary patency at 12 and 36 months) [13]. But, it has to be pointe out that hospitalization rates for vascular access problems are equally common in Europe and in the US [14].

Arteriovenous grafts

If there are no suitable veins for creating an AVF, then the creation of a synthetic arteriovenous graft (AVG) should be considered as an option. AVG are usually made of expanded polytetrafluoroethylene (ePTFE).
Anastomotic configuration of AV grafts includes [15]:
- curved brachio-axillary,
- looped axillo-axillary,
- forearm looped brachio-basilic,
- straight radial to cubital fossa vein,
- looped graft between the common femoral artery and saphenous or femoral vein.

The most common complication with AV grafts is outflow stenosis of the vein and infection that usually requires complete removal of the graft in spite of antibiotic therapy [16]. Arteriovenous graft failure is the result of a dynamic proccess involving hyperplasia of vascular smooth muscle cells that finally causes stenosis and occlusion of the vasular lumen [17].

The use of catheters

Catheters for hemodialysis can be used for short- or long-term periods. Short-term catheters can usually be placed into the internal jugular veins, the subclavian veins or the femoral veins by using the standard Seldinger technique. The use of this kind of catheters is predicted for a period of about 3 weeks and is mostly a bridging access until arteriovenous fistulas or grafts are ready for use. Long-term catheters can be plased also in the same above-mentioned veins and are designed for use for a longer period. In both cases, the preferred site of insertion should be the right jugular vein due to its lower rates of central venous stenosis, the more straight course allowing better flow rates during hemodialysis sessions and the lower complication rates in comparsion to the other insertion sites [18,19].
Taking into account the increasing number of patients with implanted pacemakers and defibrillators, usually inserted via the subclavian vein and superior vena, special consideration should be taken in the decision of where to place a central venous catheter [20].
Th meta-analysis by Ravani P. *et al*. that included 62 cohort studies comprising over 500,000 participans found that patients using hemodialysis central venous catheters had a much higher risk of death, infection, cardiovascular events and hospitalization compared to patients who used arteriovenous fistulas or grafts as a vascular access for hemodialysis [21].

Complications of the vascular access

Access failure is the most common complication. The blood flow needed for adequate dialysis is about 200-400 ml/min. Some factors that may contribute to the vascular access failure are advanced age, diabetes, female gender and forearm fistula [22] and hypotension and obesity [23].
Some future perspectives may help in maintaining AV fistula functioning, like the use of far infrared electromagnetic radiation to improve endothelial function with antiproliferative and anti-inflammatory effect [24] or transdermal glyceryl trinitrate administration that increases local blood flow in the new AV fistulas [25].
Steal phenomenon refers to ischemic lesions that result from an arterial steal phenomenon and is more frequent in eldery patients with comorbid conditions and diabetes. The first type that is also called "high-flow steal phenomenon" is mostly associated with the presence of a high-flow anastomosis, thus creating critical ischemia of the fingers. The other type of steal phenomenon involves patients with low fistula flow. In this case peripheral ischemia is a result of the occluded periheral arteries so even normal blood flow in the anastomosis will create critical ischemia in the peripheral vascular bed. According to the clinical features and level of effect, the steal syndrome is classified into four stages, from the first stage where the hands are

blue, pale, or cold without any pains, till the forth stage when there are ulcers, necrosis and gangrene lesions [26]. Therapeutic options are few and include measure for narrowing the anastomosis or closing of the fistula and insertion of a dialysis catheter. Arterial steal phenolmenon appears in 1% of AVF's and 9% of AVG's [27].

Aneurysm, a progressive desctruction of venous vessel wall and replacement of normal tissue with scar collagenous tissue resulting in the formation of aneurysms [28,29]. Major complications of aneurysms are rupture, infection and rarely embolism. Because of their tendency to progress spontaneously, sometimes it is necessary to perform a partial or complete resection of the aneurysmal sac, to correct any accompanying stenoses and to create an adequate lumen [30].

Pseudoaneurysm may occur during the placement of temporary catheter when there is an arterial puncture and consequent arterial bleeding into the surrounding subcutaneus tissue. In this case, the patient should be on bed rest and with the use of focal compression. In case of greater pseudoaneurysms, an ultrasound-guided thrombin injection into the aneurysmal neck can resolve about 75% of cases [31]. Pseudoaneurysm of arteriovenous grafts is more common. Surgical ligation is one of the treatment options for resolving this complication. It is important to note that covered stent grafts are a safe, flexible and durable treatment option for patients with AV graft pseudoaneurysms that improve graft patency [32].

Congestive heart failure is a result of hypercirculation because of the too low outflow resistance, and involves mostly patients with pre-existing cardiac problems and arteriovenous grafts. Hypercirculation is present on the field of too large anastomotic diameter that usually is the case in AV grafts and brachial artery fistulas. Banding procedures that narrow the anastomosis have been recomended but the results are poor and unpredictable. Ligation of the anastomosis is probably the most reliable procedure.

Central vein stenosis

Central stenosis is usually the result of past subclavian vein catheters, but also in rare cases of previous pacemaker cables or coagulation disorders. Clinically a central vein stenosis becomes symptomatic only when flow is increased as it is the case in AV fistula or grafts. This situation results in the swelling and cyanosis of the arm as well as the formation of collaterals on the chest wall. Therapeutic options include ligation of the anastomosis or if applicable, dilation and stenting of the stenosis using interventional techniques and rarely surgical correction [33,34].

The role of ultrasound mapping

Ultrasound examination of the veins and arteries of the upper extremities, the so called "vascular mapping" has been increasingly implemented as a standard preoperative procedure when planning and creating an arteriovenous fistula or graft. With this procedure the veins are examined for the presence of stenotic or fibrotic lesions, the vessel diameter is measured, while for the arteries factors such as diameter and the presence of atherosclerotic lesions is also examined. This approach has increased the success of arteriovenous fistula maturation and the frequency of arteriovenous fistulas [35].

Patients who benefit from vascular mapping are particular those with:

- insufficient clinical examination (absent pulses, obese, multiple previous access surgery),
- possible arterial disease (diabetes, cardiovascular disease, older age),
- possible venous disease (previous cannulation) [36].

In order to perform a good vein mapping, a proper technique should be used. Firstly, we need to examine the superficial veins using the B-mode (cephalic, basilic, median cubital vein) by checking the compressibility every 2 cm and then by measuring the diameter of the veins in transverse view. Also whenever possible, the proximal deep veins should be examined: brachial, axillary, subclavian. In order to perform a dilatation of the veins and to make a more accurate diameteres, tourniquets should be used. Accordingly, the first tourniquet is placed on the upper arm so that deeper veins are occluded, and the second is placed below the elbow to occlude the superficial veins. After B-mode, doppler spectral analysis should be performed with adjustment of an angle at 60 degrees or less and with alignment of Doppler cursor parallel to the vessel walls [37].

Vessel mapping using ultrasound has become the standard of care for preoperative planning of AV access, and Duplex Doppler ultrasound has the capability to provide functional evaluation of vascular access-fistula maturation evaluation and maturation failure thus facilitating early intervention [38].

The following factors indicate adequate vessels for creating distal radio-cephalic AV fistula [39]:

- inner diameter of radial artery $\geq$2 mm,
- inner diameter of cephalic vein $\geq$2.5 mm,
- flow velocity through radial artery VmaxS $\geq$50cm/s,
- flow through radial artery Qa.radialis $\geq$ 40 ml/m.
- Four weeks after the AV fistula creation, the following factors indicate adequately matured AV fistula and a good possibility of achieving puncture [40]:
- diameter of cephalic vein $\geq$4 mm,
- blood flow Q_{AV} $\geq$500 ml/min.

Finally, maximal blood flow velocity through AV fistula of 100-350 cm/s and blood flow of 500-1000 ml/min are the signs of a good function of AV fistula providing sufficient blood flow for hemodialysis [41].

Lockhart *et al*. showed in their study on 112 patients that there were no differences in the preoperative peak systolic velocity nor in the resistive index (RI) of successful and failed fistulas, but the measurement of the

radial artery peak systolic velocity changes after release of fist clenching identified a subset of female patients with a very low likehood for success [42].
However, Hasaballah *et al.* found an accuracy of 94.8% in 455 End-Stage Renal Disease patients of duplex based desicion in reference to intraoperative findings and post-operative results of upper arm arteriovenous fistulas. Accordingy, they suggest that preoperative duplex planning should be performed in all patients, and that brachiocephalic fistulas should be the first choice in the upper arm because of their best patency rates and lower complications. Brachiobasilic fistulas should be considered as a second option, and then grafts, which were most prone to infection (27.7%) and thrombosis (10.6%) [43].
Lauvao *et al.* in their study on 185 native arteriovenous fistula showed no significant difference in fistula maturation according to age, gender, diabetes and body-mass index, but they have underlined that vein diameter was a sole independent predictor of fistula functional maturation [44].
Also, Zadeh *et al.* in their study on 96 hemodialysis patients with AV fistula discovered that the maturation of fistula showed some correlation between duration of maturation period and vein diameter in patients with radiocephalic fistula, but did not show a correlation with arterial diameter, diabetes mellitus, gender and age [45].
It is suggested that after performing a preoperative vein mapping with ultrasonography in patients with a minimal cephalic vein size of 2.0 mm or less, a procedure other than wrist fistula should be considered for optimization of dialysis access [46].
In dialysis patients with a functioning vascular access, the following signs are indicative of malfunction and should prompt initiation of an ultrasound examination of the access [47]:

- **abnormal fistula functioning**: difficult cannulation, thrombus aspiration, elevated venous pressure greater than 200 mmHg on a 300 ml/min pump, elevated recirculation time of 15% or greater, urea reduction rate of less than 60%;
- **clinical signs and symptoms of AV access insufficiency**: access collapse suggesting poor arterial inflow, poorly matured fistula, loss or change in the intensity of thrill, clinical signs of infection, distal limb ischemia, perigraft mass, aneurysm, pseudoaneurysm.
- Duplex ultrasound evaluation of hemodialysis access should include the following examinations:
- inflow artery proximal to the fistula or graft,
- inflow artery distal to the fistula or graft,
- anastomotic sites (fistula: one site, graft: two sites),
- puncture sites,
- proximal, mid, and distal outflow vein or graft,
- axillary and subclavian veins [47].

It is important to emphasize that the sensitivity of ultrasound in the diagnosis of AV fistula and graft stenosis is very high and comparable to the fistulography especially when performed by an experienced operator [48].
In summary, ultrasound is a relatively inexpensive and readily available tool that has an important contribution for a successful placement and maintenance of dialysis access. Using it to diagnose a stenosis if a clinical problem occurs, helps the interventionist to choose a better approach for the procedure [49]. On the other hand, angiographic evaluation of the artery end veins using radiocontrast optimally visualizes both, peripheral as well as central veins, but exposes the patient to the risk of radiocontrast-induced nephropathy in pre-dialysis patients and has a greater economic cost [50].
Also, ultrasound-guided placement of a central venous hemodialysis catheter is more precise and visualizes anatomical variants and vein thrombosis in regard to landmark technique. In this way, repeated puncture can be prevented, as well as the complications like pneumothorax and arterial laceration [51]. In conclusion, many studies have demonstrated that the use of ultrasound in pre-operative mapping increases the success of AV fistula creation and patency [52,53].

Conclusions

For hemodialysis patients the selection of proper vascular access is a vital issue in regard of preventing complications and unnecessary procedures. It is known that mortality and morbidity among patients who start dialysis with a catheter is two- to three-fold higher than in those who start hemodialysis with a functioning AV fistula [54,55].
Therefore, it is important to carefully prepare and plan the right vascular access for every patient in an individual manner.
The planning, the creation and the monitoring of the vascular access in dialysis patients should involve not only the nephrologist, but also the vascular surgeon and the interventional radiologist in a multidisciplinary approach in order to achieve the maximum benefit for the patients.

References

1. Brescia MJ, Cimino JE, Appel K, Hurwich BJ. Chronic hemodialysis using venipuncture and a surgically created arteriovenous fistula. *N Engl J Med* 1966; 275: 1089-1092.
2. Tordoir J, Canaud B, Haage P, *et al*. EBPG on vascular access. *Nephrol Dial Transplant* 2007; 22(Suppl 2): ii88-117.
3. Mactier R, Davies S, Dudley C, *et al*.Summary of the 5th edition of the Renal Association Clinical Practice Guidelines (2009-2012). *Nephron Clin Pract* 2011; 118 Suppl 1: c27-70.
4. Jindal K, Chan CT, Deziel C, *et al.* Hemodialysis clinical practice guidelines for the Canadian Society of Nephrology. Canadian Society of Nephrology Committee for Clinical Practice Guidelines. *J Am Soc Nephrol* 2006; 17(3 Suppl 1): S1-27.
5. Churchill DN, Taylor DW, Cook RJ, *et al*. Canadian hemodialysis morbidity study. *Am J Kidney Dis* 1992; 19(3): 214-234.
6. Allon M. Current management of vascular access. *Clin J Am Soc Nephrol* 2007; 2(4): 786-800.

7. Sidawy AN, Spergel LM, Besarab A, *et al*. The Society for Vascular Surgery: clinical practice guidelines for the surgical placement and maintenance of arteriovenous hemodialysis access. *J Vasc Surg* 2008; 48(5 Suppl): 2S-25S.
8. National Kidney Foundation, Inc. K/DOQI Guidelines-Updates 2006. New York: National Kidney Foundation, Inc. 2001. Availablefrom: http://www.kidney.org/PROFESSIONALS/doqi/guideline_upHD_PD_VA/index.htm.
9. Miller PE, Tolwani A, Luscy CP, *et al*. Predictors of adequacy of arteriovenous fistulas in hemodialysis patients. *Kidney Int* 1999; 56(1): 275-280.
10. Miller CD, Robbin ML, Allon M. Gender differences in outcomes of arteriovenous fistulas in hemodialysis patients. *Kidney Int* 2003; 63(1): 346-352.
11. Lok CE, Allon M, Moist LM, *et al*. Risk equation determining unseccessful cannulation events and failure to maturation in arteriovenous fistulas (REDUCE FTM I). *J Am Soc Nephrol* 2006; 17: 3204-3212.
12. Venturelli C, Bandera A, Zubani R, *et al*. Vascular access in older patients: an Italian Survey. *J Nephrol* 2013; 26(6): 1122-1127.
13. Pisoni RL, Young EW, Dyxtra DM, *et al*. Vascular access use in Europe and in the United States: Results from the DOPPS. *Kidney Int* 2002; 61(1): 305-316.
14. Murad MH, Elamin MB, Sidawy AN, *et al*. Autogenous versus prostethic vascular access for hemodialysis: a systematic reviw and meta-analysis. *J Vasc Surg* 2008; 48(5 Suppl): 34S-47S.
15. Allon M, Robbin ML. Increasing arteriovenous fistulas in hemodialysis patients: problems and solutions. *Kidney Int* 2002; 62(4): 1109-1124.
16. Akoh JA. Prosthetic arteriovenous grafts for hemodialysis. *J Vasc Access* 2009; 10(3): 137-147.
17. Ponikvar R. AV fistulae and catheters for hemodialysis: how much should nephrologists be involved in vascular access for hemodialysis. *Bantao Journal* 2013; 11(9): 9-11.
18. Roy-Chaudhry P, Sukhatme VP, Cheung AK. Hemodialysis vascular access dysfunction: A cellular and molecular viewpoint. *J Am Soc Nephrol* 2006; 17(4): 1112-1127.
19. Salgado OJ, Urdaneta B, Colmenares B, *et al*. Right versus left internal jugular vein catheterization for hemodialysis: complications and impact on ipsilateral access creation. *Artif Organs* 2004; 28(8): 728-733.
20. Cimochowski GE, Worley E, Rutherford WE, *et al*. Superiority of the internal jugular over the subclavian access for temporary dialysis. *Nephron* 1990; 54(2): 154-161.
21. Santoro D, Benedotto F, Mondello P, *et al*. Vascular access for hemodialysis: current perspectives. *Int J Nephrol Renovasc Dis* 2014; 7: 281-294.
22. Ravani P, Palmer SC, Oliver MJ, *et al*. Association between hemodialysis access type and clinical outcomes: a systematic review. *J Am Soc Nephrol* 2013; 24: 465-473.
23. Roa RK, Azin GD, Hood DB, *et al*. Basilic vein transposition fistula: a good option for maintaining hemodialysis access site options. *J Vasc Surg* 2004; 39(5): 1043-1047.
24. Elsharawy MA, Moghazy KM. Pre-operative evaluation of hemodialysis access fistula. A multidisciplinary approach. *Acta chir belg* 2005; 105: 355-358.
25. Lin CC, Yang WC. Prognostic factors influency the patency of hemodialysis vascular access: literature review and novel therapeutic modality by far infrared therapy. *J Chin Medical Assoc* 2009; 72(3): 109-116.
26. Smith GE, Gohil R, Cheter IC. Factors affecting the patency of arteriovenous fistulas for dialysis access. *J Vasc Surg* 2012; 55(3): 849-855.
27. Hallett JW Jr, Mills JL, Earnshaw JJ, Reekers JA, eds. Comprehensive vascular and endovascular surgery. Edinburgh: *Mosby* 2004; p.712.
28. Peterson LA, Litzendorf M, Khabiri H, Stawicki SPA. Hemodialysis access: initial considerations and the difficult patients. In: Hemodialysis. Suzuki Hiromichi, editor. InTech. 2013.p:635-61. Available from: http://www.intechopen.com/books/hemodialysis/hemodialysis-access-initial-considerations-and-the-difficult-patient.
29. Jablonski M, Khairoune A, Martinez F. Giant aneurysm of an endogenous arteriovenous fistula. *Nephrol Dial Transplant* 2007; 22(12): 3668.
30. Lo HY, Tan SG. Arteriovenous fistula aneurysm-plicate, not ligate. *Ann Acad Med Singapore* 2007; 36(10): 851-853.
31. Konner K, Nonnast-Daniel B, Ritz E. The arteriovenous fistula. *J Am Soc Nephrol* 2003; 14: 1669-1680.
32. Pandolfe LR, Malamis AP, Pierce K, Borge MA. Treatment of hemodialysis graft pseudoaneurysms with stent grafts: institutional experience and review of the literature. *Semin Intervent Radiol* 2009; 26(2): 89-95. doi: 10.1055/s-0029-1222451.
33. Stawicki SP, Hoey BA. Lower extremity arterial thrombosis following sonographically guided thrombin injection of a femoral pseudoaneurysm. *J Clin Ultrasound* 2007; 35(2): 88-93.
34. Schillinger F, Schillinger D, Montagnac R, Milcent T. Post catheterisation vein stenosis in hemodialysis: comparative angiographic study of 50 subclavian and 50 internal jugular accesses. *Nephrol Dial Transplant* 1991; 6(10): 722-724.
35. Kovalik EC, Newman GE, Suhochi P, *et al*. Correction of central venous stenoses: use of angioplasty and vascular Wallstents. *Kidney Int* 1994; 45(4): 1177-1181.
36. Silva MB, Hobson RW, Pappas PJ, *et al*. A strategy for increasing use of autogenous hemodialysis access procedures: impact of preoperative noninvasuve evaluation. *J Vasc Surg* 1998; 27(2): 302-308.
37. Ferring M, Henderson J, Wilmink A, Smith S. Vascular ultrasound for the pre-operative evaluation prior to arteriovenous fistula formation for hemodialysis: review of the evidence. *Nephrol Dial Transplant* 2008; 23(6): 1809-1815.
38. Society for vascular ultrasound. Vascular technology proffessional performance guidelines. Upper Extremity vein mapping for placement of a dialysis access. 2009.
39. Wellen J, Shenoy S. Ultrasound in vascular access. In: Wilson SE, editor. Vascular access, principles and practice. Philadelphia: Wolters Kluwer-*Lippincott Williams and Wilkins*2010; 234-243.
40. Petrovic D. Clinical importance of color doppler ultrasonography in preoperative assesment of hemodialysis vascular access creation. *Sanamed* 2012; 7(2): 113-118.
41. Lockhart ME, Robbin ML, Allon M. Preoperative sonographic radial artery evaluation and correlation with subsequent radiocephalic fistula outcome. *J Ultrasound Med* 2004; 23(2): 161-168.
42. Hasaballah A, Elbadawy A, Khalil M. Impact of preoperative duplex mapping on patency of upper arm arteriovenous fistula for hemodialysis. *EJS* 2013; 32(3): 201-207.
43. Lauvao LS, Ihnat DM, Goshima KR, *et al*. Vein diameter is the major predictor of fistula maturation. *J Vasc Surg* 2009; 49(6): 1499-1504.
44. Zadeh MK, Gholipour F, Naderpour Z, Porkfakharan M. Relationship between vessel diameter and time to maturation of arteriovenous fistula for hemodialysis access. *Int J Nephrol* 2012; 2012: 942950.
45. Mendes RR, Farber MA, Marston WA, *et al*. Prediction of wrist arteriovenous fistula maturation with preoperative vein mapping with ultrasonography. *J Vasc Surg* 2002; 36(3): 460-463.
46. Centers for Medicare and Medicaid Servises: Empire Medical Local Coverage Determination. Available from: http://www.cmc.hhs.gov/MCD/.
47. Teodorescu V, Gustavson S, Schanzer H. Duplex ultrasound evaluation of hemodialysis access: a detailed protocol. *Int J Nephrol* 2012; 2012:508956.

48. Doelman C, Duijm LE, Liem YS, *et al*. Stenosis detection in failing hemodialysis access fistulas and grafts: comparison of color Doppler ultrasonography, contrast-enhanced magnetic resonance angiography and digital subtraction angiography. *J Vasc Surg* 2005; 42(4): 739-746.
49. Sasson T, Carson N, Voci S. The role of ultrasound in the preoperative evaluation, maturation process and postoperative evaluation of hemodialysis access. *Ultrasound Clinics* 2013; 8(2): 137-146.
50. Asif A, Ravani P, Roy-Chaudhury P, *et al*. Vascular mapping techniques: advantages and disadvantages. *J Nephrol* 2007; 20(3): 299-303.
51. Van Hooland S, Donck J, Ameye F, Aerden D. Duplex ultrasonografy and haemodialysis vascular access: a practical review. *Int J Nephrol Urol* 2010; 2(2): 283-293.
52. Ilhan G, Esi E, Bozok S, *et al*. The clinical utility of vascular mapping with Doppler ultrasound prior to arteriovenous fistula construction for hemodialsis access. *J Vasc Access* 2013; 14(1): 83-88.
53. Wong CS, McNicholas N, Healy D, *et al*. A systematic review of preoperative duplex ultrasonography and arteriovenous fistula formation. *J Vasc Surg* 2013; 57(4): 1129-1133.
54. Dhingra RK, Young EW, Hulbert-Shearon TE, *et al*. Type of vascular access and mortality in US hemodialysis patients. *Kidney Int* 2001; 60(4): 1443-1451.
55. Xue JL, Dahl D, Ebben JP, Collins AJ. The association of initial hemodialysis access type with mortality outcomes in elderly Medicare ESRD patients. *Am J Kidney Dis* 2003; 42(5): 1013-1019.

BANTAO Journal 2014; 12(1): 90-96

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Review

Kidney Complications Due to Hematopoietic Stem Cell Transplantation-A Disorder of an Increasing Incidence?

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Abstract

Hematopoietic stem cell transplantation (HSCT) is becoming an increasingly popular treatment considering that it is the only curative option for many malignant and non-malignant diseases. Many patients treated in this way have been followed for two or three decades post-transplant and are presumed to be cured. But, on the other hand, a great proportion of these patients are experiencing long-term side effects after HSCT, including non-malignant organ or tissue dysfunction, changes in quality of life, infections and secondary malignancy. Renal complications caused by HSCT are high and are associated with the development of both acute and chronic kidney failure. So, considering the increasing numbers of HSCT survivors many years after the transplantation, chronic kidney disease due to HSCT is becoming a growing problem and represents a new population of patients who are presented to nephrologists. The three most common forms of chronic kidney disease related to HSCT are: chronic calcineurin nephrotoxicity, glomerular disease after HSCT and HSCT associated thrombotic microangiopathy.

Key words: hematopoietic stem cell transplantation, acute kidney failure, chronic kidney failure

Case presentation

In January 2013 a 21-year-old man was admitted to the Department of Nephrology after experiencing pedal and facial edema for the last 14 days. His medical history began in 2007 when he was diagnosed with acute lymphoblastic leukemia (ALL). He underwent chemotherapy according to the ALL-IC-BFM 2002. After an apparent remission, three years later he presented with isolated medullary relapse. He received treatment with the ALL-REZ BFM protocol that led to cytomorphological remission. The patient underwent myeloablative allogenic peripheral stem cell transplantation with his HLA-identical sister as the donor. The conditioning regimen consisted of cyclophosphamide and 12-Gy total-body irradiation. The patient received cyclosporine and methotrexate for graft-versus-host disease (GVHD) prophylaxis. He responded well and continued further ambulatory monitoring by a hematologist. There was no sign of residual ALL on follow-up.

Results of his physical examination showed periorbital and pretibial edema. Renal function was normal; with a serum creatinine level of 80 μmol/L. He had proteinuria with protein of 9 g/24h. The kidney ultrasound was normal. He underwent a percutaneous renal biopsy that showed membranous nephropathy. Further hematological investigation showed no signs of ALL relapse.

Introduction

Hematopoietic stem cell transplantation (HSCT) is becoming an increasingly popular treatment considering that it is the only curative option for many malignant and non-malignant diseases [1]. In general, HSCT consists of three steps. In the first phase, patients are given preconditioning regimen which consists of total-body irradiation and/or chemotherapy. The decision whether to perform myeloablative or nonmyeloablative conditioning regimen depends on the patient age, co-morbid states, the underlying disease and the disease stage. Myeloablative regimens may be associated with high morbidity during the cytopenic period, and for this reason this approach is reserved for younger patients without co-morbid conditions. In the second step, the patient receives an infusion consisting of bone marrow, peripheral-blood, or umbilical cord progenitor cells which are derived from either a donor (and then we are talking about allogeneic HSCT) or the patients themselves (autologous HSCT). In the third step immunosuppressive medications are used in order to decrease the risk of graft-versus-host disease (GVHD). These are usually methotrexate or the calcineurin inhibitors

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(CNIs) cyclosporine or tacrolimus. Using the mentioned approach many patients have now been followed for two or three decades post-transplant and are presumed to be cured [1,2]. On the other hand, a great proportion of these patients are experiencing long-term side effects after HSCT, including non-malignant organ or tissue dysfunction, changes in quality of life, infections and secondary malignancy [3]. Rates of renal complications caused by HSCT have been reported as high as 92% and are associated with the development of both acute and chronic kidney failure [4]. The risk factors for kidney injury following HSCT vary depending on the types of regimens that are used in patients undergoing HSCT. Namely, a high-dose conditioning regimen is used in both myeloablative allogeneic and autologous HSCT and frequently in combination with high dose radiotherapy. Furthermore, myeloablative allogeneic HSCT also requires the use of immunosuppressive therapy post-transplant, most of the time with calcineurin inhibitors and this is not necessary in autologous HSCT [2,5].
Recently, a newly developed form of HSCT, a non-myeloablative or reduced-intensity conditioning (RIC) allogeneic HSCT is being used in older patients or in those with co-morbid medical conditions. With this procedure patients receive a lower dose of chemoradiotherapy, but post-transplant immunosuppression therapy is also required. The intensity of the conditioning regimen, especially the use of full-dose myeloablative total body irradiation (TBI) is more likely to cause late complications after allo-HSCT. On the other hand, it has been well-established that the use of RIC can reduce short-term acute toxicity, but it has also been well-documented that the probability of chronic graft-host-versus disease (cGHVD) is not reduced after implementation of this regimen, namely because this approach is used in older patients and in more advanced disease stages [1,6-8]. These observations are supported by the study of Al Hazzouri, as well [9]). In the aforementioned analysis the authors have investigated the appearance of chronic kidney disease (CKD) in patients that have received RIC versus myeloablative regimens, and they observed that there were no significant differences in terms of renal complications between two patients' groups. According to this observation and considering the increasing incidence of HSCT related nephropathy, the aim of this review is to provide an update on the recent knowledge in the approach to patients with suspected HSCT nephropathy.

Acute kidney injury (AKI) after HSCT

The incidence of AKI in the days and weeks following myeloablative regimens varies from 30% to 90%. It is significantly higher in patients receiving an allogenic HSCT, and approximately 33% of these patients require renal replacement therapy (RRT) (10). Mortality is 2 to 7 times higher in patients experiencing AKI compared to those without AKI, and when those patients require RRT, the mortality rates may eventually rise to more than 80%, mainly due to association with coexistent injury of multiple organs [11,12]. Also, the important risk factor that may be driving the sustained rates of AKI is patients' age at the time of transplantation, which is steadily increasing. The fastest growing group of patients who undergo HSCT includes patients over the age of 60. It has already been well-established that age is a risk factor for AKI. Acute kidney injury following HSCT is related to prerenal (such as fluid depletion, sepsis, drugs…), intrinsic renal (acute tubular necrosis due to ischemia, nephrotoxic drugs, acute interstitial nephritis, infection-associated kidney injury and vascular disorders) and postrenal (intratubular or extratubular obstruction) causes [2]. During the first month after HSCT the main predisposing factors for development of AKI are: sepsis, nephrotoxic drugs, obstruction, tumor lysis syndrome, hepatorenal syndrome from veno-occlusive disease, acute thrombocytopenic purpura or hemolytic uremic syndrome (TTP/HUS), acute graft-host-versus disease (aGHVD) and cytomegalovirus (CMV) reactivation. Veno-occlusive disease (VOD) usually develops within 30 days after HSCT with the incidence of approximately 10% for allogenic HSCT, and with lower incidence rate for autologous HSCT. VOD is also known as sinusoidal obstruction syndrome, and is a conditioning-related toxicity usually associated with regimens including cyclophosphamide, busulfan, and/or total body irradiation. Clinically, it is characterized by an acute onset of jaundice, ascites and painful hepatomegaly followed by azotemia, low urine sodium excretion and with bland urine. The severity of the disease varies. In mild to moderate cause hepatic injury is self-limited, but this condition can progress to multi-organ failure (MOF) [2,11,13]. Tumor lysis syndrome is characterized by hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia. Acute graft-host-versus disease (aGHVD) is the most frequent complication following allogenic HSCT and it usually occurs within the time frame of two weeks up to three months after transplantation and aGHVD causes renal injury that ranges from prerenal azotemia to thrombotic thrombocytopenic purpura-like microangiopathy [2]. TTP-like microangiopathy has a poor response to treatment with apheresis and is accompanied by a mortality rate up to 60%. When approaching a patient with AKI following HSCT, it's important to differentiate the cause of renal failure. According to this, management of AKI ranges from adequate use of fluids, antibiotics, avoidance of nephrotoxic agents, use of dialysis, etc. Treatment of hepatorenal syndrome due to veno-occlusive disease in these cases is mainly supportive [13]. Treatment of TTP/HUS because of the applied specific therapy primarily involves avoidance of the aforementioned medications. Management of

other types of TTP/HUS demands implementation of plasma exchanges and/or eculizumab [2]. There is no convincing data to support the efficiency of plasma exchange in patients who develop thrombotic microangiopathy after HSCT. This is in contrast to the well-known beneficial effect seen in most other forms of TTP-HUS. This might be partially explained by the fact that TTP-HUS following HSCT occurs due to direct injury to the kidney from nephrotoxic drugs and/or radiation. Treatment of tumor lysis syndrome consists of identifying those patients that are at risk, careful laboratory monitoring and the use of prophylactic therapy (hydration, urine alkalinization and use of xanthine oxidase inhibitors). Acute renal failure due to tumor lysis syndrome often requires some dialysis treatment (hemodialysis and/or hemofiltration) [14-16].

Chronic kidney disease (CKD) after HSCT

Within six months of transplantation some of the patients who undergo HSCT develop chronic kidney disease (CKD). The incidence of CKD related to HSCT varies worldwide and depends on the used diagnostic criteria, definition of CKD, duration of follow-up, and the type of HSCT. When we include all these factors the incidence of CKD related to HSCT ranges from 15% to as high as 60%. The growth in non-myeloablative protocols may actually increase the incidence of CKD in patients undergoing HSCT despite its milder conditioning regimen, because of older patients' age and increased baseline co-morbidities in this population of patients [2,17-18].
Independent risk factors for development of CKD include AKI in the first 100 days, previous autologous HSCT, CNI use, and chronic GVHD [2].
The three most common forms of CKD related to HSCT are: chronic CNI nephrotoxicity, glomerular disease after HSCT (chronic GVHD-associated glomerulonephritis), and HSCT associated thrombotic microangiopathy (TA-TMA) [2].

Chronic CNI nephrotoxicity

Calcineurin inhibitors, mainly cyclosporine and tacrolimus, can cause renal injury similar to that seen in other settings, such as solid organ transplantation. These are used to prevent GVHD in the period of several months after allogenic HSCT. This approach is associated with a 25% incidence of moderate to severe aGVHD. According to these observations, patients who require prolonged therapy for GVHD will receive these medications for a longer period of time and are at great risk of developing side-effects, mainly nephrotoxicity. The main pathohistological findings are non-specific and include obliterative arteriolopathy, afferent arteriolar hyalinosis, and patchy interstitial fibrosis [2,19-20].

HSCT associated thrombotic microangiopathy (TA-TMA)

Transplant-associated thrombotic microangiopathy (TA-TMA) is a severe complication of HSCT, and usually occurs within 6 to 12 months after transplantation. The kidney is the most commonly affected organ, but in some cases it may present as a systemic condition, with high mortality rate, while in milder cases there is an increased risk of a resulting chronic kidney disease [2,21-23].
Published studies have shown discrepant results in the incidence rates of TA-TMA, ranging from 0.5% to 76% which is mainly due to diagnostic uncertainty, and limited prospective data. According to the most large, retrospective studies, the incidence rate of TA-TMA is about 10-25%, which more likely represents the true burden of the disease [2,24].
The pathogenesis of thrombotic microangiopathy after HSCT is still poorly understood but it is believed that the most important setting in the pathogenesis of TA-TMA is the endothelial injury in the context of HSCT. Namely, it is believed that during the first six months after transplantation various etiological factors cause endothelium injury, which leads to endothelial inflammation. Furthermore, dysregulation of interaction between platelets and damaged endothelium results in thrombosis and fibrin deposition in the microcirculation, which in turn causes end-organ damage [2]. The most important risk factors for development of TA-TMA are: irradiation and chemotherapy, mainly the use of cyclophosphamide, busulfan, cisplatin and carmustine [24,25]. Radiotherapy is performed as a total-body irradiation or radio- immunotherapy or both treatments are implemented. TA-TMA is more common after allogeneic HSCT, but it can develop in patients who undergo autologous transplantation. Both myeloablative and reduced intensity conditioning regimens are risk factors for developing TA-TMA. Recent investigations have failed to produce a statistical difference in the prevalence of TA-TMA between reduced intensity and myeloablative conditioning regimens. Furthermore, it is known that partial renal shielding during total body irradiation may reduce the risk of TA-TMA development [2,25-27].
It is also believed that several other conditions may contribute to the development of TA-TMA, such as: scleroderma, pregnancy-related kidney disease, malignancy, numerous medications and infections (most commonly Aspergillus, cytomegalovirus, and adenovirus). It remains unclear if other potential infections (parvovirus B19, human herpes virus-6, and BK virus infection) play a role in the development of TA-TMA even though there has been a great interest in their role. It is important to emphasize that TA-TMA can occur in the presence or absence of GVHD, and with or without a triggering infection [28-30].

However, considering the complexity of the HSCT population, it's doubtful that a single etiological factor is responsible for the development of TA-TMA in all affected patients and it is more likely that TA-TMA is a consequence of several etiological factors that lead to endothelial injury of the kidney and other organs in the setting of HSCT. This hypothesis is supported by the fact that classic thrombotic microangiopathies have been successfully linked to a single etiology, such as Shiga toxin in diarrhea-positive HUS. According to these observations, TA-TMA was first thought to be TTP but as TA-TMA did not respond as well to plasma exchange as TTP did, this condition was distinct from "classic" TTP/HUS [5]. This might be partially explained by the fact that TTP-HUS following HSCT occurs because of direct injury to the kidney from nephrotoxic drugs and/or radiation. Furthermore, it is believed that deficiency of the ADAMTS-13 protease, present in classic TTP, is not involved in the pathogenesis of thrombotic microangiopathy following HSCT [2,23,24].

The pathohistological features of TA-TMA in the kidney are non-specific and include thickened capillary walls, fragmented erythrocytes, occluded vascular lumens, and endothelial separation accompanied by swelling, fibrin deposition, and necrosis [2,33]. As mentioned above, in contrast to patients with "classic" TTP, patients with TA-TMA have rarely been reported to have systemic thromboses, although recent case reports have presented the involvement of other organs, namely the lungs [32] and the gastrointestinal tract [33].

Characteristic clinical features include slowly rising plasma creatinine, hypertension, and disproportionate anemia, but some patients are experiencing a more fulminant presentation. It is important to say that hypertension is more likely due to CNI-nephrotoxicity. Proteinuria, usually in the absence of persistent hypoalbuminemia, is an important sign of renal involvement in TA-TMA. Also, urinalysis shows variable hematuria, depending on the extent of kidney involvement. In some patients, chronic TA-TMA presents as a low-grade microangiopathic hemolysis with the usual laboratory findings such as intermittent or persistent elevation in plasma lactate-dehydrogenase level, low serum haptoglobin level, anemia, thrombocytopenia, and presence of schistocytes in the peripheral blood [2,16,23,24]. Furthermore, in patients with kidney-limited TMA, the characteristic laboratory findings are missing, and hence a kidney biopsy is necessary in these patients [2].

Treatment of TA-TMA includes medical management and withdrawal of promoting medications, mainly CNIs and cisplatin. However, medical approach includes the use of antihypertensive drugs, use of recombinant erythropoietin, red blood cell transfusions, and plasma exchange. Preclinical studies indicate a beneficial effect of the angiotensin converting enzyme inhibitors (ACEI) in the treatment of HSCT-related TMA. Although the use of ACEI has not been utilized in patients with TA-TMA, it seems reasonable to believe that patients with persistent proteinuria after HSCT could benefit from this therapy. Further prospective studies are needed to confirm their beneficial effect [2,15,16].

The effectiveness of plasma exchange in the treatment of TA-TMA is unclear, and according to most studies patients who have undergone this treatment had poor response and high mortality rate [34].

According to some studies, the use of new drugs, such as daclizumab, rituximab, defibrotide, and eicosapentaenoic acid could be useful in the treatment of HSCT-related TMA [2,35-37].

Another therapeutic approach to patients with ESRD due to HSCT is kidney transplantation. In the last decade numerous cases of successful kidney transplanttation in these patients have been published [2].

In the absence of controlled trials that evaluate additional treatment modalities in patients with HSCT-related TMA, for now, discontinuation of offending agents may be the most promising therapeutic option compared to other treatment modalities.

Glomerular disease after HSCT

Nephrotic syndrome (NS) is a well-documented but rare complication after HSCT. It is mainly related to membranous nephropathy and occurs in about 75% of all cases of HSCT-associated NS [38,39]. It is less frequently related to minimal change disease, focal segmental glomerulonephrosis, diffuse proliferative glomerulonephritis or IgA nephropathy. Post-HSCT NS is characterized with immune-complex deposits, and mainly represents the consequence of GVHD. Namely, most patients with HSCT-related NS have other manifestations of cGVHD at the time of diagnosis. According to some authors this condition could represent the renal manifestation of cGVHD. This hypothesis is supported by the fact that NS usually occurs late in the course of transplantation when the patient is off immunosuppressive therapy [2,4,39-42].

It is also important to say that in adult subjects NS may represent the manifestation of different malignancy states, and the appearance of NS is an absolute indication for renal biopsy. It is necessary to exclude a clinical relapse of primary disease in HSCT patients, as well [4].

Treatment of HSCT-related NS is controversial, and in the absence of randomized controlled trials, the current therapeutic options mostly include use of cyclosporine (CSA) and corticosteroids (CS). In the majority of studies patients were treated with a high-dose steroid therapy (starting dose was 1 mg/kg, and the duration of treatment ranged from 2 months to a year) in order to reduce NS. Furthermore, in most cases the use of an additional immunosuppressive drug was necessary. Cyclosporine was the most commonly used additional drug. The duration of treatment with CSA varies from 6 to 12 months. Other immunosuppressive drugs that are repor-

ted in the setting of HSCT-related NS were mycophenolate, azathioprine, and cyclophosphamide. TNF blockers have showed a limited success, but there are promising results with the use of anti-CD 20 antibody, such as rituximab. According to these observations, the current approach in the treatment of HSTC-related NS should include the use of CSA and CS in order to control the acute manifestations of cGVHD. This is necessary as a prerequisite to the remission of NS [39-42].

Approaching the patients with HSCT-related chronic kidney disease

Patient's history important notes include the type of HSCT, the used conditioning regimen and the use of nephrotoxic drugs, mainly CNIs. General treatment should be recommended for any CKD patient. In a patient with a TA- TMA due to HSCT the hypertension control is necessary in order to reduce endothelial damage. Furthermore, patients with persistent proteinuria after HSCT could benefit from the use of ACEI. Hyperkalemia may be more common in HSCT patients than in patients with other forms of CKD. Diuretics are often needed. Considering the toxicity of CNIs, it is worthwhile to minimize their dosage or to replace them with other agents, such as m-TOR inhibitors, sirolimus or everolimus. According to some investigations, GVHD prophylaxis with sirolimus and mycophenolate mofetil has been found to be promising alternative therapy to CNIs [2,4]. A subset of patients progress to ESRD, and overall patients who undergo hemodialysis have worse survival rates than patients with ESRD due to other etiological factors. Renal transplantation is treatment option in some patients, especially in those who receive a renal-allograft from the same donor as their original HSCT, considering the fact that this approach may obviate the need for antirejection therapy because of the immunotolerance of the allograft [5,4,33].

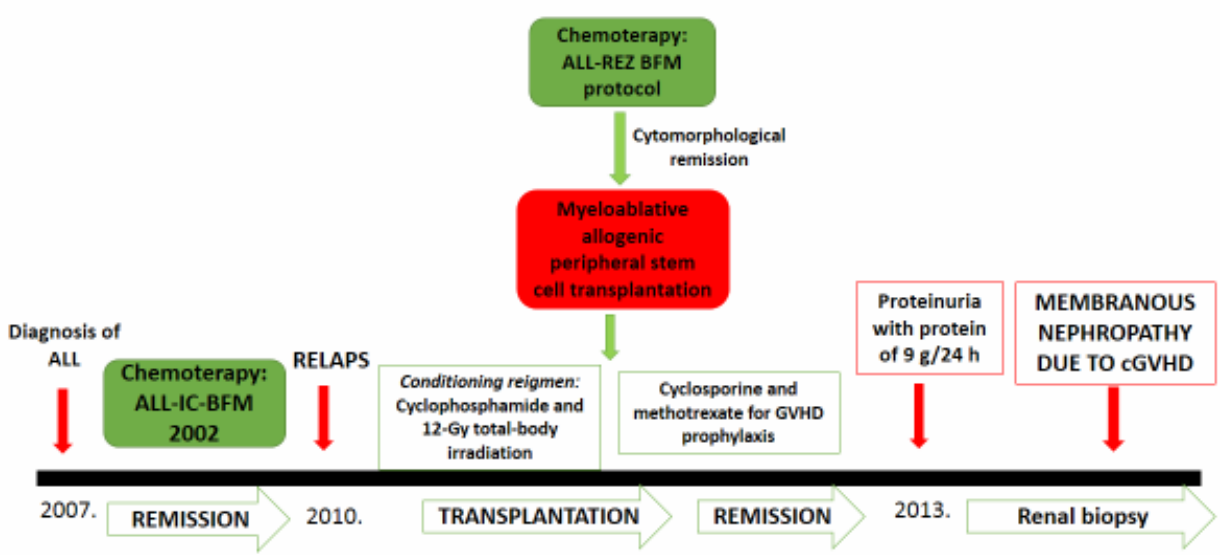

Fig. 1. Shematic view of the disease course in our patient
* acute lymphoblastic leukemia (ALL); graft-versus-host disease (GVHD); chronic graft-versus-host disease (cGVHD)

Case review

In line with the findings of kidney biopsy, nephrotic syndrome associated with membranous nephrophaty was diagnosed, probably due to cGVHD. The treatment of the patient started with an oral dose of ramipril 1.25 mg per day. This led to an improvement of hypertension and proteinuria. The patient was discharged from our Department and referred to the Hematological Department because of the need for further immunosuppressive therapy in order to control cGVHD (Figure 1).

Conclusions

Hematopoietic stem cell transplantation offers a curative treatment for many malignant and non-malignant disorders. A wide spectrum of renal involvement can be observed in these patients. Considering the increasing number of HSCT survivors many years after transplanttation, especially older patients with co-morbidities, long-term complications such as CKD and ESRD represent a growing problem. Renal biopsies are often needed to identify the underlying cause of renal failure in HSCT patients. According to this, once the underlying pathology is known, an appropriate therapeutic approach can be used in order to prevent progression to ESRD. There is a need for further research in this field in order to better define the natural history and clinical features of HSCT-related kidney injury and the treatment of this relatively new entity.

Conflict of interest statement. None declared.

References

1. Mohty B, Mohty M. Long-term complications and side effects after allogeneic hematopoietic stem cell transplantation: an update. *Blood Cancer* J2011; 1:e16; doi:10.1038/bcj.2011.14; published online 29 April 2011.
2. Singh N, McNeely J, Parikh S, *et al*. Kidney complications of hematopoietic stem cell transplantation. *Am J Kidney Dis* 2013; 61: 809-821.
3. Martin PJ, Counts Jr GW, Appelbaum FR, *et al*. Life expectancy in patients surviving more than 5 years after hematopoietic cell transplantation. *J Clin Oncol* 2010; 28: 1011-1016.
4. Panduranga SR. Nephrotic syndrome in patients with peripheral blood stem cell transplant. *Am J Kidney Dis* 2005; 45: 780-785.
5. Cohen EP. Renal failure after bone-marrow transplantation. *Lancet* 2001; 357: 6.
6. Mohty M, Bay JO, Faucher C, *et al*. Graft-versus-host disease following allogeneic transplantation from HLA-identical sibling with antithymocyte globulinbased reduced-intensity preparative regimen. *Blood* 2003; 102: 470-476.
7. Mohty M, Kuentz M, Michallet M, *et al*. Chronic graft-versus-host disease after allogeneic blood stem cell transplantation: long-term results of a randomized study. *Blood* 2002; 100: 3128-3134.
8. Mohty M, Bilger K, Jourdan E, *et al*. Higher doses of CD34+ peripheral blood stem cells are associated with increased mortality from chronic graft-versus-host disease after allogeneic HLA-identical sibling transplantation. *Leukemia* 2003; 17: 869-875.
9. Al-Hazzouri A, Cao Q, Burns LJ, *et al*. Similar risks for chronic kidney disease in long-term survivors of myeloablative and reduced-intensity allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2008; 14: 658-663.
10. Matthew JE, Uptal DP. Hematopoietic Stem-Cell Transplantation. *NEJM* 2006; 355: 10.
11. Helal I, Byzun A, Rerolle JP, *et al.* Acute renal failure following hematopoietic cell transplantation: incidence, outcome and risk factors. *Saudi J Kidney Dis Transpl* 2011; 22: 437-443.
12. Zager RA. Acute renal failure in the setting of bone marrow transplantation. *Kidney Int* 1994; 46: 1443.
13. Coppell JA, Richardson PG, Soiffer R, *et al*. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course and outcome. *Biol Blood Marrow Transplant* 2009; 15: 157-168.
14. Coiffier B, Altman A, Pui CH, *et al*. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clon Oncol* 2008; 26: 2767-2778.
15. Kersting S, Koomans HA, Hene RJ, Verdonck LF. Acute renal failure after allogeneic myeloablative stem cell transplanttation: retrospective analysis of incidence, risk factors and survival. *Bone Marrow Transplant* 2007; 39(6): 359-365.
16. Parikh CR, McSweeney P, Schrier RW. Acute renal failure independently predicts mortality after myeloablative allogeneic hematopoietic cell transplant. *Kidney Int* 2005; 67(5): 1999-2005.
17. Hingorani S. Chronic kidney disease in long-term survivors of hematopoietic cell transplantation: epidemiology, pathogenesis, and treatment. *J Am Soc Nephrol* 2006; 17: 1995.
18. Hingorani S, Guthrie KA, Schoch G, *et al*. Chronic kidney disease in long-term survivors of hematopoietic cell transplant. *Bone Marrow Transplant* 2007; 39: 223-229.
19. Cohen EP, Lawton CA, Moulder JE, *et al*. Clinical course of late-onset bone marrow transplant nephropathy. *Nephron* 1993; 64: 626-635.
20. Stewart BL, Storer B, Storek J, *et al*. Duration of immunosuppressive treatment for chronic graft-versus-host disease. *Blood* 2004; 104: 3501-3506.
21. George JN, Li X, McMinn JR, *et al*. Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome following allogeneic HPC transplantation: a diagnostic dilemma. *Transfusion* 2004; 44: 294-304.
22. Cruz DN, Perazella MA, Mahnensmith RL. Bone marrow transplant nephropathy: a case report and review of the literature. *J Am Soc Nephrol* 1997; 8: 166.
23. Changsirikulchai S, Myerson D, Guthrie KA, *et al*. Renal thrombotic microangiopathy after hematopoietic cell transplant: role of GVHD in pathogenesis. *Clin J Am Soc Nephrol* 2009; 4(2): 345-353.
24. Siami K, Kiarash K, Swisher KK, *et al.* Thrombotic Microangiopathy after Allogeneic Hematopoietic Stem Cell Transplantation: An Autopsy Study. *Transplantation* 2008; 85: 22-28.
25. Kojouri K, George JN. Thrombotic microangiopathy following allogeneic hematopoietic stem cell transplantation. *Curr Opin Oncol* 2007; 19(2): 148-154.
26. Nakamae H, Yamane T, Hasegawa T, *et al*. Risk factor analysis for thrombotic microangiopathy after reduced-intensity or myeloablative allogeneic hematopoietic stem cell transplantation. *Am J Hematol* 2006; 81(7): 525-531.
27. George JN, Li X, McMinn JR, *et al.* Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome following allogeneic HPC transplantation: a diagnostic dilemma. *Transfusion* 2004; 44(2): 294-304.
28. Uderzo C, Bonanomi S, Busca A, *et al*. Risk factors and severe outcome in thrombotic microangiopathy after allogeneic hematopoietic stem cell transplantation. *Transplantation* 2006; 82(5): 638-644.
29. Eremina V, Jefferson JA, Kowalewska J, *et al*. VEGF inhibition and renal thrombotic microangiopathy. *N Engl J Med* 2008; 358(11): 1129-1136.
30. Takatsuka H, Takemoto Y, Yamada S, *et al*. Complications after bone marrow transplantation are manifestations of systemic inflammatory response syndrome. *Bone Marrow Transplant* 2000; 26(4): 419-426.
31. Batts ED, Lazarus HM. Diagnosis and treatment of transplantation-associated thrombotic microangiopathy: real progress or are we still waiting? *Bone Marrow Transplant* 2007; 40(8): 709-719.
32. Perkowska-Ptasinska A, Sulikowska-Rowinska A, Pazik J, *et al*. Thrombotic nephropathy and pulmonary hypertension following autologous bone marrow transplantation in a patient with acute lymphoblastic leukemia: case report. *Transplant Proc* 2006; 38(1): 295-296.
33. Hewamana S, Austen B, Murray J, *et al.* Intestinal perforation secondary to haematopoietic stem cell transplant associated thrombotic microangiopathy. *Eur J Haematol* 2009; 83(3): 277.
34. Ho VT, Cutler C, Carter S, *et al.* Blood and marrow transplant clinical trials network toxicity committee consensus summary: thrombotic microangiopathy after hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2005; 11(8): 571-575.
35. Marr H, McDonald EJ, Merriman E, *et al*. Successful treatment of transplant-associated microangiopathy with rituximab. *N Z Med J* 2009; 122(1292): 72-74.
36. Carella AM, D'Arena G, Greco MM, *et al*. Rituximab for allo-SCTassociated thrombotic thrombocytopenic purpura. *Bone Marrow Transplant* 2008; 41(12): 1063-1065.
37. Au WY, Ma ES, Lee TL, *et al*. Successful treatment of thrombotic microangiopathy after haematopoietic stem cell transplantation with rituximab. *Br J Haematol* 2007; 137(5): 475-478.

38. Lin J, Markowitz GS, Nicolaides M, *et al*. Membranous glomerulopathy associated with graft-versus-host disease following allogenic stem cell transplantation. Report of 2 cases and review of the literature. *Am J Nephrol* 2001; 21: 351-356.
39. Chang A, Hingorani S, Kowalewska J, *et al*. Spectrum of renal pathology in hematopoietic cell transplantation: a series of 20 patients and review of the literature. *Clin J Am Soc Nephrol* 2007; 2: 1014-1023.
40. Terrier B, Delmas Y, Hummel A, *et al*. Post-allogeneic haematopoietic stem cell transplantation membranous nephropathy: clinical presentation, outcome and pathogenic aspects. *Nephrol Dial Transplant* 2007; 22: 1369-1376.
41. Romagnani P, Lazzeri E, Mazzinghi B, *et al*. Nephrotic syndrome and renal failure after allogeneic stem cell transplantation: novel molecular diagnostic tools for a challenging differential diagnosis. *Am J Kidney Dis* 2005; 46: 550-556.
42. Cohen EP, Drobyski WR, Moulder JE. Significant increase in end-stage renal disease after hematopietic stem cell transplanttation. *Bone Marrow Transplant* 2007; 39: 571-572.

BANTAO Journal 2014; 12(1): 97-102

BJ
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Original article

Oral and Salivary Changes in Patients with Chronic Kidney Disease

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Abstract

Introduction. Kidney disease is associated with many abnormalities in the oral health status as well as with alterations in salivary flow and composition. The aim of this study was to evaluate and to correlate oral clinical findings, salivary flow (SF) and salivary pH values in patients with chronic kidney disease (CKD) not yet on hemodyalisis treatment, those undergoing hemodialysis and in kidney transplant recipients.
Methods. In a cross-sectional study 90 patients were included. The cohort was composed of three groups: 30 patients with CKD (serum creatinine values under 120 μmol/L-group 1), 30 patients with CKD on hemodialysis (group 2) and 30 kidney transplanted patients (group 3). The control group consisted of 20 healthy individuals. Oral symptoms, signs and lesions: salivary volume, salivary pH and SF of stimulated and unstimulated saliva were evaluated.
Results. Among patients with CKD without dialysis treatment inverse relationship was found between uremic fetor, unpleasant taste and unstimulated SF and also between xerostomia and stimulated SF. Negative correlation between thirst and unstimulated salivary flow was found in both groups, patients with CKD on dialysis and kidney transplant group. Furthermore, in kidney-transplant patients a negative correlation was found between petechiae and SF, while in group of patients with CKD on hemodialysis the same negative correlation was registered between uremic fetor and stimulated SF.
Conclusions. Salivary flow was significantly lower in hemodialysis patients, while the highest was in the kidney-transplant recipients accompanied with improvement in the other oral clinical findings observed in our study.

Key words: hemodialysis, kidney transplantation, oral findings, salivary flow

Introduction

Patients with chronic kidney disease (CKD) often present systemic complications such as anemia, coagulation and platelet function disorders [1]. Some of them manifest oral symptoms and signs [2]. Oral symptoms may be more or less prevalent in the oral mucosa [3,4]. It has been proven that approximately 90% of the patients with CKD have soft tissue changes [5]. Besides changes in the soft tissue, in these patients there is an increased risk of caries which is considered to be a multifactorial disease.
Several studies have reported the connection of the salivary flow with periodontal, dental and oral status in CKD patients [6,7]. It has been also reported that in CKD patients saliva has important protective properties, participating in the maintenance of oral mucosa and hard tissues integrity, that is in the physiological balance within normal condition. Any deviation may influence the condition of the tissues in the oral cavity [8]. Salivary buffer capacity is an important parameter in maintaining pH of saliva, thereby reflecting on the integrity of soft and hard tissue in the oral cavity [9-11].
According to Bots *et al.* [6] any disorder which influences on the established equilibrium of all components in the oral cavity leads to a reduction in salivary flow, which may cause symptoms and signs of xerostomia and atrophic changes on the oral mucosa. It is considered that determination of some biomarkers in saliva can be effective alternative method for monitoring the efficacy of the treatment with dialysis in CKD patients [12]. In that context Blicharz *et al.* [12] believe that saliva sample represents a revolution in diagnostic and therapeutic monitoring strategies in CKD patients and those suffering from other chronic diseases.
Considering these facts the aim of our study was to find the association between salivary flow and oral clinical findings in patients with chronic kidney disease.

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Material and methods

Ninety patients with diagnosed CKD from the University Department of Nephrology, University of Skopje and the eponymous hemodialysis center were included in the study. Complete anamnestic procedure and clinical examination were performed at the University Department of Oral Pathology and Periodontology, and laboratory investigations were performed at the Department of Medical and Experimental Biochemistry in Skopje. Twenty healthy subjects without any kidney disease were included in the control group.

Patients with CKD included in the study were divided into three groups. The first group (group 1) consisted of 30 patients with CKD and serum creatinine level below 120 μmol/L. The second group (group 2) consisted of 30 patients with CKD undergoing hemodialysis, and the third group (group 3) consisted of 30 kidney transplant patients.

Our cohort was predominantly female (52 women) with mean age of 46±14 years. The frequency of hemodialysis was three times per week with duration of four hours per session in the group of patients undergoing hemodialysis (group 2). Kidney transplanted patients (group 2) received standard triple immunosuppressive therapy which include micophenolate mophetil, prednosine and cyclosporine at a daily dose of 100-175 mg (neoral 3-4 mg/kg/day). All subjects were informed about the procedure and agreed to participate in the study. Information about oral health status of all patients included in the study was obtained from the anamnesis and clinical examination. Oral changes were followed on the entire mucosal surface of the oral cavity and were classified into subjective and objective findings.

The anamnestic data gave the following most common subjective oral symptoms and signs: uremic fetor, unpleasant taste, thirst, xerostomia and burning tongue.

Uremic fetor was recorded as a urine-odor breath, and unpleasant taste as a lack of normal perception of different tastes in food. Diagnosis of xerostomia was made based on the patients' report of dry mouth and during oral inspection when dental instrument was sticking to the oral mucosa.

The objective clinical finding based on the examination of the oral mucosa revealed changes and lesions such as: pale mucosa, dry fissured lips, coated tongue, petechiae and ecchymoses, uremic stomatitis and angular cheilitis.

Oral lesions in our study were registered according to acknowledged clinical diagnostic criteria [13,14]. Dry and fissured lips were recorded when smaller or larger squamous formations on mildly erythematous vermilion surface were observed. Coated tongue was recorded as dirty white plaque formations on the dorsal surface with present elongated filiform papillae. Uremic stomatitis was registered as irregular erythematosus areas covered with grayish white pseudomembranes localized on lateral borders and dorsum of the tongue or buccal mucosa accompanied with painful sensations.

In all subjects included in our study, stimulated and unstimulated saliva samples were obtained, and salivary pH and salivary flow were determined. In patients on hemodialysis treatment (group B) saliva samples were taken immediately before the dialysis session, and in the other subjects samples of saliva were collected in the morning before breakfast, according to the spitting method. The collection of saliva started with instruction to the subjects to abstain from smoking, eating, drinking, and tooth brushing for one hour prior collection. All subjects were advised to rinse the mouth with water before the collection of saliva. The collection period lasted for five minutes. Stimulated saliva was collected by using chewing gum.

During preparation of saliva samples, the test tubes were kept on ice. The volume of saliva was determined gravimetrically (assuming 1 g=1 ml) and the pH was determined within five minutes after collection by electrolyte analyzer (Humalyte Plus [5], Human, Germany).

Statistical analysis

The obtained data were statistically analyzed, presented as mean values with standard deviation. The significance of differences in the salivary flow and salivary pH values among all studied groups were assessed by using the Kruskall-Wallis-test. The Mann-Whitney U-test was used to examine the significance of difference between two groups. Correlations between salivary findings and oral changes were performed using the Spearman's rank test. A p-value <0.05 was considered as statistically significant.

Results

The examined groups had different flow rates of saliva, with or without stimulation. As expected, the lowest flow rate of unstimulated saliva was evident in patients undergoing hemodialysis (Table 1). Mann-Whitney test showed that unstimulated salivary flow was significantly

Table 1. Salivary flow and salivary pH in control and examined groups

Laboratory results		Control group	Examined group			p
			Group A	Group B	Group C	
Salivary flow ml/min	Unstimulated	0.54±0.20	0.36±0.09	0.31±0.21	0.37±0.27	p<0.05
	Stimulated	1.90±0.42	0.95±0.31*	0.59±0.35	1.02±0.55	p<0.001
Salivary pH	Unstimulated	7.34±0.05	7.37±0.19	7.26±0.35	7.32±0.47	NS
	Stimulated	6.78±0.32	6.88±0.16	6.91± 0.35	6.72±0.38	NS

* Mann-Whitney A/B p<0.05; NS = not significant

lower (p<0.001) in both, the group A (patients on predialysis phase) (0.36±0.09 ml/min) and group B (patients on hemodialysis) (0.31±0.21 ml/min) when compared to the control group (0.54±0.20 ml/min).
There was no statistically significant difference in pH values of stimulated and unstimulated saliva among examined and control groups in our study.
Furthermore, the obtained data from laboratory findings of stimulated saliva indicated that patients on hemodialysis had the lowest salivary flow rate, and significant difference between the groups for flow rate of stimulated saliva was found (p<0.001).
Additionally, significant difference (p<0.001) in stimulated salivary flow rate between group B (lower) versus other groups (group A, group C and control group) (higher), and significant difference (p<0.01) between group A (lower) and control group (higher) was found.
The obtained results for the correlation between oral and salivary flow changes are shown in Table 2 and Table 3.
In pre-dialysis patients (group A) a negative correlation between uremic fetor and unstimulated salivary flow (r =-0.686; p<0.001) was found, which was not found in patients on hemodialysis (group B) nor in kidney transplant patients (group C).

Table 2. Correlation between unstimulated salivary flow and oral changes in patients with CKD

Oral symptoms, signs, changes and lesions	Salivary flow rate of unstimulated saliva					
	Group A		Group B		Group C	
	Spearman Rank Test	*p*	Spearman Rank Test	*p*	Spearman Rank Test	*p*
Uremic fetor	*r* =-0.686	<0.001	*r* =-0.352	NS	*r* =0.184	NS
Unpleasant taste	*r* =-0.686	<0.001	*r* =-0.70	NS	*r* =0.084	NS
Thirst	*r* =-0.718	<0.001	*r* =-0.617	<0.001	*r* =-0.075	NS
Xerostomia	*r* =-0.533	<0.01	*r* =-0.512	<0.01	*r* =-0.283	NS
Burning tongue	*r* =- 0.046	NS	*r* =-0.639	<0.001	*r* =0.046	NS
Dry, fissured lips	*r* =-0.087	NS	*r* =0.014	NS	*r* =-0.309	NS
Coated tongue	*r* =-0.224	NS	*r* =0.215	NS	*r* =-0.010	NS
Angular cheilitis	*r* =-0.759	<0.001	*r* =-0.165	NS	*r* =-0.313	NS
Pale mucosa	*r*=0.107	NS	*r*=0.105	NS	*r*=0.108	NS
Petechiae/ecchymosemoses	*r*=-0.268	<0.05	*r*=-0.381	<0.001	*r*=-0.228	<0.05
Uremic stomatitis	*r*=-0.034	NS	*r*=-0.062	NS	*r*=-0.025	NS

Table 3. Correlation between stimulated salivary flow and oral changes in patients with CKD

Oral symptoms, signs, changes and lesions	Salivary flow rate of stimulated saliva					
	Group A		Group B		Group C	
	Spearman Rank Test	*p*	Spearman Rank Test	*p*	Spearman Rank Test	*p*
Uremic fetor	*r* =-0.277	<0.01	*r* =-0.300	<0.001	*r* =-0.240	<0.05
Unpleasant taste	*r* =-0.188	NS	*r* =-0.120	NS	*r* =-0.084	NS
Thirst	*r* =-0.121	NS	*r* =-0.115	NS	*r* =-0.117	NS
Xerostomia	*r* =0.092	NS	*r* =0.008	NS	*r* =-0.157	NS
Burning tongue	*r* =-0.119	NS	*r* =-0.121	NS	*r* =-0.125	NS
Dry, fissured lips	*r* =-0.218	<0.05	*r* =-0.255	<0.05	*r* =-0.206	<0.05
Coated tongue	*r* =-0.160	NS	*r* =-0.158	NS	*r* =-0.120	NS
Angular cheilitis	*r* =-0.128	NS	*r* =-0.119	NS	*r* =-0.121	NS
Pale mucosa	*r* =-0.101	NS	*r* =-0.107	NS	*r* =-0.115	NS
Petechiae / ecchymoses	*r* =-0.405	<0.001	*r* =-0.398	<0.001	*r* =-0.348	<0.001
Uremic stomatitis	*r*=-0.034	NS	*r* =-0.049	NS	*r* =-0.055	NS

Furthermore, a negative correlation between unpleasant taste and unstimulated salivary flow (r=-0.686; p<0.001); was found in the group A, nor in the other two groups.
Moreover, we found a negative correlation between thirst and unstimulated salivary flow in group A (r=-0.718; p<0.001) and group B (r=-0.617; p<0.001). In groups A and B we also found a negative correlation between xerostomia or oral dryness and unstimulated salivary flow.
However, the correlation between unstimulated salivary flow and burning tongue did not reach statistically significant level in patients from group A, while in patients from group B burning tongue negatively correlated with unstimulated salivary flow (r =-0.639; p<0.001).
In all of the three studied groups, a significant correlation between angular cheilitis and unstimulated salivary flow was found only in patients of group A (r=- 0.759; p<0.001).
There was no correlation between unstimulated salivary flow with dry fissured lips, coated tongue, pale mucosa and uremic stomatitis in either of the examined groups.
Furthermore, in our study we found a negative correlation between petechiae and ecchymoses with unstimulated salivary flow in all examined groups. In kidney-transplant patients (group C) with unstimulated salivary flow we found a negative correlation between petechiae and ecchymoses, which was not the case between the other oral changes.

As shown in table 3, stimulated salivary flow was negatively correlated with uremic fetor (r=-0.277; p<0.01), dry fissured lips (r=-0.218; p<0.05), petechiae and ecchymoses (r=-0.405; p<0.001) in pre-dialysis patients from group A. Similarly, a negative correlation was found between stimulated salivary flow and the same listed oral changes in hemodialysis patients from group B and kidney- transplant patients from group C.

Discussion

The improved health care, pharmacological progress and extended life span have increased the number of patients living with chronic kidney disease seeking dental treatment. In most of them a wide range of oral manifestations as gingivitis, xerostomia, uremic fetor, pale mucosa etc. were observed [15,16]. Here, according to Bots *et al*. [6] the saliva has a crucial role. Changes in the flow of saliva, pH values and biochemical composition are reflected on the oral clinical finding. In this study, patients with CKD had reduced flow of stimulated and unstimulated saliva, compared to the control group. In group A (patients with serum creatinine 120 μmol/L) there was a negative correlation between uremic fetor, unpleasant taste, thirst, xerostomia and unstimulated salivary flow. Similarly, in group B (hemodialysis patients) a negative correlation between thirst, xerostomia, burning tongue and unstimulated salivary flow was found. Thus, we assume that thirst in hemodialysis patients is a result of fluid restriction implemented in order to prevent fluid overload between dialysis sessions, and consequently to prevent the occurrence of hypertension. The presence or occurrence of thirst in patients in pre-dialysis phase and patients on hemodialysis might be explained as a consequence of the present hyposalivation; in our study confirmed by the negative correlation between thirst and unstimulated salivary flow in groups A and B (r=-0.718, p<0.001; r=-0.617, p<0.001). Hence, it means that reduction of the salivary flow in groups A and B, results with the emergence of thirst. Abuleo *et al*. [17] reported high levels of serum sodium, angiotensin II, rapid rise of urea in serum, as well as psychological factors as possible reasons for thirst in CKD patients. In patients with kidney transplantation (group C), although they had nearly the same values of unstimulated saliva as patients from group A (0.37±0.27 ml/min vs 0.36 ml/min), there was no association between thirst and their average amount of unstimulated salivary flow (r=0.695; p>0.05). The authors believe that the reason for presence of thirst in kidney-transplant patients is of a complex nature. In fact, despite the determined hyposalivation, dominant role belongs to the synergistic side effect of the maintenance immunosuppressive and corticosteroid therapy [3,6,11].

According to Hamid *et al*. [1], except thirst, xerostomia appears as a quite frequent oral symptom in CKD patients. On the other side, Dirschabel *et al*. [18] registered a high prevalence of oral lesions, such as xerostomia and coated tongue in hemodialysis and renal transplant patients.

Our experience showed that xerostomia and thirst are the most common oral discomforts, which patients in pre-dialysis phase and patient undergoing haemodialysis face. Bots *et al*. [6] after a two-year period of monitoring of CKD patients, showed that the prevalence of xerostomia and thirst remained the same quantity during the period of follow-up in patients on dialysis treatment. In contrast, in the same study, patients who carried out renal transplantation were characterized with decreased oral dryness, thirst and increased salivary flow. In line with the previous observation, in our study we did not find any statistically significant correlation between oral dryness with either stimulated or unstimulated salivary flow (r=-0.157; r=-0,283; p>0.05) in renal transplant patients. However, we found a negative correlation between unstimulated salivary flow and xerostomia (r=-0.533; r=-0.512; p<0.01) between the groups A and B. Besides the reduced salivary flow in patients with CKD, we assume that oral dryness could further exacerbate by the applied medicament therapy. It has to be pointed out that patients included in this study, despite their main immunosuppressive regimen, were treated with ACE-inhibitors, antidepressants and sedatives.

On the other side, in this study an inverse correlation between unpleasant taste and unstimulated salivary flow in pre-dialysis patients from group A was found. Actually, the reduced salivary flow causes the oral dryness, which initiates a changed taste perception in these patients. It is well-known that the sensitivity of taste perceptions is altered for all four basic types of flavor, due to insufficient solubility which reacts to oral chemoreceptors, causing an unpleasant metallic taste and the taste perception is impaired in all uremic patients, regardless of the type of treatment [17].

In our study, an inverse correlation between uremic fetor and unstimulated salivary flow in patients from group A (r=-0.686 p<0.001) and between uremic fetor and stimulated saliva in patients from groups A (r=-0.277 p<0.01) and B (r=-0.240 p<0.05) was found. Therefore, we think that the reduced salivary flow in this category of patients abounded with urea metabolites, especially ammonia that could be accepted as a main factor for the occurrence of uremic fetor. Keles *et al*. [19] and Martins *et al*. [20] reported identical findings. However, this correlation is interpreted differently by Mason *et al*. [21]. In fact, along with the reduction of salivary flow there is an increase in the concentration of uric acid. So, in patients with reduced salivary flow and subsequently increased concentration of uric acid in saliva, an increased presence of uremic fetor may occur. In CKD patients, despite previously mentioned reasons, the poor oral hygiene and dental plaque accumulation, due to their lack of motivation and less priority to maintain oral health, are accepted as additional factors that emphasize the uremic fetor.

Among all of our studied groups, a negative correlation between salivary flow of unstimulated saliva and the burning tongue in hemodialysis patients from group B was found. We assume that the major reason for appearance of burning tongue is dehydrated oral mucosa. The reduced salivary flow affects the vulnerability of oral mucosa, making it too sensitive, thereby emphasizing the symptom of burning sensation. Additionally**,** the dry and vulnerable mucosa, insufficient humidity in mouth and lost elasticity, make the oral mucosa to be easily traumatized, which is clinically manifested by occurrence of petechiae and ecchymoses. Petechiae and ecchymoses of oral mucosa, in all of our studied groups were negatively associated with unstimulated and stimulated flow of saliva ($p<0.001$). These results do not match with those of Skorecki *et al*. [22], Kerr *et al*. [23] and Ziccardi *et al*. [24]. According to these authors petechiae and ecchymoses are common oral clinical finding seen in patients with CKD, as a result of altered platelet aggregation in conditions of uremia. Kho *et al*. [25] and Chuang *et al*. [26] claim that reduced salivary flow, heparin and other anticoagulants that patients on dialysis receive, are the primary reason for petechiae and ecchymoses. In agreement with these data and the results from the current study, we think that all previously mentioned reasons may mutually contribute to the occurrence of petechiae and ecchymoses in patients with CKD.

Furthermore, in this study we found a negative correlation between angular cheilitis and unstimulated salivary flow in patients from group A. Unfortunately, in the literature there are poor data and hence, we could not compare our findings. In support of our findings are the results reported by Klassen *et al*. [27]. They found a prevalence of 4% angular cheilitis in dialysis patients. On the other side, in the studies of Obry *et al*. [28] and Holmstrup *et al*. [29] an association between angular cheilitis and anemia and candidiasis was reported. However, we consider that with the reduced amount of saliva and lost humidity of oral epithelium there is a reduced local defense mechanism in patients with CKD. We confirmed in our study that the lower flow of saliva impaired keratinization and decreased immunity, and created an ideal base for development of fungal or bacterial infection on the corner of the lips, especially in the immunocompromised CKD patients.

In our study, flow rate of both stimulated and unstimulated saliva was not associated with coated tongue, uremic stomatitis and pale mucosa among all participants. In hemodialysis patients salivary flow of unstimulated saliva was inversely associated with xerostomia, thirst, burning tongue, petechiae and ecchymoses. On the other side, salivary flow of unstimulated saliva was inversely associated with thirst, uremic fetor, unpleasant taste and angular cheilitis, in pre-dialysis patients, while in kidney-transplant patients, petechiae and ecchymoses salivary flow of unstimulated saliva was not associated with any other oral changes.

Conclusions

In conclusion, the reduced salivary flow in patients with CKD negatively affects their oral health, resulting in occurrence of many oral symptoms, changes and lesions. In this study, salivary flow rates were found to be the lowest in patients on hemodialysis, and the highest in kidney-transplant patients. Hence, renal transplantation as a treatment of choice in patients with irreversible renal failure not only restores renal function, but has also influence on increased flow of saliva and reduced incidence of oral changes.

Conflict of interest statement. None declared.

References

1. Hamid MJAA, Dummer CD, Pinto LS. Systemic conditions, oral findings and dental management of chronic renal failure patients: General considerations and case report. *Braz Dent J* 2006; 17: 166-170.
2. Rossi SS, Glick M. Dental considerations for the patients with renal disease and renal disease receiving haemodyalisis. *J Amer Dent Assoc* 1996; 19: 127-211.
3. Mosannen Mozaffari P, Amirchaghmaghi M, Mortazavi H. Oral Manifestations of Renal Patients Before and After Transplantation: A Review of Literature. *DJH* 2006; 1(1): 1-6.
4. Summers SAA, Tilakaratne WMB, Fortune FB, Ashman NA. Renal disease and the mouth. *Am J Med* 2007; 120: 568-573.
5. Davidovich E, Davidovits M, Eidelman E, *et al*. Pathophysiology, therapy, and oral implications of renal failure in children and adolescents: an update. *Pediatr Dent* 2005; 27(2): 98-106.
6. Bots CP, Brand HS, Poorterman JH, *et al*. Oral and salivary changes in patients with end stage renal disease (ESRD): a two year follow-up study. *Br Dent* 2007; 27: 202(2): E3.
7. Bayraktar G, *et al*. Oral health and inflammation in patients with end-stage renal failure. *Perit Dial Int* 2009; 29(4): 472-479.
8. Schuller AA, Holst D. Oral status indicators DMFT and FS-T: reflections on index selection. *Eur J Oral Sci* 2001; 109: 155-159.
9. Kao CH, Hsieh JF, Tsai SC, *et al*. Decreased salivary function in patients with end-stage renal disease requiring hemodialysis. *Am J Kidney Dis* 2009; 36: 1110-1114.
10. Roberson TM, Lundeen TF. Cariology: the lesion, etiology, prevention and control. In: Roberson TM, Heymann HO, Swift JREJ, eds. *Sturdevant's Art and Science of Operative Dentistry. Mosby, St. Louis:* 2002; 63-130.
11. Postorino M, Catalano C, Martorano C, *et al*. Salivary and lacrimal secretion is reduced in patients with ESRD. *Am J Kidney Dis* 2003; 42(4): 722-728.
12. Blicharz TM, Rissin DM, Bowden M, *et al*. Use of colometric test strips for monitoring the effect of hemodialysis on salivary nitrite and uric acid in patients with end-stage renal disese: a proof of principle. *Clin Chem* 2008; 54: 1473-1480.
13. Cohen SG. Enfermedades renales En: Lynch MA, Brightman VJ, Greenberg MS eds. Medicina bucal de Burket. *McGraw-Hill Interamericana Editores, Mexico:* 1996; 492-514.
14. Proctor R, Kumar N, Stein A, *et al*. Oral and dental aspects of chronic renal failure. *J Dent Res* 2005; 84: 199-20.
15. Gavalda C, Bagan J, Scully C, *et al*. Renal hemodialysis patients: oral, salivary, dental and periodontal findings in 105 adult cases. *Oral Dis* 1999; 5: 299-302.

16. Atassi F. Oral home care and the reasons for seeking dental care by individuals on renal dialysis. *J Contemp Dent Pract* 2002; 3: 31-41.
17. Abuleo JG. Large interdialytic weightvgains. Causes, consequences and corrective measures. *Semin Dial* 1998; 11: 25-32.
18. Dirschnabel AJ, *et al*. Clinical oral findings in dialysis and kidney-transplant patients. *http://www.ncbi.nlm.nih.gov/pubmed/21359247* 2001; 42(2): 127-123.
19. Keles M, Tozoglu U, Uyanik A, *et al*. Does peritoneal dialysis affect halitosis in patients with end-stage renal disease? *Perit Dial Int* 2011; 31(2): 168-172.
20. Martins C, Siqueira WL, Guimaraes Primo LS. Oral and salivary flow characteristics of a group of Brazilian children and adolescents with chronic renal failure. *Pediatr Nephrol* 2008; 23(4): 619-624.
21. Mason KD, Boylie JA, Harden RM, *et al*. The influence of low rate on the concertation of uric aceid in human parotid and submandibular saliva. *J Dent Res* 1996; 45: 1439.
22. Skorecki K, Green J, Brenner BM. Chronic renal failure. En: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, eds. Harrison´s Principles of Internal Medicine, *McGraw-Hill, New York:* 2005; 1653-1663.
23. Kerr AR. Update on renal disease for the dental practitioner. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; 92: 9-16.
24. Ziccardi VB, Saini J, Demas PN, Braun TW. Management of the oral and maxillofacial surgery patient with end-stage renal disease. *J Oral Maxillofac Surg* 1992; 50: 1207-1212.
25. Kho HS, Lee SW, Chung SCh, Kim YK. Oral manifestations and salivary flow rate, pH, and buffer capacity in patients with end-stage renal disease undergoing hemodialysis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, 1999; 88:316-9.
26. Chuang SF, Sung JM, Kuo SC, *et al*. Oral and dental manifestations in diabetic and nondiabetic uremic patients receiving hemodialysis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; 99: 689-695.
27. Klassen JR, Krasko BM. The dental health status of dialysis patients. *J Can Dent Assoc* 2002; 68(1): 34-38.
28. Obry F, Belcourt AB, Frank RM, *et al*. Biochemical study of whole saliva from children with chronic renal failure. *ASDC J Dent Child* 1987; 54(6): 429-432.
29. Holmstrup P, Axell T. Classification and clinical manifestations of oral yeast infections. *Acta Odontol Scand* 1990; 48: 57-59.

BANTAO Journal 2014; 12(1): 103-107

BJ
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Original article

Are we Treating or Curing Tuberculosis? Profile of Secondary Renal Amyloidosis in Patients Receiving Anti Tubercular Treatment

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Abstract

Introduction. Secondary renal amyloidosis due to tuberculosis is a debilitating disease with considerable mortality and morbidity due to renal failure and other manifestations of both amyloidosis and renal failure. Most patients with amyloidosis have been adequately treated with DOTS (Directly observed treatment, Short Course strategy). The aimof our study was to analyze the epidemiological and demographic profile of patients undergoing renal biopsy and found to have renal amyloidosis secondary to tuberculosis.
Methods. In this study, retrospective renal biopsy data was collected from 2009-2012 and patients with amyloidosis were identified and their clinical and biochemical parameters were analyzed.
Results. Incidence of amyloidosis was 4.66% (n=24/514) among total renal biopsies. Among this, secondary amyloidosis constituted 87.5% of total amyloidosis. The commonest etiology in these patients was pulmonary tuberculosis (73.5%). All patients with tuberculosis had previously received DOTS treatment. 47.5% of patients with amyloidosis had renal impairment and 10.5% developed end-stage renal disease over 12 months and were dialysis dependent.
Conclusions. Amyloidosis due to tuberculosis is a well-established, yet under-diagnosed complication of tuberculosis. The duration and treatment status of tuberculosis does not influence the occurrence of amyloidosis, as most of the patients were treated appropriately with DOTS. There are no predictive factors in patients who will develop secondary amyloidosis. At present there is no specific treatment apart from supportive therapy. The prognosis is poor, as most of these patients inexorably progress towards end-stage renal disease (ESRD) with significant mortality and morbidity. To conclude, at present we are only treating tuberculosis, we are yet to cure tuberculosis.

Key words: secondary renal amyloidosis, pulmonary tuberculosis, end-stage renal disease (ESRD), DOTS, supportive treatment

Introduction

Tuberculosis is an overwhelming public health problem of the 21st century in India. The incidence of tuberculosis in India is 1.96 million new cases annually and the prevalence was 3.8 million cases in 2000 [1]. The annual mortality due to tuberculosis is 3,30,000 deaths per year [1]. Among various long-term complications of tuberculosis, secondary amyloidosis is perhaps the rarest and one of the most debilitating [2-4]. Apart from the sequelae of tuberculosis, the patient suffers from various manifestations of amyloidosis like edema, anemia, renal failure, malnutrition (due to proteinuria and losses from gastrointestinal tract), cardiac failure and autonomic neuropathy [5-7]. In this study, retrospective data was collected from 2009 to 2012 of all patients undergoing renal biopsies. Renal amyloidosis cases were identified and their clinical and biochemical parameters were analyzed.

Material and methods

We have analyzed the demographic and epidemiological profile of patients undergoing renal biopsy and found to have renal amyloidosis secondary to tuberculosis.
Retrospective renal biopsy registry data from 2009 to 2012 was analyzed.
All renal biopsies found to have amyloidosis were identified and retrospectively analyzed. All renal biopsies were found to be adequate [7] .They were reported by a fixed panel of pathologists. The biopsies were analyzed with standard light microscopy stains like hemotoxylin & eosin, congo red, Masson's trichome, Periodicacid-Schiff, silver methenamine stain. All congo red positive samples were subsequently examined with polarizing microscope and apple green birefringence was confirmed in all of the samples. Immunohistochemical staining to differentiate primary from secondary amyloidosis was not performed. Demographic, clinical, treatment history

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and biochemical data of these patients were analyzed using standard analytical methods.
Ethical approval was not needed because of the retrospective nature of the study.

Results

A total of 514 biopsies were available for analysis from 2009 to 2012, out of which a total of 24 patients (4.66% of the total biopsies) were found to have renal amyloidosis (Figure 1). Among these patients, secondary renal amyloidosis was found in 21 patients (87.5% of total amyloidosis patients). The remaining 3 patients (12.5% of total amyloidosis patients) had primary amyloidosis, 1 patient had AL amyloidosis and the remaining 2 patients had multiple myeloma.

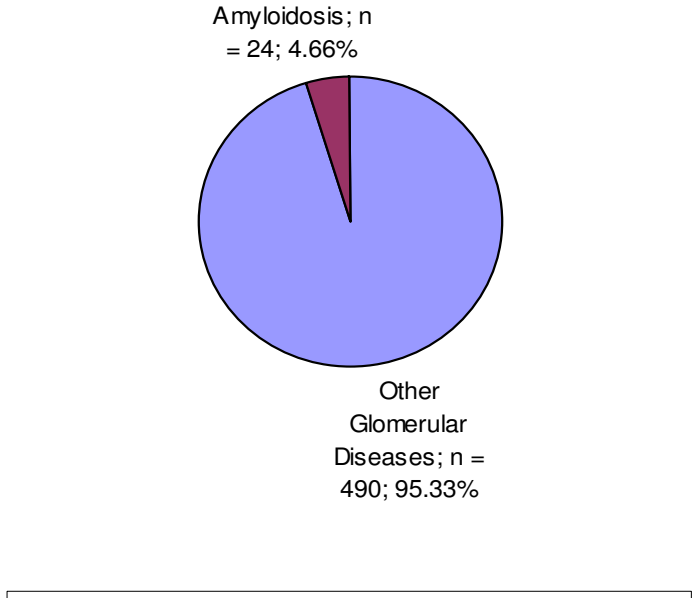

Fig. 1. Percentage of patients having amyloidosis among total renal biopsies

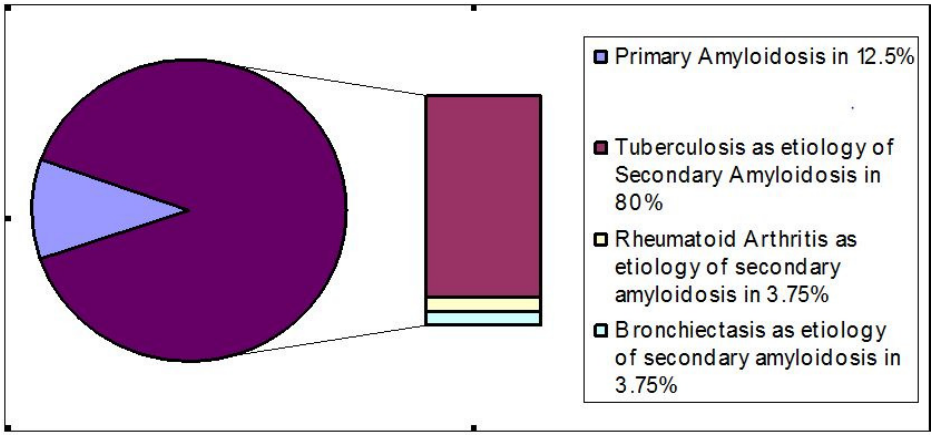

Fig. 2. Various etiologies of amyloidosis

Among the 21 patients deemed to have secondary renal amyloidosis, 19 patients had definite history of tuberculosis in the past, 1 patient had evidence of rheumatoid arthritis and 1 patient had bronchiectasis (Figure 2).
The demographic profile of the patients with secondary amyloidosis due to tuberculosis is given in Table1.
All patients had received anti-tuberculosis treatment according to DOTS, at sometime during the course of their illness. Among these, 6 out of 19 patients (31.5% of total secondary amyloidosis patients) were defaulters and 3 out 6 of the defaulters had received 2 or more courses of anti-tuberculosis treatment. The remaining 13 patients were declared to be cured of tuberculosis. Except for 1 patient who had active pulmonary TB, receiving Anti Tubercular Treatment (ATT) at the time of diagnosis, none of the patients had any clinical features suggestive of active TB at the time of diagnosis of amyloidosis.
The clinical profile of these patients is given in Table 2.
None of the patients had significant hematuria, hyperlipidemia or evidence of any other glomerular diseases.
Nine (9) patients (47.2%) had deranged renal functions, defined as serum creatinine of more than 1.3 mg/dl at the

Table 1. Demographic profile of patients with secondary amyloidosis due to tuberculosis

Age of patients	
a) Mean age	38 years
b) Range of age	13 years to 66 years
Sex	
Male: Female	11: 8 (n = 19)
History of tuberculosis prior to presentation	
a) Mean duration of history of tuberculosis	3.5 years
b) Range of duration of history of tuberculosis	2 months* to 16 years

*1 patient was diagnosed with pulmonary tuberculosis 2 months prior to the diagnosis of amyloidosis and he was already on anti tuberculosis treatment

time of presentation. Two (2) patients presented with uremic symptoms, requiring dialysis at the time of presentation. Glomerular amyloid deposition was present in 17 patients (90%), tubular deposition in 2 (10.5%) patients and arteriolar deposition in 3 (15.7%) patients.

Table 2. Clinical and biochemical profile of patients; n = 19

1) Site of tuberculosis		
i) Pulmonary		14 (73.68%)
ii) Extrapulmonary		5 (26.31%)
a) Lymphadenopathy		1 (5.25%)
b) Gastrointestinal tract		1 (5.25%)
c) Bone and joint		1 (5.25%)
d) Disseminated tuberculosis		2 (10.5%)
2) Clinical features at presentation		
a) Edema		16 (84.2%)
b) Anemia		11 (57.9%)
c) Fatigue and malaise		11 (57.9%)
d) Fever		2 (10.5%)
e) Anorexia		3 (15.7%)
f) Dyspnea on exertion		7 (36.8%)
g) Ascites		12 (63.1%)
h) Autonomic dysfunction		1 (5.2%)
i) Cardiac failure		2 (10.5%)
j) Uremic symptoms (Any combination of: Oliguria, asterexis, anorexia, pericardial rub, nausea & vomiting)		2 (10.5%)
k) Hypertension		3 (15.7%)
3) Degree of renal dysfunction at presentation		
a) Mean Serum Creatinine (mg/dl)	1.66	(Range: 0.9-5.8)
b) Mean 24 hour Proteinuria (grams)	2.8	(Range: 1.6-6.2)
c) Mean hemoglobin (g/dl)	10.6	(Range: 7.7-13.4)
d) Mean serum albumin (g/L)	2.6	(Range: 1.8-3.6)
4) Patients developing ESRD over 12 months		2 (10.5%)

Discussion

In this study, the incidence of amyloidosis in patients with glomerular disease was found to be 4.66%, which was concordant with data from similar studies [2-4,11-13]. Not surprisingly, tuberculosis was the most common etiology of amyloidosis in our study and primary amyloidosis was rare in our study as in similar studies from Indian sub-continent with AL amyloidosis and multiple myeloma being fairly uncommon causes of amyloidosis [2,12,13]. Tuberculosis is an overwhelming public health problem in India. It causes significant mortality and morbidity, often afflicting the most productive age group, thus affecting the physical health and also the socio-economic status of the family and the community [1]. Amyloidosis is a serious and debilitating complication of tuberculosis and its incidence and prevalence among tuberculosis patients in India is not known. Pulmonary tuberculosis was the commonest site of tuberculosis and extra-pulmonary sites being uncommon in our study. In western countries chronic rheumatologic diseases [5,6,9] are common etiologies of secondary renal amyloidosis, however they are distinctly uncommon causes of amyloidosis in our country as found in our study and in other similar studies [2,4,11,13]. This could be due to low incidence of rheumatologic diseases in India when compared to western countries and also the long duration of illness required (often more than 20 years) to cause secondary amyloidosis. None of the patients had chronic bronchiectasis, which has been often implicated

in pulmonary tuberculosis as the source of persistent inflammation despite apparent cure of TB [4,11,14].
The duration of tuberculosis required to cause amyloidosis ranged from 2 months to 16 years, thus implying that even remote history of tuberculosis is enough to trigger amyloidosis; the flip side being that patients having tuberculosis for a short duration can also suffer from amyloidosis. As already mentioned, all of the patients had received some form of anti-tuberculosis treatment (DOTS) prior to the diagnosis of amyloidosis and up to 70% of the patients were declared to be cured of tuberculosis, after which they subsequently went on to develop amyloidosis. This raises a few pertinent questions regarding tuberculosis and its treatment. Firstly, do dormant mycobacterium bacilli continue to be a focus of inflammatory stimuli without producing clinical disease? Secondly, the often quoted time interval of decades [5,7,10] required prior to the development of amyloidosis was not seen in patients suffering from amyloidosis secondary to tuberculosis; so, does this imply that mycobacterial infection causes more rapid and higher levels of serum amyloid A protein (SAA) production leading to early amyloidosis?
Amyloidosis is a systemic disease affecting many organs and can be fatal or extremely debilitating due to the involvement of gastrointestinal tract, cardiovascular system and kidneys [6,7,17,18]. Amyloidosis formation is a nucleation-initiation process [8,9], in some cases of disseminated tuberculosis and destroyed lung due to tuberculosis, large quantity of SAA is constantly produced. These act as a constant source of inflammation and may accelerate deposition of amyloid fibrils on a pre-existing nidus and may perpetuate amyloidosis, even after apparent cure [9-11]. This, however, remains conjectural at present and needs to be proven.
Diagnosis of amyloidosis in a patient with remote history of tuberculosis also causes dilemma with respect to treatment of these patients. The obvious treatment of secondary amyloidosis is to treat the underlying inflammatory disorder, which may include specific measures like using DMARD's/biological agents in patients with rheumatoid arthritis [20-23], treatment of chronic osteomyelitis etc, depending on the specific underlying cause. These measures are known to slow or even completely stop the progress of amyloidosis. However most of the patients in our study did not have any evidence of active tuberculosis, so there is often no justification in starting anti-tuberculosis treatment. It is ironical that even though we have effective treatment for tuberculosis, we cannot offer any definitive treatment in secondary amyloidosis. Hence, we are often left with the only option of offering supportive treatment and to closely monitor the patient for progression of the disease.
A significant number of these patients inexorably progress towards ESRD, requiring some form of renal replacement therapy. These patients often have difficulty in tolerating hemodialysis [24-26] due to frequent episodes of hypotension due to cardiomyopathy and autonomic neuropathy. Continuous ambulatory peritoneal dialysis (CAPD) is often the preferred modality in these patients [24-28]. Renal transplant can also be offered to these patients; however the incidence of recurrence of amyloidosis in the transplanted kidney and duration of graft survival has not been studied in any large studies [29-31]. There is also the possibility of re-activating tuberculosis in these patients after initiation of immunosuppressants. Apart from routine measures used in chronic kidney disease (CKD) patients, drugs like colchicines [5,6,19] often used in familial amyloidosis, have not been found to be useful in this group of patients. Newer drugs like dimethylsulfoxide and eprosidate are yet to be tried in this group of patients [6,9,19,32].
In India, it is a well-established fact that tuberculosis is the commonest etiology of amyloidosis. The clinical features and pattern of organ involvement have been well-established in many studies [4,11,12]. The latency between the infection with tuberculosis and initiation of the amyloidosis is not known clearly. Patients may be totally asymptomatic till the establishment of pedal edema. It is the importance of diagnosing amyloidosis, which needs to be highlighted. As shown in our study, edema may be absent in a few patients (15%) and hypertension may be present in a few patients (15%). Highlighting these exceptions to the general practitioners and to inculcate a high index of suspicion in them towards diagnosing amyloidosis will go a long way in managing these patients. Given the tremendous public health importance of tuberculosis and its re-emergence in a more severe form due to its association with HIV and the emergence of multidrug and extensively drug-resistant tuberculosis (MDR&X-DR TB), any disease sequelae due to tuberculosis should be taken seriously. Even though there is no definite data on the incidence and prevalence of secondary amyloidosis in tuberculosis patients, it should be given due importance because of the sheer number of patients afflicted with TB in India [1].
Limitations of this study include retrospective nature of the data, with limited follow-up. Patients with non-renal manifestations were not included in this study. The criteria for renal biopsy was not uniform, patients with sub-nephrotic range proteinuria were not universally biopsied, hence possibly leading to under-diagnosing those patients with sub-nephrotic proteinuria and non-glomerular amyloidosis deposition.

Conclusions

Amyloidosis due to tuberculosis is a well-established, yet under-diagnosed complication of tuberculosis. The duration and treatment status of tuberculosis does not influence the occurrence of amyloidosis, as most of the patients were treated appropriately with DOTS. Education regarding the typical and atypical manifestations of amyloidosis is important in establishing the diagnosis.

As shown in our study, in many patients amyloidosis develops after apparent cure of tuberculosis, and even in patients currently receiving treatment for tuberculosis. There are no predictive factors in patients who will develop secondary amyloidosis

Once established, there is no specific treatment for amyloidosis due to tuberculosis, there is no role of anti-tuberculosis treatment in a large majority of patients, as they usually do not have evidence of active tuberculosis. Only supportive treatment and management of CKD can be offered to these patients. Large multicentric studies with long follow-up are needed to identify the subset of tuberculosis patients who are prone to develop amyloidosis in future, and to answer the various questions raised in this study regarding management of these patients. To conclude, at present we are only treating tuberculosis, we are yet to cure tuberculosis.

Conflict of interest statement. None declared.

References

1. Mohan A, Sharma SK. History. In: Sharma SK, Mohan A (editors). Tuberculosis. New Delhi, *Jaypee Brothers Medical Publishers, 2nd edition* 2009;5-13.
2. Jai Prakash, Takhellambam Brojen, Surendra Singh Rathore, *et al*. The Changing Pattern of Renal Amyloidosis in Indian Subcontinent: Two Decades of Experience from a Single Center. *Ren Fail* 2012; Vol. 34, No.10: Pages 1212-1216.
3. SK Agarwal, SC Dash. Spectrum of Renal Diseases in Indian Adults. *J Assoc Physicians India* 2000; 48(6): 594-600.
4. Chugh KS, Datta BN, Singhal PC, *et al*. Pattern of renal amyloidosis in Indian patients. *Post Graduate Medical Journal* 1981; 57: 31-35.
5. Helen J Lachmann, Hugh JB Goodman, Janet A Gilbertson, *et al*. Natural History and Outcome in Systemic AA Amyloidosis. *N Engl J Med* 2007; 356: 2361-2371.
6. Bouke PC, Hazenberg. Amyloidosis. *Rheumatic Disease Clinics of North America* 2013; 39(2): 323-345.
7. Dember L. Amyloidosis associated Kidney Disease. *J Am Soc Nephrol* 2006; 17: 3458-3471.
8. Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. *N Engl J Med* 2003; 349: 583-596.
9. Giampaolo Merlini, David C Seldin, Morie A Gertz. Amyloidosis: Pathogenesis and New Therapeutic Options. *J Clin Oncol* 2011; 29(14): 1924-1933.
10. Gillmore JD, Lovat LB, Persey MR, *et al*. Amyloid load and clinical outcome in AA amyloidosis in relation to circulating concentration of serum amyloid A protein. *Lancet* 2001; 358: 24-29.
11. Ramakant Dixit, Rakesh Gupta, Lokendra Dave, *et al*. Clinical profile of patients having pulmonary tuberculosis and renal amyloidosis. *Lung India* 2009; Vol 26(2): 41-45.
12. Shah VB, Phatak AM, Shah BS, *et al*. Renal amyloidosis-A clinicopathological study. *Indian J Pathol Microbiol* 1996; 39(3): 179-185.
13. Mehta HJ, Talwalkar NC, Merchant MR, *et al*. Pattern of renal amyloidosis in western India-A study of 104 cases. *J Assoc Physicians India* 1990; 38(6): 407-410.
14. Tank SJ, Chima RS, Shah V, *et al*. Renal amyloidosis following tuberculosis. *Indian J Pediatr* 2000; 67: 679-81.
15. Simons JP, Al-Shawi R, Ellmerich S, *et al*. Pathogenetic mechanisms of amyloid A amyloidosis. *Proceedings of the National Academy of Sciences* 2013; 110(40): 16115-16120.
16. Le Roux DM, Pillay K, Nourse P, *et al.* Systemic amyloidosis complicating multidrug-resistant tuberculosis in childhood. *Pediatric Infectious Disease Journal* 2012; 31(9): 994-997.
17. Dubrey SW, Comenzo RL. Amyloid diseases of the heart: current and future therapies. *QJM*: *An International Journal of Medicine* 2012; Vol 105, Issue 7: 617-631.
18. Ambruzs JM, Walker PD, Larsen CP. The histopathologic spectrum of kidney biopsies in patients with inflammatory bowel disease. *Clin J Am Soc Nephrol* 2014; 9(2): 265-270.
19. Nelson Leung, Samith H Nasr and Sanjeev Sethi. How I treat amyloidosis: the importance of accurate diagnosis and amyloid typing. *Blood* 2012; 120: 3206-3213.
20. Gottenberg JE, Merle-Vincent F, Bentaberry F, *et al*. Anti–tumor necrosis factor α therapy in fifteen patients with AA amyloidosis secondary to inflammatory arthritides: A follow up report of tolerability and efficacy. *Arthritis & Rheumatism* 2003; 48: 2019-2024.
21. Elkayam O, Hawkins PN, Lachmann H, *et al*. Rapid and complete resolution of proteinuria due to renal amyloidosis in a patient with rheumatoid arthritis treated with infliximab. *Arthritis & Rheumatism* 2002; 46: 2571-2573.
22. Ippei Miyagawa, Shingo Nakayamada, Kazuyoshi Saito, *et al*. Study on the safety and efficacy of tocilizumab, an anti-IL-6 receptor antibody, in patients with rheumatoid arthritis complicated with AA amyloidosis. *Modern Rheumatology* 2013; 1-5.
23. Castellano I, Gomez-Martino JR, Hernandez MT, *et al*. Remission of nephrotic syndrome caused by renal amyloidosis secondary to pulmonary tuberculosis after tuberculostatic treatment. *Nefrologia* 2001; 21: 88-91.
24. Guillaume Bollee, Bruno Guery, Dominique Joly, *et al*. Presentation and Outcome of Patients with Systemic Amyloidosis Undergoing Dialysis. *CJASN* 2008; (2): 375-381.
25. Gertz MA, Kyle RA, O'Fallon WM. Dialysis support of patients with primary systemic amyloidosis: A study of 211 patients. *Arch Intern Med* 1992; 11: 2245-2250.
26. Martinez-Vea A, Garcia C, Carreras M, *et al*. End-stage renal disease in systemic amyloidosis: Clinical course and outcome on dialysis. *Am J Nephrol* 1990; 4: 283-289.
27. Sanai T, Nanishi F, Nagata M, *et al*. Role of amyloidosis in determining the prognosis of dialyzed patients with rheumatoid arthritis. *Rheumatol Int* 2007; 363-367.
28. Kuroda T, Tanabe N, Sato H, *et al*. Outcome of patients with reactive amyloidosis associated with rheumatoid arthritis in dialysis treatment. *Rheumatol Int* 2006; 12: 1147-1153.
29. Claudio Ponticelli, Gabriella Moroni and Richard J. Glassock. Recurrence of Secondary Glomerular Disease after Renal Transplantation. *Clin J Am Soc Nephrol* 2011; 6: 1214-1221.
30. Pinney JH, Lachmann HJ, Sattianayagam PT, *et al*. Renal Transplantation in Systemic Amyloidosis-Importance of Amyloid Fibril Type and Precursor Protein Abundance. *American Journal of Transplantation* 2013; 13: 433-441.
31. Vivekanand Jha, Vinay Sakhuja, Kim Vaiphei, *et al*. An Unusual Case of Recurrence of AA Amyloidosis in the Renal Allograft. *Renal Failure* 2004; 26(1): 89-92.
32. Dember LM, Hawkins PN, Hazenberg BP, *et al*. Eprodisate for the Treatment of Renal Disease in AA amyloidosis Trial Group. *N Engl J Med* 2007; 356: 2349-2360.

BANTAO Journal 2014; 12(1): 108-113

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Original article

Correlation of B-type Natriuretic Peptide (BNP) with Left Ventricle Systolic Function Echocardiographic Parameters in Patients with Chronic Kidney Disease (CKD)

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Abstract

Introduction. BNP plasma levels are significantly increased in heart failure and have an excellent negative predictive value for left ventricular dysfunction. Measurement of BNP level is useful for "screening" in high-risk populations. It is suitable for detection of left ventricular hypertrophy (LVH) and/or dysfunction and risk assessment in the sub-acute phase of acute myocardial infarction in hypertensive patients. The aim of our study was to find whether BNP may correlate with the left ventricular systolic function, i.e. its echocardiographic parameters in chronic kidney disease (CKD) patients.
Methods. In a prospective study performed at the Department of Nephrology and Clinic for hemodialysis at the Clinical Center in Sarajevo we followed-up 80 patients stratified in three separate groups according to CKD stage (Stage III, IV and V) for two years, regardless of their cardiovascular symptoms. We analyzed levels of BNP before and after diuretic therapy or hemodialysis and echocardiographic characteristics of the left ventricle.
Results. There was a strong negative correlation between BNP values and the size of the EF before (rho=-0.692, $p<0.0001$) and after diuretic therapy (rho=-0.683, $p<0.0001$) for patients in CKD stage III, stage IV (rho=-0.314, $p>0.05$) and after diuretic therapy (rho=-495, $p<0.05$) Similarly, a negative correlation was found for BNP and EF values before (rho=-0.432, $p<0.05$) and after hemodialysis (rho=-0.556, $p<0.01$) for stage V CKD.
Conclusions. Our study confirmed that the value of BNP in CKD patients may represent a measure of left ventricular systolic function with a strong negative correlation with ejection fraction. BNP measurement is a reliable parameter for further follow-up and prognosis in patients with established left ventricular dysfunction, acute coronary syndrome and for estimation of the left ventricular dysfunction.

Key words: BNP, left ventricle systolic function, chronic renal disease

Introduction

B-type natriuretic peptide (BNP) is a hormone which is secreted from the ventricle in response to elevated volume and filling pressures. Levels of BNP depend on the presence or absence of chronic kidney disease (CKD). Along with the aging of the left ventricle (LV) and developed stiffness an increase in BNP is observed until it develops systolic or diastolic LV dysfunction. Cardiac and atrial natriuretic peptide (ANP) as well as the brain natriuretic peptide (BNP) act as key regulators of homeostasis of body fluid volume and blood pressure, by decreasing the retention of salt and water inhibiting the intensive action of the sympathetic nervous system and vasoconstrictor hormone secretion [1]. BNP plasma levels are significantly increased in heart failure. Measurement of BNP level is useful for "screening" in high-risk populations [2]. In addition, BNP has an excellent negative predictive value for left ventricular dysfunction. It is also suitable for "screening" in hypertensive patients for detection of left ventricular hypertrophy (LVH) and/or dysfunction (LVD) and risk assessment in the sub-acute phase of acute myocardial infarction. Measurement of BNP level is also useful for treatment monitoring and optimization of the heart failure therapy [3].
The question might be why, when and in which population we should determine the BNP? Of course it's not necessary to determine the BNP level in the entire population, but only in patients with positive cardiovascular (CV) anamnesis and in presence of CV risk factors. That's why the European Society of Cardiology guides for LVH diagnosis with BNP in these patients as an early diagnostic procedure.

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The normal value of BNP(<100pg/ml) is associated with high probability that the patient is without LVD. In cases of increased BNP values another diagnostic procedures should be carried out in order to establish a more detailed morpho-functional characteristics of the damaged myocardium.
However, BNP levels cannot replace echocardiography and similar techniques, because these methods provide different information. Thus, for cardiologists determination of the natriuretic peptides is a useful complementtary parameter to the standard clinical investigation of patients with LVD [4,5].

Material and methods

In a prospective study performed at the Department of Nephrology and Clinic for hemodialysis at the Clinical Center in Sarajevo we followed-up 80 patients stratified in three separate groups according to CKD stage (Stage III, IV and V) for two years, regardless of their cardiovascular symptoms. We analyzed levels of BNP before and after diuretic therapy or hemodialysis and echocardiographic characteristics of the left ventricle.
Group A: 28 patients, CKD stage III (GFR 30-60 ml/min/1.73m²), 12 males, mean age 65.3±19.36 years and 16 females, mean age 67.7±13.51 years.
Group B: 25 patients, CKD stage IV (GFR 15-29 ml/min/1.73m²), 15 males, mean age 58.3±13.51 years and 10 females, mean age 69.2±11.41 years.
Group C: 27 hemodialysis patients, CKD stage V (GFR< 15 ml/min/1.73m²), 16 males, mean age 50.5±16.52 years and 11 females, mean age 62.6±17.70 years.
All patients were subjected to detailed personal medical history, physical examination, BMI calculation, ECG, echocardiography at the beginning and end of study, and laboratory tests (BNP and TnII) before/after diuretic therapy and hemodialysis.
Hemodialysis of bicarbonate type, and low and high-flow dialyzers with programmed ultrafiltration (UF) were used.
Echocardiography was performed on the machine Hewlett Packard 5500 Sonors, Philips Inc.
Left ventricle mass as a sign of myocardial hypertrophy was determined based on the formula for calculation of left ventricle mass by the Penn convention:

$$\textbf{LV mass}=1{,}04\,[(\text{LVIDd}+\text{IVS}+\text{LVPWd})^3-(\text{LVIDd})^3]+13{,}6\ \text{g}$$

where LVIDd-left ventricle in diastole dimension, IVS-interventricular septum thickness in diastole and LVPW-posterior wall thickness in diastole. Left ventricle volume as a sign of myocardial hypertrophy was determined using the following formula:

$$\textbf{Volume LV (RWT)} = 2x\ (\text{LVPWd}/\text{LVIDd})$$

where LPWd-posterior wall thickness in diastole, LVIDd-left ventricle in diastole dimension.
BNP concentration was determined by immunoassay (quantitative determination of BNP in human plasma), centrifuged at room temperature at 3000 rpm for 3 minutes (ARCHITECTE 2000 SR machine).
We used descriptive and analytical method for statistical analysis. The groups were compared with the Student's *t*-test for normally distributed variables; the Mann Whitney U-test was used for skewed variables distribution and x^2 test for categorical values. SPSS statistical software (version 13.0 SPSS) was used for the analysis, and $p<0.005$ level was considered significant. Data were presented as mean ± standard deviation.

Results

Out of 80 patients**,** 19 patients had normal value of BNP (BNP<100) and regular EF (EF 53-66%). Five patients with normal values of BNP had a lower EF (EF approximately 52-40%).

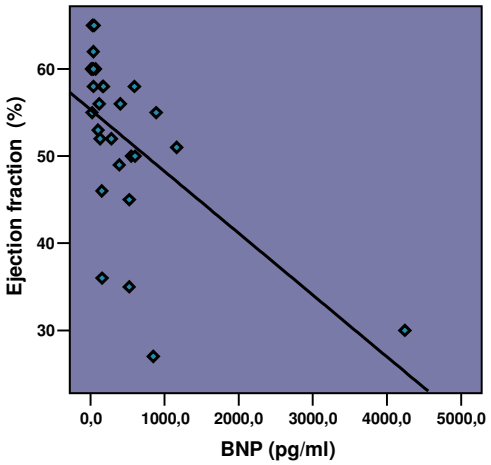

Fig. 1. Correlation between BNP and ejection fraction size in stage III CKD before therapy (rho=-0,692; p<0,0001). Results of the individual values of BNP (pg/ml) compared to the size of the ejection fraction (%) of patients in stage III CKD, before the use of diuretic therapy

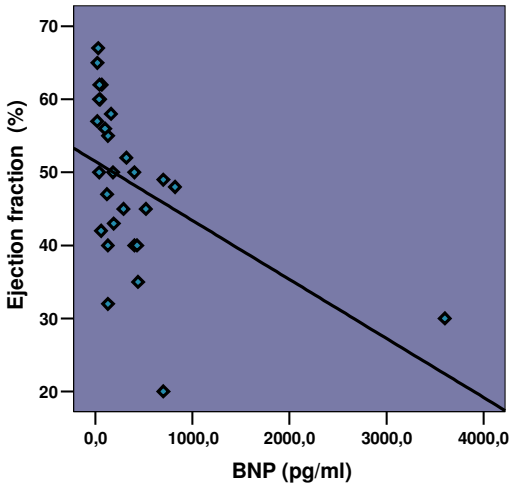

Fig. 2. Correlation between BNP and ejection fraction size in stage III CKD after therapy (rho=- 0,683; p<0,0001). Results of the individual values of BNP (pg/ml) compared to the size of the ejection fraction (%) of patients in stage III CKD after the use of diuretic therapy

None of the patients with normal values of BNP had extremely low EF (EF <40%).
Based on the results of this study, the total number of patients (80) 22 patients with normal BNP value (BNP<100) did not have verified LVH on echocardiography, while three of them with normal BNP value had verified LVH.
Thirteen (13) patients with an elevated BNP value (BNP>100) did not have verified LVH, while 42 of them with elevated BNP value had verified LVH on echocardiography.
Based on the assumption of investigated association between the value of BNP and EF (LVEF) we present some interesting observations.
In patients with stage III CKD before use of diuretic therapy there was strong negative correlation between BNP and EF values (rho=-0.692; p<0.0001) (Figure 1.).

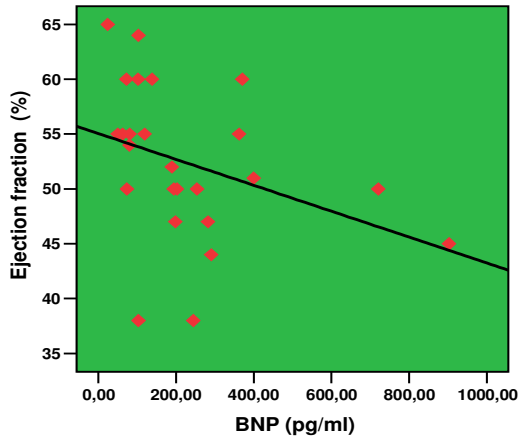

Fig. 3. Correlation between BNP and ejection fraction size in stage IV CKD after therapy (rho=-0.495; p<0.05). Results of a single value of BNP (pg / ml) compared to the size of the ejection fraction (%) of patients in stage IV CKD and after the use of diuretic therapy.

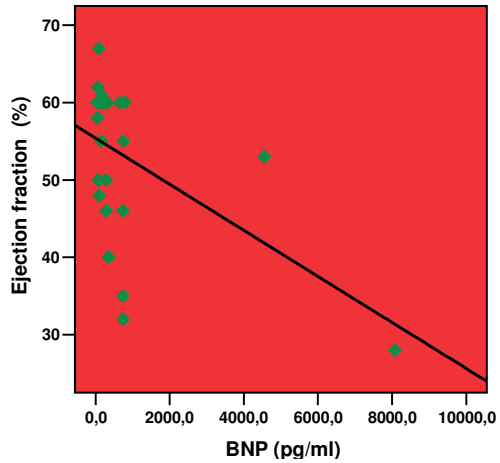

Fig. 4. Correlation between BNP and ejection fraction size in HD patients before dialysis (rho=-0.432; p<0.05). Eesults of a single value of BNP (pg/ml) compared to the size of the ejection fraction (%) in HD patients before hemodialysis.

In these patients, even after the use of diuretic therapy negative correlation between BNP values and the size of the EF was confirmed (rho=-0.683, p <0.0001) (Figure 2).

In CKD patients with stage IV before diuretic therapy the correlation between BNP and EF (rho=-0.314, p>0.05) was not found. However, after the administration of adequate diuretic therapy in these patients a strong, negative correlation between BNP and EF values (rho=- 0.495, p<0.05) was demonstrated (Figure 3).
In CKD patients with stage V before HD therapy there was strong, negative correlation between BNP and EF values (rho=-0.432, p<0.05) (Figure 4), which was maintained after dialysis (rho=-0.556, p<0.01) (Figure 5).

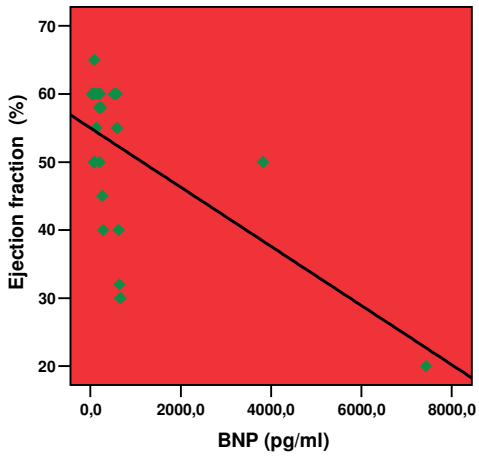

Fig. 5. Correlation between BNP and ejection fraction size in HD patients after hemodialysis (rho=- 0.556; p<0.01). Results of a single value of BNP (pg/ml) compared to the size of the ejection fraction (%) in HD patients after hemodialysis.

In order to verify LVH on echocardiography in addition to EF, the following parameters were also measured: left ventricular mass, volume of the left ventricle and left ventricular shortening fraction (FS).
Mean BNP level in serum of patients with CKD stage III with LVH before diuretic therapy (654.31±223.07) was significantly higher than mean BNP level in serum of patients without LVH (58.43±15.48, p<0.0005).
Similar pattern of mean BNP level in serum of CKD stage III patients with LVH after the use of diuretic therapy (530.73±188.24) was significantly higher than the mean BNP level in serum of patients with CKD stage III without LVH (59.28±13.68, p<0.0005).
In addition, we observed that CKD stage III patients with elevated BNP levels (BNP>100 pg/ml) have LVH, whereas patients with baseline values of BNP (BNP≤100 pg/ml) didn't have LVH on echocardiography. The mean BNP value in patients with LVH was greater compared to mean BNP level in patients without LVH before and after diuretic therapy.
In contrast, there was no correlation between the BNP levels and LVH parameters in patients with CKD stage III before use of diuretics, neither between BNP levels and left ventricular volume, nor between BNP and fractional shortening.
Nevertheless, in patients with CKD stage III we found a strong, positive correlation between fractional shortening (FS) and left ventricular volumes before and after ad-

ministration of diuretic therapy (rho=0.587, p<0.001 (Figure 6) before diuretic therapy; rho=0.592, p<0.001 after diuretic therapy) (Figure 7).

Mean BNP level in serum of CKD stage IV patients with LVH before use of diuretic therapy (464.00±100.34) was significantly higher compared to CKD stage IV patients without LVH (125.22±32.65, p<0.001).

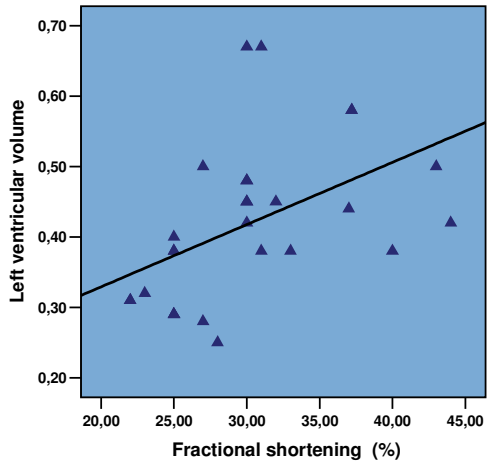

Fig. 6. Correlation between fractional shortening and left ventricular volume (rho=0,587; p<0,001). Values of fractional shortening (FS) and left ventricular volume (LVV) in patients in stage III CKD before diuretic therapy.

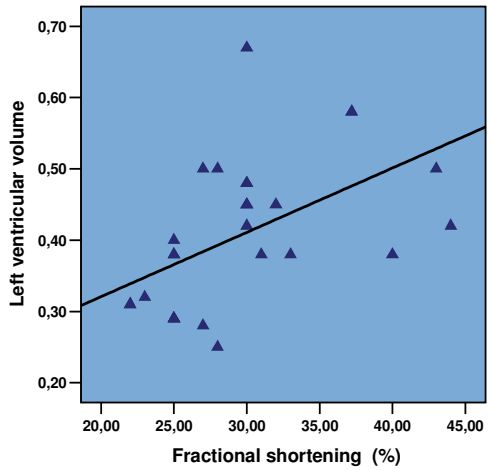

Fig. 7. Correlation between fractional shortening and left ventricular volume (rho=0.592; p<0.001). Values of fractional shortening (FS) and left ventricular volume (LVV) in patients in stage III CKD after diuretic therapy.

Mean BNP levels in CKD stage IV patients with LVH after the use of diuretics (359.85±71.52) was significantly higher compared to patients with CKD stage IV without LVH (118.77±25.16, p<0.001).

The mean BNP levels in serum of patients with CKD stage V (HD) with LVH before hemodialysis (1173.59±530.35) was significantly higher than those in CKD patients stage V (HD) without LVH (119.28±19.12, p<0.0005).

The mean BNP levels in patients with CKD stage V (HD) with LVH after hemodialysis (1025.63±481.16) was significantly higher compared to the mean BNP levels in CKD stage V patients (HD) without LVH (115.32±16.76, p<0.0005).

There was no correlation between BNP levels and left ventricular mass, left ventricular volume and fractional shortening in patients with CKD stage V (HD) before hemodialysis. However, a strong negative correlation between values of fractional shortening and left ventricular mass in HD patients before hemodialysis (rho=-0.680, p<0.0001 (Figure 8)), as well as a negative correlation between values of fractional shortening and left ventricular mass in HD patients after hemodialysis (rho=- 0.748, p <0.0001) was observed (Figure 9).

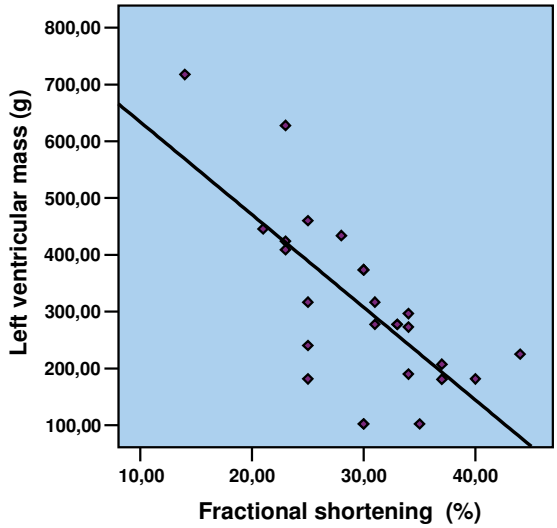

Fig. 8. Correlation between fractional shortening and left ventricular mass (rho=-0.680; p<0.0001). Values of fractional shortening (FS) and left ventricular mass (LVM) in HD patients before hemodialysis.

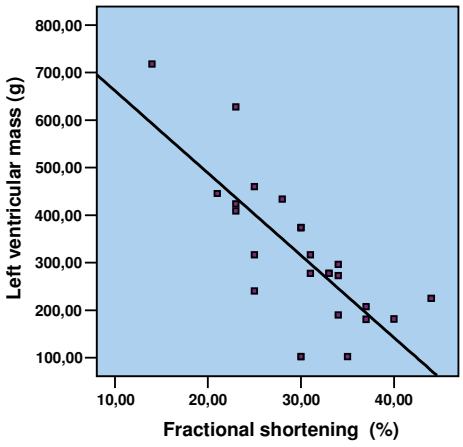

Fig. 9. Correlation between fractional shortening and left ventricular mass (rho=-0.748; p<0.0001). Values of fractional shortening (FS) and left ventricular mass (LVM) in HD patients after hemodialysis.

Discussion

These results have shown that an increase in BNP concentrations in serum of CKD patients with stage III before and after administration of diuretic therapy, lead

to a reduction in the size of the EF. Patients with CKD (stage III, IV and V) have elevated BNP levels compared to healthy population at the same age, even in the absence of congestive heart failure. This might be due to decreased renal clearance, increased stress on the myocardium, left ventricle hypertrophy, subclinical ischemia and remodeling, and fibrosis. However, the limited value of BNP in diagnosis of congestive heart failure should be adjusted in patients with GFR <60 ml/min.
According to the study of Forfia *et al.*, who monitored 40 patients in an Intensive Care Unit, 63% of patients in various CKD stages and without diagnosed congestive heart failure had BNP values between 100-250 pg/ml [6]. Hence and in addition to our observations, BNP value in patients with different stages of CKD associated with congestive heart failure has only a limited value for BNP of 200 pg/ml instead of 100 pg/ml as previously considered. Hence, BNP of 390 ng/L might be considered a weak predictor of adverse cardiovascular events in patients on hemodialysis [6].
As expected, the HD patients have higher BNP levels compared to patients in other CKD stages (III and IV) [7] that might be explained by the high prevalence of left ventricle structural and functional abnormalities.
We have confirmed the positive correlation between BNP levels and LVH and an inverse correlation with the ejection fraction (EF) [7-9]. Naganuma *et al*. have prospectively monitored a cohort of 164 patients for 36 months, showing the BNP correlation with LVH, cardiovascular diseases and diabetes mellitus [8]. Zoccali *et al*. monitored the levels of ANP and BNP and performed echocardiography in 246 CKD patients, without clinical evidence of congestive heart failure. They showed significant association between both natriuretic peptides and left ventricle mass index, LVH and ejection fraction [9].
Our results showed a negative correlation between BNP levels and ejection fraction in all groups of patients before and after diuretic therapy or hemodialysis, except in patients with CKD stage III, before diuretic therapy, where the correlation was not significant. However, we could not find any correlation between BNP and left ventricle mass, left ventricle volume and fraction shortening. Hence, the question is what might be the reason for such an inconsistency in correlations between the above-mentioned parameters in our study. The first possible explanation might be the insufficient number of patients included in the study (n=80). Another reason may be the drug effect that was not recorded when personal history data were collected, and finally the intraobserver variation i.e. the individual approach in determining of the parameters of LVH on echocardiography.
Given that BNP is secreted in response to the increase in myocardial wall stretch, it is hypothesized that the circulating BNP might be a useful marker of volume status. A few studies have investigated the relationship between BNP levels and volume load, but the direct evidence still lacks [10].
Several limitations should be considered in interpreting our results. Firstly, we used a single baseline measurement for BNP at the start and end of the study. We did not use average values during the follow-up. Secondly, we considered only plasma levels of BNP, we did not measure plasma levels of NT-pro-BNP. Thirdly, the follow-up period was relatively short, only two years (a longer follow-up period might produce more relevant results).

Conclusions

Study results show that the BNP value in CKD patients may represent a measure of left ventricular systolic function and correlate well with echocardiographic parameters. BNP levels correlate directly with left ventricular mass index and left ventricular hypertrophy, and negatevely with ejection fraction. Correlation of the BNP levels and ejection fraction is negative and statistically significant. The BNP level may be useful for risk stratification and administered therapy in CKD patients. Measurement of the BNP level is important in the prognosis of the outcome in patients with established left ventricle dysfunction, acute coronary syndrome and for estimation of the likelihood of ventricle dysfunction.
Testing of natriuretic peptides (BNP) is perhaps the greatest advance in the diagnosis of congestive heart failure since theintroduction of echocardiography. However, tests of BNP can not be used independently, they provide additional information.
Their sensitivity and negative predicitive value makes them suitable for elimination of congestive heart failure with high certainty. Conversely, increasing their levels goes in line with the increase of their specificity and positive predictive value.

Conflict of interest statement. None declared.

References

1. LaPointe MC. Molecular regulation of the brain natriuretic peptide gene. *Peptides* 2005; 26(6): 944-956.
2. Dries DL, Exner DV, Domanski MJ, *et al.* The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with ventricular systolic dysfunction. *J Am Coll Cardiol* 2000; 35: 681-689.
3. Parfrey PS. Cardiac disease in dialysis patients:diagnosis, burden of disease, prognosis, risk factors ana management. *Nephrol Dial Transplant* 2000; 15(Suppl 5): 58-68.
4. Foley RN, Parfrey PS, Harnett JD, *et al.* Serial change in echocardiographic parameters and cardiac failure in end-stage renal disease. *J Am Soc Nephrol* 2000; 11(5): 912-916.
5. Abbot KC, Bakris GL. Kidney Failure and Cardiovascular Disease. *Circulation* 2003; 108(16): 114-115.
6. Forfia PR, Watkins SP, Rame JE, *et al.* Relationship between B-type natriuretic peptides and pulmonary capillary wedge pressure in the intensive care unit. *J Am Coll Cardiol* 2005; 45: 1667-1671.
7. Mark PB, Stewart GA, Gansevoort RT, *et al*. Diagnostic potential of circulation natriuretic peptides in chronic kidney disease, *Nephro Dial Transplant* 2006; 21: 402-410.

8. Naganuma T, Sugimura K, Wada S. The prognostic role of brain natriuretic peptides in hemodialysis patients. *Am J Nephrol* 2002; 22: 437-444.
9. Zoccali C, Mallamaci F, Benedetto F. Cardiac natriuretic peptides are related to left ventricular mass and function and predict mortality in dyalsis patients. *J Am Soc Nephrol* 2001; 12: 1508-1515.
10. Wang AY, Lai KN. Use of cardiac biomarkers in end stage renal disease. *J Am Nephrol* 2008; 19: 1643-1652.

BANTAO Journal 2014; 12(1): 114-118

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Original article

Vitamin D Status has no Influence on the Incidence of Recurrent Urinary Tract Infections after Kidney Transplantation

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Abstract

Introduction. Recurrent urinary tract infections (rUTIs) after kidney transplantation (KT) are associated with significant decrease in graft survival. There is a growing body of evidence for the pleiotropic effects of vitamin D (VD), including immunomodulatory and antibacterial effect. The number of studies on VD's pleiotropic effects in kidney transplant recipients (KTRs) however is low. The aim of our study was to assess the influence of VD on the incidence of recurrent UTIs after KT.
Methods. The KTRs were tested for 25-hydroxyvitamin D (25VD) between 1.05.2012 and 30.11.2012. Patients within 12 months of transplantation, performed parathyroidectomy, concomitant intake of calcineurin inhibitors and mTOR inhibitors, advanced liver disease and VD supplementation were excluded from the study. Recurrent UTIs were defined as more than 3 episodes of active UTI within the last 12 months of testing for 25VD. Statistical analysis was carried out with SPSS version 22.0 and included descriptive statistics, Mann-Whitney U test. Determination of total 25VD was performed by a validated LC-MS/MS method.
Results. A total of 275 patients met the above-mentioned criteria (males 182, females 93). The mean 25VD in patients with rUTIs (n=14) was 51.41±25.17 nmol/L, whereas in the group without rUTIs (n=261) the level was 60.35±23.29 nmol/L. After matching the two groups for seasonal factors (sampling for 25VD in July, August, September) and gender 169 patients were selected, and 11 were with rUTIs. No significant difference was detected in the 25VD level in the two groups (53.30±18.37 vs 49.08±21.04 nmol/L), p=0.342.
Conclusions. Despite the higher 25VD in the KTRs without rUTIs, the difference between the two groups remained insignificant.

Key words: 25-hydroxyvitamin D, pleiotropic effects, recurrent urinary tract infections, renal transplantation

Introduction

Urinary tract infections (UTIs) are one of the most common complications after kidney transplantation (KT), with prevalence peaking up to 80% [1]. UTIs, including recurrent UTIs, are associated with graft failure, risk for rejection episode and decreased patient survival [2,3]. On the other hand, vitamin D is getting more and more popular for its pleiotropic effects-renoprotection, control of diabetes mellitus and hypertension, immunomodulation. One of these non-skeletal effects is stimulating protective immunity [4-6]. Low VD level predicts higher incidence of recurrent UTIs (rUTIs) in premenopausal women [7]. A recent study by Lowery *et al.* has revealed that poor VD status is linked to higher infection rate after lung transplantation [8]. However, there is still no data proving the protective role of VD in reducing the risk for infection, including UTI after KT. Therefore, the aim of our study was to assess the association between rUTIs and VD status after KT, measured by the serum level of 25-hydroxyvitamin D [25(OH)VD], as generally accepted [9].

Material and methods

Subjects

Three hundred ninety five kidney transplant recipients (KTRs) in our transplant center were tested for 25(OH)D between 01.05.2012 and 30.11.2012. The following selection criteria were applied: KTRs less than 36 months after kidney transplantation were excluded, patients with performed parathyroidectomy and unstable kidney function were also excluded from the study; subjects with advanced liver disease (Child-Pugh score B and over) and with vitamin D supplementation were not taken into consideration, as well as outliers for BMI and 25(OH)D (absolute value for Z-score greater than 3.29). Our study was approved by the Institutional Ethics Committee, and was in accordance to the Helsinki Declaration of 1975 (as revised in 2000). All participants gave their informed consent prior to inclusion in the study. Recurrent UTIs were defined as more than 3 episodes of UTI

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within 12 months before testing for 25(OH)D. In order to assess the link between VD status and rUTIs the patients in both groups (with and without rUTI) were matched for gender and months of sampling for VD, due to the influence of these factors on 25(OH)D [10-12].

Methods

Analysis of 25(OH)D

Determination of 25(OH)D was performed by a validated LC-MS/MS method developed in-house, utilizing extraction with hexane, d325(OH)D3 as internal standard, isocratic elution on C18 analytical column, positive-ion electrospray ionization, and selected reaction monitorring for the respective m/z transitions: 401→383 for 25(OH)D3, 413→395 for 25(OH)D2, and 404→386 for d325(OH)D3. This method was calibrated with the use of commercial, NIST (National Institute of Standards and Technology, USA) 972 traceable reference materials and was validated according to FDA guidance requirements, with documented selectivity and matrix effect, accuracy and precision within 7.5%; extraction recoveries averaging 57-73%; linearity range 3.0-300.0 nmol/L, R2>0.99, freeze-thaw stability for three cycles of 24 h, post-preparative stability for 96 h at 10°C, short-term stability at ambient temperature for 24 h in the dark and for 2 h at daylight; stock solution stability and long-term stability in plasma for 5 days at 4-8°C, and for 99 days at -20°C. It participated in DEQAS (UK Vitamin D External Proficiency Testing Scheme) external proficiency testing scheme with achieved certification for 2012.

Microbiological analysis

Conventional biochemical methods were used to identify different strains of uropathogens-automatic and semi-automatic biochemical identification systems-miniApi (bioMerieux, France) and BBL Crystal (BD). The antibiotic sensitivity was determined via disc-diffusion method, according to the accepted CLSI standard in Bulgaria.

Statistical analysis

Descriptive statistics, Fisher`s exact test and Mann-Whitney U test were used to investigate the association between 25VD and recurrent UTIs. Level of significance was set at P<0.05, SPSS 22.0 Software (SPSS Inc, Chicago, IL, USA) was used. In order to avoid distortions of parameter and statistic estimates, we screened the data for BMI and 25(OH)D level for outliers using the Z-score method, with cut-off values lower than /-3.29/ and higher than /+3.29/.

Results

Two hundred and twenty two patients were shortlisted after the selection criteria were applied. Males outnumbered the females (145 vs 77). The baseline characteristics of the group are depicted in Table 1.

Table 1. Basic characteristics of the study subjects, n=222

	Males n=145	**Females n=77**
Age (years)	43.67±13.08	43.51±11.42
Time after TR * (months)	112.49±54.83	121.25±53.73
eGFR † (ml/min/1,73m^2)	62.59±22.02	62.73±26.54
Vit.D concentration‡ (nmol/L)	65.77±24.12	52.58±21.57

*TR-transplantation, †eGFR-estimated glomerular filtration rate-CKD-EPI formula, ‡ total 25(OH)D

In almost 80% of the subjects suboptimal 25(OH)D levels were established (Figure 1). Out of 222 patients 8 were detected with recurrent UTIs. Two out of 47 VD sufficient kidney transplant recipients (KTRs) were detected with rUTIs (4.3%), compared to 6 KTRs with rUTI out of 175 patients with suboptimal VD status (3.4%). The difference was found to be insignificant, p=0.678 (Fisher's exact test, Figure 2).

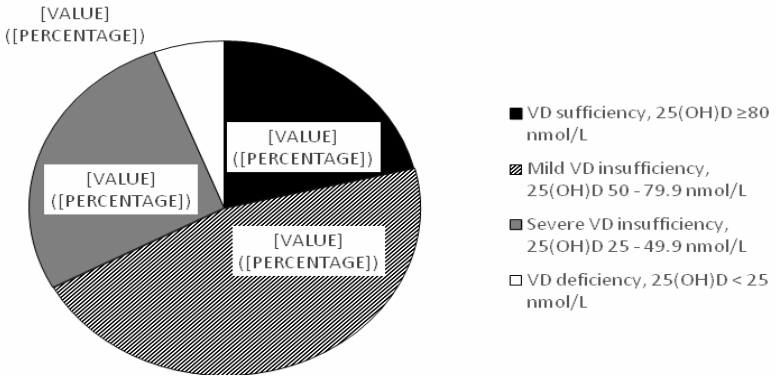


Fig. 1. VD status of the assessed KTRs, n=222; VD-vitamin D

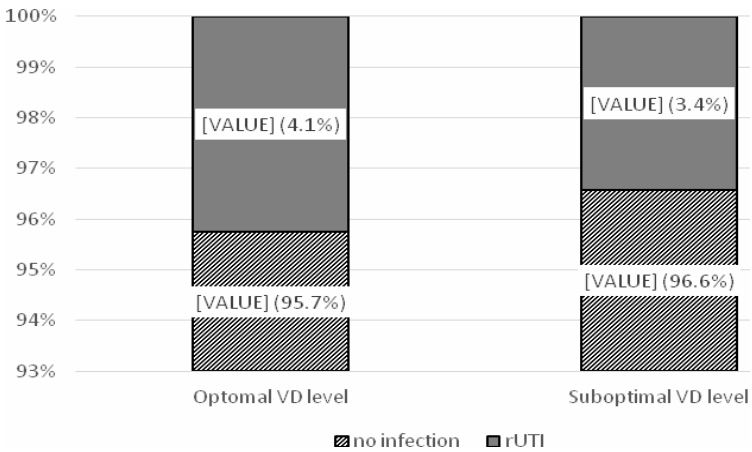
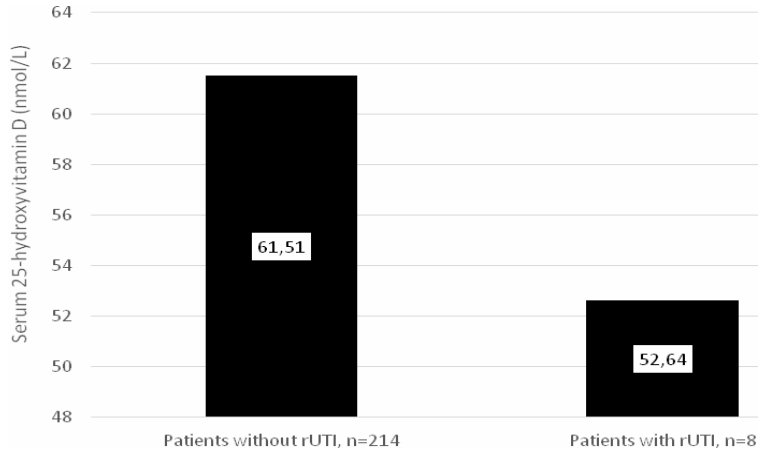


Fig. 2. rUTI incidence rate KTRs with optimal VD (n=47) vs KTRs with suboptimal VD level (n=175) VD-vitamin D, rUTI-recurrent urinary tract infection

In addition, VD status between patients with and without rUTIs was compared. The mean 25(OH)D for patients with rUTIs was 52.64±30.59 nmol/L, whereas in the group without infection-61.51±23.81nmol/L (Figure 3). The difference was insignificant, p=0.490 (Mann-Whitney U test). In order to assess the link between VD level and rUTI incidence rate more accurately, the patients were matched according to gender and month of sampling. Patients



rUTI – recurrent urinary tract infections

P=0.490

Fig. 3. Mean 25-hydroxyvitamin D levels in patients with rUTI and without rUTI

tested for 25VD in July, August, September were excluded due to the significant influence of summer testing on VD status. After the second selection was performed 56 patients were shortlisted. Five [5] out of 56 were with rUTIs. The mean 25(OH)D level for patients without infection was 48.25±18.19 nmol/L vs 48.24±26.26nmol/L. The difference was statistically insignificant (Mann-Whitney U test, p=0.978). The result is summarized in Figure 4.

Discussion

Considering the relationship between rUTIs and VD status we should bear in mind two basic considerations. UTIs are a frequent and important complication after KT, with various clinical presentations. The major risk factors for development of rUTIs are female gender, immunosuppression, in-dwelling catheters, anatomical abnormalities of the native kidneys or the graft, diabetes mellitus, urologic procedures, elderly patients, antibiotic resistance of the bacterial strains [2,13]. The influence of these factors gradually decreases with the increase of time interval after KT. In order to exclude most of the above-mentioned predictors for UTI incidence we deliberately selected patients with longer period of time after KT. In our study no significant association was established between VD status and rUTI incidence. It is possible that our results reflect the persistent influence of the well-known predictors in the course of time after KT, thus being the more important cause for higher rUTIs incidence rather than 25(OH)D level.

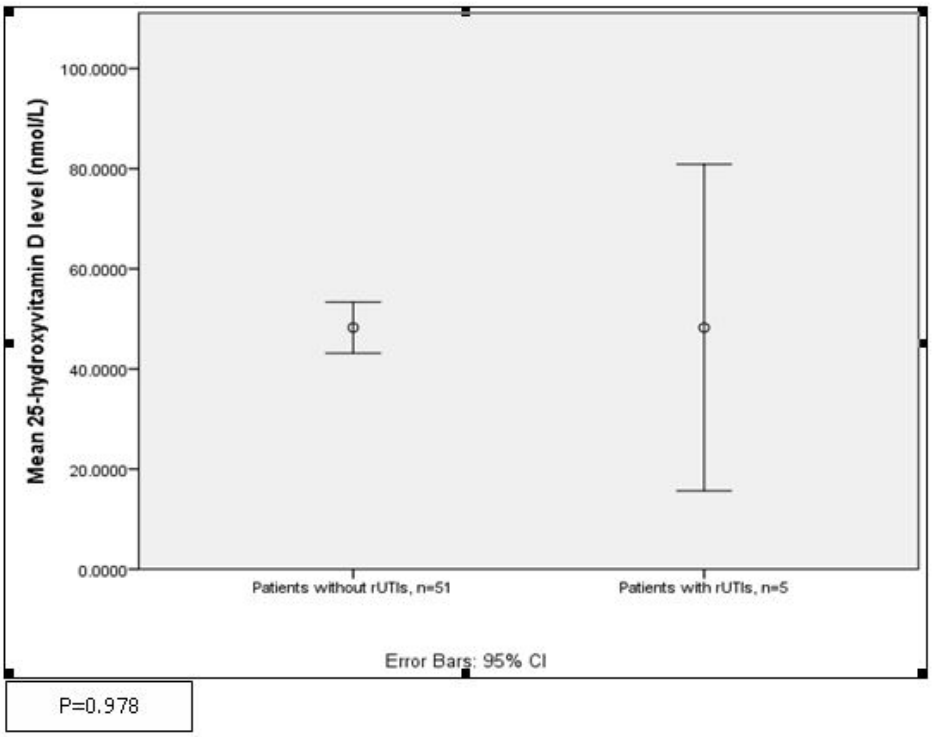


Fig. 4. Mean 25-hydroxyvitamin D, gender and season matched group, n=56
rUTI-recurrent urinary tract infections

Furthermore, the impact of 25(OH)D on infection rate after kidney transplantation is still unclear [14]. Indeed, several in vitro studies proved that calcitriol leads to an increased synthesis of cathelicidin, an antimicrobial peptide, by macrophages [15]. Calcitriol was also associated with increased production of interleukin 1 and monocyte proliferation [16,17]. Vitamin D3 supplementation reduced influence infection rate in humans and improved antiviral response in hepatitis C infected patients [18,19]. A retrospective study however failed to detect beneficial effect of regular VD supplementation on infectious mortality rate in patients on hemodialysis [20]. In addition, the number of reports linking VD status and infection rate after solid organ transplantation is small and insufficient. Therefore we can conclude that further data must be gathered in order to evaluate any potential relationship between 25(OH)D level and rUTIs after KT.
The major drawback of our study is its retrospective model and the relatively small number of patients with rUTIs. However, the studies assessing the pleiotropic effects after KT are mainly observational, except for 2 small studies reporting of the immunomodulatory effect of 25(OH)D in kidney transplant recipients [14,21,22)]. Evidently, larger prospective multicenter controlled studies with adequate VD supplementation are needed to evaluate the link between VD status and urinary tract infection rate in kidney transplant recipients.

Conflict of interest statement. None declared.

References

1. Rubin RH. Infectious disease complications of renal transplantation. *Kidney Int* 1993; 44: 221-36.
2. Saemann M, Horl WH. Urinary tract infection in renal transplant recipients. *Eur J Clin Invest* 2008; 38 Suppl 2: 58-65.
3. Golebiewska JE, Debska-Slizien A, Rutkowski B. Urinary tract infections during the first year after renal transplantation-one centre's experience and a review of the literature. *Clin Transplant* 2014; doi: 10.1111/ctr.12465. [Epub ahead of print].
4. Cannell JJ, Vieth R, Umhau JC, *et al*. Epidemic influenza and vitamin D. *Epidemiol Infect* 2006; 134(6): 1129-1140.
5. Bodnar LM, Krohn MA, Simhan HN. Maternal vitamin D deficiency is associated with bacterial vaginosis in the first trimester of pregnancy. *J Nutr* 2009; 139(6): 1157-1161.
6. Rodríguez M, Daniels B, Gunawardene S, Robbins GK. High frequency of vitamin D deficiency in ambulatory HIV-Positive patients. *AIDS Res Hum Retroviruses* 2009; 25(1): 9-14.
7. Nseir W, Taha M, Nemarny H, Mograbi J. The association between serum levels of vitamin D and recurrent urinary tract infections in premenopausal women. *Int J Infect Dis* 2013; 17(12): 1121-1124.
8. Lowery EM, Bemiss B, Cascino T, *et al*. Low vitamin D levels are associated with increased rejection and infections after lung transplantation. *J Heart Lung Transplant* 2012; 31: 700-707.
9. KDIGO Clinical Practice Guidelines for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder. *Kidney Int* 2009; 76 (Suppl 113): S22-S49.
10. van Dam RM, Snijder MB, Dekker JM, *et al*. Potentially modifiable determinants of vitamin D status in an older population in the Netherlands: the Hoorn Study. *Am J Clin Nutrq* 2007; 85: 755-761.

11. Филипов Ж, Златков Б, Паскалев Е, Хубанов Н, Свинаров Д. Сезонни вариации в нивото на 25-хидроксивитомин Д при български пациенти с бъбречна трансплантация. *Медицински преглед*, 2014, 50: 37-42.
12. Nesby-O'Dell S, Scanlon KS, Cogswell ME, *et al*. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988-1994. *Am J Clin Nutr* 2002; 76(1): 187-192.
13. Kubak MB, Holt CD. Infectious Complications in Kidney Transplantation and their Management. In: *Handbook of Kidney Transplantation, ed. G. M. Danovitch, 2 ed., Boston, A Little, Brown* 1996; 187-213.
14. Courbebaisse M, Souberbielle, Thervet E. Vitamin D and transplantation. In: R.R. Watson (ed.), Handbook of vitamin D in human health: Prevention, treatment and toxicity. *Human Health Handbooks Wageningen Academic Publishers* 2013, 4: 566-587.
15. Liu PT, Stenger S, Li H, *et al*. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 2006; 311: 1770-1773.
16. Ohta M, Okabe T, Ozawa K, *et al*. 1 alpha,25-dihydroxyvitamin D3 (calcitriol) stimulates proliferation of human circulating monocytes in vitro. *FEBS Lett* 1985; 185: 9-13.
17. Bhalla AK, Amento EP and Krane SM. Differential effects of 1, 25-dihydroxyvitamin D3 on human lymphocytes and monocyte/macrophages: inhibition of interleukin-2 and augmentation of interleukin-1 production. *Cell Immunol* 1986; 98: 311-322.
18. Aloia JF and Li-Ng M. Re: Epidemic influenza and vitamin D. *Epidemiol Infect* 2007; 135: 1095-1096.
19. Abu-Mouch S, Fireman Z, Jarchovsky J, *et al*. Vitamin D supplementation improves sustained virologic response in chronic hepatitis C (genotype 1)-naïve patients. *World J Gastroenterol* 2011; 17: 5184-5190.
20. St Peter WL, Li S, Liu J, *et al*. Effects of monthly dose and regular dosing of intravenous active vitamin D use on mortality among patients undergoing hemodialysis. *Pharmacotherapy* 2009; 29: 154-164.
21. Ardalan MR, Maljaei H, Shoja MM, *et al*. Calcitriol started in the donor, expands the population of CD4+CD25+ T cells in renal transplant recipients. *Transplant Proc* 2007; 39: 951-953.
22. Ahmadpoor P, Ilkhanizadeh B, Ghasemmahdi L, *et al*. Effect of active vitamin D on expression of co-stimulatory molecules and HLA-DR in renal transplant recipients. *Exp Clin Transplant* 2009; 7: 99-103.

BANTAO Journal 2014; 12(1): 119-121

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Case report

Membranoproliferative Glomerulonephritis Type 1 Secondary to an Infected Ventriculoperitoneal Shunt: a Case Report

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Abstract

Ventricular shunting is the usual method for treatment of congenital or acquired hydrocephalus. Immune-mediated glomerulonephritis (shunt nephritis) is a rare but life-threatening complication of this neurosurgical technique. Intraglomerular deposition of circulating immune complexes and the subsequent activation of the classical pathway of serum complement's cascade result in glomerular inflammation. Membranoproliferative gomerulonephritis is the most common histologic pattern observed in renal biopsy. The diagnosis needs high suspicion and is based on clinical and laboratory findings. Deterioration of renal function in association with signs of infection and low levels of serum complement's proteins C3 and C4 make the diagnosis possible. The prognosis is variable and depends on the time of diagnosis after the onset of glomerular injury. The optimal treatment includes timely removal of the infected shunt in combination with aggressive antibiotic therapy. In this paper we present the case of a membranoproliferative glomerulonephritis type 1 in a patient with a ventriculoperitoneal shunt. Although this type of shunting is considered safer than the ventriculoatrial one, the risk of complications such as an immune-mediated glomerulonephritis still exists.

Key words: hypocomplementemia; membranoproliferative glomerulonephritis; shunt nephritis; ventriculoperitoneal shunt

Introduction

Ventricular shunting is the usual method for treatment of congenital or acquired hydrocephalus. Ventriculoatrial (VA) and ventriculoperitoneal (VP) shunts are commonly used for the drainage of CSF into the right atrium or the peritoneal cavity, respectively. Each type of shunting presents a series of potential complications. Among them, infections are frequent with an average incidence of 10-15% [1]. They usually occur during the first months after surgery. Clinical manifestations of an infected shunt may be variable, ranging from an asymptomatic infection to severe clinical conditions such as sepsis, ventriculitis, intraabdominal collections, peritonitis, glomerulonephritis (GN) or cor pulmonale [2]. However, in terms of durability and severity of complications, the VA shunt is considered to be a safer choice than the VP one [2-4]. Shunt nephritis, an immune-mediated GN, is a relatively rare complication of an infected shunt, with an estimated incidence of 0.7-2.25% [5]. Since its first description in 1965 [6], several hundreds of cases have been reported in the literature, mostly associated with an infected VA shunt [7,8]. However, its frequency tends to be lower in the last years, mostly due to better preventive measures taken perioperatively. In this report we describe a case of a shunt nephritis which complicated an infected VP shunt.

Case report

A 51-year-old female patient was admitted to the Nephrology Department for investigation of low-grade fever, headache and acute renal failure. Her medical history included hydrocephalus with intracranial hypertension syndrome secondary to CNS echinococcosis and placement of the first VP shunt 10 years earlier. Since then the patient underwent multiple neurosurgical operations for shunt malfunction, including placement of two new shunts, one VA 9 years ago and one VP 4 years ago, respectively, as well as various revisions of the latter. The VP shunt was still functional on her admission.

The patient was presented in our outpatient department well orientated in time and space, hemodynamically stable (BP 120/80 mmHg, 90 pulses/min) and with low-grade fever. She reported recurrent episodes of fever and headache during the last six months responding to simple antipyretics and analgesics. The clinical examination was unremarkable with the exception of mild dysarthria and generalized muscle weakness. No edema, rash or palpable lymphadenopathy was present.

The initial laboratory workup revealed anemia (Hb 8.6 g/dl, Hct 26.5%) with high erythrocyte sedimentation rate (59 mm/h) and moderate renal dysfunction (urea=64 mg/dl, creatinine 2.05 mg/dl). On urinalysis there was

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microscopic hematuria (60 dysmorphic red blood cells per high-power field with few erythrocyte casts) and proteinuria (+++) without leucocyturia. Twenty-four hours urine collection revealed proteinuria within nephrotic range (4349.1 mg/24h). The immunological tests showed mildly increased IgG (1786 mg/dl, normal 700-1600), positive rheumatoid factor (44.3 IU/ml, normal <20) and decreased serum complement´s proteins C_3 (35 mg/dl, normal 82-17) and C4 (6 mg/dl, normal 10-40). The rest of the immunological tests (ANA, anti dsDNA, anti ENA, c-ANCA, p-ANCA, HBs Ag, anti-HCV, cryoglobulins, Coombs' tests) were negative. The renal ultrasound showed kidneys and cortex of normal size, with diffuse hyperechogenicity without signs of obstruction. The chest X-ray was normal and the echocardiogram excluded infective endocarditis showing only a small pericardial effusion. All the initial blood cultures as well as the urinary culture were negative.

Based on the medical history and the clinical and laboratory findings the suspicion of shunt nephritis was set. Thus, the patient underwent renal biopsy which showed hypertrophic glomeruli with lobular appearance and endocapillary hyperplasia. Glomerular basement membranes (GBM) appeared segmentally thickened and reduplicated (double contour) (Figure 1). Immunofluorescence revealed granular, mesangial and intra-membranous deposits of IgM, C3, C1q and λ light chains. There were a few atrophic tubules and interstitial fibrosis to a small extent (<10% of the cortex). The histologic pattern was type 1 membranoproliferative GN.

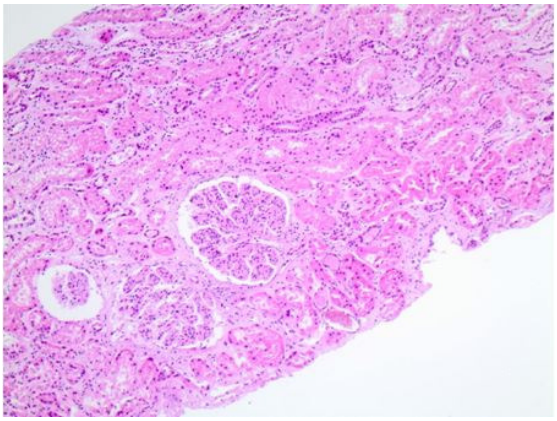

Fig 1. Two glomeruli with increased lobulation and hypercellularity. Hyperplasia of endothelial and mesangial cells (H-E staining x 62,5).

Three days after the admission the clinical condition of the patient was deteriorated with high fever (40^0C) and signs of intracranial hypertension (vomiting, headache and confusion). The cranial CT scan showed dilatation of the third and fourth ventricles secondary to shunt's malfunction (Figure 2). The examination of cerebrospinal fluid (CSF) revealed marked leucocytosis and hypoglycorrhachia (1600 cells/mm^3, PMNn=90%, glucose=64 mg/dl, protein=12.5mg/dl). Cerebrospinal fluid and blood cultures were sent for analysis while an empirical antibiotic therapy was initiated (Vancomycine 1 gr / 48h iv and Rifampicin 600 mg / 24h iv). In the meantime the obstructed shunt was removed and a temporary external CSF drainage was placed.

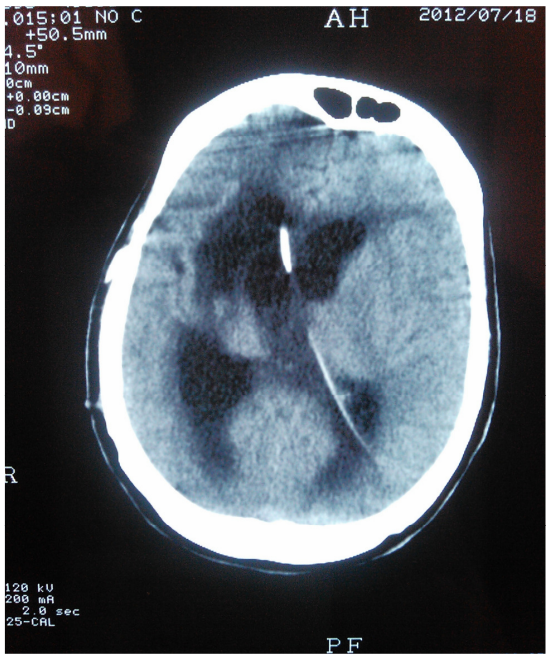

Fig. 2. Cranial CT

Staphylococcus aureus in both blood and CSF cultures as well as at the tip of the shunt was detected. Progressively a decline of the number of cells was observed in the CSF examination and a new cranial CT scan showed decongestion of the ventricles and thus a new ventriculoperitoneal shunt was placed. Renal function and proteinuria were normalized on the 17th and 36th day, respectively. After 68 days in the ICU the patient was transferred to the Internal Medicine Department in stable condition.

Discussion

Shunt nephritis is an immune-mediated GN, which rarely complicates an infected ventricular shunt. Colonization of the distal tip of the shunt and passage of the nephritigenic strains into the bloodstream are the initial pathophysiological events. Persisting bacteremia stimulates the formation of circulating immune complexes. Intraglomerular deposition of the complexes and the subsequent activation of the classical pathway of the serum complement induce glomerular injury [7]. The presence of bacterial antigens in the renal tissue has been described [9].

In our case *Staphylococcus aureus* was isolated from blood and CSF cultures. Staphylococcus species are responsible for the majority of shunts' infections. *Staph. epidermidis* accounts for about 40% and *Staph. aureus* for another 20% of all cases respectively [2]. Staphylococcus has a high affinity for the material of the shunt and produces a biofilm which protects the strains from the bactericide antibiotic effect [10]. Other bacteria of the normal skin flora such as gram positive cocci, gram

positive anaerobic bacilli, gram negative bacilli or yeasts may also infect a ventricular shunt causing nephritis [11,12].

The clinical condition of our patient was initially dominated by renal dysfunction in the context of recurrent febrile episodes but rapidly complicated by intracranial hypertension. Indeed, the clinical picture of shunt nephritis includes signs and symptoms of infection such as recurrent fever, purpuric rash, hepato-splenomegaly or arthritis [13] as well as cerebral manifestations (vomiting, changes of behavior, seizures). The renal manifestations are variable, including microscopic or macroscopic hematuria (88-100%), non-nephrotic range proteinuria (64-100%) or nephrotic syndrome (28-43%), arterial hypertension (10-64%) and renal failure (46-61%) [7,8].

The laboratory work-up is helpful for the diagnosis. Anemia and increased markers of inflammation (leucocytes, CRP and erythrocyte sedimentation rate) are observed. A characteristic finding is hypocomplementemia (C3, C4, CH50), which reflects the activation of the classical pathway of the serum complement. Antinuclear antibodies and serological markers suggestive of circulating immune-complexes such as rheumatoid factor or cryoglobulines may be positive. Cases of shunt nephritis with positive titers of proteinase-3 ANCA have also been reported [14]. Blood and cerebrospinal fluid cultures as well as cultures of the removed shunt's tip can determine the causative agent, guiding accordingly the antibiotic therapy. Brain imaging (CT or MRI scan) can confirm the presence of shunt obstruction.

Histologically, the membranoproliferative pattern is dominant in renal biopsy. Hypertrophic glomeruli with mesangial expansion and hypercellularity, duplication of the GBM and granular, mesangial, subendothelial or intramembranous depositions, predominantly of IgM, IgG and C3 are common findings. Pure mesangioproliferative lesions as well as endocapillary hyperplasia or extracapillary proliferation with crescents have also been reported [11].

Shunt nephritis must be differentiated from subacute infective endocarditis, glomerulopathies with low serum complement levels such as poststreptococcal GN, lupus nephritis or C3 glomerulopathy as well as other secondary causes of membranoproliferative GN (i.e. HCV-related cryoglobulinemic GN or light chain deposit disease).

Although the initial colonization of the shunt usually occurs within the first months after the operation, glomerulonephritis may develop after several months or even years. In our case the diagnosis was made 4 years after the last operation for shunt's placement. The patient complained of low-grade fever and intermittent episodes of headache during the previous six months. This clinical information in association with the histologic finding of the preponderance of IgM glomerular depositions was suggestive of a relatively recent inflammatory process with good prognosis.

In general, the time of removal of the shunt after the onset of the infection has influence on the prognosis of the disease. The optimal treatment consists of complete shunt removal and temporary external drainage of CSF, in combination with the appropriate antibiotics administered intravenously and intraventricularly for at least 10 days [8]. A new shunt must be placed only after clinical remission. In our patient the removal of the infected ventriculoperitoneal shunt and the antibiotic course rapidly normalized her renal function.

Conclusions

Although the therapy of hydrocephalus with placement of a VP shunt has fewer complications in comparison with a VA one, glomerulonephritis should be considered in patients with VP shunt, signs of infection and coexisting deteriorated renal function. The therapeutic approach includes removal of the shunt combined with aggressive antibiotic therapy. The aforementioned may improve the prognosis of the renal injury.

Conflict of interest statement. None declared.

References

1. Blount JP, Campbell JA, Haines SJ. Complications in ventricular cerebrospinal fluid shunting. *Nuerosurg Clin North Am* 1993; 4: 633-656.
2. Weprin BE, Swift DM. Complications of ventricular shunts. *Techniques in Neurosurgery* 2002; 3: 224-242.
3. Fernell E, von Wendt L, Serlo W, *et al*. Ventriculoatrial or ventriculoperitoneal shunts in the treatment of hydrocephalus in children? *Z Kinderchir* 1985; 40(Suppl 1): 12-14.
4. Borgbjerg BM, Gjerris F, Albeck MJ, *et al*. A comparison between ventriculo-peritoneal and ventriculo-atrial cerebrospinal fluid shunts in relation to rate of revision and durability. *Acta Neurochir* 1998; 140(5): 459-464.
5. Narchi H, Taylor R, Azmy AF, *et al*. Shunt nephritis. *J Pediatr Surg* 1988; 23: 839-841.
6. Black JA, Chaacombe DN, Ockenden BG. Nephrotic syndrome associated with bacteraemia after shunt operations for hydrocephalus. *Lancet* 1965; 2: 921-924.
7. Arze RS, Rashid H, Morley R, *et al*. Shunt nephritis. Report of two cases and review of the literature. *Clin Nephrol* 1983; 19: 48-53.
8. Haffner D, Schindera F, Aschoff A, *et al*. The clinical spectrum of shunt nephritis. *Nephrol Dial Transpl* 1997; 12: 1143-1148.
9. Groeneveld ABJ, Nommensen FE, Mullink H, *et al*. Shunt nephritis associated with Propionibacterium acnes with demonstration of the antigen in the glomeruli. *Nephron* 1982; 32: 365-369.
10. Pople IK, Bayston R, Hayward RD. Infection of cerebrospinal fluid shunts in infants: a study of etiological factors. *J Neurosurg* 1992; 77: 29-36.
11. Shapino S, Boaz J, Kleinmem M, *et al*. Origins of organisms infected ventricular shunts. *Neurosurgery* 1988; 22: 868-872.
12. Kiryluk K, Preddie D, D'Agati VD, *et al*. A young man with Propionibacterium acves-induced shunt nephritis. *Kidney Int* 2008; 73: 1434-1440.
13. Legoupil N, Ronco P, Berenbaum F. Arthritis-related shunt nephritis in an adult. *Rheumatology* 2003; 42: 698-699.
14. Iwata Y, Ohta S, Kawai K, *et al*. Shunt nephritis with positive titers for ANCA specific for proteinase 3. *Am J Kidney Dis* 2004; 43(5): e11-16.

BANTAO Journal 2014; 12(1): 122-124

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Case report

Drusen Formation in Type II Membranoproliferative Glomerulonephritis after Renal Transplantation

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Abstract

Type II membranoproliferative glomerulonephritis (MPGN) is a systemic disease that almost invariably recurs in renal allografts. This is a case of a 45-year-old woman with biopsy proven type II MPGN that led to renal failure 10 years after diagnosis. During the fifth month after cadaveric transplantation she was treated with pulse doses of methylprednisolone owing to acute T-cell mediated rejection without pathohistological signs of type II MPGN recurrence. One month later the patient was hospitalized due to acute bilateral vision deterioration. Ophthalmoscopy showed bilateral, multifocal drusen, concentrating in the posterior pole, and exudative ablation of the retinal pigment epithelium. Ocular coherence tomography (OCT) revealed focal retinal pigment epithelial elevation and detachments. The patient was treated with methylprednisolone (1 mg/kg) for 3 days. Therapy led to regression of exudation and flattening of the pigment epithelial detachments with discrete subjective visual improvement. Type II MPGN almost invariably recurs and leads to graft failure in 50% of cases. Our patient had evident chronic eye changes due to type II MPGN leaving allograft function intact during the first year of follow-up. Considering these potentially devastating effects of the disease, type II MPGN patients should be observed carefully from both the renal and eye point of view, because the severity of ocular changes, like in our case, is not always in line with allograft function.

Key words: type II membranoproliferative glomerulonephritis, drusen

Introduction

Type II membranoproliferative glomerulonephritis (MPGN) is a systemic disease of insufficiently understood origin [1]. The pathognomonic feature of type II MPGN is the presence of white-yellowish spots or drusen, extracellular dense depositions within the glomerular basement membrane (GBM), the choriocapillaris-Bruch's membrane-retinal pigment epithelial interface and the sinusoidal basement membranes of the spleen [2]. The first clinical report of fundus changes with "drusen-like" deposits was made by Duvall-Young in 1989 and since then drusen and retinal pigment epithelium damage have been recognized as features of type II MPGN [3]. Recent reports describe similar changes in type I MPGN [4]. Type II MPGN almost invariably recurs morphologically in renal allografts and, although progression to end-stage renal disease is not inevitable, half of the allografts ultimately fail [5].

Case report

We report a case of a 45-year-old woman with biopsy proven type II MPGN that led to renal failure 10 years after being diagnosed. After a year of hemodialysis she received a renal allograft from a cadaveric donor. Induction therapy consisted of antithymocyte globulin (9 mg/kg) followed by maintenance with tacrolimus (0.15 mg/kg), mycophenolate sodium and prednisone. During the fifth month after transplantation she was treated with pulse doses of methylprednisolone due to an episode of biopsy proven acute T-cell mediated rejection, without pathohistological signs of type II MPGN recurrence. At discharge allograft function was stable (Table 1).

Table 1. Allograft function during ocular drusen formation

	At the onset of visual deterioration	At discharge	One year later
scr (µmol/l)*	97	88	86
ccr (ml/min)**	89	98	79
Proteinuria (g/day)	0.2	0.12	0.04

*scr=serum creatinine, **ccr=creatinine clearance

One month later the patient was hospitalized due to acute bilateral vision deterioration. Blood tests revealed normal allograft function without any evidence of sys-

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temic inflammation (Table 1). There were no signs of vasculitis or recent history of accelerated hypertension. The NMR excluded expansive processes in the endocranium. Ophthalmoscopy showed bilateral, multifocal drusen, concentrating in the posterior pole and exudative ablation of the retinal pigment epithelium (Figure 1). In addition, ocular coherence tomography (OCT) revealed focal retinal pigment epithelial elevation and detachments (Figure 2). The patient was treated with methylprednisolone (1 mg/kg) for 3 days, with graduated dose reduction. The control OCT 4 months later showed

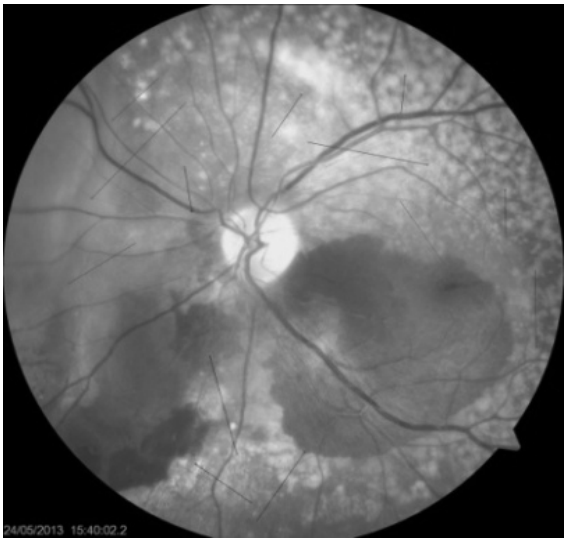

Fig. 1. Ophthalmoscopy: drusen and subretinal hemorrhage of the left eye

regression of exudation and flattening of the pigment epithelial detachments followed by discrete subjective visual improvement. During the follow-up of 1 year there were no reported signs of allograft function deterioration or proteinuria (Table 1).

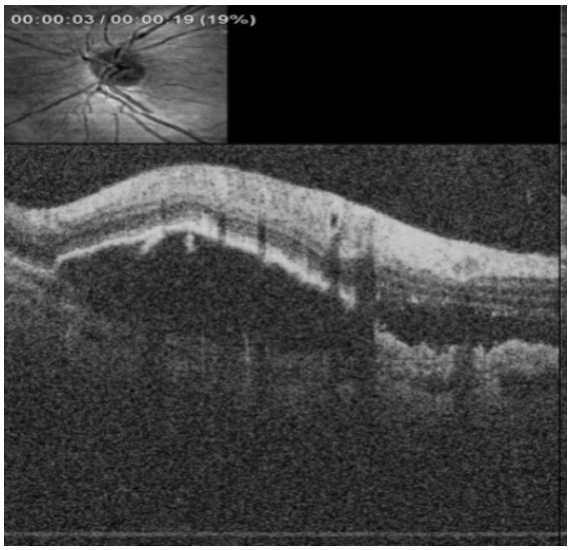

Fig. 2. Ocular coherence tomography: retinal pigment epithelial elevation of the left eye

Discussion

Type II MPGN is an uncommon renal condition leading to end-stage renal failure in 6 to 10 years [6)]. Its systemic nature lies in the fact that the electron dense deposits may also be found in the spleen, choriocapillaris and Bruchs membrane of the eye and because the disease has a tendency of recurring in allografts [7]. Unlike ocular drusen in age-related macular degeneration, typically seen in patients over 50 years old, those in type II MPGN occur at an early age and correlate with the duration of the renal disease [7,8]. These deposits initially have little impact on visual acuity. However, long-term visual deterioration caused by subretinal neovascularisation, macular detachments and central serous retinopathy occurs in approximately 10% of patients with type II MPGN [1].

There is no correlation between disease severity in the kidney and in the eye, so an ophthalmologic examination at the time of diagnosis including periodical fundoscopic assessments as part of the patient's treatment is suggested [9)]. Our patient had posterior pole drusen deposition with hemorrhagic ablation of the retinal pigment epithelium and acute vision deterioration suggesting bleeding from subretinal choroidal neovascular membranes and a chronic nature of the eye deposition. There is no universally effective treatment for type II MPGN, including the eye changes [1]. There are data suggesting spontaneous and significant improvement in the anatomical and clinical picture in the retina of patients suffering from type II MPGN [10]. We treated our patient with pulse doses of corticosteroids for 3 days and subsequent low doses of prednisone. Therapy led to relative improvement of vision acuity and OCT findings. Type II MPGN almost invariably recurs morphologically in renal allografts leading to graft failure in 50% of cases [1]. In our case, the patient had only evident chronic eye changes due to type II MPGN, leaving allograft function intact during the first year of follow-up. Segmental areas of retinal pigment epithelium detachments associated with secondary exudation following organ transplantation were first described in 1992 and it was suggested that local intravascular coagulation induced by subclinical graft rejection may have some impact on the ocular symptoms [11].

However, some results of long-term monitoring indicated that renal transplantation did not appear to increase the risk of progression of drusen and choroidal neovascularisation in patients with type II MPGN [7, 9].

Conclusions

Considering the potentially devastating effects of the disease, type II MPGN patients should be observed carefully from both renal and eye points of view, although the severity of ocular changes, like in our case, is not always in line with allograft function.

Conflict of interest statement. None declared.

References

1. Appel G, Cook H. T, Hageman G, Charles J, *et al.* Membranoproliferative glomerulonephritis Type II (Dense Deposit Disease): An Update. *J Am Soc Nephrol* 2005; 16: 1392-1404.
2. Colville D, Guymer R, Sinclair RA, Savige J. Visual impairment caused by retinal abnormalities in mesangiocapillary (membranoproliferative) glomerulonephritis type II ("dense deposit disease"). *Am J Kidney Dis* 2003; 42: E2-E5.
3. Duvall-Young J, Short CD, Raines MF, *et al.* Fundus changes in mesangiocapillary glomerulonephritis type II: clinical and fluorescein angiographic findings. *Br J Ophthalmol* 1989; 73: 900-964.
4. Han DP, Sievers S. Extensive drusen in Type I membranoproliferative glomerulonephritis. *Arc Ophthalmol* 2009; 127: 577-579.
5. Moritz MJ, Burke JF, Jarrell BE, Carabasi RA. The incidence of membranoproliferative glomerulonephritis in renal allografts. *Transplant Proc* 1987; 19: 2206-2207.
6. Brenner BM (ed). Pathogenesis of renal disease. In: Brenner and Rectors. *The Kidney*, Vol 1, 7th ed. WB Saunders: London, 2004; 1322-1327.
7. McAvoy CE, Silvestri G. Retinal changes associated with type 2 glomerulonephritis. *Eye* 2005; 985-989.
8. Paulus T, De Jong M. Age-related macular degeneration. *N Engl J Med* 2006; 355: 1474-1485.
9. D'Souza Y, Short CD, McLeod D, Bonshek RE. Long-term follow-up of drusen-like lesions in patients with type II mesangiocapillary glomerulonephritis. *Br J Ophthalmol* 2008; 950-953.
10. Empeslidis T, Imrani U, Vardarinos A, *et al.* Spontaneous resolution of retinal pigment epithelial detachments and visual improvement in a patient with MPGN II: A case report. *Case Reports in Ophthalmol Med* 2012; Volume 2012, Article ID 864198.
11. Gass JDM, Slamovits TL, Fuller DG, *et al.* Posterior chorioretinopathy and retinal detachment after organ transplantation. *Arch Ophthalmol* 1992; 110: 1717-1722.

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3. Rycroft RJG, Calnan CD. Facial rashes among visual display unit (VDU) operators. In: Pearce BG, ed. *Health hazards of VDUs.* Wiley, London, UK: 1984; 13-15
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