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НИРКИ KIDNEYS

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Шановні друзі і колеги!

Слоган цього номера: «Вчись вибирати». Ось до нього невеличка історія.

В одному зоопарку жив слон. Звичайний африканський слон, анітрохи не гірший і не кращий за інших.

Але одного разу прийшли люди, виміряли його в усіх напрямках, а потім сказали:

— Цей слон має найбільші вуха серед усіх слонів, які живуть у зоопарках.

Слон одразу запишався.

— Ви чули, — казав він, — у мене найбільші вуха з усіх слонів, які мешкають у зоопарках!

І він вимагав, щоб усе це було написане на його клітці. Відтоді біля його вольєра стало збиратися найбільше народу. Ще б пак, адже це був не звичайний слон, а слон із найбільшими вухами. Навіть дуже важливі люди — міністри та посли — хотіли познайомитися з ним.

— Послухай, — казали йому друзі, — у цьому немає жодної твоєї заслуги. Ти маєш бути найскромнішим і наймилішим слоном з усіх слонів, які живуть у зоопарках.

Але хоч у слона були найбільші вуха, він нізащо не хотів слухати поради друзів. Недарма ж йому давали найкращі вольєри, його знімали в кіно, його обрали почесним слоном у всіх зоопарках світу.

Більше того, до нього було приставлено спеціальну людину, яка мила його і доглядала його великі вуха.

Якось ця людина перестаралася. Вона так сильно виполоскала вуха слона, що вони після прання зсілися.

Люди стали дивуватися:

— А чому цей слон займає найкращий вольєр?

— Бо мав найбільші вуха.

— То ж були…

І слона відправили у спільний вольєр, до його старих друзів. Але слон не хотів жити із друзями. Він дуже звик до популярності. Тому він пішов із зоопарку і став блукати найближчими полями та ущелинами. Від мандрівного життя він скоро схуд, змарнів і взагалі став більше схожим на верблюда.

Невідомо, чим усе це скінчилося б, якби до нього знову не підійшли люди. Вони розмовляли з ним, а потім сказали:

— Цей слон — найдурніший слон з усіх слонів, які мешкають у зоопарках.

Путівник одразу підбадьорився.

— Чули, — похвалявся він, — я найдурніший слон з усіх слонів, з якими розмовляли!

Він знову повернувся до зоопарку, і йому знову надали найкращий вольєр.

Так він і живе в ньому досі. Він усім задоволений, але найбільше у світі тепер боїться одного: як би несподівано не порозумнішати.

(«Четверо під однією обкладинкою», Едуард Успенський, 1966 р.)

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Nephrological care in the conditions of martial law in Ukraine

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Abstract. *During armed conflicts (AC) and other disasters, the elderly, women, children, the infirm and the chronically ill patients are the most vulnerable population, with a high risk to health and life. Chronically ill people with kidney diseases, including those with kidney failure, deserve special attention due to their complete dependence on available functional infrastructure, and access to vital drugs and well-trained personnel. Currently, there is little information on the effects of AC on patients with kidney damage compared to the available data about the effects of other disasters. Mechanisms of injuries in AC and natural or man-made disasters have similar and distinctive features. Distinctive features: during AC — mainly gunshot and mine blast injuries, bleedings, poisonings by toxic substances, during disasters — hypothermia or burns, mechanical injuries, etc. Similar features include damage to infrastructure, particularly health care facilities, shortage of medicines, medical personnel, humanitarian and other crises, and a large number of injured and traumatized people in the hospitals. In this article, we systematized the material obtained during the military conflict, as well as reviewed domestic and foreign articles on this topic in order to optimize the work of nephrologists in the conditions of martial law and limited resources.*

Keywords: *martial law; chronic kidney disease; refugees; nuclear conflict; renal replacement therapy; dialysis; kidney transplantation; humanitarian crisis*

Background

Emmanuel Macron, at the beginning of the full-scale invasion by Russia, said: "That nothing will be like before". Most people will probably agree with this quote. But there is another famous quote: "War is barbarism when attacking a peaceful neighbour, but it is a sacred duty when defending the Motherland" (Guy De Maupassant). All too often, in recent times, armed conflicts (AC) with violence and mass damage and killing of civilians, and non-combatants have occurred [1]. More than 70 wars are currently going on in the world, which means that there are more than 400 million children in conflict zones [2].

International or inter-ethnic conflicts (wars) are force options, with the use of armed forces, to resolve disputed issues between two or more parties. The number of active conflicts in 2020 reached a record level since the Second World War. The United Nations (UN) constantly calls on all conflicting parties to cease fire, but, despite this, more than one billion people (in 2022) are at health and life risk of active conflicts (Africa, Syria, Ukraine and others) [3, 4].

The war is a catastrophe that has seriously affected and continues to negatively affect the lives of all patients. About 2.7 million people with disabilities are registered in Ukraine. Broken infrastructure creates significant barriers for patients to receive by them vital treatments. Patients are at high risk regardless of whether they remain in affected areas or move elsewhere, putting themself at risk in the absence of appropriate care, resulting in increased morbidity and mortality [5–8].

The war artificially creates a defect in chronic care for our patients [9]. Military actions induce long-term consequences for the health of all Ukrainians. Children, the sick, the elderly and senile, women, the poor and refugees suffer the most [10].

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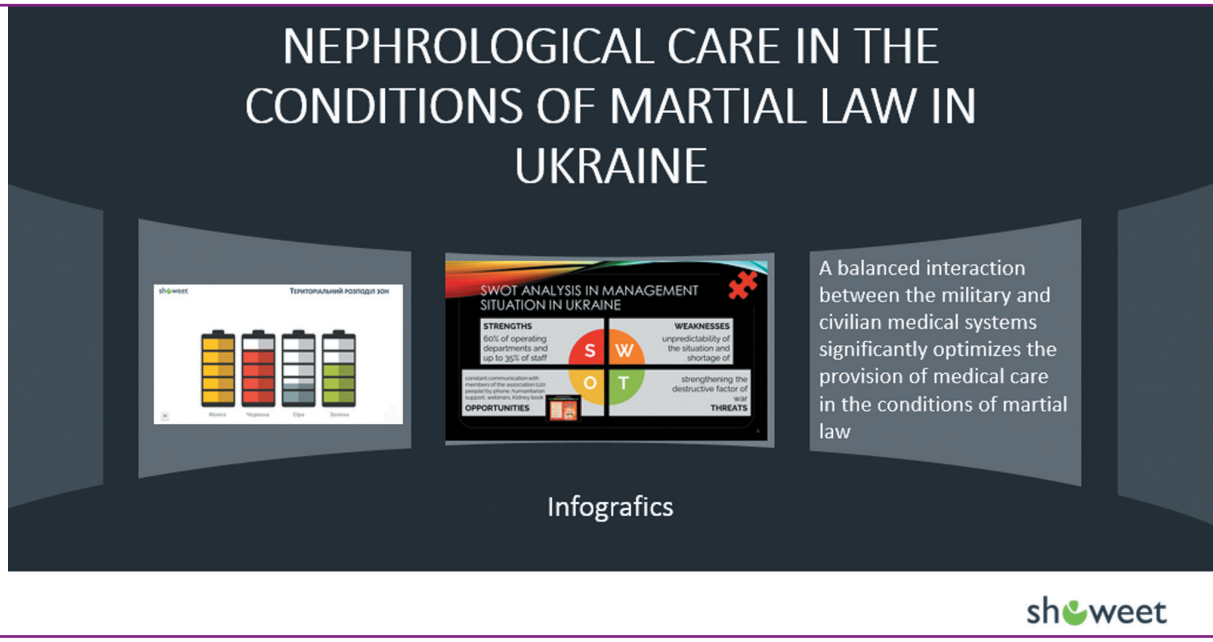

Figure 1

Zone D. This is an annexed or temporarily occupied territory that is currently under the control of Ukraine. Russia bears full responsibility for providing the population with medical aid

Zone A. The territory where active hostilities are taking place. As a rule, nephrological care is needed by patients (wounded) with prolonged soft-tissue crush syndrome, dehydration (acute and chronic), those who were exposed to toxic effects during the destruction of chemical enterprises of Ukraine, or the military/population with a severe exacerbation of CKD

Classification of Ukrainian territory during martial law in 2022

Zone C. Characterized by the absence of active hostilities, a low risk of missile strikes, provision of nephrological patients with all types of medical care in conditions of limited military resources

Zone B. This is a front-line area that is subject to evacuation and is subject to active enemy military intervention in the form of rocket and artillery bombardment and disruption of logistical processes, which negatively affects the provision of medicine and medical care to nephrology patients. In this zone, a large number of patients (migrants, transit, from zone A) who need RRT can be observed

Figure 2. Classification of Ukraine territory zones during ML in 2022

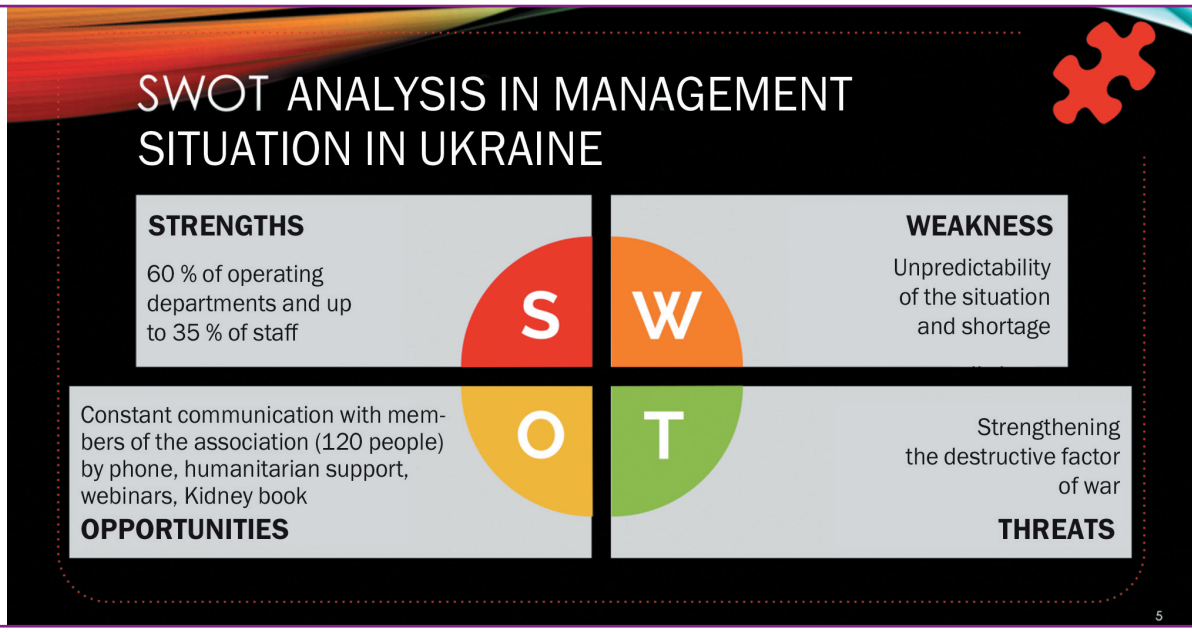

Figure 3

Personal problems

The increase in the burden on medical personnel, the shortage of medical personnel and the lack of algorithms and protocols of action during ML in various situations worsen the quality of nephrological care for patients [3].

From the professional point of view of a nephrologist, we have conditionally divided the territory of Ukraine into four zones (Figure 2):

— Zone A (red). The territory in which active hostilities take place. As a rule, nephrological care is needed for patients (wounded) with prolonged soft-tissue crush syndrome, dehydration (acute and chronic), those who were exposed to toxic effects during the destruction of chemical enterprises of Ukraine, or the military/population with a severe exacerbation of CKD. Patients with acute kidney injury who need RRT can receive it at the nearest dialysis units [3, 11];

— Zone B (orange). This is a frontline area that is subject to evacuation and is subject to active enemy military intervention in the form of missile and artillery bombardment and disruption of logistical processes, which negatively affects the provision of drugs and medical care to nephrology patients. In this zone, a large number of patients (refugees, transit, from zone A) who need RRT may be observed [3, 11];

— Zone C (green) — characterized by the absence of active hostilities, low risk of missile strikes, and provision of nephrological patients with all types of medical care in conditions of limited resources of the ML [3, 11];

— Zone D (grey) is an annexed or temporarily occupied territory that is not currently under the control of Ukraine. Russia is fully responsible for providing the population with medical care [3, 11].

Patients of the most vulnerable category are the first to suffer: dialysis patients, who will have logistical problems with visiting their centers and receiving a dialysis procedure (air alarms, lack of drugs or consumables, etc.), kidney transplant patients, who may be left without vitally necessary drugs [9].

Mortality is expected to be higher in CKD patients compared to healthy people, due to logistical problems, unsatisfactory medical care, etc. Of course, the highest risks are seen in patients receiving dialysis or after a kidney transplant. 4 million CKD patients (10–15 % of the population) in Ukraine are at risk of the consequences of ML [3].

During the period from February 24 to August 1, almost 600 patients with CKD stage 5D left Ukraine. The authors gained their own experience by remotely consulting such patients, helping them to solve organizational issues with conducting RRT abroad and continuing to provide dialysis care on the territory of Ukraine, with extremely limited opportunities (lack of supply of consumables, difficulties in transportation to dialysis, etc.).

In order to improve the provision of medical care in Ukraine, we analyzed the experience of acute kidney injury (AKI) according to the data on the Korean military conflict [9]. During the Korean War, the mortality rate was 53 % among AKI patients (dialyzed and non-dialyzed). In recent wars, despite some improvement, the mortality rate is still 22 % [3]. Chronic, long-term disasters (the 11th year of the Syrian war) [12] have a greater negative impact on the course of CKD than short-term conflicts.

Table 1. Military-Induced Factors Affecting KD [5]

		Medical factors	Logistic factors
Specific KD Patients with acute kidney injury	Patients with acute kidney injury	The cause of the disease can be bleeding (when wounded), crushing and other injuries, exposure to harmful gases/agents	Shortage of nephrological personnel, medical appliance and materials, technical capabilities of dialysis
	Patients with CKD, pre-dialysis stage	High risk of complications through to interruption of treatment due to suboptimal conditions	There is limited or no access to immunosuppressive, hypoglycemic, antihypertensive and other drugs necessary for routine treatment of CKD
	Patients with CKD stage 5D	Complications due to inadequate dialysis	The shortage of dialysis personnel and consumables for its implementation leads to inadequate dialysis
	Kidney transplant patients	Complications due to interruption of treatment, high risk of developing infections (due to living in unhygienic conditions and immunological imbalance)[1]	There is limited or no access to immunosuppressant drugs and transplant doctors
Non-specific		High risk of medical problems due to prolonged stay in an “unhealthy” environment (hypothermia, etc.)[1], inadequate and/or inappropriate nutrition and treatment	Damage to general infrastructure and health care infrastructure, shortage of nephrologists and other medical personnel, necessary materials and medicines, limited or no access to vital resources/means

Note: [1] — Subway tunnels, basements, open-air tents, etc.

The mortality rate of dialysis patients who remained in the conflict zone during the Iraq-Kuwait war was 42 %, which is significantly higher than for patients who left the country (12.7 %). Sick and elderly patients may not have had the opportunity to leave. Insufficient weekly dialysis doses due to damaged health infrastructure likely also contributed to these negative outcomes in regions affected by AK [3].

During the period of limited conditions for the provision of medical care (February 24 — May 31, 2022), the number of patients receiving RRT in Kyiv decreased by 34 %, some patients were transferred to dialysis 2 times a week, and the number of erythropoietin, immunosuppressant, antihypertensive drugs was reduced. An increase in average daily BP levels was recorded: SBP by 12.2 ± 2, DBP by 6 ± 2 mm Hg.

Traffic in the city was limited, and in some areas — absent, due to the bombing. In Kyiv, almost the entire nongovernmental dialysis service has stopped working due to a shortage of medical personnel and disruption of logistical processes (see slide). Prof. D. Ivanov's nephrology clinic (clinical base of the Department of Nephrology and RRT of the Shupyk National Healthcare University of Ukraine) worked all this time. During the period from February 24 to August 1, there was an increase in consultations, diagnostic examinations (invasive and non-invasive) and hemodialysis (HD) sessions for patients who could not receive care at the place of their previous observation. The entire team of the clinic, including employees of the department, who are attached to the clinical base, remained at their workplace almost in full. Thanks to the courage and dedication of the employees of the clinic and the Department of Nephrology and RRT, all patients of the clinic received proper nephrological care [3, 11].

Picture 3 presents a SWOT analysis of the management situation in Ukraine [3, 11, 13].

In Kyiv, the city's largest clinical children's hospital was closed, and the staff was reduced by 70 %. The supply of medicines was stopped, and there was a defect in nephrological care due to a decrease in the number of paediatric nephrologists in the field and disruption of the logistical chains of providing medical care to the children population [3, 11]. We were forced to reduce the doses of immunosuppressive drugs due to their shortage, to transfer children with nephrotic syndrome to rituximab due to a shortage of hormones and mycophenolate mofetil, to reduce the dialysis dose for children on dialysis due to a shortage of consumables, to reduce the prescription of erythropoietin, drugs affecting bone metabolism, to increase doses of antihypertensive drugs, as hypertension, that possibly caused by stress, increased by 34 %. In approximately 70 % of cases, such temporary changes did not lead to a fatal outcome, in 20 % they significantly worsened the condition, and in 10 % they ended tragically.

Paediatric population

Until February 24, 2022, two Ukrainian centers — Lviv and Kyiv — provided RRT for children. Until February 24, 17 children were receiving RRT at the OHMATDYT National specialized children's hospital Ministry of Health of Ukraine (OHMATDYT NSCH) base, 8 children were on HD and 13 were on peritoneal dialysis (PD) at the West Ukrainian Specialized Medical Center. In March, the situation in Kyiv was very tense, in this regard, on March 8, 2022, children receiving RRT at the OHMATDYT NSCH were evacuated to the Western Ukrainian specialized children's medical center (WUSCMC). After evacuation from other regions of Ukraine, the number of patients increased to 22 on HD and 30 on PD, some children went abroad for treatment.

Almost all children with CKD stage 5D from the city of Kyiv were evacuated to Western Ukraine and abroad, only 3 children remained in OHMATDYT NSCH. Today, more than 2/3 of them have returned to Ukraine. Approximately 30 % moved to safer regions. This process of displacement within the borders of Ukraine continues even now, this is determined by the map of the activity of military actions [3, 11]. The evacuation from Kyiv of almost all children who received RRT allowed them to continue their specialized nephrological treatment. Although we would feel safer if we had mobile dialyzers, which are needed during the transportation of children to their temporary evacuation site.

During the first 3 months of ML, 29 children on RRT together with 40 family members crossed the border: 13 were on PD, 10 on HD and 4 after kidney transplantation and 3 patients with syndromes: congenital nephrotic syndrome, atypical hemolytic-uremic syndrome and nail-patella syndrome. 26 children were referred to Polish nephrology centers (Warsaw, Krakow, Lublin, Gdansk, Wroclaw, Białystok, Poznań, Szczecin), and 3 children were referred for further treatment to Germany (Marburg, Cologne and Hamburg).

Since the beginning of ML in Lviv, 5 kidney transplants have been performed for children, in particular, 3 transplants have been performed at the WUSCMC. Fruitful cooperation has been established with children's nephrology centers in Warsaw, Krakow, Gdansk, and the Charite Clinic. We express our sincere thanks for the constant support and provision of humanitarian aid for Ukrainian children in the form of medicines and consumables for HD.

During the period of ML, 133 patients, internally displaced persons (IDPs) from the affected regions were treated at the Kyiv city center of nephrology and dialysis and 8 kidney transplants were performed, of which 4 were family, and 4 were donors.

The Institute of Nephrology of the Academy of Medical Sciences of Ukraine has developed recommendations for the organization of treatment of HD patients in wartime (cooperation with military administrations, disinfection of HD devices in conditions of water and time shortages, an algorithm for emergency disconnection of patients if necessary and optimization of isolation of patients with COVID-19) [14].

Disruptions in the health care system create a serious long-term risk for patients, especially those with CKD, chronic cardiovascular disease (CVDs), and oncology. Military actions cause a shortage of personnel and an increase in the burden on personnel and patients. Many medical work-

ers were injured, killed or forced to flee their homes, leading to shortages of medical personnel and disruption of logistics processes [10].

Care by general practitioners

It is difficult to underestimate the nephrology care provided by primary health care. Basically, the majority of patients over 60 years of age with early-stage CKD seek primary care (prevalence of almost 30 %). In only a small number of patients, CKD progresses to end-stage renal disease (ESRD) requiring RRT. It is known that referral to a nephrologist one to six months before the start of dialysis reduces mortality and hospitalization, and also has a positive effect on the quality of preparation for dialysis [15]. Wartime family medicine is more than just primary care. In addition to the fact that family doctors take care of the health of their patients, they have a load, including volunteer work. In addition, our family doctors provide medical care to the wounded.

Internationally, there are differences in health care systems regarding referral to specialized nephrology services, which are reflected in many clinical practice guidelines and recommendations for the treatment of CKD with different criteria. In most guidelines (British guidelines of The National Institute for Health and Care Excellence (NICE, 2014), The KD: Improving Global Outcomes (KDIGO, 2012), and The German College of General Practice and Family Medicine (DEGAM, 2019)), the patient is referred to a nephrologist from stage 4 (estimated glomerular filtration rate (eGFR) < 30 ml/min). Also, referral with GFR 30–59 ml/min is recommended, if additional criteria are present. The German Society of Nephrology (Deutsche Gesellschaft fur Nephrologie (DGfN)) and The German Society of Internal Medicine (Deutschen Gesellschaft für InnereMedizin (DGIM)) recommend referral with GFR < 45 ml/min (Guideline with recommendations, 2015). In 2021, a KF risk equation was proposed for clinical practice to estimate the 5-year risk of RRT need (NICE, 2021). A risk of 5 % is suggested as a threshold for referral to a nephrologist [15].

Many Ukrainians are used to waiting until the last thing to do when it comes to taking care of their health, and during hostilities, their own health always takes the last place on their agenda. Therefore, the role of family doctors should also be to draw the attention of all their patients who have signed declarations that ML is not a reason not to worry about their health. On the contrary, we have a great burden on the psychological health of each person, we may not diagnose the development or exacerbation of chronic diseases in advance, or miss the optimal time to start treatment.

All this can be done by contacting a family doctor. This is important now because after ML we will have many people who will need a large amount of time to bring their health back to the level it was before ML. Military time is exactly the time when you need to go to the family doctor to check your health again and prevent health problems.

Avoiding the unnecessary referral of patients to a nephrologist at low risk of KF is not usually a primary goal, but given the high incidence of CKD, the shortage of nephrologists, and the additional financial burden on health care in an ML environment, it is essential [15].

In the first months, mostly forcibly displaced Ukrainians, who were often in a state of stress and in need of external support, turned to medical institutions. Therefore, the specifics of the work of family doctors have changed, because, despite various diseases, patients also needed the consultation of a psychologist. In the conditions of ML, family doctors also provide psychological help.

Family physicians continue to issue electronic prescriptions to their patients. During ML, about three million Ukrainians were issued electronic prescriptions, which means that family doctors are in constant contact with their patients. They consult remotely, in particular, by phone. And this makes it possible to keep the entire medical system in good shape.

For patients with a nephrological profile who are shown specialized treatment and patients with a high risk of progression of CKD to the ESRD, ensuring timely and full access to a nephrological service, in the conditions of ML and limited resources, is a priority, and unified criteria for referral to a nephrologist, significantly facilitate the work of the primary link [15].

Damage to HCF in Ukraine has a negative impact on the health of citizens. The World Health Organization (WHO) recorded more than 200 attacks on HCF by the end of April 2022, including 54 injuries and 75 deaths among medical personnel and patients [10]. On April 28, the UN High Commissioner for Human Rights reported 6,009 civilian casualties (including 2,829 dead and 3,180 wounded) as a result of the AC in Ukraine, the real number is expected to be much higher [16]. During the 3 weeks of the AC, according to the Ministry of Health (MoH), 117 hospitals were damaged (including maternity centers) [7, 10, 16–18].

It is expected that the number of non-working HCF will increase. According to the assessment of the former Deputy Minister of Health of Ukraine, the damage caused to the medical facilities of Ukraine is enormous: the medical infrastructure of entire cities was destroyed, and roads were damaged and mined, which further limited access to medical facilities [10].

A particular problem is dialysis refugee patients, who are often on the move for several days, with limited or no access to their usual therapeutic resources and are deprived of nephrologist follow-up, who always need support in an unfamiliar area, because of communication problems (foreign culture or/and language) [5, 7, 19].

Refugee CKD patients

Refugee-hosting countries have implemented a large number of short-term emergency measures to support refugees. Long-term measures to integrate refugees into the life of the local population remain problematic. These countries, acting as a transit for the transportation of goods and essential items to and from Ukraine, feel the need for coordinated cooperation between all interested parties [20].

During an AC, patients with KD, like the general population, may stay in the war zone or move to other safer re-

gions of Ukraine, IDPs, or leave for other countries (refugees) [3, 21].

In 2021, the number of displaced persons reached 89.3 million. The Syria crisis has led to 6.9 million IDPs and another 5.6 million refugees after 11 years of war [12].

On March 19, 2022, 2.0107 million refugees from Ukraine arrived in Poland, 518.3 thousand — in Romania, 359.1 thousand — in Moldova, 299.3 thousand — in Hungary, 240.0 thousand — in Slovakia, 184.6 thousand — in Russia, and 2.5 thousand arrived in Belarus [22].

On March 29, more than 4 million refugees left Ukraine (over 1.5 million children), and about 7 million IDPs. The majority of refugees (76 %) arrived in Poland [22–26].

At the beginning of May 2022, more than 5.8 million refugees left Ukraine. Found asylum in neighboring countries: 3.2 million — in Poland, 0.86 million — in Romania and 0.56 million — in Hungary, but a much larger number is IDPs [10, 24–26].

6.8 million Ukrainians became refugees as of May 31, 2022. IDPs during this period — another 8.0 million Ukrainians who remained in Ukraine. A total of 14.8 million Ukrainians (33.5 % of the country's 44.1 million citizens) were forced to leave their homes within three months. Due to the AC in Ukraine, the world's number of displaced persons increased from 84 million to 99 million (a total increase of 17 %). Children and women make up almost 90 % of refugees from Ukraine. As of May 31, 2022, only one-third of the 7.5 million Ukrainian children under the age of 18 remained at home. The remaining two-thirds of children (over 2.2 million) migrated to European countries, and 3 million became IDPs [4]

As of June 9, 2022, the Office of the United Nations High Commissioner for Refugees (UN HCR) reported on its website the number of refugees from Ukraine registered for temporary protection in Europe — was 3.207 million [https://interfax.com.ua/news/general/838562.html].

As of June 14, 2022, during the Ukrainian disaster, the number of IDPs (7.1 million) and refugees (4.9 million). During displacement and in destination countries, refugees may face more dangerous conditions than those who remain at home. Difficulties in using a foreign health care system and problems in communication due to language or cultural barriers negatively affect the provision of medical care, the number of medical errors, etc. [3, 7, 19, 27, 28].

Most of the Ukrainian refugees went to Poland and several other border countries. The support provided by European countries and their people is extraordinary. However, the local therapeutic infrastructure, near the Polish border, maybe overwhelmed [5, 24–26].

In Poland, a law was adopted that guarantees legal stay and employment for 18 months, and also provides access to health care and social security systems (funds for children's education) [20]. Providing one million refugees with access to health care is estimated at 200 million zlotys per month (US$47 million) [7].

According to UN HCR data, the largest number of refugees with the status of temporary protection is in Poland — 1 million 152.36 thousand, despite the fact that, according to the data of the Polish border service, 3.865 million people arrived in the country from Ukraine from the beginning of the war until June 9, and in the reverse direction, 1.738 million people travelled to Ukraine [https://interfax.com.ua/news/general/838562.html].

For Ukrainians, Canada issued 112,035 temporary visas (241,620 people applied), and 32,201 refugees were registered as of May 18, 2022. There are 2 ways to enter Canada for Ukrainians: for those who wish to become permanent residents (family reunification) or as temporary residents with a 3-year visa (Canadian-Ukrainian Emergency Travel Authorization (CUAET)). Citizens of Ukraine, under the CUAET program, can obtain visas within 14 days, without any processing fees, with a term of up to 3 years, for temporary residence. Residents have the right to apply for a free open work permit, attend primary and secondary schools, and receive provincial health insurance [29].

In general, according to the UN, about 10 million people have left Ukraine since the beginning of ML, while 2.388 million have returned (without data from Hungary, the Russian Federation, and Belarus). According to this information, the total number of refugees since the beginning of ML is estimated by the UN to be approximately 4.8 million people [https://interfax.com.ua/news/general/838562.html].

In addition to the deep concern about the increase in the cost of energy and gas, and the recession of the economy, which will significantly affect the cost of providing care to our patients, the world media, from the first days, talked about humanitarian corridors and helping refugees [9, 30].

The "Directive on Temporary Protection", which came into force on March 4, 2022, provides for social security in any EU member state, granting Ukrainians residence permits, access to work, access to education for minors, and the possibility of family relocation [20].

On March 8, 2022, the legislative act "Program for Cohesion for Refugees in Europe (CARE)" was adopted, which allows the financing of humanitarian measures [20].

WHO, UN agencies and the International Federation of Red Cross and Red Crescent Societies (IFRC) also actively support Ukraine and neighbouring countries, provide first aid, transport people, and organize humanitarian aid and basic training [20, 31].

The International Movement of the Red Cross in Poland, Hungary, Romania, Moldova, and Slovakia has centres at border posts with rescue teams that provided assistance to arriving refugees [20].

Organizations such as the International Red Cross or Doctors Without Borders provide medical assistance to people who find themselves in disputed parts of Ukraine, as well as to IDPs and refugees. Also, they provide fresh water, food, shelter, emergency medicine and treatment [10].

To monitor the impact on public health in Ukraine, the Association of Schools of Public Health in the European Region (ASPHER) created a working group to prevent, prepare for and respond to the AC in Ukraine [32].

For Ukrainian refugees in the countries, humanitarian benefits have been introduced:

1. Free treatment of military personnel injured as a result of hostilities.

2. Free psychologist consultations, medical examinations, and dental and medical services.

3. Registration of children in preschool and school institutions.

4. Organization of information centers, specialized sites, and hotlines in Ukrainian and Russian.

5. Free prescription drugs that were issued in Ukraine or in the host country.

6. One-time cash payment to arrive refugees and host families.

7. Establishing guardianship over unaccompanied minors, etc.

8. Free public transport.

9. Creation of medical teams at border checkpoints to examine people and domestic animals [20].

In EU countries, there are doctors and nurses among the refugees from Ukraine. In many countries, in their own health care systems, programs have been created to optimize the work of refugee doctors and nurses [7].

According to the provided results of the estimates of the International Organization for Migration, from March 9 to 16, 2022, about 6.5 million Ukrainians were IDPs, and 53 % of displaced persons were women. Ukraine ranked ninth among IDPs in the world, even before the Russian invasion. It has been recorded how IDPs faced deliberate beatings, rapes, kidnappings, murders, bombings and attacks by the Russian military [20, 33]. Another vulnerable population group is stateless persons, almost 40,000 such people live in Ukraine according to UNHCR estimates. Also, there are more than 5,000 refugees and persons who have received additional state protection in Ukraine, their fate is not yet determined. These vulnerable population groups need more attention and help [20].

Adult patients

In 2019, 10,250 patients received RRT (European Renal Association (ERA) 2019) in Ukraine; of them on HD or hemodiafiltration — 7869, 922 — on PD and 1459 with a transplanted kidney (mainly from living donors) [5]. In Ukraine, at the beginning of 2021, 11,181 patients (268 per million) received RRT, of which 6,017 were treated with HD, 2,700 with hemodiafiltration, and 931 with PD, and 1,533 underwent kidney transplantation [14].

The number of patients with HD and after kidney transplantation has increased significantly in recent years (2021–2022) due to the implementation of medical reform. A register of kidney transplant recipients was created (more than 300 kidney transplants from cadaveric donors) [14].

Before the start of hostilities, all patients after kidney transplantation received immunosuppressants, iron preparations, erythropoietin, and phosphate binders in full. Patients with CKD stage 5 could freely choose the method of RRT and the dialysis center, if there were restrictions on choice, they were of a purely medical nature [14].

Now, especially in some regions, the state of nephrology and dialysis services has changed. The problem of delivery of consumables for HD comes to the fore, as well as limited or no access to the dialysis center for patients and medical personnel due to bombing and rocket attacks. Dozens of patients have problems getting to their dialysis centers and there are even those who have not received dialysis for more than a week [14].

Currently, some dialysis centers and departments have been evacuated, some are not working, and some are at risk of becoming inoperable. Some part (no one knows the exact numbers) of 10,250 patients moved to another place in Ukraine, or, in general, abroad. Nephrologists of Ukraine and neighbouring countries have probably already felt the burden [5].

Patients receiving RRT in conditions of ML, limited resources, constant rocket bombardment and curfews are the most vulnerable category [14]. Every day, risking their lives, our nephrologists and nurses and other staff do everything possible and impossible to provide patients with adequate HD. The entire Ukrainian nephrology community is united now, more than ever [14]. In Ukraine, from an ordinary medical workers to the president, the workplace courage index (which defines 11 forms of behaviour) (Detert, 2021) is impressive [34].

As of April 22, 2022, the population of Ukraine is 44.1 million people, of which 4.99 million people (11.31 %) are already infected with COVID-19 and more than 0.1 million deaths from COVID-19 have been recorded. In Ukraine, 15 million people (33 %) are vaccinated against COVID-19 (WHO), despite the fact that vaccination campaigns against COVID-19 and routine immunization have practically stopped throughout the country [35–39].

So far, many offers have been received from several countries to treat our dialysis patients and fortunately many of our patients are now continuing their treatment in Poland, Germany and other countries [14].

As the present shows, the nephrology sector suffered the most from military operations. The reasons are different: the need for intact general and medical infrastructure and special equipment risks to the life and health of nephrologists and their families, and a large number of patients with complications of AKI and CKD [5].

The proper work of a nephrologist depends on teamwork (dialysis nurses, engineers, technicians and laboratory technicians, nutritionists, psychologists), where everyone faces the same problems and overloads as nephrologists themselves. Also, for effective work, nephrologists often need the consultation of related specialists, such as intensive care specialists, surgeons, traumatologists, and emergency physicians, which significantly increases their workload. Burnout during the period of military operations among nephrologists is a common phenomenon, which has a very negative effect on the nephrology and dialysis services of Ukraine [5].

Patients with CKD are very vulnerable and there is a high risk that they may be injured during military operations. Because access to dialysis, immunosuppressive and other drugs for them may be limited or absent, which may lead to their death. The CKD patient community requires uninterrupted access to dialysis, transplantation, and medical care. There is solidarity between the various kidney disease communities and they are all willing to support each other [5].

The international nephrology community must be ready to organize support for affected nephrology patients and nephrologists. Unfortunately, there are no patient algorithms

and routes and other information (instructions, protocols, recommendations) in the conditions of military operations and a shortage of medical resources and other material and technical problems in nephrology [5].

The following are examples of possible solutions during wartime:

1. Everyone must be prepared, at all levels, from the nephrologist to the MoH, to respond effectively to disasters and military operations to ensure adequate nephrology care for all who need it [5].

2. Reduced demand for dialysis during hostilities may result in fewer dialysis sessions per week, reducing the burden on the dialysis service. In this case, patients should be recommended a special low-protein diet and other dietary restrictions to reduce intoxication, electrolyte disorders and hyperhydration [5].

3. Telemedicine and drones for the delivery of medicines, etc., are a very good option for optimizing the work of a nephrologist, but there may be obstacles such as cyberattacks, lack of Internet, computers, phones, or an insufficient level of computer skills [5].

4. The principles of treatment of victims during military operations may differ from standard nephrological practice in peacetime; it is necessary to use as simple and pragmatic recommendations as possible in the treatment of both AKI and CKD during military actions [5].

5. Nephrology of catastrophes should be included in the curricula of teaching nephrology, as well as in the scientific programs of international and national annual congresses [5].

The first humanitarian aid to the central and eastern regions of Ukraine, to Kyiv, began to arrive approximately 3 weeks after the start of the conflict. For the Ukrainian Association of Paediatric Nephrologists/Ukrainian Association of Nephrologists, the first to provide humanitarian aid were ESPN, the nephrology associations of Germany, Belgium, and France. It should be noted that their help with medicines and consumables for dialysis was the most significant [3, 11].

Many EU universities have supported their Ukrainian students with scholarships, exemption from accommodation fees, providing psychological counselling and providing temporary housing for the family [20].

Many private European companies helped and continue to help Ukrainian refugees and Ukraine, along with airlines that provided Ukrainians with discounted (including free) fares [20].

But, unfortunately, despite the efforts and measures taken, many legal, material, technical and organizational problems remain [20].

Among our foreign colleagues, we should note, first of all, Prof. Lars (Pape), President-Elect, International Paediatric Transplant Association, Prof. Dr. Jun Oh, Prof. Dr. Elena Levtchenko, MD, PhD, FESPN, Prof. Dr. Lutz T. Weber, Prof. Dr. Hermann Pavenstädt President of the German Society of Nephrology, Prof. Arnaud Devresse MD, PhD, Prof. Dr. Lionel Rostaing, MD, PhD, Prof. Rukshana Shroff, Prof. Dr. Andrzej Więcek, MD, Prof. Dr. Justine Bacchetta, MD, PhD. Prof. D. Ivanov was awarded the IPNA Humanitarian Award 2022 [3, 11].

The Ukrainian Association of Paediatric Nephrologists jointly with the Institute of Nephrology of the Medical Academy of Ukraine held a kidney day on March 10 (152 participants). The Ukrainian Association of Nephrologists together with the Department of Nephrology and RRT spent WKD on April 2. The number of participants — 201, the number of speakers — 16 (from 3 countries of the world) and the number of issued certificates for participation in scientific medical forums — 217. Ukrainian Association of Nephrologists/Ukrainian Association of Paediatric Nephrologists and the staff of the Department of Nephrology and RRT of Shupyk National Healthcare University of Ukraine, with the help of these measures, doctors were allowed to feel mutual support and agree on their actions [3, 11].

It should be noted that all employees of the Department of Nephrology and RRT did not leave the territory of Ukraine during the entire period of ML, remained and remain at their workplaces within the city of Kyiv and the Kyiv region. During the period from February 24 to August 1, they consulted 348 patients face-to-face and conducted 61 sessions of chronic HD, 25 kidney biopsies (according to a unique technique that increases the verification of the diagnosis and reduces the risk of trans- and post-puncture complications in patients) at the clinical base of the Department of Nephrology and RRT — "Clinic of Prof. D. Ivanov" [3, 11].

Also, employees of the department held telephone consultations with nephrologists in other cities of Ukraine (mostly in Zaporizhzhia) regarding the examination and treatment of nephrological patients. One employee of the department even went to Zaporizhzhia, where, in addition to consulting work, he organized humanitarian aid for refugees from Mariupol and other regions [3, 11].

Despite the technical difficulties, the publication of the specialized KIDNEYS magazine, video conferences and consultations were continued with our own funds, which also became a certain test for our specialists.

International assistance

It should be noted that international support was provided by ERA, which organized Task Forse Ukraine (Prof. Serhan Tuglular, members Mehmet Sukru Sever, Raymond Vanholder, Valerie Luyckx, Kai-Uwe Eckardt, MykolaKolesnyk, Andrzej Wiecek, Ewa Pawlowicz-Szlarska, Daniel Gallego, Rukshana Shroff, Andrej Škoberne, Ionut Nistor, Mohamed Sekkarie, Dmytro Ivanov, Edita Noruišiene, the Renal Disaster Relief Task Force of the ERA) [3, 11].

This group is responsible for the consistent analysis of the nephrological situation in Ukraine and the organization of humanitarian aid. Members of the group developed a questionnaire for refugee patients with CKD and staff of RRT departments, which are filled out by our doctors and patients. Consultation webinars were introduced every Monday (moderated by Prof. D. Ivanov) for clinical analysis of cases and discussion of modern treatment recommendations. Experts were colleagues from Germany (Sharite) and members of Task Forse Ukraine. Two documents have also

been prepared, which define the modern understanding and algorithm of actions during the AC in Ukraine [3, 11].

The situation in wartime is constantly changing, there are new issues in providing nephrological care that requires immediate resolution. Nephrologists of Ukraine work selflessly to preserve the health and lives of patients [3, 11].

The support of foreign colleagues is important to us, but, unfortunately, most European medical workers have little experience of working in the conditions of military operations and related threats [5].

Treatment of patients with AKI or CKD with KF requires increased attention, as the quality of life and survival of patients depends on advanced technologies and professional personnel. Patients with CKD, in addition to drug therapy, must follow a special diet; PD requires an uninterrupted supply of materials and is impossible without auxiliary medical means; HD requires special conditions: a significant amount of energy, water and general infrastructure; patients with a transplanted kidney vitally need immunosuppressants to prevent transplant rejection. Military actions create problems for providing nephrological care to patients in full, there is a high risk of not only medical but also material and technical problems [5]. Treatment of CKD 1–4 stages in Ukraine is carried out exclusively at the expense of the patient or through insurance [40].

Today presents difficult challenges to Ukraine and to every Ukrainian. Not least among them are crises: health crises, economic crises and humanitarian crises, and other crises. It is frightening how quickly we get used to them and the inability of many of us to cope with them. Our medical duty is to support our patients, provide them with timely help, and prevent their health from deteriorating [9, 30, 41].

Another high risk of a terrible catastrophe is nuclear terrorism. Examples, the seizure of the Chornobyl and Zaporizhia nuclear power plants (NPP), the termination of electricity supply to the Chornobyl NPP, the dangerous firefights near Zaporizhzhia (the largest NPP in Europe), and the fire at the Zaporizhia NPP, the location of dangerous explosive materials on the territory of the Zaporizhia NPP, all this creates the danger of a terrible ecological disaster during ML in Ukraine. Intentional or unintentional damage to a NPP due to gunfire, or due to interruptions in the supply of electricity or cooling of spent radioactive fuel rods, can lead to a disaster [27, 42]. And, of course, there remains the danger of Russia using tactical or strategic nuclear weapons on the territory of Ukraine [2, 42, 43].

It should not be forgotten that in the East of Ukraine there is the storage of radioactive water, which was used during the Cold War for the development of nuclear weapons. Damage to these underground structures will lead to contamination of groundwater with radioactive water, and, as a result, contamination of agricultural fields and an increase in the background radiation exposure of the region for decades [42].

Before the start of military actions, the MoH of Ukraine provided information on the availability of individual first-aid kits and medicines for 120 % and 72 % of the available personnel, respectively, in the areas of the Joint Forces Operation (JFO) in Ukraine (Donbas). The shortage of drugs (antiviral drugs, antibiotics, dressing material, cardiovascular drugs, etc.) can adversely affect the current ML scenario and, in the future, increase the percentage of servicemen with KD [20].

The health care system of Ukraine (the Semashko health care system) was inherited from the USSR (it provides free general access to medical care for everyone). The existing health care system based on the Semashko model has a controversial assessment. In 2017, the Verkhovna Rada of Ukraine launched a series of reforms to create a new patient-oriented healthcare system [17, 44].

Between 2016 and 2020, the government published nine documents on medical support. These documents reflect the provisions and implementation of NATO (North Atlantic Treaty Organization) standards. From 2019 to 2020, more than 180 armoured medical vehicles and sanitary vehicles were purchased. The Ukrainian Military Medical Academy created a special course in medical psychology and introduced a program of psychological rehabilitation of servicemen (over 42,000 servicemen used it) [20].

In 1994, Ukraine established an office at WHO. To coordinate cooperation between Ukraine and WHO, two-year agreements are regularly mutually signed. Another document was signed on January 31 [38].

In order to optimize primary and secondary healthcare services (including in the nephrology sector) [13] during ML, it is possible to involve medical students in more active actions. Unfortunately, the current curriculum does not meet modern needs. It is necessary to provide medical students with the opportunity of voluntary service in “hot” zones, in order to gain the necessary experience [20, 45]. A special course on conflict and disaster management in medicine, with an appropriation, identification and management, of vulnerable populations and resources, should be included in routine training programs. Before sending the students, a mandatory briefing should be conducted to better understand the tasks and goals. Similar strategies can be applied, also, for nurses, psychologists and other professionals. But when implementing such a strategy, many ethical and legal problems will arise [20].

In the context of military actions, the classical ethical principles “do no harm”, “do good”, fair distribution and respect for autonomy should be applied, but some principles of medical ethics may require different approaches. For example, the balance between individual benefit/autonomy and fair distribution of resources among the population [3, 46].

Do not forget about primary and secondary prevention of CKD. During military operations, prevention becomes more relevant than ever. The main non-communicable diseases (NCDs) that can cause CKD are diabetes mellitus, hypertension and other CVDs, gout, systemic autoinflammatory diseases, urolithiasis and others. These NCDs are the target of preventive measures.

Until February 24, 2022, NCDs were the cause of 91 % of deaths in Ukraine (CVDs — 67 %). This is due to the high prevalence of NCDs risk factors, which has the highest level, according to WHO data, in the European region. Alcohol and tobacco use is one of the risk factors [10, 47].

Before the full-scale invasion, of Ukraine, CVDs mortality was nearly 800/100,000 for men and 1,000/100,000 for women, compared with 328/100,000 and 311/100,000 in high-income European countries and 449/100,000 and 458/100,000 in middle-income European countries (According to data from the European Society of Cardiology (ESC)) [10].

In 2019, almost a quarter of Ukrainians suffered from obesity, the prevalence of overweight was 59 %. From 2010 to 2013, a survey of adolescents and children in Ukraine revealed an obesity rate of 17.2 %. An increase in the level of total cholesterol in the blood (norm ≥ 5.0 mmol/l) was found in more than 40 % of the population. Only 11 % achieved the lipid target, and among high-risk secondary prevention patients, only 9 % achieved the target. Among the adult population, the prevalence of diabetes is 7.1 % [10, 47].

Almost 35 % of the population of Ukraine suffers from systemic hypertension. In 85 % of cases, antihypertensive therapy with incomplete blood pressure control. In order to improve the cardiovascular health of the population, the nationwide program for the prevention and treatment of hypertension (1999–2005) (Decree of the President of Ukraine dated February 4, 1996, № 117/99) and the state program for the prevention and treatment of CVDs and cerebrovascular diseases were implemented for decades (2006–2010) (Resolution of the Cabinet of Ministers of May 31, 2006 No. 761) [10].

The prevalence of hypertension has changed little, in the male population, the overall risk factor has increased. The number of men with one risk factor decreased by 2.6 times, but the number of men with three or more risk factors increased by five times [10].

For comparison, in Western Europe, approximately 30 % have hypertension and 5 % of the population suffer from diabetes, 10 % of the adult population is diagnosed with kidney damage, and about 1 in 1,000 is shown RRT [9].

Data on the health status of newly arrived refugees (75 % of all emigrants, 92 different nationalities) are registered in the medical information system (The electronic Personal Health Record (ePHR)), which was introduced in eight European countries (Italy, Croatia, Cyprus, Bulgaria, Romania, Greece, Slovenia and Serbia). A cross-sectional study (2016–2019) of the health status and health problems of all refugees was introduced at the reception points. In the period from January 2016 to October 2019, 19,564 clinical episodes in 14,436 patients were registered in ePHR: 2,531/19,564 (12.9 %) episodes of infectious diseases (283/2,531 (50.7 %) — pharyngotonsillitis, 529 (20.9 %) — scabies, 158 (6.2 %) — viral hepatitis and 156 (6.1 %) lower respiratory tract infections) and NCDs — 2462 persons (17.1 %) (821 (5.7 %) CVD, 1,183 (8.2 %) neurological diseases, 644 (4.5 %) diabetes mellitus and 212 (1.5 %) KD) [48].

Also, according to PRISMA recommendations (PROSPERO CRD420201970430), a literature review was conducted (Al-Oraibi A., 2022). The search was conducted from January 1, 2011, to November 1, 2021, in the PubMed, CINAHL, MEDLINE, and EMBASE databases. The selected reviewed studies included data on the prevalence of five NCDs among Syrian refugees (adults) living in Turkey, Jordan or Lebanon.

466 references were found (237,723 Syrian refugees): prevalence of hypertension — 24 %, type 2 diabetes — 12 % (8–15), CVDs — 5 % (3–7), chronic respiratory diseases — 4 % (3–5) and arthritis was 11 % (7–14). In primary care institutions, the prevalence of hypertension — 35 % (33–36) and type 2 diabetes — 48 % (24–72) was significantly higher [49].

Primary health care, screening and immunization programs are failing. Patients with chronic diseases, such as CKD, coronary heart disease, heart failure, diabetes, etc., with international medical support, risk not receiving adequate treatment, or not receiving any treatment at all [10].

The search for new "early" biomarkers of the onset and progression of CKD is very relevant and promising [50, 51].

Patients with CKD often have comorbidities, including clinical frailty, cognitive dysfunction, mobility limitations, and CVDs, which significantly increase the risk of complications and/or decompensation of the underlying disease and impair quality of life [3].

The clinical syndrome of weakness is determined by a decrease in the functional reserve and susceptibility to negative consequences, which is complicated by the existing CKD. Clinical decision-making and pre-treatment planning by a nephrologist should follow a clinical frailty assessment. Weakness is a common clinical syndrome among patients with CKD (7 % in patients with mild CKD, 19 % with mixed CKD, 42.6 % with severe CKD and 53.8 % in the pre-dialysis population), the largest share is in dialysis patients (from 30 to 73–82 %), especially the elderly (over 65 — 14–24 %), especially when hospitalized — up to 90 % [52].

Frailty is an independent risk factor for conversion to dialysis/death. Rockwood proposed a 9-point clinical frailty scale (CFS) ("frailty indices" (FI) gives a quantitative characteristic), in which each increase of 1 point is associated with a mortality risk ratio of 1.22, regardless of comorbidity, modality dialysis and old age. Risk factors include diabetic nephropathy, peripheral arterial disease, and obesity, which independently increase the risk of frailty in patients receiving HD. There is evidence of a direct pathogenic role of uraemia. In almost 60 % of patients with CKD, there is a lack of physical activity (increasing the risk of mortality by 56 %) — one of the criteria of Fried's weakness. A decrease of 0.1 m/s in gait speed is associated with a 26 % increase in the risk of mortality, and an increase of 1 s in the Timed Up-and-Go test is associated with an 8 % increase in the risk of death [52].

Gait disturbances in patients with CKD are caused not only by metabolic factors but also by brain changes that affect motor control. Treatment of CKD should include correction of cognitive impairment [53].

Strict dietary restrictions (medical recommendations or related to dysgeusia), as well as chronic molecular stress, in patients with CKD, affect the pathogenesis of clinical weakness [52, 54].

Clinical supervision of patients outside the HCF is not possible. Patients suffering from chronic diseases, due to limited or no access to medical care, such as insulin therapy, antiplatelet, lipid-lowering and antihypertensive therapy, may require immediate medical care when crossing a border with another country. As statistics show, for every direct victim of military operations, there can be many more indirect

victims. The victims need urgent global action to receive immediate medical and humanitarian assistance [10, 30].

Unexpectedly, high rates of KF and other NCDs requiring continuous treatment were found among refugees. A significant number of patients with severe conditions requiring long-term special treatment (RRT) were successfully evacuated to neighbouring countries for continued treatment. Unfortunately, among refugees or hospitalized Ukrainians, there are cases of sudden death (arrhythmia, myocardial infarction, heart failure) and worsening of major diseases, including CKD, which are often not provided with assistance due to a lack of personnel and/or resources [10].

During hostilities, for various reasons (economic, security, or logistical), many planned medical issues were ignored; therefore, whenever possible, delayed medical problems should be addressed as soon as possible (screening, diagnosis and treatment), not forgetting about mental health [3].

In order to avoid repeating mistakes in the event of new natural or man-made disasters, it is necessary to analyse the experience gained to identify defects in the response to disasters [3].

Conclusions

The ML in Ukraine has shown how vulnerable the current concept of dialysis is, with its high consumption of water and energy. As never before, the question of early detection and prevention of progression of CKD with leakage into the ESRD is becoming acute. The search for new "early" biomarkers of the onset and progression of CKD is very relevant and promising.

The concept of dialysis probably needs to be changed. Perhaps it makes sense to pay more attention to the widespread introduction into the practice of "home" dialysis, which is the best option for patients. A flexible health care system is more productive and viable in the event of disasters such as hurricanes, COVID-19, and other disasters (earthquakes, etc.).

During military actions and disasters, unlike healthy people, people with KD have a higher risk of adverse consequences. This category of patients is extremely vulnerable due to forced displacement (internally or abroad), total dependence on life-saving therapies, functioning infrastructure, advanced technologies and well-trained personnel.

The doctor's duty is to ensure the right of every patient to health care. World Kidney Day (2022) with the slogan "Kidney Health for All" has undoubtedly given much attention to this issue.

Our country should be ready for anything, but with the threat of Russia using weapons of mass destruction during military actions, support and assistance at the international level are no less important.

A balanced interaction between the military and civilian medical systems significantly optimizes the provision of medical care in the conditions of the Armed Forces.

Possible appropriate measures, in our opinion, include:

1. The need for a bomb shelter in which children with their mothers and medical personnel could be/live.

2. The need for mobile devices for HD and PD.

3. The need for at least a 3-month supply of consumables and accompanying medicines.

4. Rapid interchangeability of personnel to replace absent doctors and nurses and their training directly at the patient's bedside.

5. Communicating with foreign nephrologists and nephrology societies that could quickly help with humanitarian aid.

6. Communication with foreign specialists, to whom our patients have been referred, to ensure continuity of patient treatment.

7. It would be rational to have the possibility of additional funding for the payment of medical personnel, outside of local sources of funding, to maintain personnel in hot regions.

8. Humanitarian aid with food would be very useful, both for patients and for staff.

There is a need to plan in advance how to deal with such situations and constantly search for new successful solutions to improve and preserve health, and optimize the work of the health care service at all levels and stages.

Our collective of authors condemns all criminal military actions of Russia, the mass murder of people, children, and other vulnerable categories of the population. And we know and feel the support of the whole world, including our foreign colleagues.

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Нефрологічна допомога в умовах воєнного стану в Україні

Резюме. Під час збройних конфліктів (ЗК) і інших катастроф люди похилого віку, жінки, діти, немічні й хронічно хворі є найбільш вразливою категорією населення з високим ризиком для здоров'я і життя. Хронічно хворі люди із захворюваннями нирок (у тому числі з нирковою недостатністю) заслуговують на особливу увагу через повну залежність від доступного функціоналу інфраструктури й доступу до життєво важливих ліків і добре навченого персоналу. На даний час є мало інформації про наслідки ЗК для хворих з ураженням нирок порівняно з наявними даними про вплив інших катастроф. Механізми уражень при ЗК і природних або техногенних катастрофах мають схожі й відмінні риси. Відмінні риси: при ЗК переважають вогнепальні й мінно-вибухові поранення, кровотеча, отруєння токсичними речовинами, при катастрофах — переохолодження або опіки, механічні травми тощо. Спільне — пошкодження інфраструктури, у тому числі закладів охорони здоров'я, дефіцит ліків, медичного персоналу, гуманітарні та інші кризи, велике навантаження пораненими й травмованими закладів охорони здоров'я. У цій статті ми систематизували отриманий під час воєнного конфлікту матеріал, а також зробили огляд вітчизняних і іноземних статей з даної тематики, щоб оптимізувати роботу нефрологів в умовах воєнного стану й обмежених ресурсів.

Ключові слова: воєнний стан; хронічна хвороба нирок; біженці; ядерний конфлікт; нирково-замісна терапія; діаліз; трансплантація нирки; гуманітарна криза

НИРКИ KIDNEYS

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Effect size of Dna-j heat shock protein family B member 9 (DNAJB9) biomarker in kidney biopsy specimens on kidney outcomes in fibrillary glomerulonephritis

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Abstract. ***Background.*** *Fibrillary glomerulonephritis is a rare glomerular disease that presents with hypertension, hematuria, nephrotic syndrome and renal insufficiency. The purpose of this research was to assess effect of DNAjB9 staining marker in kidney biopsy specimens on kidney outcomes.* ***Materials and methods.*** *In this analytic (experimental) clinical study with randomized clinical trial design in meta-analysis article, 72 patients with biopsy-proven fibrillary glomerulonephritis were investigated. Clinical features, laboratory data at initial presentation, management and outcomes were collected. The paper has written based on searching PubMed Central and Google Scholar to identify potentially relevant articles. Median, percentage, mean ± standard deviation (SD), two-tailed t and Chi-square, two proportion difference meta-analysis and Kaplan-Meier analysis were used for statistical evaluation. Moreover, relative risk, odds ratio, Spearman's correlation for statistical analyses were used.* ***Results.*** *The median and interquartile range of age of patients with fibrillary nephropathy at the time of diagnosis were 55 and 18 years, respectively. There was no statistically significant difference between two sex groups of males and females in current research (p-value: 0.35). There was significant statistical correlation between elevated serum creatinine level and time of last serum creatinine measurement with p-value of 0.01 and confidence interval (CI) of 0.7820 to –0.1258 during follow-up. Relative risk of kidney failure progression to kidney replacement therapy (↑ ≥ 2-fold in serum creatinine or dialysis or kidney transplant) in DNAjB9-positive (group I) and DNAjB9-negative patients (group II) was assessed 2.67 with 95% CI of 1.128 to 6.3044 and p-value of 0.025. Odds ratio of kidney failure progression to kidney replacement therapy (↑ ≥ 2-fold in serum creatinine or dialysis or kidney transplant) was assessed 4.33 with 95% CI of 0.9464 to 19.8417 and p-value of 0.058. There was statistically significant difference when comparing group I and group II for mortality probability (Kaplan-Meier analysis) during follow-up (P < 0.0001).* ***Conclusions.*** *The present study revealed high mortality in DNAjB9-negative (8/64, 12.5%) versus DNAjB9-positive patients (0/8) with statistically significant level. Relative risk and odds ratio of kidney failure progression to kidney replacement therapy were assessed 2.67 and 4.33, respectively.*

Keywords: *DNAjB9 marker; electron microscopy; end-stage kidney disease; fibrillary glomerulonephritis; MEST-C score*

Introduction

Fibrillary glomerulonephritis (FGN) or fibrillary glomerulopathy (FGP) is a glomerulopathy that is classified into two groups of congophobic and congophilic fibrillary glomerulonephritis. Diagnosis of fibrillary glomerulonephritis is made by kidney biopsy. The commonest light microscopic finding is membranoproliferative glomerulonephritis. Mesangial proliferation, endocapillary proliferation and diffuse glomerulosclerosis are the other histologic patterns in light microscopy. Membranous nephropathy, cellular of fibrocellular crescents and interstitial fibrosis may be present in histologic presentation of disease. In immunofluorescence microscopy, all patients are stained with immunoglobulins, C3 and C1q, kappa and lambda chains. The

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texture of staining was smudged without linearity or granularity. Ultrastructural evaluation of kidney specimens is done by presence of fibrils as random orientation, width of < 30 nanometer (nm), no hollow cores in magnifications more than × 30000 and positive immunoglobulins by immunofluorescence (IF) staining [1]. Dna-j heat shock protein family B member 9 (DNAjB9) that, namely known as endoplasmic reticulum-localized DnaJ homologs 4 (ERdj4) or mdg-1, is a 223 amino acid member of the DNAJ family of proteins that act as co-chaperones for the heat shock protein 70 family members including binding immunoglobulin protein (BiP). The heat shock protein (HSP) 70 family members are thought as important chaperones in the endoplasmic reticulum (ER) and involve in protein folding, unfolding, translocation and degradation [2]. The J-domain of Dnaj has a histidine-proline-aspartic acid motif which stimulates hydrolysis of adenosine triphosphate (ATP) [3]. DnaJB9 was first discovered in 2002 and there is in ER organs such as liver, placenta and kidneys. There is no specific treatment for fibrillary glomerulonephritis and renal prognosis is poor. Patients achieve to end-stage kidney disease (ESKD) with mean average of 4 years after diagnosis. Kidney transplantation is an option for ESKD patients and recurrence can occur post renal transplant period.

Objectives

Research questions

Why DNAjB9 marker is diagnostic biomarker

DNAjB9 histochemical marker is abundantly detected in glomeruli of fibrillary glomerulopathy, in glomeruli of healthy persons and not in glomeruli of other glomerular diseases. This marker distinguishes congophilic fibrillary glomerulonephritis from amyloidosis in kidney biopsy specimens. Hence, it accounts as a 100% specific and sensitive survey in fibrillary glomerulopathy and can be used as quick and specific diagnostic method for this disease in the absence of ultrastructural evaluation.

What DNAjB9 biomarker does

DNAjB9 immunohistochemical biomarker is a member of molecular chaperone gene family that is analyzed using mass spectrometry or laser microdissection-assisted shotgun proteomics in glomeruli of kidney specimens in patients with fibrillary GP. As previously mentioned, DNAjB9 involves in BIP as a co-chaperone, assisting in protein folding and degradation of misfolded protein as unfolded protein response (UPR). In other words, DNAjB9 involves in recognition of misfolded protein and marks them for degradation. It may inhibit apoptotic effect of p53 on cells with stress and this function indicates that increased expression of DNAjB9 may be a marker for increased ER stress. DNAjB9 is found in low levels in ER in most of cell types such as cytoplasm of neurons, gastrointestinal (GI), gynecologic, pulmonary, breast epithelium and lymphocytes. In the normal kidney, DNAjB9 is detected in renal tubular epithelial cells, podocytes, mesangial and endothelial cells. Existing large amounts of DNAjB9 marker in extracellular deposition distinguishes it from other glomerular diseases and this finding is specific for this disease.

Materials and Methods

Eligibility Criteria

Type of Studies

The search identified 3045 full-text articles via electronic search in google scholar (2690), PubMed central (318) and other databases (37). Therefore total records of 3045 full-text articles were identified and five articles were deduplicated (3040). So total 3040 articles screened based on title and abstract. Then 66 full-text articles were eligible and 2974 articles were excluded due to not related subject. Therefore, 72 participants in 62 published articles included and 4 articles were discarded due to non-case reports. These 62 articles included 72 case reports that were examined 72 patients of kidney disturbation as decreased estimated glomerular filtration rate (eGFR) or elevated serum creatinine. These participants were enrolled for systematic review and meta-analysis.

Type of Participants

All patients with biopsy-proven fibrillary glomerulopathy were considered in this research.

Type of Outcomes

Primary end-points. Proportion of acute kidney injury (AKI), acute kidney disease (AKD), chronic kidney disease (CKD) and non-kidney disease (NKD), graft loss, proteinuria, relative risk (RR) and Odds ratio (OR) of kidney failure progression to kidney replacement therapy (KRT), death probability and effect of DNAjB9 marker on outcome of fibrillary glomerulopathy were considered as primary end-points.

Secondary end-points. Decreased estimated glomerular filtration rate, positive anti-nuclear antibodies (ANA), positive cryoglobulins, low complement levels, positive viral infection, low platelet counts and high hepatic enzyme levels are considered as secondary end-points.

Information Sources. The paper has written based on advanced searching via PubMed and Google Scholar databases to identify articles published since 1975 to January 2022.

Search methods for identification of studies

Electronic search

The mentioned search performed with search terms of fibrillary deposition And (Boolean) kidney impairement, also with term of fibrillary glomerulopathy in this research.

Searching other resources

The author reviewed references of all included articles and performed handsearching of related journals to identify the additional relevant studies.

Study selection

The search strategy was used to obtain titles and abstracts of articles in databases. Total 3045 titles and abstracts were identified via electronic search in PubMed and Google Scholar by author. Total records of 3045 articles were identified and eventually 3040 articles identified after dedupli-

cation. Therefore, 3040 articles screened in this research. Of these, 2974 articles were excluded due to non-related subject, review articles, others and 66 full-text articles were considered for eligibility. However studies and reviews that might include relevant data or information on studies were retained initially. Four articles were excluded and then 62 published articles were included for qualitative and quantitative synthesis. These 62 published articles were enrolled 72 patients with fibrillary glomerulonephritis with kidney specimens in current research.

Data collection and analysis

Data extraction and management

Data extraction was carried out by author and studies which reported in journals as non-English language were translated before assessment. Where more than one publication of a study existed, reports were grouped together and the publication with the most complete data was included.

Data items

All patients with clinical, laboratory and pathologic presentations of fibrillary GN, decreased eGFR and tissue biopsy-proven kidney specimens were considered in this research. Demographic and clinical features such as age, sex, different symptoms and physical signs were extracted from this study. Furthermore, biochemical variables of serum creatinine (SCr), eGFR, urine protein at initial presentation and following days, imaging, management and outcomes were collected.

Definition of kidney dysfunction

AKI, AKD and CKD, NKD can form a continuum whereby initial kidney injury can lead to persistent injury eventually leading to CKD. AKI is defined as an abrupt decrease in kidney function occurring over 7 days or less whereas CKD is defined by the persistent of kidney disease for a period of > 90 days. AKD is defined as acute or subacute damage and/or loss of kidney function for duration of seven and 90 days after exposure to an AKI initiating event. Recovery from AKI within 48 h of the initiating event typically heralds rapid reversal of AKI [16th workgroup of acute disease quality initiative (ADQI) consensus report in 2017]. Kidney disease: improving global outcomes (KDIGO) in August 2020 convened a consensus conference for kidney disease definition as functional and/or structural abnormalities of the kidney and classified kidney disease (KD) according to cause, severity of structural and functional abnormalities and duration of those abnormalities (KDIGO consensus conference 2020, published in July 2021). Based on this classification, KD can be classified to AKI, AKD, CKD and NKD. CKD is classified according to eGFR and kidney damage such as proteinuria (> 200 mg/day or protein to creatinine ratio > 200 mg/g creatinine) or albuminuria (urinary albumin excretion ≥ 30 mg/day or albumin to creatinine ratio ≥ 30 mg/g creatinine) using SCr. Kidney disease outcomes: quality initiative (KDOQI) guidelines 2009 classified CKD to stage 0 (no CKD) corresponded to eGFR ≥ 90 ml/min/1.73 m^2 without proteinuria, Stage 1 to eGFR ≥ 90 mL/min/1.73 m^2 with proteinuria, Stage 2 to eGFR ≥ 60–90 mL/min/1.73 m^2, Stage 3 to eGFR ≥ 30–60 mL/min/1.73 m^2, Stage 4 to eGFR ≥ 15–30 mL/min/1.73 m^2 and Stage 5 to eGFR ≤ 15 mL/min/1.73 m^2 or end-stage renal disease (ESRD) requiring the initiation of chronic dialysis therapy [4]. 2012 KDIGO CKD guidelines classified CKD to cause of disease, level of GFR (6 categories), and level of albuminuria (3 categories), collectively classified with mnemonic of CGA. Of course this key point must be said that term of nephrology-related conditions must be used instead of kidney diseases [5]. Estimated GFR is defined according to creatinine clearance (CrCl), CockGroft-Gault equation, modification of diet in renal disease (MDRD) and chronic kidney disease-epidemiology collaboration (CKD-EPI). CrCl in 24-hr urine collection is expressed using urine creatinine (mg per deciliter or micromole per liter) multiplication by urine volume (milliliter or liter) divided on plasma creatinine (milligram per deciliter or micromole per liter) multiplied 1440 and its unit is expressed with milliliter per minutes (ml/min). Cockcroft-Gault equation is expressed as CrCl = (140 − age) × wt divided on SCr × 72, multiplication by 0.85 if female. MDRD equation given by: estimated GFR = 175 × Standardized $SCr^{-1.154}$ × $age^{-0.203}$ × 1.212 [if black] × 0.742 [if female] where eGFR is expressed as ml/min/1.73 m^2 of body surface area and SCr is expressed as mg per dl. The CKD-EPI equation, expressed as a single equation, is eGFR = 141 × min (Scr/κ,1)$^{\alpha}$ × max (Scr/κ, 1) − 1.209 × 0.993^{age} × 1.018 [if female] − 1.159 [if black], where κ is 0.7 for females and 0.9 for males, α is −0.329 for females and 0.411 for males, min indicates the minimum Scr/k or 1 and max indicates the maximum of Scr/κ or 1. Proteinuria, albumin-to-creatinine ratio (ACR) is greater than 2.5 mg/mmol in men or 3.5 mg/mmol in women, or a protein-to-creatinine ratio (PCR) is greater than 15 mg/mmol is sufficient for diagnosis of CKD (random PCR < 15 mg/mmol: normal; 15–49 mg/mmol: trace proteinuria; 50–99 mg/mmol: significant proteinuria; 100–300 mg/mmol: high proteinuria; > 300 mg/mmol: nephrotic range proteinuria). Albuminuria may be classified as moderately increased albuminuria (3–30 mg/mmol creatinine) or severely increased albuminuria (greater than 30 mg/mmol creatinine). The normal PCR in children and adolescent is less than 0.3. In infants and younger children, the PCR is higher with the upper normal limit of 0.5. PCR above 3 is found in patients with nephrotic syndrome. The daily protein excretion rate (PER) can be determined from spot urine PCR, based on sex, age and weight using the following equations: PER (g/m^2/day) = 0.63* (PCR).

Markers of fibrillary glomerulonephritis

DNAjB9 is a 223-aminoacid protein that is a member of the DNAj family of chaperons with a predicted 23-aminoacid signal peptide. It is a heat shock protein in ER/unfolded response pathway and binds to aggregation-prone peptides. DNAjB9 is present in glomerular and extraglomerular immune deposits of patients with fibrillary glomerulopathy [6]. DNAJ proteins influence on many of cellular processes by regulating the ATPase activity of 70-kD heat shock proteins. DNAjB9 is involved in ER stress and the UPR and it is a cochaperone for Bip/Grp78, a master regulator of the URP.

DNAJB9 is upregulated by ER stress, nitric oxide and other inflammatory mediators, protects against cell death, protects hematopoietic stem cells during stress and is required for normal B cell development and antibody production. DNAJB9 also specifically binds aggregation-prone regions in proteins. Methods for detecting DNAjB9 marker in kidney biopsy specimens are by liquid chromatography/tandem mass spectrometry and laser microdissection-assisted shotgun proteomics [7]. DNAjB9 is a useful diagnostic marker for diagnosis of atypical forms of fibrillary glomerulopathy. Patients patients with fibrillary glomerulonephritis were classified into groups I and II in the current research. Group I was considered as DNAjB9-positive tissue and group II was considered as DNAjB9-negative tissue in biopsy-proven kidney specimens.

Definition of normal values of serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), serum immunoelectrophoresis (SIEP), urine immunoelectrophoresis (UIEP), serum immune fixation (SIF), and urine immune fixation (UIF)

The monoclonal components are usually identified and quantified by electrophoresis and immunofixation of serum (SPE + sIFE) and urine (UPE + uIFE) proteins. Normal range for serum immunoglobulins in SIEP are defined with serum immunoglobulin A (IgA) of 70–350 mg/dl, immunoglobulin D (IgD) of 0–14 mg/dl, immunoglobulin E (IgE) of 1–87 IU/ml, immunoglobulin G (IgG) of 700–1700 mg/dl (IgG1of 270–1740 mg/dl; IgG2 of 30–630 mg/dl; IgG3 of 13–320 mg/dl; IgG4 of 11–620 mg/dl) and immunoglobulin M (IgM) of 50–300 mg/dl. In serum and urine protein electrophoresis, normal value for albumin is defined 3.5–5.5 (50–60 %), globulin 2–3.5 g/dl (40–50 %), alpha1 0.2–0.4 g/dl (4.2–7.2 %), alpha2 0.5–0.9 g/dl (6.8–12 %), beta 0.6–1.1 g/dl (9.3–15 %) and gamma globulin is 0.7–1.7 g/dl (13–23 %). Normal range for serum free light chain kappa (sFLCκ) level is 3.3 to19.4 mg/l, for serum free light chain lambda (sFLCλ) level is 5.7 to 26 mg/dl, for kappa to lambda ratio is 0.26 to 1.65 in one reference and in other reference 1.47–2.95. Reference range of ratio in this article has been considered 0.26 to 1.65. Normal value for urine free light chain kappa (uFLCκ) is considered < 2.5 mg/dl and for urine free light chain lambda (uFLCλ) levels is defined < 5 mg/dl. Normal value for urine bence jones protein is considered undetectable. Normal serum beta-2 microglobulin (β-2 MG) is considered 0.7–1.8 mg/l and 1.1 to 2.4 mg/l in male and female, respectively. Normal 24-hr urine excretion of β-2 MG is mentioned < 120 μg/day and normal concentration of urinary β-2 MG is reported less than 300 μg/l in scientific references. Free heavy chains are called α, δ, ε, ϒ, μ and normal values for these subtypes is defined negative.

Definition of normal values of autoantibodies and complement system

Normal range of complement 3 (C3) is considered 88–201 mg/dl and normal range for complement 4 (C4) is defined 16–48 mg/dl or 0.16 to 0.48 gram per liter. Fifty percent hemolytic complement (CH50) level is defined 150 to 250 units per milliliter. Serum factor H (FH) autoantibody is defined 0.3 to 0.6 g/l and as percent normal range for it is defined 0–7.3 %. Serum Factor B (FB) level is in range of 17–22 mg/dl. Positive anti-nuclear antibodies is defined more than or equal to 1 over 160 titer and positive anti-double stranded deoxynucleic acids antibodies (Anti-DS DNA Abs) is considered more than or equal 1 over 10. Normal levels of autoantibodies are considered for cytoplasmic antineutrophil cytoplasmic antibodies (C-ANCA) < 2.8 unit over milliliter (U/ml), perinuclear antineutrophil cytoplasmic antibodies (P-ANCA) < 1.4 U/ml, anti-glomerular basement membrane antibodies (anti-GBM Abs) < 5U/ml, anti-parietal cell antibody at 1over 20 (1 : 20) titer and anti-smooth muscle antibody titer of 1/20. Normal ranges for anti-mitochondrial antibody titer, anti-smith antibody, anti-ribonucleoprotein antibody (anti-RNP), anti-Scl 70 antibody (anti-topoisomerase I), anti-platelet antibody, anti-R0 antibody, anti-Jo-1 antibody (anti-histidyl) and anti-La antibody are considered negative. Normal value for serum rheumatoid factor and anti-citrulinated peptide/protein antibodies (ACPA) such as anti-cyclic citrulinated peptide antibody (anti-CCP) is considered < 30 IU/ml and < 20 Unit, respectively. Reference Range in UpToDate for Anti-CCP antibody is considered level < 20 EU/ml (negative), 20–39 EU/ml (weakly positive), 40–59 EU/mL (moderately positive), > 60 EU/mL (strongly positive or at least three times the upper limit of normal). Another alternative test for anti-CCP antibody is called anti-mutated citrulinated vimentin.

Definition of non-albumin proteinuria (NAP)

NAP is calculated as non-albumin protein to creatinine ratio (NAPCR) is equal with urinary protein to creatinine ratio (UPCR) minus urinary albumin to creatinine ratio (UACR). Cut-off value for NAP is 120 mg/g and isolated NAP (iNAP) is defined with UPCR ≥ 150 mg/g and UACR < 30 mg/g. NAP is used as complementary diabetic kidney disease (DKD) marker to albuminuria. Researchers found NAP was significantly associated with CKD progression that defined as decline in CKD stage with decrease of ≥ 25 % in eGFR from the baseline [8].

Assessment of risk of bias and quality in included articles

Case reports were analyzed using criteria developed by the Joanna Briggs Institute Critical Appraisal tool for case reports that has different assessment tools for each study design in question. The evaluation tool has 8 items for case reports.

Statistical analysis

Data were entered in Microsoft Excel 2010 software. Categorical variables are recorded as frequency (N) and percentage (%). The continuous variables were determined as to whether they were normally distributed using the Kolmogorove-Smirnov or Shapiro-Wilk test. Continuous variables with normal distribution reported as mean ± standard deviation (SD). Nonparametric variables are expressed as

median and interquartile range (Q1, Q3 and IQR). Comparisons between continuous variables with normally distributed (ND) data assessed by two-tailed t test analysis. Effect size of variable on outcome was analyzed using two proportion meta-analysis. Kaplan-Miere analysis was used for mortality probability. Correlation between two non-parametric variables were assessed using spearman's tests. Moreover, relative risk and odds ratio for statistical analyses were used. Significance was assessed with p-value of < 0.05.

Results

Description of studies

Results of the search and study selection

Author identified 3045 records after searching electronic databases. Alongside, five articles were removed (N = 5) and total 3040 titles and abstracts identified. Then 3040 articles screened and author discarded 2974 full-texts articles due to non-related subject. Thereafter 66 articles were eligible and 4 articles were discarded due to non-case reports. Of these, 62 published articles (72 case reports) were included and enrolled as participants in this study.

Included studies (criteria)

Sixty-two published articles (72 case reports or participants) were considered for inclusion in this research.

Study characteristics

Study design

This research categorized as analytic (experimental) prospective study type with randomized control trials (RCTs) design in systematic review and meta-analysis article. Retrospective data were collected via electronic method in this research.

Sample sizes

Sample sizes of 72 patients or participants were considered in this study.

Setting

Participants were referred to single center or multi-center settings (emergency room or hospital or clinic) in this research.

Participants

All patients with biopsy-proven kidney specimens infavor of fibrillary GP included in this study. In those patients, structural or functional marker for kidney damage such as elevated serum creatinine levels or decreased eGFR, significant proteinuria and active urinalysis were noticed. Moreover, staining for DNAjB9 protein in kidney specimens was done.

Excluded studies (criteria)

Patients were excluded from the study if they were suspected to or not diagnosed as fibrillary glomerulopathy in kidney biopsy at initial time or during follow up except in one case report that kidney biopsy was not performed due to death in familial fibrillary glomerulonephritis (father) and DNAjB9 marker was not performed in two brothers. So it was supposed that each three case be put in DNAjB9 negative groups.

Risk of bias and quality in the included studies

Assessment of risk of bias and quality of included articles performed using Joanna Briggs Institute critical appraisal tools for case reports. Based on these criteria, six out of seventy-two case reports obtained eight score (6/72, 8.3 %), fifty out of seventy-two case reports had seven score (50/72, 69.4 %), twelve out of seventy-two case reports achieved to six score (12/72,16.6 %), three out of seventy-two patient attained five score (3/72, 4.1 %) and one out of seventy-two patients reach to three score (1/72, 1.3 %).

Results of case studies

Patients' Characteristics

Among 3045 full-text articles obtained in this research paper, five articles deduplicated and total 3040 articles identified. In current research, 3040 articles screened and 2974 articles were excluded due to unrelated subject, review articles and other studies. Then 66 full-text articles were eligible and 4 articles were excluded due to non-case reports (n = 4). Finally 62 published articles that contained 72 participants were included in this study because one published article may contain more than one case report (Fig. 1). The sixty-two published articles (examined seventy-two case reports) were interrogated clinical, laboratory, imaging data and biopsy-proven kidney specimens of patients with fibrillary glomerulopathy in the current research [9–70]. Forty out of seventy-two patients were male (40/72, 55.5 %) and thirty-two of them female (32/72, 44.4 %). Eight of seventy-two patients (8/72, 11.1 %) were Caucasian, six of seventy-two patients (6/72, 8.3 %) belonged to white descent, four out of seventy-two patients (4/72, 5.5 %) were Japanese and African American ethnicity, one out of seventy-one (1/72, 1.3 %) belonged to Korean race and Non-Hispanic ethnicity. The median and IQR of age of patients with fibrillary nephropathy at time of diagnosis was 55 and 18 years old, respectively.

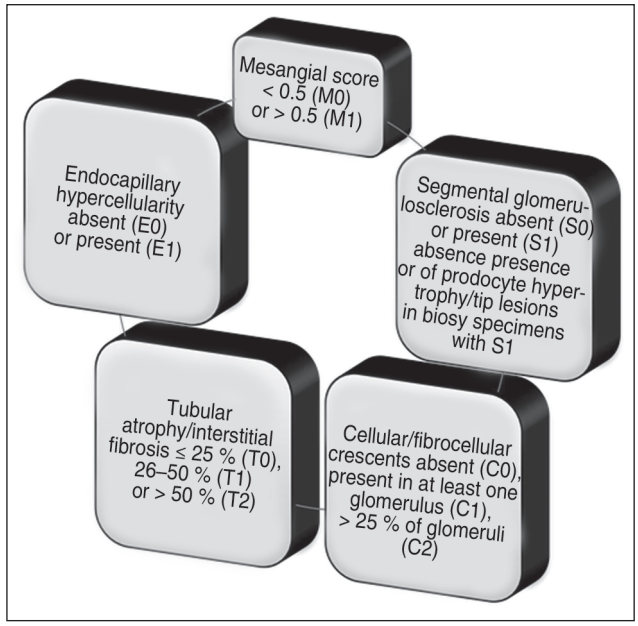

Figure 1. Pathologic classification of fibrillary glomerulonephritis with mimicry of immunoglobulin A nephropathy (IgAN)

The mean average of age in male and female patients were 53.55 ± 13.78 and 56.29 ± 15.8 years old (range from 1 to 80 years) respectively. There were no statistical significant level between two sex groups in current research (p-value: 0.35).

Patients' Complains

The patients with fibrillary glomerulopathy were presented with various symptoms. These symptoms comprise lower leg extremity edema in seventeen out of seventy-two patients (17/72, 23.6 %), nausea and dyspnea in six out of seventy-two patients (6/72, 8.3 %), abdominal pain and headache in four out of seventy-two patients (4/72, 5.5 %). Twenty-seven out of seventy-two patients (27/72, 37.5 %) had history of hypertension and fourteen out of seventy-two patients (14/72, 19.4 %) referred with history of diabetes mellitus. Seven out of seventy-two patients with fibrillary glomerulopathy (7/72, 9.7 %) had history of obesity. Four out of seventy-two patients (4/72, 5.5 %) gave history of smoking and three out of seventy-two patients (3/72, 4.1 %) patients had history of dyslipidemia, weakness and asthenia in the current research. Two out of seventy-two patients (2/72, 2.7 %) had history of gastroesophageal reflux disorders (GERD), weight gain, loss of appetite, red-colored urine, skin lesions, pale conjunctiva and ankle swelling. In sign of patients with fibrillary glomerulopathy, twenty-four out of seventy-two patients (24/72, 33.3 %) were manifested with hypertension and fourteen of seventy-two patients (14/72, 19.4 %) presented with lower extremity edema. Four out of seventy-two patients with fibrillary glomerulopathy (4/72, 5.5 %) revealed abnormal chest auscultation, obesity and three out of seventy-two patients (3/72, 4.1 %) showed high temperature. Two out of seventy-two patients (2/72, 2.7 %) showed abnormal general appearance and one out of seventy-two patients (1/72, 1.3 %) developed overweight.

Laboratory data

In fifty-six out of seventy-two patients (56/72, 77.7 %) was performed urinalysis. Proteinuria was found in thirty-five out of fifty-six patients (35/56, 62.5 %) and nephrotic-range proteinuria detected in two out of thirty-five patients (2/35, 5.7 %) in dipstick. Red blood cells detected in forty-eight of fifty-six patients (48/56, 85.7 %) and occult blood found in three out of fifty-six patients (3/56, 5.3 %) in urinalysis. Dysmorphic red blood cell (RBC) found in five out of forty-eight patients (5/48, 10.4 %) in urine of patients in current study. Pyuria was measured in twelve out of fifty-six patients (12/56, 21.4 %) and significant pyuria was seen in six out of twelve (6/12, 50 %). Urine eosinophil more than 5 percent found in one out of twelve patients (1/12, 8.3 %) in urinalysis. Granular cast was found in six out of fifty-six patients (6/56, 10.7 %), hyalin cast in five out of fifty-six patients (5/56, 8.9 %), fatty and RBC cast in two out of fifty-six patients (2/56, 3.5 %), oval fat body cast and waxy cast in one out of fifty-six patients (1/56, 1.7 %) in urinalysis. Urine epithelial cells were seen in one out of fifty-six patients (1/56, 1.7 %) in dipstick. Serum creatinine was measured in sixty-seven out of seventy-two patients (67/72, 93 %) and elevated SCr was seen in forty-nine out of sixty-seven patients (49/67, 73.1 %) with median of 2.17 and IQR of 1.86 mg/dl (Q3-Q1 = 3.55–1.69). Blood urea nitrogen was measured in twenty-four of seventy-two of patients (24/72, 33.3 %) and elevated serum blood urea nitrogen was seen in seventeen of twenty-four patients (17/24, 70.8 %) with median of 39.2 and IQR of 62.7 mg/dl. Serum urea was measured in seven out of seventy-two patients (7/72, 9.7 %) and five of seven patients (5/7, 71.4 %) revealed elevated serum urea with the mean average of 89.96 ± 35.34 mg/dl. Estimated GFR was measured in fifteen out of seventy-two patients (15/72, 20.8 %) and decreased eGFR was seen in thirteen of fifteen patients with fibrillary glomerulopathy (13/15, 86.6 %) with the mean average of 58.83 ± 16.99 ml/min/1.73 m^2 in the present research. Serum hemoglobin was measured in twenty-four of seventy-two patients (24/72, 33.3 %) that anemia was seen in twenty-two patients (22/24, 91.6 %) with the mean average of 9.52 ± 1.92 g/dl. Leukocyte count was measured in twenty-two out of seventy-two patients (22/72, 30.5 %) and leukocytosis was observed in five out of twenty-two patients (5/22, 22.7 %) with the mean average of 15 450 ± 3971.46 cells/10^3. Two out of twenty-two patients (2/22, 9 %) had leukopenia with the mean average of 4040 ± 130 cells/10^3 in the present research. Platelets count was measured in twenty out of seventy-two patients (20/72, 27.7 %) and thrombocytopenia was seen in two out of twenty patients (2/20, 10 %) with the mean average of 70 850 ± 45 860.08 cells/10^3. Serum albumin was measured in thirty-seven out of seventy-two patients (37/72, 51.3 %) and hypoalbuminemia (serum albumin < 3.5–4 g/dl) has been seen in twenty-eight out of thirty-seven patients (28/37, 75.6 %) with the mean average of 2.61 ± 0.48 g/dl with fibrillary glomerulopathy in the present research. Erythrocyte sedimentation rate (ESR) was measured in ten out of seventy-two patients (10/72, 13.8 %) and elevated erythrocyte sedimentation rate (ESR) was seen in eight out of ten patients (8/10, 80 %) with the mean average of 48.44 ± 27.22 mm/hr in current research. 24-hr urine protein was measured in fifty-eight out of seventy-two patients (58/72, 80.5 %) and fifty-seven out of fifty-eight patients (57/58, 98.2 %) showed significant proteinuria with the median of 4200 mg and IQR of 5900 mg (Q3-Q1 = 8000–2100) in 24-hrs. Spot UPCR was measured in sixteen out of seventy-two patients (16/72, 22.2 %) and elevated spot urine protein to creatinine ratio was seen in fifteen of sixteen patients (15/16, 93.7 %) with the mean average of 3924.25 ± 2556.76 mg/g in the present research. Non-albumin PCR (NAPCR) with value of 2083.91 mg/g found in one out of seventy-two patients (1/72, 1.3 %) and elevated NAPCR was seen in 100 % of patients in current research. DNAjB9 detected in eight of seventy-two patients (8/72, 11.1 %) that two out of eight patients (2/8, 25 %) found in kidney renal recipients and six out of eight patients (6/8, 75 %) found in non-transplant patients. Serum protein electrophoresis was measured in thirty-four out of seventy-two patients (34/72, 29.4 %) and abnormal serum protein electrophoresis was seen in ten out of seventy-two patients (10/34, 13.8 %). There are low gamma fraction in two out of twenty-four patients (2/24, 8.3 %) in protein electrophoresis in current research. UPEP was measured in sixteen out of seventy-two patients (16/72, 22.2 %) and there was abnor-

mal urine protein electrophoresis in four out of sixteen (4/16, 25 %) in current research. Serum IgG in SIEP was measured in eleven out of seventy-two patients (11/72, 15.2 %) in the present research. Elevated immunoglobulin (IgG) levels were seen in two out of eleven patients (2/11, 18.1 %) and low IgG levels were seen in three out of eleven patients (3/11, 2.7 %) in the current research. Serum IgM in SIEP was measured in ten out of seventy-two patients (10/72, 13.8 %) in current research. Elevated serum IgM levels were seen in three out of ten patients (3/10, 3 %) and low IgM levels was seen in one out of ten patients (1/10, 10 %) in the present research. In this research, SIF was measured in thirty-six out of seventy-two patients (36/72, 50 %) and there are abnormal serum immunofixation in ten out of thirty-six patients (10/36, 27.7 %). Serum free kappa levels in SIF was measured in seven out of seventy-two patients (7/72, 9.7 %) and there are elevated free kappa levels in seven out seven (7/7, 100 %) with median of 1000 and IQR of 3320.73 mg/l. Serum free lambda levels in SIF was measured in six out of seventy-two patients (6/72, 8.3 %) and elevated free lambda levels was seen in five out six patients (5/6, 83.3 %) with the mean average of 95.26 ± 70.71 mg/l. Free kappa to lambda levels was measured in nine out of seventy-two patients (9/72, 12.5 %) and high free kappa to lambda levels (κ/λ ratio) was seen in three out of nine patients (3/9, 33.3 %) with the mean average of 3.82 ± 2.26 in the present research. UIF was measured in thirty out of seventy-two patients (30/72, 41.6 %) and there are abnormal UIF in nine out of thirty patients (9/30, 30 %) in the present research. Anti-HCV antibody was measured in ten out of seventy-two patients (10/72, 13.8 %) and positive anti-HCV Ab was seen in five out of ten patients (5/10, 50 %) in the present research. HCV RNA PCR was measured in three out of seventy-two patients (3/72, 4.1 %) and positive HCV RNA PCR were seen in two out of three patients (2/3, 66.6 %) in current research. ANA was measured in thirty-seven out of seventy-two patients (37/72, 51.3 %) and there is positive anti-nuclear antibody titer (≥ 160) in six out of thirty-seven patients (6/37, 16.2 %) with median of 1/320 and the IQR of 1 to 320 titer in the present research. C-ANCA was measured in sixteen out of seventy-two patients (16/72, 22.2 %) and P-ANCA was measured in seventeen out of seventy-two patients (17/72, 23.6 %) in current research. Positive C-ANCA was seen in one out of sixteen patients (1/16, 6.25 %) and C-ANCA was seen in one out of seventeen patients (1/17, 5.8 %). Anti-GBM antibody was measured in eleven out of seventy-two patients (11/72, 15.2 %) and positive test was seen in two out of eleven patients (2/11, 18.1 %) in current research. Serum C3 level was measured in forty-four out of seventy-two patients (44/72, 61.1 %) and there is low C3 in nine out of forty-four patients (9/44, 20.4 %) in current research. Serum C4 level was measured in forty-two out of seventy-two patients (42/72, 58.3 %) and low C4 level in three out of forty-two patients (3/42, 7.1 %) in current research. Serum CH50 level was seen in five out of seventy-two patients (5/72, 6.9 %) and decreased CH50 level was seen in three out of five patients (3/5, 60 %) with the mean average of 32.56 ± 10.39 mg/l. High Factor H antibody was measured in two out of seventy-two patients (2/72, 2.7 %) and elevated FH antibody level was seen in one out of two patients (1/2, 50 %) in the present research. Serum CRP level was measured in six out of seventy-two patients (6/72, 8.3 %) and high CRP was seen in five out of six patients (5/6, 83.3 %) patients with median and IQR of 5.9 and 8162.65 mg/l, respectively. Serum β-2 microglobulin level was measured in two out of seventy-two patients (2/72, 2.7 %) and elevated β-2 microglobulin was in two out of two patients (2/2, 100 %) with the mean average of 1000.65 ± 995.35 mg/l. Urinary β-2 microglobulin concentration was measured in one out of seventy-two patients (1/72, 1.3 %) and elevated urinary β-2 microglobulin concentration was seen in one out of one patient (1/1,100 %) in current research. M-spike was seen in two of seventy-two patients (2/72, 2.7 %) with the mean average of 1159.5 ± 1140.5 mg/l. Creatinine clearance (CrCl) was measured in fifteen out of seventy-two patients (15/72, 20.8 %) in current research. There were decreased creatinine clearance in eight of out fifteen patients (8/15, 53.3 %) with median and IQR of 27 and 37 ml/min/1.73 m^2, respectively. Elevated creatinine clearance was seen in two out of fifteen patients (2/15, 13.3 %) with the mean average of 121.7 ± 21.4 ml/min/1.73 m^2 in the present research. eGFR was measured in fifteen out of seventy-two patients (15/72, 20.8 %) and decreased estimated glomerular filtration rate (eGFR) was seen in thirteen out seventy-two patients (13/15, 86.6 %) with the mean average of 58.80 ± 16.99 ml/min/1.73 m^2 in the present research. There was raised eGFR in two out of fifteen patients (2/15, 13.3 %) with the mean average of 111.45 ± 3.25 ml/min/1.73 m^2 in the current research. Serum blood sugar was measured in four out of seventy-two patients (4/72, 5.5 %) that there was hypoglycemia and hyperglycemia in one out four patients (1/4, 25 %) patients in the current research. Serum chloride was measured in six out of seventy-two patients (6/72, 8.3 %) and hyperchloremia was seen in three out of six patients (3/6, 50 %) with the mean average of 112.30 ± 3.39 mEq/l. Lower limit of normal range for serum chloride was seen in one out of six patients (1/6, 16.6 %) in the present research. Serum uric acid was measured in six out of seventy-two patients (6/72, 8.3 %) and there was hyperuricemia in four out of six patients (4/6, 66.6 %) with the mean average of 8.85 ± 0.85 mg/dl in the present research. Serum sodium was measured in seven out of seventy-two patients (7/72, 9.7 %) and hyponatremia was seen in two out of seven patients (2/7, 28.5 %) with the mean average of 130.25 ± 1.75 mEq/l in current research. Serum potassium was measured in eight out of seventy-two patients (8/72, 11.1 %) and hyperkalemia were seen in two out of eight patients (2/8, 25 %) with the mean average of 6.42 ± 0.42 mEq/l in current research. Serum transaminases were measured in eleven out of seventy-two patients (11/72, 15.2 %). Elevated aminotransferase above 22 IU/l were seen in six out of eleven patients (6/11, 54.5 %) with median of 37.5 IU/l and IQR of 40 IU/l for AST, median of 43 and IQR of 41 IU/l for ALT in current research. Serum cholesterol was measured in nineteen out of seventy-two patients (19/72, 26.3 %) in current research. There was elevated total cholesterol in thirteen out of nineteen (13/19, 68.4 %) with medi-

an of 247 mg/dl and IQR of 126 mg/dl. Fibril size was measured in sixty-nine out of seventy-two patients (69/72, 83.3 %) with median size of 15 nm and IQR of 6.5 nm (Q3-Q1 = 18.5–12.4) in the present research.

Pathologic findings

Working group updated oxford classification of IgA nephropathy in 2016 year and five parameters of MEST-C score were considered for this classification. Based on this workshop, kidney specimens must contain at least eight glomeruli number. Number of glomeruli with endocapillary hypercellularity, necrosis, extracapillary hypercellularity (cellular/fibrocellular crescents), global glomerulosclerosis and segmental glomerulosclerosis in this classification must be considered (Fig. 2). Kidney biopsy was performed in seventy-one out of seventy-two patients (71/72, 98.6 %) in the present research. Kidney biopsy was not performed in one patient (1/72, 1.3 %) due to death in current research. According to Oxford MEST-C classification, there was M0 score in twenty-two of seventy-one patients (22/71, 30.9 %), M1 score in four out of seventy-one patients (4/71, 5.6 %), undetermined mesangial score in eight out of seventy-one patients (8/71, 11.2 %) in current research. E1 score found in fifteen out of seventy-one patients (15/71, 21.1 %), E0 in three out of seventy-one patients (3/71, 4.2 %) and undetermined E score in one out of seventy-one patients (1/72, 1.3 %) in the present research. There was C2 in eight out of seventy-one patients (8/71, 11.2 %), C1 in five out of seventy-one patients (5/71, 7 %) and three out of seventy-one patients (3/71, 4.2 %) in current research. S1 found in thirty-nine out of seventy-one patients (39/71, 54.9 %) in the present research. T0 found in thirty of seventy-one patients (30/71, 41.7 %), T1 in nine out of seventy-one patients (9/71, 12.6 %), T2 in seven out of seventy-one patients (7/71, 9.8 %) in current research. Double contour glomerular basement membrane (GBM) detected in six out of seventy-one patients (6/71, 8.4 %) and DNAjB9 marker found in kidney biopsies of eight out of seventy-one patients (8/71, 11.2 %) in current research. In renal allograft recipients, there was mm0 in two out of seventy-one patients (2/71, 2.8 %), i1, t1, v0, g1, ptc3, c4d3, ci0, cv1, cv3, cg1b, mm3 in one out of seventy-one patients (1/71, 1.4 %) patients in current research. Undetermined ci, cv, ct and mm and mesangial proliferation found in one out of seventy-one patients (1/71, 1.4%) in the present research (Table 1).

Imaging techniques

Chest x-ray in the present research revealed different abnormalities such as bilateral pleural effusion in two out of seventy-two patients (2/72, 2.7 %), bulky left hilum, bilateral cottony interstitial infiltrates, mild interstitial lung disease

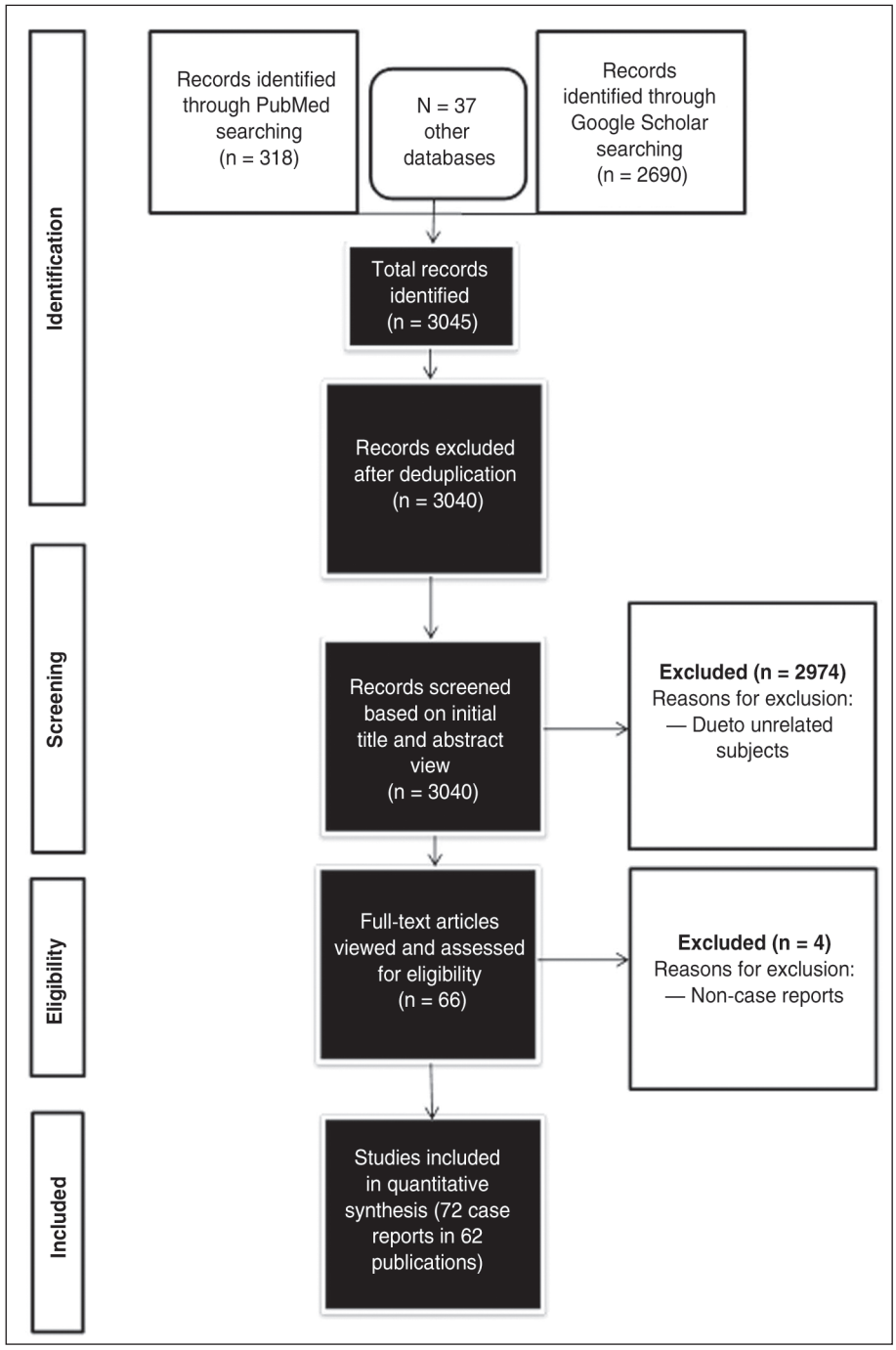

Figure 2. Workflow of current research

Table 1. Pathologic characteristics of patients with biopsy-proven fibrillary glomerulopathy in current research

Pathologic classification of MEST-C Score								
Score / Author	Mesangial score (M0 or M1)	Endocapillary Hypercellularity (E0 or E1)	Segmental glomerulosclerosis (S0 or S1)	Tubular atrophy/ Interstitial Fibrosis (T0 or T1 or T2)	Cellular/fibrocellular crescents (C0 or C1 or C2)	Glomeruli number		
1	2	3	4	5	6	7	8	9
Park		E1	S1	T0		21		
Fisher	M0	E1	S1	T0				
Javaid	M0		S1	T0	C0	9		
Pliquett			S1					
Navaro-Antolin	M0			T0				
Adapa	M0	E1	S1	T0		27		
Sung	M0		S1	T0				KWN
Her	M0		S1	T0		12		
Joffy	M1		S1	T0		15		
Watanabe 1	M0					90		
Watanabe 2	M1					49	Double contour	
Watanabe 3				T0				
Lodhi	M1		S1	T1	C1			
Gielen	M0	E1				12		
Momose	+	E1	S1	T0		17		
Garcia			S1		C2	49	DNAJB9	
Nebuloni	M1		S1 (3)		C2 (9)	20		
Cheungpasitporn	M0		S1		C2 (1 = fibrocellular; 1 = fibrous crescent)	7		
Nilajgi	+	+	S1	T1	C2	19		
Sanjeeve			S1	T2	C2	17		
Kfoury	M0		S1	T1 (30 %)		8		
Shah	M0	E1		T0–T1	C1	12		
Huerta 1	M0		S1	T0		15		
Huerta 2	M0		S1	T0		21		

Table 1 continuation

1	2	3	4	5	6	7	8	9
Mendez	+					16		
Marin				T1		19		
Churg 1	M1		S1	T0		11		
Churg 2	M1	E1	S1			36		
Uchida	M0	E1	S1	T0		27	Double contour; DNAJB9	
Alpers	M0		S1	T0		16		
Amir-Ansari	M1			T0–T1				
Lerner	M2		S1	T1		48	Kim-melstiel nodule; double contour; DNAJB9	
De larrea	+, MH				C1		Nodular ME	
Leiber	M1			T0		14		
Gandhi			S1	T2		3	DNAJB9	
Masson	M1			T0				
Kornblihtt								
Wu	M1	E1	S1	T0		11	Double contour	
Sain-pretzel								
Sekulic	M1	E1	S1	T0	C0	14		
Maroz	M1			T2		39		
Cantillo	M1	E1	S1	T2			Double contour	
Yumura	M0	E0	S1	T0		15		
Suzuki	+			T0			Double contour	
Sundaram	+		S1	T1		10	Lobulated	
Sehgal	M1			T2				

Table 1 continuation

1	2	3	4	5	6	7	8	9
Chaudhary 1	M1		S1	T0		16		
Chaudhary 2	+		S1	T1		32	Kim-melsteil wilson nodule	
Dussol	M1		S1			25		
Ichikawa	M0			T0		10		
Coroneos	M1	E0		T0	C0	51		
Ray	M0		S1					
Kim	M0							
Soma	M0	E1	S1	T2		22		
Asakawa					C2	13	DNAJB9, segmental duplication	
González-Cabrera 1	M1		S1	T0		14		
González-Cabrera 2	M0		S1	T0	C2	18		
González-Cabrera 3	M0		S1	T1		15		
González-Cabrera 4			S1			11		
Tsui	M1	E0		T0			DNAJB9	
Adey	M1			T2	C2		Double contour	
Rostagno		E1	S1	T1	C1	17		
Hsu 1	M1			T0	C1			
Hsu 2	M1							
Bircan	M1	E1				40	Duplication	
SF Cheung	+	E1		T0		15	Focal double contour	
Khorsan	M1							

End of table 1

Author \ Banff classification	Banff lesion score in renal allograft																
	Interstitial inflammation (i)	Tubulitis (t)	Intimal arteritis (v)	Glomerulitis (g)	Peritubular Capillaritis (ptc)	C4d	Interstitial fibrosis (ci)	Tubular atrophy (ct)	Vascular fibrous intimal thickening (cv)	GBM double contours (cg)	Mesangial matrix expansion (mm)	Arteriolar hyalinosis (ah)	Hyaline arteriolar thickening (aah)	Total inflammation (ti)	Inflammation in the area of IFTA (i-IFTA)	Glomeruli number		Banff grade
Nasr	i1	t1	v0	g1	Ptc3	C4d3					mm0						Active Ab-mediated rejection, DNAJB9	borderline (i1t1v0)
Fillippone							+	+	+		+							
Jeyabalan							ci0		cv1	Cg1b	mm0, MP						DNAJB9	
Cheung									cv3		mm3					36		

***Notes:** DNAJB9 — DnaJ heat shock protein family (Heat shock protein 40) member 9; GBM — glomerular basement membrane; i-IFTA — inflammation-interstitial fibrosis/tubular atrophy; KWN — kimmelsteil Wilson nodule; MEST-C — mesangial expansion/endocapillary hypercellularity/segmental sclerosis/tubular fibrosis/atrophy-crescent; MP — mesangial proliferation.*

(ILD), diffuse interstitial process and atelectasis of left lower lobe, mild cardiomegaly in one out of seventy-two patients (1/72, 1.3 %) in current research. Abnormal kidney ultrasonography was seen in thirteen out of seventy-two patients (13/72, 18 %) in current research. There were various kidney abnormalities in ultrasonography as increased parenchymal echogenicity, scattered cyst, simple cyst, enlarged kidney sizes, bilateral small kidney, single kidney with compensatory hypertrophy of other kidney, enlarged kidneys with multiple cyst, bilateral kidneys with increased echogenicity and irregular surface, bilateral kidneys with increased echogenicity, irregular surface and normal sizes in the present research. A small benign cyst was seen in ultrasound scan of one out of seventy-one patients (1/72, 1.3 %) in the present research. Abdominal sonography in one out of seventy-two patients (1/72, 1.3 %) revealed ascites, gall bladder stone and bilateral pleural effusion. Upper GI endoscopy was performed in two out of seventy-two patients (2/72, 2.7 %) that in one case (1/72, 1.3 %) revealed macroscopic evidence of gastritis with polypoid mass and central ulceration on the anterior wall of the stomach. Another case showed chronic antral gastritis and duodenitis with superficial erosions. Two abnormal findings were seen in echocardiography (2/72, 2.7 %) as mild mitral regurgitation (MR) and slight left ventricular hypertrophy (LVH) in the present research. Chest computed tomography (CT) scan in one out of seventy-two patients (1/72, 1.3 %) revealed bilateral interstitial pulmonary infiltration and abdominal CT scan showed renal atrophy, ascites and multiple liver abscesses.

Treatment modalities

Therapeutic modalities comprise oral steroids in forty-two out of seventy-two patients (42/72, 58.3 %), IV methylprednisolone in thirty-two out of seventy-two patients (32/72, 44.4 %), immunosuppressive agents in forty patients (40/72, 55.5 %) that include cyclophosphamide (CPA) in fifteen cases (15/40, 37.5 %), azathioprine in eight cases (8/40, 20 %), cyclosporin in five cases (5/40, 12.5 %), mycophenolate mofetil (MMF) in four cases (4/40, 10 %), tacrolimus, chlorambucil and undetermined immunosuppressive agents in three cases (3/40, 7.5 %), sirolimus in 1 case (1/40, 2.5 %). Rituximab was used in ten out of seventy-two patients (10/72, 13.8 %) and plasmapheresis in seven out of seventy-two patients (7/72, 9.7 %). Interferons were used in three out of seventy-two patients (3/72, 4.1 %) that consist interferon, interferon alpha and interferon alpha 2A. Immunoglobulins were used in three out of seventy-two patients (3/72, 4.1 %) in the present research. Angiotensin-converting enzyme inhibitors (ACEIs) were used in twenty-five out

of seventy-two patients (25/72, 34.7 %), angiotensin receptor blockers (ARBs) were used in eight out of seventy-two patients (8/72, 15.2 %) and dual renin angiotensin system (RAS) blockades in three out of seventy-two patients (3/72, 4.1 %). Diuretics were consumed in fourteen out of seventy-two patients (14/72, 19.4 %). Calcium channel blockers were used in eight out of seventy-two patients (8/72, 11.1 %) and beta-blockers in four out of seventy-two patients (4/72, 5.5 %). H_2-blockers were used in four out of seventy-two patients (4/72, 5.5 %) patients with fibrillary glomerulopathy. Fifteen out of seventy-two patients (15/72, 20.3 %) underwent hemodialysis (HD) in current research and two out of seventy-two patients (2/72, 2.7 %) underwent peritoneal dialysis (PD). Undetermined dialysis (2/72, 2.7 %) performed in one out of seventy-two patients (1/72, 1.3 %) in the present research.

Outcomes and follow up

Characteristics of patients during follow up has been recorded in Table S8 in current research.

Primary end-points

Serum creatinine was measured in forty out of seventy-two patients (40/72, 55.5 %) and in accordance with SCr, three out of forty patients (3/40, 7.5 %) found AKI, four out of forty patients (4/40, 10 %) found AKD, fourteen out of forty patients (14/40, 35 %) developed CKD during follow up in current research. NKD found in one out of forty patients (1/40, 2.5 %) based on eGFR calculation. Elevated SCr was seen in twenty-eight out of forty patients (28/40, 70 %) with median of 2.18 mg/dl and IQR of 4 mg/dl (Q3-Q1 = 5.65–1.55) during time of follow up (time of the last serum creatinine measurement) in the present research. There was significant statistical correlation between elevated SCr and follow up time with *p* value of 0.01 and confidence interval of 0.7820 to –0.1258 during follow up (Fig. 3). Relative risk of kidney failure progression to KRT (≥ 2 fold elevation in SCr or dialysis or kidney transplant) in exposed to DNAjB9 positive patients (Group I) and DNAjB9 negative patients (Group II) was assessed 2.67 with 95% CI of 1.128 to 6.3044 and *p* value of 0.025. Odds ratio of kidney failure progression to KRT (≥ 2 fold elevation in SCr or dialysis or kidney transplant) was assessed 4.33 with 95% CI of 0.9464 to 19.8417 and *p* value of 0.058 in current research (Table 2). Twenty-two out of seventy-two patients (22/72, 30.5 %) stayed on dialysis and two out twenty patients (2/20, 10 %) underwent PD during follow up period. Kidney disturbation was occurred in the median time of 6.5 hours and IQR of 14.5 hrs (Q3-Q1 = 17.5–3). Serum Bun was measured in six out of seventy-two patients (6/72, 8.3 %) and three out of six patients (3/6, 50 %) found elevated blood urea nitrogen with the mean average of 69.0 ± 23.8 mg/dl in current research. Creatinine clearance was measured in three out of seventy-two patients (3/72, 4.1 %) and two out of three patients (2/3, 66.6 %) found decreased creatinine clearance with the mean average of 20.2 ± 11.5 milliliter per minute (cc/min). Estimated GFR was measured in five out of seventy-two patients (5/72, 6.9 %) and five out of five patients (5/5, 100 %) patients developed declined eGFR with the mean average of 42.02 ± 18.94 ml/min/1.73 m^2 in current research. 24-hr urine protein collection was measured in twenty-one out of seventy-two patients (21/72, 29.1 %) and significant 24-hr proteinuria was seen in fourteen out of twenty-one patients (14/21, 66.6 %) with mean of 1.09 ± 0.75 g/24 hr in current research. UPCR was measured in nine out of seventy-two patients (9/72, 12.5 %) and eight out of nine patients (8/9, 88.8 %) developed elevated UPCR proteinuria with median of 800 mg/g and IQR of 12 600 mg/g (Q3-Q1 = 13 000–400) during follow up. Urinary bence jones protein (BJP) was measured in one out of seventy-two patients and elevated free BJP (free kappa protein) was seen in one out of one patient (1/1, 100 %) in the present research. Free kappa to lambda ratio was measured in two out of seventy-two patients (2/72, 2.7 %) and two out of two patients (2/2, 100 %) found elevated free kappa to lambda ratio in the present research. Eight out of seventy-two patients (8/72, 11.1 %) died in current research. Proportion of death in DNAjB9 positive patients (Group I) was assessed zero out of eight patients (0/8) and proportion of non-died patients in DNAjB9 positive patients was assessed eight out of eight patients (8/8,100 %). Proportion of death in DNAjB9 negative patients (Group II) was assessed eight out of sixty-four patients (8/64, 12.5 %) and proportion of non-died patients in DNAjB9 negative patients was assessed fifty-six out of sixty-four patients (56/64, 87.5 %) in current research. There was nonsignificant statistical level in comparison between DNAjB9-positive and DNAjB9-negative patients (proportion between two groups) during follow up in current meta-analysis ($p = 0.29$). There was statistical significant level at comparison between group I and group II for mortality probability (Kaplan-Miere analysis) during follow up in the present research ($p < 0.0001$) (Fig. 4). KRT (renal transplant) was seen in four out of seventy-two patients (4/72, 5.5 %) in current research. Two out of eight DNAjB9 positive staining in kidney biopsy specimens found kidney transplantation (2/8, 25 %) and six out of eight DNAjB9 positive staining were not received kidney transplantation (6/8, 75 %). Proportion difference was assessed 21.9 % in this research. Comparison of these value was assessed 0.011 (p-value of 0.011) with confidence interval of 2.51 to 56.05. Two out of sixty-four DNAjB9 negative staining in kidney biopsy specimens found kidney transplantation (2/64, 3.1 %) and sixty-two out of sixty-four DNAjB9 negative staining were not received kidney transplantation (62/64, 96.8 %). Two out of seventy-two patients (2/72, 2.7 %) developed recurrence of disease in fibrillary glomerulonephritis. Graft loss was seen in two out of four patients (2/4, 50 %) post-transplant period during follow up. There was not significant correlation between histologic marker of segmental glomerulosclerosis (S1) and DNAjB9 staining on kidney biopsy specimens (p-value of 0.11; correlation coefficient: 0.7).

Secondary end-points

Three out of seventy-two patients (3/72, 4.1 %) patients found ESKD in the present research. HCV RNA was measured in one out of seventy-two patients (1/72, 1.3 %) and it disappeared in one out of one patient (1/1, 100 %) during

follow up. Herpers zoster was measured in one out seventy-two patients (1/72, 1.3 %) and found in one out one patient (100 %) in the present research. Serum transaminases were measured in two out of seventy-two patients (2/72, 2.7 %) and elevated serum transaminases found in one out of two patients (1/2, 50 %) in current research. C3 was measured in three out of seventy-two patients (3/72, 4.1 %) and low C3 was seen in one of three patients (1/3, 33.3 %) in current research. C4 was measured in two out of seventy-two patients patients (2/72, 2.7 %) and normal C4 detected in two out of two patients (2/2, 100 %). Platelet count was measured in two out of seventy-two patients and thrombocytopenia found in two out of two patients (100 %) in current research. Antinuclear antibodies was measured in one out of seventy-two patients (1/72, 1.3 %) and elevated ANA titer was seen in one out one patient (1/1, 100 %) in the present research.

Discussion

Fibrillary glomerulonephritis is a rare glomerular disease that has been found in less than 1 % of native kidney biopsies. This disease first described by Rosenmann and Eliakim in 1977 year [71]. Fibrillary GP is diagnosed by ultrastructural finding of arranged straight fibrils measuring to 10 to 30 nm in thickness in electron microscopy. Depositions in FGN are in the mesangium and GBM or both in electron microscopy. On immunofluorescence (IF) staining, the deposits stain for polyclonal IgG and complement indicating immune complex deposition. Somewhat ill-defined smudged deposits that stain most intensely for IgG, usually accompanied by C3, κ, λ and sometimes also associated with staining for C1q, IgM and/or IgA. In 5 % of cases, IF deposits stain by κ or λ but not both and such light chain restriction is related to dysproteinemia [3]. Morphologic features of FGN in IF staining consist mesangial expansion/hypercellularity with or without GBM duplication. Other morphologic features include endocapillary glomerulonephritis and crescentric glomerulonephritis. These patients present with proteinuria (most often with nephrotic syndrome), hematuria, renal insufficiency and hypertension that in 50 % of cases culminate in to end-stage kidney disease. In our research 19.4 % (14/72) of patients presented with lower leg extremity edema and 85.7 % (48/56) presented with micro-

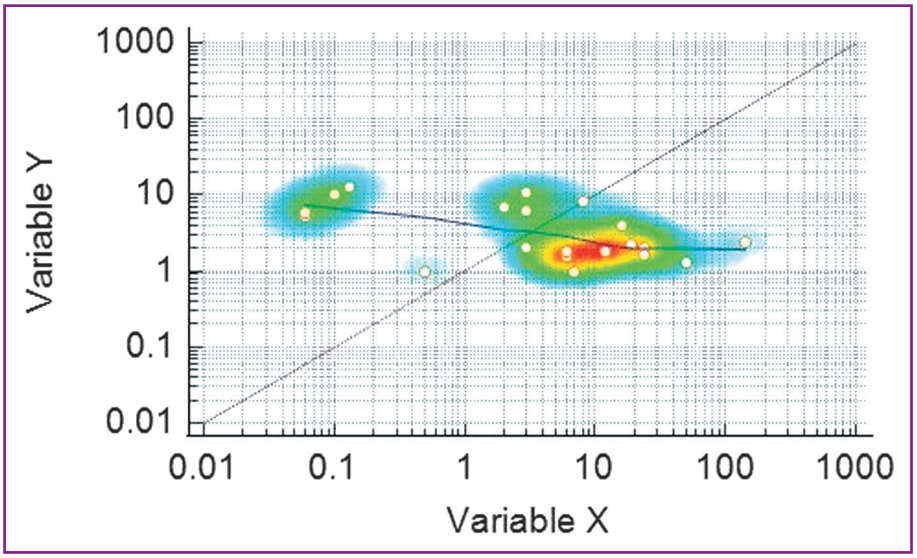

Figure 3. Correlation between serum creatinine and time on outcomes of patients with fibrillary glomerulopathy in current research. SCr, serum creatinine. Variable X indicates time of the last serum creatinine measurement in patients with fibrillary glomerulonephritis during follow up and variable Y depicts serum creatinine level

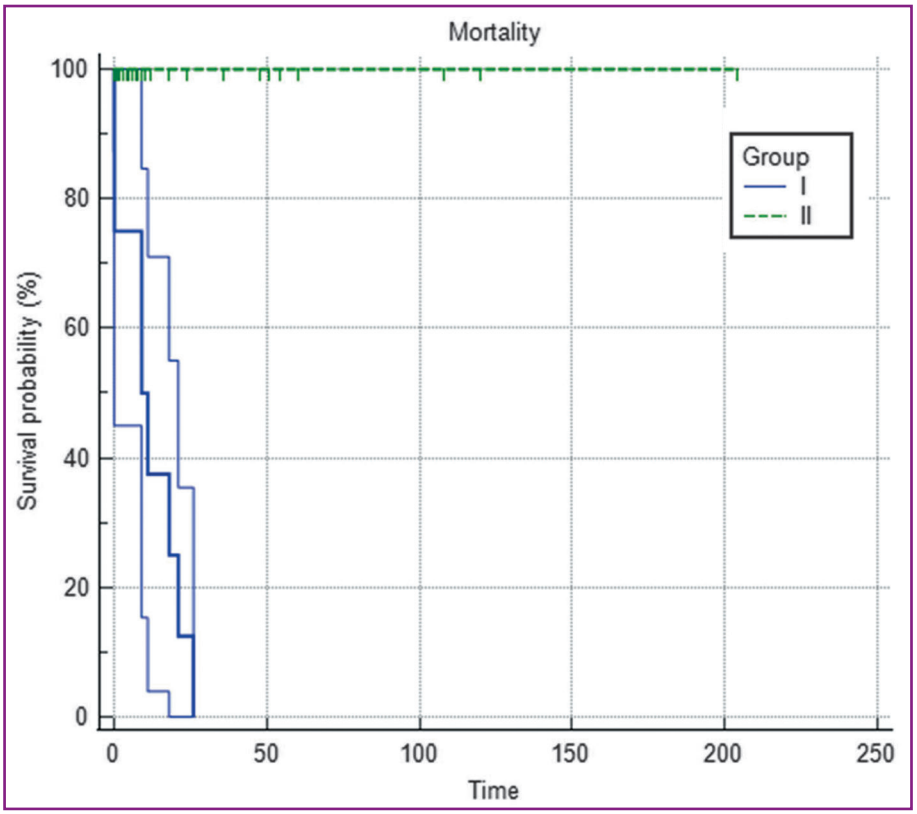

Figure 4. Kaplan-Miere curve of death and time of follow up of patients with fibrillary glomerulopathy in current research. Group I indicates death in DNAjB9 positive patients and Group II depicts death in DNAjB9 negative patients

scopic hematuria. Clinical features of 33.3 % (24/72) of our patients were hypertension and there was proteinuria in one hundred (100%) patients. 33.3 % of our patients developed ESKD during 1 year follow up that was in disagreement with study by Andeen et al. that 53 % progressed to ESKD during 24 months follow up. DNAjB9 is a novel biomarker for FGN and DNAjB9 expression in the glomeruli is highly specific and sensitive for FGN. Whether serum DNAjB9 marker can be used for FGN or not, one study by Nasr et al. revealed that serum levels of DNAjB9 staining could be valuable marker to predict FGN with the complement kidney biopsy for the diagnosis of FGN [72]. Inherited FGN or familial FGN is reported in few cases and genetic background can play a role in pathogenesis of FGN because human leukocyte antigens (HLAs) involve in inherited risk factors for emerging FGN. HLA associated with FGN is seen in other kidney diseases. HLA-DR7 and HLA-DQ2 have been associated with steroid sensitive nephrotic syndrome and HLA-B-35 is seen in IgA nephropathy/Henoch-schoenline purpura (HSP) [73]. Moreover, association between FGN and HLAs have been reported as HLA-B35, HLA-DR-7 and DQ2 antigens. Lower frequency with HLA-DR4 has reported in FGN. Notably, association between hepatitis C virus infection and fibrillary glomerulonephritis has been reported in several studies. Positive HCV RNA PCR was seen in two out of three patients (2/3, 66.6 %) and positive anti-HCV Ab was seen in five out of ten patients (5/10, 50 %) in the present research that those values are approximately in agreement with studies by Nasr et al. and Said et al. arisen positive hepatitis C infection. That study revealed positive Hepatitis C PCR in two out of forty-seven patients (2/47, 4.2 %) while study by said et al. revealed positive hepatitis C infection in one out of seventeen patients (1/17, 5.8 %) [74]. Association of this virus with FGN in black people in another study has been documented by Schober et al. that this value was higher in black people rather than white people [75]. Another finding in this research must be noticed that is age of patients with FGN. The median age of patients with FGN was 55 years old and there was slight male predominance (male to female ratio: 1.25) that was agreement with Study by Nasr et al. The mean age of patients at kidney biopsy was 53 years and female predominance was detected in that study. Another association of this disease has been reported with dysproteinemia and autoimmune diseases such as cryoglobulinemia and test for cryoglobulin must be performed before diagnosis of fibrillary GP. In our research, high free kappa and free lambda levels found in 100% (7/7) and 83.3 % (5/6) of patients with FGP, respectively. Moreover, high free kappa to lambda levels (κ/λ ratio) was seen in three out of nine patients (3/9, 33.3 %) with the mean average of 3.82 ± 2.26 in the present research. Two out of seventy-two patients (2/72, 2.7 %) had M-spike protein while in study by Nasr et al., was assessed eleven out of sixty-three patients (11/63, 17.4 %). Moreover, study by Marinaki et al. revealed negative monoclonal paraproteinemia, chronic viral infection and serologic tests for other autoimmune disorders in ten patients [76]. Positive ANA was seen in six out of thirty-seven patients (6/37, 16.2 %) and with median of 1/320 and the IQR of 1 to 320 titer and this value was disagreement with study by Said et al. that this value was assessed higher (3/14, 21.4 %). Low C3 in nine out of forty-four patients (9/44, 20.4 %), low C4 in three of forty-two (3/42, 7.1 %) patients and low CH50 were seen in three out of five patients (3/5, 60 %) were detected while it was inconsistent with study by Said et al. that serum C3 and C4 were normal in all sixteen patients. Positive C-ANCA was seen in one out of sixteen patients (1/16, 6.25 %) and C-ANCA was seen in one out of seventeen patients (1/17, 5.8 %). Positive anti-GBM antibody was seen in two out of eleven patients (2/11, 18.1 %) in current research. Other finding in this research was presence of high relative risk and Odds ratio of fibrillary glomerulonephritis on outcome of kidney failure progression to KRT (persistent dialysis or kidney transplantation or ≥ 2-fold elevation in SCr) that assessed 2.67 and 4.33, respectively. The key points in this discussion are death probability in DNAjB9-negative patients and effect of this marker on outcomes of fibrillary glomerulonephritis. Survival probability of DNAjB9 negative patients with fibrillary GP was assessed 12.5 % vs. probability of 0 in DNAjB9-positive patients with significant statistical level (< 0.0001). Till to now based on my to my best knowledge, such study hasn't been found in literature review and advanced searching. Because DNAjB9 is accounted as the fourth most abundant protein in FGN glomeruli, therefore can be said that it is the most common protein involving in its pathogenesis [77]. Hence it is possible that in the absence of ultrastructural evaluation (EM), this immunohistochemical marker can diagnose the fibrillary GN [3]. In conclusion, relative risk of kidney failure progression to KRT in exposed to DNAjB9 positive patients (Group I) and DNAjB9 negative patients (Group II) was assessed 2.67. There was statistical significant level at comparison between group I and group II for mortality probability (Kaplan-Miere analysis) during follow up in the present research.

Ethics Approval and consent to participate. Authors of published articles (case reports) stated that research was

Table 2. Relative risk and odds ratio of kidney failure progression to KRT

Disease +/– / Exposure +/–	Kidney failure progression to KRT	Non-kidney failure progression to KRT	Total	Relative Risk	Odds ratio
DNAjB9 positive patients (Group I)	4 (a)	4 (b)	8 (n1)	a/a + b ÷ c/c + d 4/4 + 4 = 0.5 12/12 + 52 = 0.18 0.5 ÷ 0.187 = 2.67	a × d/b × c 52 × 4 = 208 12 × 4 = 48 208 ÷ 48 = 4.33
DNAjB9 negative patients (Group II)	12 (c)	52 (d)	64 (n0)		
	16 (m1)	56 (m0)	72 (N)	2.67	4.33

Note: KRT — kidney replacement therapy.

conducted ethically in accordance with the World Medical Association Declaration of Helsinki. They described that subjects (or their parents or guardians) were given their informed consent and study protocol was approved by the institute's committee on human research.

Consent for publication. Not applicable.

Availability of data and material. Author put the dataset (supplementary data) with http://doi.org/10.6084/m9.figshare.20530224 in figshare repository after publication.

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Dataset of manuscript entitled «Effect of FN1 mutation on outcomes of fibronectin glomerulopathy in a systematic review and meta-analysis» that has been published on 23 May 2022, located in figshare repository with Doi: 10.6084/m9.figshare.20532126.This repository is active.

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Вплив біомаркера Dna-j білка теплового шоку члена 9 родини B (DNAJB9) у зразках біопсії нирки на ниркові результати при фібрилярному гломерулонефриті

Резюме. Актуальність. Фібрилярний гломерулонефрит — рідкісне захворювання клубочків, що проявляється гіпертензією, гематурією, нефротичним синдромом і нирковою недостатністю. **Мета дослідження:** оцінити вплив маркера забарвлення DNAjB9 у зразках біопсії нирок на ниркові результати. **Матеріали та методи.** У цьому аналітичному (експериментальному) клінічному дослідженні з дизайном рандомізованого клінічного випробування (метааналітична стаття) були обстежені 72 пацієнти з підтвердженим біопсією фібрилярним гломерулонефритом. Вивчені клінічні ознаки, лабораторні дані при первинному зверненні, методи лікування та наслідки. Стаття написана на основі пошуку в базах PubMed Central і Google Scholar для виявлення потенційно релевантних статей. Медіана, відсоток, середнє ± стандартне відхилення (SD), двовибірковий t-критерій і хі-квадрат, двопропорційний метааналіз різниць та аналіз Каплана — Меєра використовувалися для статистичної оцінки. Крім того, для статистичного аналізу враховували відносний ризик, співвідношення шансів, кореляцію Спірмена. **Результати.** Медіана та інтерквартильний діапазон віку пацієнтів із фібрилярною нефропатією на момент встановлення діагнозу дорівнювали 55 і 18 років відповідно. У поточному дослідженні не було статистично значущої різниці між групами чоловіків і жінок (p = 0,35). Існувала значуща статистична кореляція між підвищеним рівнем креатиніну сироватки, часом останнього вимірювання креатиніну сироватки і значенням p = 0,01 та довірчим інтервалом (ДІ) від 0,7820 до –0,1258 під час спостереження. Відносний ризик прогресування ниркової недостатності до використання замісної ниркової терапії (↑ ≥ 2 рази рівня креатиніну в сироватці крові або діаліз чи трансплантація нирки) у DNAjB9-позитивних (група I) та DNAjB9-негативних пацієнтів (група II) оцінювався як 2,67 із 95% ДІ від 1,128 до 6,3044 і значенням p = 0,025. Співвідношення шансів прогресування ниркової недостатності до замісної ниркової терапії (↑ ≥ 2 рази рівня сироваткового креатиніну або діаліз чи трансплантація нирки) було оцінено як 4,33 із 95% ДІ від 0,9464 до 19,8417 і значенням p = 0,058. Виявлено статистично значущу різницю при порівнянні групи I та групи II щодо ймовірності смертності (аналіз Каплана — Меєра) під час подальшого спостереження (p < 0,0001). **Висновки.** У цьому дослідженні виявлено високий ризик смертності серед DNAjB9-негативних пацієнтів (8/64, 12,5 %) порівняно з DNAjB9-позитивними пацієнтами (0/8) зі статистично значущим рівнем. Відносний ризик і співвідношення шансів прогресування ниркової недостатності до замісної ниркової терапії оцінювалися як 2,67 і 4,33 відповідно.

Ключові слова: маркер DNAjB9; електронна мікроскопія; термінальна стадія хвороби нирок; фібрилярний гломерулонефрит; шкала MEST-C

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Structure and features of the dynamics of primary disability in the adult population of Ukraine as a result of non-oncological urological diseases

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Abstract. ***Background.*** *The purpose of the work: to study the structure and features of the dynamics of primary disability among the adult population of Ukraine as a result of non-oncological urological diseases.* ***Materials and methods.*** *The reporting form No. 14 of the State Statistics Service of Ukraine, the statistical sources of the Ukrainian State Research Institute of Medical and Social Problems of Disability, documentation of regional centers for medical and social expertise are used.* ***Results.*** *There is a tendency to reduce the number of people recognized as disabled for the first time due to genitourinary diseases. It has been confirmed that prolonging temporary disability contributes to this. The official reporting of the causes of disability by the class of genitourinary diseases is presented only for chronic glomerulonephritis and chronic pyelonephritis; for 5 years, the incidence of the first nosology increased by 13.0 % (to 43.8 % among 1,549 registered), the second — decreased by 37.4 % (to 20.0 % in all regions except Kyiv). At the same time, there was a tendency to reduce the incidence of disability retirement for reasons classified as "others" (36.2 ± 2.0 % vs. 39.0 ± 1.8 % in 2016, and in the Central and Northeastern regions it reached 49.2 ± 2.8 % and 49.6 ± 4.7 %, respectively). Apart from the two above-mentioned pathologies, the structure of disability causes is as follows: the first three places belonged to urolithiasis, polycystic kidney disease, single kidney, the next three — hydronephrosis, congenital malformations and urethral stricture. With age, the incidence of urolithiasis, polycystic kidney disease, hydronephrosis, urethral stricture increases and the incidence of congenital malformations and a single kidney decreases. Over the years, the assignment of the second group of disability decreases (18.1 ± 3.1 % in 2020 vs. 20.4 ± 2.6 % in 2016), with an increase of the third group (67.8 ± 3.8 % vs. 65.3 ± 3.1 %), and stabilization of the first group (14.1 vs. 14.3 %).* ***Conclusions.*** *During the 5-year observation period, 12.9 % more patients avoided disability and 4.7 % less received groups I and II. A decrease by 37.4 % (to 20.0 %) in the share of chronic pyelonephritis as a cause of disability was observed in all regions except Kyiv. Structure of other causes of disability: urolithiasis — 45.0 %, polycystic kidney disease — 22.1 %, single kidney — 18.8 %, hydronephrosis — 15.4 %, congenital defects — 12.1 %, urethral stricture — 4.7 %. Against the background of the general increase in disability assignments with age, group III disability among others was more common (7.7 % — at the age of up to 39 years, 63.1 % — at pre-retirement age, 67.8 % — at retirement age).*

Keywords: *primary disability; non-oncological urological diseases; structure; dynamics*

Introduction

Public health, according to the World Health Organization, is a set of organizational measures aimed at preventing disease and prolonging human life. Investments in health cover a wide range of costs for prevention, payment for medical services, rehabilitation [1–4]. A separate, relevant area is the management of people with disabilities who are among the most active users of medical care in outpatient clinics and hospitals and need social services. The World Health Organization emphasizes the prevalence of disability over the years, along with the growing elderly and senile population and the consequent reduction in healthy life expectancy with significant economic damage. No country

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can avoid it. Therefore, the formation of social and economic policy in each of them is determined not only by the degree of understanding the problem, but also the development of the health care system and by socio-economic situation [5, 6].

The predominance of people with disability groups III (55 %) and II indicates untreated patients who were referred to the medical and social expert commissions (MSEC) by doctors from medical control commissions. Hence the importance of coordinated work of medical and social examination and outpatient services in the rehabilitation of patients with chronic debilitating diseases. At present, the practice of medical and social expertise, the principles of classification and criteria for establishing disability, types of medical and social care need to be improved [7]. Reorganization of medical care aimed at prevention, early diagnosis, post-hospital therapy with rehabilitation in outpatient and sanatorium conditions, adaptation at the social level are the main principles for solving disability problems [8–10]. The above justifies the need to study the regional dynamics of the causes of disability, in this case due to genitourinary diseases.

Purpose: to study the structure and features of the dynamics of primary disability due to non-oncological urological diseases among the adult population of Ukraine.

Materials and methods

Several sources of information are used in the work. The first was the reporting form No. 14 "Report on the causes of disability, indications for medical, professional and social rehabilitation", approved by the Order of the Ministry of Health of Ukraine No. 378 dated 10.07.2007 by agreement with the State Statistics Service of Ukraine (chapter 4 "Distribution of people newly diagnosed with a disability by disease classes and individual nosological forms", chapter 5 "Of the total number of people newly diagnosed with a disability"). The class of genitourinary diseases in the document is represented by only two nosological forms: chronic glomerulonephritis and chronic pyelonephritis [11, 12]. The statistical sources of the Ukrainian State Research Institute of Medical and Social Problems of Disability of the Ministry of Health of Ukraine were selected as the second source of information [13, 14].

On a contract basis, the materials of the following regional MSECs were also used: Ivano-Frankivsk, Ternopil (Western region), Cherkasy (Central), Sumy (Northeast), Dnipropetrovsk (Southeast), Mykolaiv, Odesa, Kherson (South). The total adult population of these areas in 2020 was 10,066,417 people of both sexes, which was 29.4 % of the total population of Ukraine (34,198,849). Among them, 27.9 % (6,662,304) were urban residents (23,883,921) and 33.0 % (3,404,113) — rural (10,314,928).

The indicators of 2020 and 2016 were analyzed and compared: absolute values and calculated intensive, extensive coefficients, average values and mean errors. The latter was used to determine Student's criterion for assessing the significance of the differences between the two statistical coefficients.

Results and discussion

The issue of disability of people of working age due to non-oncological urological diseases, despite its relevance, was last discussed in the literature available to us in 1991 [15, 16]. The analysis of the current state of the problem showed that in Ukraine, the total number of people disabled due to genitourinary diseases is reducing over the years. Thus, in 2020, 1,549 people were recognized as disabled for the first time, which was 13.0 % less than in the previous year (1,782) and 13.7 % for five consecutive years (1,795). Moreover, in 2016–2020, the process affected all regions: in the West — by 5.1 % to 479, in the Center — by 8.8 % to 301, in the Northeast — by 2.3 % to 115, in the Southeast — by 23.3 % to 385, in the South — by 12.0 % to 162 and in Kyiv — by 13.0 % to 108 people. In 2016, the most cases occurred in the Western and Southeastern regions (505 and 502 people), they shared the first place (28.1 ± 1.6 % and 28.0 ± 1.0 %, respectively). The second was Central region, where 18.4 ± 0.9 % (330) was concentrated, the third was Southern — 10.2 ± 0.2 % (184), followed by Northeastern (8.4 ± 0.6 %) and the capital (6.9 ± 0.6 %). In 2020, the distribution remained the same, but with an increase in the share of the contingent in the Western region and its decrease in the Southeast (to 31.0 ± 1.3 % and 24.9 ± 1.0 %, respectively), i.e. it became clearer. At the same time, it is worth pointing out the significant fluctuations in the number of people recognized as disabled for the first time in some administrative territories. According to their number, Kyiv and four regions (Lviv, Dnipropetrovsk, Kharkiv, Odesa) attracted attention in 2016, with the exception of Kharkiv region in 2020. They accounted for 39.2 ± 1.1 % and 36.5 ± 1.2 %, respectively, i.e. 704 of 1,795 and 566 of 1,549 people ($p < 0.05$).

It has been confirmed that in addition to effective inpatient treatment with subsequent rehabilitation in outpatient settings (outpatient-polyclinic, sanatorium, etc.), one of the most important and effective means for preventing disability is the extension of sick leaves through MSEC. In recent years, this principle of treating patients with urological diseases has become more common and sophisticated, as shown in Table 1.

So, if in 2016 there were 49 such cases and this number is taken as 100 %, then with each year they increased by 36.7, 16.3, 4.1 %, and in 2020 by 51.0 % (74 people). The share of patients who completed treatment in each current year is also growing, namely by 41.2, 11.8, 20.6 and 94.1 % according to the value of the coefficient, provided that 34 cases in 2016 are accepted as 100 %. This nature of change indicates the feasibility of the existing approach. At present, more patients have returned to active life and daily work without restrictions and have not been considered disabled. The share of such people over the years was 73.5, 54.2, 55.3, 63.4 and 86.4 %, respectively, for 2016–2020. It is worth noting that most people considered disabled were assigned group III. In particular, in 2016, there were 9 of 34 such patients after completion of treatment (26.5 %), in subsequent years, 19 of 48 (39.6 %), 17 of 38 (44.7 %), 12 of 41 (29.3 %) and 8 of 66 (12.1 %), respectively. Meanwhile, 3 people received group I–II in 2017 (6.2 %), 3 (7.3 %) in 2019 and 1 (1.5 %) in 2020.

Probably, the fact that the share of primary disability due to genitourinary diseases in Ukraine for many years is low (in 2016 and 2020, it was 1.4 and 1.5 and 1.3 and

Table 1. The results of treatment of urological patients after extension of sick leaves

Indicators	Years				
	2016	2017	2018	2019	2020
Extended sick leave, total	49	67	57	51	74
Treatment completed by the next year	34	48	38	41	66
Of these, not considered disabled, abs. (%)	25 (73.5)	26 (54.2)	21 (55.3)	26 (63.4)	57 (86.4)
Considered disabled, total	9	22	17	15	9
Including disability group I–II, abs. (%)	–	3 (6.2)	–	3 (7.3)	1 (1.5)
Disability group III, abs. (%)	9 (26.5)	19 (39.6)	17 (44.7)	12 (29.3)	8 (12.1)
Continue treatment	9	19	19	10	8

1.4 %, respectively, for the adult and working-age population, or 0.6 and 0.7 and 0.5 and 0.6 per 10 thousand), explains the special shortage of available statistics on certain nosological forms. Information is limited to chronic glomerulonephritis and chronic pyelonephritis. In 2016, they accounted for 33.5 ± 1.9 % and 27.5 ± 2.0 %, respectively, in Ukraine as a whole. Over 5 years, the share of chronic glomerulonephritis has significantly increased and the share of chronic pyelonephritis has decreased (in 2020, 43.8 ± 1.9 % and 20.0 ± 2.2 %, respectively). An increase in chronic glomerulonephritis is due to an increase in cases in the West (from 31.5 ± 1.9 % to 49.7 ± 2.2 %; $p < 0.05$), Southeast (from 35.2 ± 2.1 % to 41.6 ± 2.5 %; $p < 0.05$), South (from 35.3 ± 3.5 % to 55.6 ± 3.9 %; $p < 0.05$) and in the capital (from 13.7 ± 3.0 % to 45.4 ± 4.7 %, $p < 0.05$). In the other two regions, the nature of the changes was reversed. At the same time, the proportion of chronic pyelonephritis has decreased significantly in all regions except Kyiv. The data hidden under "other reasons" are of particular interest. Their share with a declining trend remains high across the country (from 39.0 ± 1.8 % in 2016 to 36.2 ± 2.0 % in 2020). At the same time, in the Central and Northeastern regions, the indicator reaches almost 50 % (49.2 ± 2.8 % and 49.6 ± 4.7 % vs. 39.7 ± 2.6 % and 33.3 ± 3.8 % in 2016; $p < 0.05$). This prompted to expand the study with the results of the MSEC operational data of eight regions, with an emphasis on detailing and clarifying other reasons.

Table 2 shows that the number of people recognized as disabled for the first time in the defined territory was 582 in 2016, 492 in 2020, i.e. 32.4 and 31.8 % of their number in Ukraine, respectively. Involvement of more than a third of cases testifies to the representativeness of the sample. Proof of this is the preservation of the general sign of disability reduction (for 5 years by 15.5 %). In addition, the same nature of changes in indicators can be seen in all observations, as well as their close values. In particular, the percentage of chronic glomerulonephritis as a cause of disability is growing (36.4 ± 1.9 % and 44.3 ± 2.2 % in 2016 and 2020, respectively; $p < 0.05$), it is lower, but still remains high among "others" (39.7 ± 2.0 % and 30.3 ± 2.0 %; $p < 0.05$). The incidence of chronic pyelonephritis remains similar (23.9 ± 1.7 % and 25.4 ± 1.9 % vs. 27.5 ± 2.0 % and 20.0 ± 2.2 % in Ukraine as a whole in 2016 and 2020, respectively). This situation is quite acceptable given its course and prevalence both as an independent disease, and as a complication of almost all infectious and inflammatory diseases.

The results of the study on the causes of primary disability among the adult population of Ukraine due to urological pathology depending on age and nosology (except for chronic pyelonephritis) according to MSEC materials of eight regions are presented in Table 3. It was found that urolithiasis occupies a leading position. However, its share decreased significantly, from 45.0 ± 3.2 % in 2016 to 26.8 ± 3.6 % in 2020; $p < 0.05$. The age-specific feature of disability of patients with urolithiasis has been established. It was manifested by a decrease in the number of people under 39 years, those of pre-retirement and retirement age, but significantly in the first two categories (39.5 ± 4.7 % vs. 19.6 ± 6.2 %, 47.5 ± 4.8 % vs. 31.0 ± 6.2 % and 55.6 ± 4.8 % vs. 50.0 ± 6.2 %, respectively).

There were significantly fewer patients whose disability was due to nephrectomy (7.4 ± 2.1 % in 2020 vs. 24.2 ± 2.8 % in 2016) and the results of surgery (3.3 ± 1.4 % vs. 6.9 ± 1.6 %, respectively). This should be considered a consequence of achievements in the diagnosis, treatment and metaphylaxis of the disease. However, the presence of stones in both kidneys tends to increase among the causes of disability (from 13.9 ± 2.2 % to 16.1 ± 3.0 %).

The second place in the structure of the causes of disability is occupied by polycystic kidney disease with a tendency to increase over the years: in 2016 — 19.0 ± 2.5 %, in 2020 — 22.1 ± 3.3 % ($p > 0.05$). There is an increase in such cases among the younger population. Thus, if in 2016 the above three age categories accounted for 16.0 ± 5.5 %, 19.8 ± 6.0 % and 33.3 ± 7.0 %, then in 2020, 19.6 ± 7.0 %, 23.8 ± 7.4 % and 25.0 ± 7.5 %, respectively. Given the nature of the course of polycystic kidney disease, this can be explained by its late detection in the stage of decompensation.

Third place in 2020 belonged to a single kidney as a cause of disability, which accounted for significantly more cases than in 2016: 18.8 ± 3.2 % vs. 8.7 ± 1.8 % (five years after, this place belonged to congenital malformations — 17.7 ± 2.5 %). It is noteworthy that the number of patients with a single kidney as a cause of disability decreases with age: from 21.3 % under the age of 39 to 17.8 % at the age of 40–55 and 40–60 years among women and men, respectively. The reverse nature of changes against the background of significantly lower indicators was observed in 2016, namely: 7.4, 10.0 and 11.1 %, respectively, for three age periods.

Table 2. Dynamics of primary disability among the adult population by some forms of non-oncological urological diseases in the regions of Ukraine by nested sampling

Region	2016								2020							
	Total	Chronic glomerulonephritis	Chronic pyelonephritis	Total		Others			Total	Chronic glomerulonephritis	Chronic pyelonephritis	Total		Others		
				Abs.	%	Abs.	%	m				Abs.	%	Abs.	%	m
Ivano-Frankivsk	73	32	15	47	64.4	26	35.6	3.1	75	24	18	42	56.0	33	44.0	4.0
Dnipropetrovsk	158	52	24	76	48.1	82	51.9	3.2	124	48	47	95	76.6	29	23.4	3.4
Mykolaiv	40	14	8	22	55.0	18	45.0	3.2	29	16	5	21	72.4	8	27.6	3.6
Odesa	101	33	28	61	60.4	40	39.6	2.6	110	56	27	83	75.5	27	24.5	3.5
Ternopil	48	16	14	30	62.5	18	37.5	3.2	36	20	9	29	80.6	7	19.4	3.2
Sumy	52	24	10	34	65.4	18	34.6	3.1	38	13	7	20	52.6	18	47.4	4.0
Cherkasy	67	23	25	148	71.6	19	28.4	2.9	57	23	9	32	56.1	25	43.9	4.0
Kherson	43	18	15	33	76.7	10	23.3	2.7	23	18	3	21	91.3	2	8.7	2.3
Total	582	212	139	351	60.3	231	39.7	2.0	492	218	125	343	69.7	149	30.3	2.0
Ukraine	1.795	602	494	1.096	61.0	699	39.6	1.8	1.549	679	309	988	63.8	561	36.2	2.0

Table 3. Dynamics of the structure of the causes of primary disability due to non-oncological urological diseases depending on age (except for chronic pyelonephritis) among the adult population of Ukraine

Disease	2016									2020								
	Up to 39 years		Women aged 40–55; men aged 40–60		Women aged > 55, men aged > 60		Total			Up to 39 years		Women aged 40–55, men aged 40–60		Women aged > 55, men aged > 60		Total		
	Abs.	%	Abs.	%	Abs.	%	Abs.	%	m	Abs.	%	Abs.	%	Abs.	%	Abs.	%	m
Urolithiasis, total	32	39.5	67	47.5	5	55.6	104	45.0	3.2	12	19.6	26	31.0	21	50	40	26.8*	3.6
Urolithiasis, operated	7	8.6	9	6.4	–	–	16	6.9	1.6	2	3.3	3	3.6	–	–	5	3.3*	1.4
Urolithiasis, single kidney	16	19.7	35	24.8	5	55.6	56	24.2	2.8	4	6.5	6	7.1	1	25.0	11	7.4*	2.1
Urolithiasis of both kidneys	9	11.1	23	16.3	–	–	32	13.9	2.2	6	9.8	17	20.2	1	25.0	24	16.1	3.0
Polycystic kidney disease	13	16.0	28	19.8	3	33.3	44	19.0	2.5	12	19.6	20	23.8	1	25.0	33	22.1	3.3
Congenital malformations	23	28.4	17	12.1	–	–	41	17.7	2.5	10	16.4	8	9.5	–	–	18	12.1*	2.6
Single kidney	6	7.4	14	10.0	1	11.1	20	8.7	1.8	13	21.3	15	17.8	–	–	28	18.8*	3.2
Hydronephrosis	5	6.2	10	7.1	–	–	15	6.5	1.6	12	19.6	10	12.0	1	25	23	15.4*	2.9
Urethral stricture	2	2.5	5	3.5	–	–	7	3.0	1.1	2	3.3	5	6.0	–	–	7	4.7	1.7
Total	81	100.0	141	100.0	9	–	231	100.0	–	61	100.0	84	100.0	4	–	149	–	–

Note: * — the difference is significant between the indicators until 2016 (p < 0.05).

As for birth defects, they lost their third place in 2016, taking fifth place in 2020. Their share was 17.7 ± 2.5 % vs. 12.1 ± 2.6 %; $p < 0.05$. However, twice as many cases with age are a common feature for them: in 2016, 28.4 and 12.1 % among people under 39 and 40–55 and 40–60 years (women, men), and in 2020, 16.4 and 9.5 %, respectively. This confirms the latent nature of the course, and hence the untimely detection of pathology with such adverse consequences.

Hydronephrosis was the most common cause of disability. It ranks fourth in 2020 and fifth in 2016 (15.4 ± 2.9 % and 6.5 ± 1.6 %, respectively; $p < 0.05$). Urethral stricture among the causes of disability consistently occupies the last sixth place, its share was 4.7 ± 1.7 % and 3.0 ± 1.1 % in 2020 and 2016, respectively. The multifactorial etiology, duration and complexity of treating patients explain an increase in such cases with age and years of follow-up (from 3.3 to 6.0 %, respectively, in people under 39 and at pre-retirement age in 2020, while in 2016, 2.5 and 3.5 %, respectively).

Over the years, the share of cases of group II disability decreases (18.1 ± 3.1 % in 2020 vs. 20.4 ± 2.6 % in 2016; $p > 0.05$), there is a tendency to increase the figure with group III (67.8 ± 3.8 % vs. 65.3 ± 3.1 %, respectively) with stabilization of the frequency of assignment of group I (14.1 vs. 14.3 %, respectively). There is also an age dependence in the form of a less frequent assignment of group III, more frequent — of group II and even more clearly — of group I.

If in 2016 rural residents predominated (52.4 ± 4.5 % vs. 47.6 ± 4.7 % of urban residents; $p > 0.05$), then in 2020, on the contrary, there were 53.7 ± 5.5 % of urban residents vs. 46.3 ± 6.0 % of rural ($p > 0.05$). In addition, patients of pre-retirement age dominated in rural areas (97.5 vs. 94.5 % in urban areas), while in 2020, the situation has changed — among urban residents, younger people dominated (97.5 vs. 94.2 %).

The distribution by sex has also differed. In 2016, males who were recognized as disabled for the first time prevailed significantly, namely 58.3 ± 3.2 % vs. 41.7 ± 3.2 % of females; in 2020, the difference between the indicators decreased to 53.6 ± 4.1 % and 46.4 ±4.0 %, respectively ($p > 0.05$).

Conclusions

1. The effective application of the approach of extended sick leaves led to a 51.0% increase in the number of patients who complete treatment in each current year, which, in turn, allowed 12.9 % more patients to avoid disability and 4.7 % less (only 1.5 vs. 6.2 % in 2017) — to be assigned group I–II.

2. According to official reports, chronic glomerulonephritis and chronic pyelonephritis together accounted for 1,096 of 1,795 cases (61.0 %) in 2016, and 988 of 1,549 (63.8 %) in 2020. A decrease in the share of chronic pyelonephritis as a cause of disability by 37.4 % (to 20.0 %) was observed in all regions except Kyiv.

3. According to the results of a nested sampling from 8 regions of Ukraine, 582 and 492 people were recognized as disabled for the first time due to diseases of the urinary and male reproductive systems, which accounted for 32.4 and 31.7 % of their total number in Ukraine in 2016 and 2020, respectively. The following structure of disability causes was determined (with the exception of chronic glomerulonephritis and chronic pyelonephritis): urolithiasis — 45.0 % in 2020 vs. 26.8 % in 2016; polycystic kidney disease — 22.1 vs. 19.0 %; single kidney — 18.8 vs. 8.7 %; hydronephrosis — 15.4 vs. 6.5 %; congenital defects — 12.1 vs. 17.7 %; urethral stricture — 4.7 vs. 3.0 %, respectively.

4. The general feature of an increase in the number of patients recognized as disabled for the first time in the following pathologies was established: urolithiasis — 19.6 % under 39 years, 31.0 % at pre-retirement age, 50.0 % at retirement age; polycystic kidney disease — 19.6, 23.8, 25.0 %, respectively; hydronephrosis — 19.6 % under the age of 39 and 25.0 % at pre-retirement age; urethral strictures — 3.3 and 6.0 %, respectively. A decrease was noted for congenital defects — from 16.4 to 9.5 % in those under 39 years and at pre-retirement age; single kidney — from 21.3 to 17.8 %, respectively.

5. Over the years, a decrease was noted in the assignments of disability group II (18.1 % in 2020 vs. 20.4 % in 2016), an increase in group III (67.8 vs. 65.3 %), with stabilization of group I (14.1 vs. 14.3 %). At the same time, it was found that group III was assigned more frequently with age (7.7 % — up to 39 years old, 63.1 % — at pre-retirement age, 67.8 % — at retirement age), the number of group II assignments increased (14.3, 28.2 and 25.0 %, respectively) and even more clearly — of group I (8.2, 16.7 and 30.0 %, respectively).

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Структура й особливості динаміки первинної інвалідності дорослого населення України внаслідок неонкологічних урологічних захворювань

Резюме. Мета дослідження: вивчити структуру й особливості динаміки первинної інвалідності серед дорослого населення України в результаті неонкологічних урологічних захворювань за формуючими її хворобами. **Матеріали та методи.** Використано форму звітності № 14 Держкомстату України, статистичні збірники ДУ «Український державний НДІ медико-соціальних проблем інвалідності» й документацію регіональних медико-соціальних експертних комісій. **Результати.** Виявлено тенденцію до зменшення кількості осіб, уперше визнаних інвалідами внаслідок хвороб сечостатевої системи (ССС). Підтверджено, що цьому сприяє продовження тимчасової втрати працездатності. Офіційна звітність щодо причин інвалідності за класом хвороб ССС стосується лише хронічного гломерулонефриту й хронічного пієлонефриту: за 5 років частка першої нозології збільшилася на 13,0 % (до 43,8 % серед 1549 зареєстрованих), другої — зменшилася на 37,4 % (до 20,0 % у всіх регіонах, крім м. Києва). Одночасно спостерігалася тенденція до зменшення частки виходу на інвалідність з причин, віднесених до «інших» (36,2 ± 2,0 % проти 39,0 ± 1,8 % у 2016 р., а в Центральному і Північно-Східному регіонах — 49,2 ± 2,8 % і 49,6 ± 4,7 % відповідно). За винятком двох вищезгаданих патологій, структура причин інвалідності така: перші три місця посідали сечокам'яна хвороба (СКХ), полікістоз, єдина нирка, наступні три — гідронефроз, уроджені вади й стриктура сечівника. З віком збільшується частота випадків при СКХ, полікістозі, гідронефрозі, стриктурі сечівника й зменшується — при уроджених вадах і єдиній нирці. З роками зменшується також частка призначення II групи інвалідності (18,1 ± 3,1 % у 2020 р. проти 20,4 ± 2,6 % у 2016 р.) і відбувається збільшення частки III групи (67,8 ± 3,8 % проти 65,3 ± 3,1 %) при стабільних показниках I групи (14,1 проти 14,3 %). **Висновки.** За 5-річний період спостереження на 12,9 % більше пацієнтів уникли інвалідності і на 4,7 % менше отримали I і II групу. Зменшення частки хронічного пієлонефриту як причини інвалідності на 37,4 % (до 20,0 %) спостерігалось у всіх регіонах, окрім м. Києва. Структура інших причин інвалідності: сечокам'яна хвороба — 45,0 %, полікістоз нирок — 22,1 %, єдина нирка — 18,8 %, гідронефроз — 15,4 %, уроджені вади — 12,1 %, стриктура сечівника — 4,7 %. На тлі загального зростання призначень інвалідності з віком частіше призначалася інвалідність III групи (7,7 % — до 39 років, 63,1 % — у передпенсійному віці, 67,8 % — у пенсійному).

Ключові слова: первинна інвалідність; неонкологічні урологічні захворювання; структура; динаміка

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Проблеми нирково-замісної терапії: чи є вибір у пацієнта?

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Резюме. *Сьогодні проблема нирково-замісної терапії гостро стоїть в усьому світі. Основними методами зараз є діаліз та ниркова трансплантація. Разом із тим для багатьох регіонів один чи більше методів є недосяжними, що зумовлене економічними, соціальними та іншими чинниками. Гемодіаліз та перитонеальний діаліз є рівнозначними за ефективністю методиками, однак навіть за умови доступності обох видів буває нелегко здійснити вибір на користь того чи іншого. Для кожного пацієнта, що вибирає метод нирково-замісної терапії, стоїть питання, який шлях вибрати. Моральний і соціальний аспекти такого вибору є досить складними. Тому роль лікаря, окрім кваліфікованого виконання нирково-замісної терапії, є багато в чому дорадчою та потребує терпіння й розуміння пацієнта. Важливо підняти рівень інформованості пацієнтів, освіту медичного персоналу та забезпечити рівномірний доступ до усіх видів нирково-замісної терапії у світі.*

Ключові слова: *нирково-замісна терапія; гемодіаліз; перитонеальний діаліз; ниркова трансплантація; хронічна хвороба нирок*

Нирково-замісна терапія (НЗТ) — спосіб лікування пацієнтів із хронічною хворобою нирок (ХХН), що, згідно з настановами KDIGO, рекомендовано розпочати в пацієнтів зі стадією ХХН 4–5 (рШКФ < 29 мл/хв/1,73 м^2) [1].

Одним із найбільш поширених у всьому світі методів НЗТ є діаліз, який KDIGO пропонує розпочинати за наявності одного симптому або більше: ознаки термінальної недостатності функції нирки (аномалії кислотно-основного обміну, серозити, свербіж); неможливість консервативного регулювання рівня артеріального тиску та волемії; прогресивне порушення стану харчування, що не коригується дієтою; порушення когнітивної функції. Найбільш поширеними такі симптоми є у пацієнтів із ХХН 5-ї стадії, що є термінальною (рШКФ ≤ 15 мл/хв/1,73 м^2) [1].

Окрім діалізу, іншим менш поширеним методом НЗТ є ниркова трансплантація. KDIGO пропонує розглянути цей метод при рШКФ < 20 мл/хв/1,73 м^2, за наявності доказів прогресивної необоротної ХХН у попередні 6–12 місяців. Найчастіше трансплантація нирки проводиться від живого донора [1].

Імовірно, на сьогодні у всьому світі надається перевага саме трансплантації нирки як методу НЗТ, однак існує низка проблем та перешкод у широкому його запровадженні. До основних причин, що утруднюють світове поширення трансплантації, відносять нерівність соціальних та економічних умов у різних регіонах, обмежений людський ресурс та рівень підготовки медиків як для проведення операції, так і для післяопераційного догляду. Деякі частини світу також стикаються із юридичними та культурними бар'єрами, що потребують рішень та, імовірно, політичного втручання для ефективного впровадження трансплантації [1, 2].

Лідерами у забезпеченні населення адекватною НЗТ, за даними 2020 року, є п'ять країн: США, Японія, Німеччина, Бразилія та Італія, що становить лише 12 % від світової популяції. Країни із середнім рівнем достатку мають значний тягар витрат на лікування ХХН переважно методом діалізу, а країни із

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низьким рівнем доходу нерідко не можуть дозволити собі жодного методу НЗТ взагалі, що призводить до загибелі понад 1 мільйона осіб щорічно [3].

Зрозуміло, що в більшості країн із низьким рівнем доходу трансплантація є досі недосяжним методом, однак і розвинені країни мають складнощі в її впровадженні.

Так, у Сполучених Штатах Америки трансплантація нирки є методом вибору для меншості пацієнтів із термінальною ХХН. Дані United Network for Organ Sharing (UNOS) за 2021 рік вказують, що протягом останніх років більшість пацієнтів із термінальною ХХН жодного разу не зверталися за оцінкою з приводу трансплантації нирки і мають до 70 % 5-річної смертності на діалізі.

При цьому впровадження імуносупресивної терапії з комбінацією азатіоприну та стероїдів у 1963 році та циклоспорину в 1983 році значно покращило наслідки для пацієнтів із трансплантованими органами, мінімізуючи ризики відторгнення. Подальші інновації — моноклональні та поліклональні антитіла проти Т-клітин та винайдення нових імуносупресантів (такролімус, сиролімус, мікофенолат тощо) здійснили прорив у показниках однорічного виживання пересадженого органа та пацієнта (> 90 %). Таким чином, у країнах із більш високим достатком трансплантація нирки вважається більш кошторис-ефективною альтернативою діалізу. Із 1988 року у США було здійснено понад 515 000 трансплантацій нирки із рекордним показником у 2019 році (24 502) [4–8].

У Європі за 2019 рік були здійснені 28 053 ниркові трансплантації, а в Африці, наприклад, лише 470 [9].

Одним зі світових лідерів у трансплантації нирки на сьогодні є Турція з одним із найкращих показників однорічного виживання трансплантата та пацієнтів після трансплантації від живого донора [10].

Загалом у світових звітах із ниркової трансплантації наголошується на необхідності вдосконалення програм та законодавчої бази з трансплантації від живих та померлих донорів, із залученням зовнішнього та доброчинного фінансування, посиленим навчанням медичного персоналу та створенням освітніх програм для населення.

Обмежений доступ до діалізу та трансплантації значно утруднює підтримку здоров'я та якості життя пацієнтів із ХХН у країнах із низьким рівнем доходу. За статистикою 2019 року, показник трансплантації у цих країнах залишається дуже низьким, що відображається у світових показниках захворюваності та смертності від ХХН [10–15].

З огляду на невтішний світовий стан трансплантації як методу НЗТ при ХХН 4–5-ї стадій більшість країн все ще надають перевагу методу діалізу, при цьому перитонеальний діаліз (ПД) та гемодіаліз (ГД) використовуються однаково успішно та з подібними наслідками. Перші два роки від початку діалізу ПД та ГД демонструють рівну ефективність, однак бракує даних досліджень для оцінки віддалених наслідків [1, 2, 11, 16].

Вибір методу діалізу не завжди є легким завданням для лікуючого лікаря, адже це залежить не лише від загального стану пацієнта, а і від наявних ресурсів системи охорони здоров'я, економічних, освітніх, законодавчих та логістичних чинників. Країни із низьким рівнем доходу значно частіше надають перевагу ПД з огляду на суттєво менші вимоги до його до ресурсів — економічних, технологічних та людських [16–18].

Цікавим є досвід розвинених країн із тактикою «початкового ПД», коли пацієнти мали можливість самостійного вибору між двома методами діалізу після консультації із лікарем. Близько 25 % пацієнтів обирали ПД, що супроводжувалося відповідною освітньою програмою, та ефективно його дотримувались [18].

Серед переваг, що зазначені пацієнтами на ПД, були: покращення якості життя, близькість до родини, зручне самостійне управління процедурою із вибором часу та ефективне управління анемією через нижчі крововтрати порівняно з ГД [11, 18]. Старші пацієнти із термінальною ХХН, що за критеріями та наявними можливостями мали вибір між тим чи іншим методом діалізу, також мали вищу мотивацію до ПД завдяки комбінації нормального ритму життя із можливістю самостійно та успішно управляти процедурою, приділяючи більше часу звичній активності [19].

Пандемія COVID-19 також внесла корективи в управління діалізом: пацієнтам на ПД було легше отримати доступ до лікування, водночас уникаючи надмірних соціальних контактів через необхідність переміщення та перебування в центрах ГД. Кількість пацієнтів на ПД у цей період зросла також через подовження часу очікування в листах ниркової трансплантації, запобіжні заходи з урахуванням порушення імунологічної толерантності у донорів та отримувачів трансплантата та через посилення протоколів безпеки хірургічних та терапевтичних відділень. Більшість рішень із трансплантації у 2019–2021 роках приймались з огляду на досвід центрів та лікуючих лікарів, віддалені наслідки яких будуть оцінені належним чином у більш пізньому терміні. Було розроблено спеціальні інноваційні програми із «віддаленого управління пацієнтом» (Remote patient management), що було асоційоване зі сприятливими наслідками для пацієнтів, яким призначали ПД. Як результат, покращився контроль артеріального тиску, знизились рівні госпіталізації та тривалість перебування в лікарні [11, 18, 20–22].

Окремим питанням, вартим розгляду, є вибір методики діалізу перед нирковою трансплантацією, адже більшість пацієнтів у світі, як зазначалось, не мають доступу до своєчасної трансплантації, навіть за її наявності, тому вимушені проводити діаліз під час перебування в листі очікування.

У США, де щорічно зростає кількість пацієнтів із термінальною ХХН, більшість пацієнтів до трансплантації обирають ГД, хоча найновіші дослі-

дження свідчать про переваги саме ПД у передтрансплантаційному періоді з огляду на нижчі ризики госпіталізацій, зниження витрат системи охорони здоров'я та смертності. Ці дані 2019 року змінюють наше попереднє уявлення про однакові рівні смертності при обох методах діалізу у передтрансплантаційному періоді [23].

У світі приблизно 10–20 % дорослих отримувачів ниркового трансплантата та 40 % педіатричних отримують ПД до ниркової трансплантації. Найбільша увага в передопераційному медичному догляді приділяється управлінню катетером ПД [24].

Одразу після трансплантації ПД часто використовується для підтримки віддаленого функціонування трансплантата (ВФТ), що потребують близько 20 % пацієнтів після проведеної операції, особливо в центрах із розширеними донорськими критеріями. ПД порівняно з ГД був асоційований із нижчим ризиком виникнення ВФТ *de novo* та серцево-судинної смертності. Дані щодо тромбозу у трансплантаті протягом перших 5 та 10 років, однак, неоднозначні та потребують подальшого вивчення [23, 24]. Рекомендовано залишати катетер ПД у пацієнтів, які не мали порушення цілісності очеревинної порожнини після операції та виконувати ПД у супінованій позиції із низьким об'ємом. Хоча на сьогодні не існує єдиного світового консенсусу в догляді за катетером ПД після ниркової трансплантації, наголошується на важливості активного догляду за ним та найшвидшого його видалення при зникненні потреби у ПД для профілактики інфекційних ускладнень [24].

Повідомляється про загальний брак рандомізованих контрольованих досліджень із вибору методики діалізу до трансплантації та його подальшого впливу на стан трансплантата в найближчий та віддалений час та впливу на якість життя, але ПД вважається недооціненим методом у передопераційному періоді, і нижчий рівень його використання порівняно із ГД, імовірно, спостерігається через недостатність освітніх програм [23].

У будь-якому випадку запропоновано надавати перевагу ПД у посттрансплантаційному періоді, адже ГД має вищі інфекційні ризики через наявність центрального венозного катетера, що потенційно є джерелом більшої інфекційної небезпеки для пацієнтів, які знаходяться на імуносупресії, та небезпеки кровотечі [25].

Для кращого вибору методу діалізу важлива двостороння комунікація та співпраця лікаря та пацієнта. Нові дослідження направлені на розробку інструментів самостійної оцінки пацієнтами для полегшення вибору методики діалізу при ХХН. Зазначається, що вищий рівень поінформованості пацієнтів дає кращі результати лікування на діалізі, більш ефективне дотримання того чи іншого методу та зростання показників якості життя [26].

Одне з досліджень показало позитивні результати використання таких шкал оцінки, у яких максимальна оцінка в прийняті рішення була 100 і загальний середній рівень задоволення у прийнятті рішення пацієнтами становив 86. Різниця у виборі між домашнім та внутрішньолікарняним діалізом була незначною та все ж схилялась на користь домашнього (97 проти 83 %, p = 0,627). Пацієнти, які обирали домашній метод, мали вищий рівень обізнаності порівняно з тими, які обирали внутрішньолікарняний (84 проти 75 %, p = 0,006), хоча рівень готовності був практично однаковим (87 проти 84 %, p = 0,908). Наявні можливості та обізнаність пацієнтів призвели до досягнення високого рівня задоволеності пацієнтів рішенням — 83 % [27].

Подібні дані були отримані Ghodsian et al. (2021), що оцінювали 300 пацієнтів на діалізі (218 на ГД та 82 на ПД) у двох діалізних центрах. Було встановлено золотий стандарт пацієнт-орієнтованого догляду — «спільне прийняття рішення» (Shared decision making (SDM)). Пацієнти проходили опитування, за результатами якого середній бал SDM був вищим в осіб на ПД (33,11 ± 10,08), ніж у тих, які перебували на ГД (17,14 ± 74,24) (p < 0,001). Цікавою ідеєю, що підсумовувала дослідження, була пропозиція спільного прийняття рішення про можливий метод діалізу заздалегідь — на ранніх стадіях ХХН [28].

Попереднє дослідження Zee та ін. (2018) підтверджує, що пацієнти, які перебувають на ПД, відчувають себе більш задіяними та інформованими порівняно з пацієнтами на ГД [29].

Schellartz та колеги (2021) зіткнулись із протилежною проблемою. Опубліковано статтю за даними опитування 590 пацієнтів, які перебували на ГД у двох діалізних центрах у Німеччині. Пацієнтам було запропоновано подібне опитування стосовно розуміння ними обраної методики діалізу, адже ГД та ПД вважаються еквівалентними методиками для лікування термінальної ХХН. Німецькі лікарі зобов'язані інформувати своїх пацієнтів щодо переваг та недоліків того чи іншого способу, але, незважаючи на численні переваги ПД, вживаність його залишається низькою.

Вражаючі результати вказали на те, що лише 56 % пацієнтів зазначили, що були поінформовані про той чи інший метод діалізу, при цьому краще поінформованими були пацієнти, молодші за 65 років (на 61 %, p < 0,001). Пацієнти із вищим рівнем освіти мали на 47 % більше шансів на отримання інформації (p = 0,030). Інформовані пацієнти мали вищий бал загального задоволення лікуванням (76,9 проти 44,2; p < 0,001). Було зроблено висновок, що більша частка розглянутих пацієнтів на ГД, а саме пацієнти похилого віку та/або з низьким рівнем освіти, не усвідомлювали наявні опції та їх різницю до початку діалізу [30].

Багато сучасних даних вказують на вищу оцінку діалізу пацієнтами, які знаходяться на ПД, порівняно із ГД. Тому важливо покращувати інформованість та задіяність гемодалізних пацієнтів [31].

Найновіше дослідження Kobe et al. (2022) з аналізу національної бази даних у Японії показало, що із рос-

том поінформованості пацієнтів все більше пацієнтів переходять на ПД [32].

Центр у Північній Індії у 2021 році проаналізував методи НЗТ у 13 дітей із термінальною ХХН, установив хронічний ПД найбільш прийнятним методом для педіатричної категорії за неможливості трансплантації через складнощі венозного доступу для ГД. Основні проблеми, які були висвітлені в публікації, — протидія інфекціям та подолання затримки росту [33].

Іншою важливою перевагою ПД, за новими даними, стало зниження функціонального класу серцевої недостатності та кількості госпіталізацій, пов'язаних із серцево-судинними подіями в пацієнтів без ХХН із застійною серцевою недостатністю. ПД мав позитивний вплив для завершення станів, що характеризувались перевантаженням рідиною [34].

Загалом, за результатами аналізу 57 досліджень та 68 оригінальних статей MEDLINE (PubMed) та ClinicalTrials.gov, установлено використання множинних адаптивних методів дизайну досліджень для поліпшення ефективності лікування в популяції, що знаходиться на діалізі. Тенденція вказує на зростання частоти використання цих методів для отримання більш вірогідних даних та їх ефективність для статистичного аналізу та формування подальших рекомендацій із ведення пацієнтів на НЗТ [35].

Продовжуються нові дослідження із застосуванням новітніх методів для кращої стратифікації із покращенням ефективності ведення пацієнтів у подальшому. Наприклад, протеомні дослідження встановили дисрегуляцію молекулярних процесів у пацієнтів на ПД, які можуть призводити до ПД-асоційованих ускладнень. Знайдені порушення взаємодії рецептор — ліганд та експресія певних генів відповідають біологічним процесам ангіогенезу, клітинної адгезії та організації позаклітинного матриксу та можуть бути прогностичними факторами ускладнень, пов'язаних із ПД за умови гіперекспресії.

Дослідження на глибоких клітинному та молекулярному рівнях можуть ознаменувати нову сторінку у виборі того чи іншого методу НЗТ, але найважливішим для таких пацієнтів є усвідомлення можливості вибору та доступу щонайменше до одного з методів.

Сучасній світ вносить певні обмеження в процес надання нирково-замісної терапії [37]. До них слід віднести COVID-19 [38] та військові дії. Слід також окремо відзначити, що під час військових дій може виникати ціла низка проблем, що потребують від лікаря та пацієнта правильного вибору. На сьогодні, спираючись на особистий досвід, можна запропонувати алгоритми дій у таких обставинах [39].

Висновки

Діаліз та трансплантація нирки є сучасними методами нирково-замісної терапії.

Оскільки трансплантація є досі недоступним методом у багатьох країнах світу, основним вибором для більшості пацієнтів із термінальною хворобою нирок є діаліз, тоді перед лікарем та пацієнтом постає питання про вибір перитонеального чи гемодіалізу. Вибір зазвичай базується скоріше на доступних технічних та фінансових ресурсах, аніж на особистих побажаннях та статусі пацієнта. Дослідження вказують, що важливим компонентом нирково-замісної терапії за будь-якого її вибору є поінформованість та навчання пацієнта, що покращує показники дотримання терапії та оцінку якості життя самими пацієнтами. Перитонеальний діаліз як метод сьогодні переживає відродження із поновленням більш широкого впровадження серед населення завдяки зручності та низці інших переваг.

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Renal replacement therapy: does the patient have a choice?

Abstract. Nowadays there is an emerging problem with renal replacement therapy in the world. Its main methods include dialysis and renal transplantation. However, many regions in the world do not have access to one or more therapy methods due to numerous economic, social, and other factors. Hemodialysis and peritoneal dialysis are shown to be equally efficient, however, it may be difficult to choose one. For each patient who is faced with the choice of a method of renal replacement therapy, the question is which way to choose. The moral and social aspects of such a choice are quite complex. Therefore, the role of a doctor, in addition to the qualified performance of renal replacement therapy, is largely advisory and requires patience and understanding of a patient. It is important to raise the awareness of patients and the level of medical staff education as well as provide equal access to all renal replacement therapy types in the world.

Keywords: renal replacement therapy; hemodialysis; peritoneal dialysis; renal transplantation; chronic kidney disease

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Distance learning in the system of higher education in Kazakhstan (based on main platforms and services)

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Abstract. *In this article, the author considers distance learning as a new stage in the development of education. The author focuses on the latest achievements in the educational process, as well as the impact of the self-isolation process on the introduction of distance learning. The main advantages and disadvantages of distance learning technology are determined. The basic principles that a teacher needs to master for conducting distance learning of students are considered. The main educational platforms and services are presented, such as Microsoft Teams, Moodle, Zoom, Cisco Webex, Google Classroom. The main features of each platform and service for distance learning are highlighted. The strengths and weaknesses of each of the above platforms and services are considered.*

Keywords: *distance learning; platform; service; Microsoft Teams; Moodle; Zoom; Cisco Webex; Google Classroom*

At present, the use of information technologies in the educational process brings education to a new stage of development.

The variety of modern technical teaching aids has led to greater accessibility of education. The latest achievements of modern science and technology are used to create new and improve long-standing forms and methods of teaching. Among such developments is distance learning. The recent regime of self-isolation and the forced transition of universities and schools to distance learning has prompted many teachers to thoroughly delve into the process of organizing and implementing distance learning.

"Distance learning is a new form of organization of the educational process, combining traditional and new information technologies of education, based on the principle of self-acquisition of knowledge, mainly involving the telecommunication principle of delivering basic educational material to the student and interactive interaction between students and teachers both directly in the learning process, and in assessing the knowledge and skills they acquired in the process of learning" [1].

Distance learning is a new learning format that has been gaining popularity in recent years. This format of training undoubtedly has a number of advantages:

— saving time and money on the way to the educational institution;

— learning in a comfortable environment;

— the ability to study from anywhere in the world with the Internet and a gadget;

— Continuity of education during pandemics and martial law.

In addition to its advantages, distance learning is not without its drawbacks. Among the main shortcomings, I would like to highlight the following:

— a large load on the organs of vision;

— lack of direct contact between the teacher and the student;

— no guarantee of independent fulfilment of educational tasks;

— the impossibility of learning in the absence of the Internet and a gadget.

Having considered the positive and negative aspects of distance learning, we can say that a lot depends on the attitude of teachers and students themselves to the learning process. An important task of the student is to take classes responsibly, to complete training tasks in a timely manner and with high quality, and to be able to distribute study time in order to reduce the load on their body.

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Distance learning is a process of transferring and mastering knowledge, skills and types of human cognitive activity into a specialized educational environment, which is based on modern psychological, pedagogical and information and communication technologies [6].

In turn, the teacher needs to improve his skills, be responsible for conducting online classes, interest students in interesting tasks, and establish contact and feedback with students.

In the educational process, the teacher needs to master at the highest level not only the basic teaching technologies but also improve his knowledge, mastering the newly emerging technologies.

Every day, distance learning technologies are improving and becoming more accessible in the learning process.

Technologies for conducting training sessions are determined by many factors. From the point of view of managing the educational process, the choice of technologies is determined by the teacher of the university.

A large number of methods have been described that provide the possibility of transferring knowledge at a distance. Basically, they can be divided into two groups: 1) training in the format of real regulated time; 2) training in an individual independent mode [7].

The educational process in distance learning includes all the main forms of the traditional organization of the educational process: lectures, seminars and practical classes, a laboratory workshop, a control system, research and independent work of students [2].

In order to give students the opportunity to make an informed choice, it is necessary to gradually introduce them to the available forms of education — to provide some topics for self-study on the Internet, and to consolidate the results in classroom seminars. Thus, it will be possible to evaluate the results of online learning, and identify and fill educational gaps. The most suitable means of online learning for students are educational platforms [3].

To date, many educational platforms have been developed for conducting online classes. The most popular are Microsoft Teams, Moodle, Zoom, Cisco Webex, and Google Classroom.

Microsoft Teams is a service that is part of the Office365 cloud platform that allows you to organize online learning, collaboration and interaction between students and teachers.

This application can be downloaded to a computer or smartphone, after registering, you will have access to the capabilities of this service. The service provides great opportunities for organizing online learning and allows you to:

— create Teams for conducting training sessions for students in groups;

— organize webinars, video lectures, as well as practical online seminars;

— create virtual classrooms, giving students the opportunity to make various presentations or share a digital whiteboard;

— teachers and students can interact using text, audio or video;

— provide students with access to educational materials and files;

— add and check individual and group assignments, issue them to students, track timely completion and carry out verification, and students — find out deadlines, turn in work and receive an assessment.

Currently, a virtual learning environment based on Moodle is widely used in the higher education system. Moodle is a web platform that refers to free software environments with open source code, i.e. is open source under the GNU Public License. Thanks to the open source, this system can be easily adapted to the goals of an educational project [4].

Leading institutes, universities, and colleges are deploying distance learning systems so that anyone can get an education from them, regardless of citizenship [8].

Moodle is a modular object-oriented dynamic learning environment. It is a free and open source platform that does not need to be installed on the server yourself. On smartphones and tablets, Moodle can be opened in Chrome and Safari mobile browsers or used with the Moodle Mobile app, making it more accessible for learning.

Among the capabilities of this platform, I would like to highlight the most useful and most used in the learning process:

— the ability to upload any type of content: text (including PDF and XLS), images, presentations, tests and courses, videos;

— the ability to create training plans;

— the interaction of students with each other and with the teacher through forums and chats;

—— to carry out the transfer of knowledge in electronic form using various types of files, archives, web pages, and video lectures;

— conduct knowledge testing and training using tests and tasks of various types, and students can send completed tasks in text form or in the form of files;

— the ability to track their own achievements in the course of studying a particular course by a student, and the teacher of the achievement of each student in the course of studying the taught discipline.

A definite leader among these programs is Zoom. Today, this program has, perhaps, the richest functionality, including the basic version. Zoom is a service for video conferencing, online meetings and distance learning. With it, it is possible to hold large interactive events with the broadcasting of video, sound and screens (up to 100 participants can participate in the free version of the program) [4].

Service features include:

— demonstration of presentations, images, graphs and documents for all participants in the educational process;

— communication between participants, both by voice and through messaging forms or by using the show of hands function;

— the teacher and students can write on the interactive whiteboard and communicate through the message board, which is located in the “screen sharing” section;

— conducting a survey with a different number of answers, the ability to make it anonymous;

— conducting sessions at a low Internet connection speed.

A significant disadvantage of the demo version of Zoom is the limited session time of 45 minutes.

Cisco Webex Meetings is an online meeting service that runs on PCs, smartphones, and tablets as a web application.

Allows you to create conferences for up to 1000 people. A tab is available in which it is possible to schedule video conferences in advance and make a mailing list in instant messengers or e-mail links to the meeting.

To conduct seminars, students connected in groups using the link sent earlier, at the appointed time. The teacher's screen displayed all those present in the form of window panels. The teacher was the moderator of the videoconference. The teacher conducted a survey of each student. Those present heard this answer and, if necessary, could supplement it or enter into a discussion. The function in the program "Raise your hand" was very helpful in this [5]. In the Cisco WebEx Meetings service, as well as the previously mentioned platforms and services, training rooms are created, and you can exchange presentations, text files and applications. It is also possible to record the lesson conducted by the teacher. For feedback from students and teachers, the service has a chat.

Another online learning service is Google Classroom. This service allows you to create courses, conduct webers and test students.

The service developed by Google is suitable for schools, technical schools, universities and non-profit organizations. Google Classroom is available for free. You can create 30 courses per day and open access to them for 200 people, which is an undoubted advantage of this service.

On the platform, the teacher can create his own course, organize the registration of participants, share the necessary materials with the training, propose tasks for completion and evaluate their performance.

Among the useful features of the Google Classroom service, I would like to highlight:

— the course can be divided into theoretical and practical parts;

— the ability to combine ready-made text documents, videos, presentations, and pictures into a course;

— use of tasks of different types: with the choice of one or more correct answers, writing an essay, task-picture, open-ended questions;

— setting evaluation criteria and deadlines for assignments;

— the possibility of holding video meetings lasting up to 60 minutes.

Info communication technologies help to optimize the learning process, freeing teachers from routine operations for the development and maintenance of educational materials, simplifying the control procedure and other processes that can be automated [9].

Distance learning has entered the 21st century as one of the most effective systems for training high-level specialists. It makes it possible to implement the underlying principles of DL: the first is "education for all", the right of everyone to start studying and receive a secondary or higher education without entrance examinations; and the second — learning with minimal contact with the teacher when the emphasis is on independent work [8, 10].

In the course of the analysis of existing platforms and programs for distance learning, I would like to highlight the availability of the functionality and capabilities of the above platforms. All of the listed platforms and services have standard functionality necessary for conducting classes, with the help of which you can use video lectures, use presentations, and text files.

Thus, for better online classes and deep assimilation of academic disciplines, the standard functions of platforms and services are not enough. In addition to standard capabilities, it is necessary to use various types of test tasks in the educational process, evaluate the quality of their implementation, and use various educational materials. The platforms and services of Microsoft Teams, Moodle, and Google Classroom have such functions.

Summing up, it should be said that distance learning is a technology that is certainly convenient and useful, but, despite a large number of positive aspects, this technology also has negative aspects to minimize, which require work. When choosing a platform and service for distance learning, teachers should have knowledge about the capabilities of each platform, and relying on this knowledge, choose a platform whose capabilities will help in the implementation of specific pedagogical tasks.

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Дистанційне навчання в системі вищої освіти Казахстану (на підставі основних платформ і сервісів)

Резюме. У цій статті автор розглядає дистанційне навчання як новий етап розвитку освіти. Автор наголошує на останніх досягненнях освітнього процесу, а також впливі процесу самоізоляції на впровадження дистанційного навчання. Визначено головні переваги й недоліки технології дистанційного навчання. Розглядаються базові принципи, які необхідно засвоїти викладачеві для проведення дистанційного навчання студентів. Наведені основні освітні платформи й послуги, такі як Microsoft Teams, Moodle, Zoom, Cisco Webex, Google Classroom. Висвітлено головні можливості кожної платформи і сервісу для проведення дистанційного навчання. Виділено сильні й слабкі сторони кожної з наведених вище платформ і сервісів.

Ключові слова: дистанційне навчання; платформа; сервіс; Microsoft Teams; Moodle; Zoom; Cisco Webex; Google Classroom

НИРКИ KIDNEYS

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Хронобіологічні аспекти діяльності видільної системи (огляд літератури)

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Резюме. *У статті розглядаються питання функціонування циркадних ритмів і їх значення в регуляції фізіологічних процесів у видільній системі. Приділяється увага питанням десинхронозу, його причинам і впливу на фізіологічні процеси діяльності видільної системи в дітей. Показана практична значимість хронобіологічних аспектів, залежність їх від індивідуальних і популяційних факторів, динамічність таких порушень і їх актуальність у віковому аспекті. Підкреслено значущість хронобіологічних аспектів діяльності видільної системи й доцільність продовження науково-практичних досліджень у цьому напрямку медичної науки.*
Ключові слова: *циркадні ритми; десинхроноз; видільна система; діти*

Життєдіяльність організму людини можлива лише за умови підтримання постійного складу внутрішнього його середовища — гомеостазу. Упродовж останнього десятиріччя зростає увага клініцистів до патології нирок, що пов'язується зі зростанням патології видільної системи (нирок), а також вагомою роллю нирок у гомеостатичних реакціях людського організму (рис. 1). Не менш важлива роль нирок щодо виведення з організму продуктів азотистого обміну, токсичних речовин: порушення основних гомеостатичних констант екскреції речовин — один з основних проявів розвитку ниркової недостатності в разі їх безпосереднього пошкодження або внаслідок дії позаниркових чинників. Нирки — не лише екскреторний, але й важливий інкреторний орган, який бере участь у регуляції судинного тонусу, еритропоезу, згортання крові тощо [1–7].

Хронобіологія — науковий напрямок, що вивчає біологічні ритми (загальні властивості, механізми, еволюцію, можливості практичного застосування) на всіх рівнях ієрархічної організації живої матерії (від молекулярно-субклітинного до біогеоценотичного). У наукових дослідженнях і клінічній медичній практиці аналізуються близько 300 функцій організму людини з добовою періодичністю [8–12], серед яких циркадний ритм є найпотужнішим добовим коливанням усіх ендокринних і гематологічних показників, обмінних процесів, показників функціональної активності нервової, серцево-судинної, дихальної, видільної і травної систем; цьому ж ритму підпорядкована й рецепторна чутливість даних органів і систем організму до різноманітних гуморальних факторів [9, 13–16]. Значення добових ритмів у багатьох випадках важливе і для підбору доз і часу прийому лікарських препаратів — хронотерапії [17–20].

Видільна система (нирки) характеризуються чіткою часовою збалансованістю функцій, і на сьогодні особливості циркадної організації і механізми біоритмічної регуляції ниркових функцій викликають жваву наукову зацікавленість [21–26]. Як відомо, у групу захворювань із високим ризиком ураження серцево-судинної системи (ССС) входять різні нозологічні форми патології нирок [27–31].

Вторинна артеріальна гіпертензія (АГ) у дітей у переважній більшості випадків має нефрологічне походження, а підвищений артеріальний тиск (АТ) є одним із симптомів хвороби нирок, переважно гломерулонефриту (ГН). Якщо на початковому етапі ГН — це імунозапальне захворювання нирок з ураженням клу-

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бочків, канальців та інтерстицію, то в подальшому досить швидко розвиваються порушення механізмів регуляції кровотоку, які призводять до системного ураження органів, і в першу чергу ССС [32–35]. АГ часто супроводжує хронічну хворобу нирок (ХХН) або нефропатії при інших захворюваннях; поряд із забезпеченням контролю позаклітинного об'єму рідини в організмі нирки продукують вазоконстрикторні речовини (ренін, ендотелін, простагландин Е) і вазодилататори (оксид азоту, простагландин F1α і кініни) і є відповідальними за стан периферичного судинного опору [36, 37].

Для центральної і периферичної гемодинаміки у хворих на ГН з АГ є характерним прогресивне зменшення ударного об'єму й ударного індексу і, як наслідок, низькі показники хвилинного об'єму кровотоку й об'ємної швидкості викиду крові; найбільш значущих змін зазнає загальний периферичний опір, що обумовлює швидкий розвиток ремоделювання й дилатації міокарда в пацієнта [32, 37]. У той же час для АГ при нефропатіях характерною є мала амплітуда між систолічним і діастолічним тиском, менш виражені прояви гіпертрофії серцевого м'яза й порушення його скорочувальної функції, що виникає значно пізніше [38, 39].

АГ при ХХН супроводжується вищим АТ із порушенням його циркадних коливань і вірогідно меншим значенням величини ранкового підйому, що прискорює виникнення структурно-функціональних змін із боку органів-мішеней. Рівень АТ і його добова крива при АГ, обумовленій ХХН, залежать від зниження ролі вегетативної нервової системи й переважання гуморальних факторів, у тому числі ренін-ангіотензинової системи; у більшості хворих показники, що характеризують навантаження на ниркові судини і ССС загалом впродовж доби, суттєво вищі за середні значення при недостатньому ступені зниження АТ у нічний час [34, 36, 37]. Саме тому призначення антигіпертензивних препаратів при захворюваннях нирок передбачає застосування більшої дози на ніч, а при одноразовому прийомі — також увечері [45].

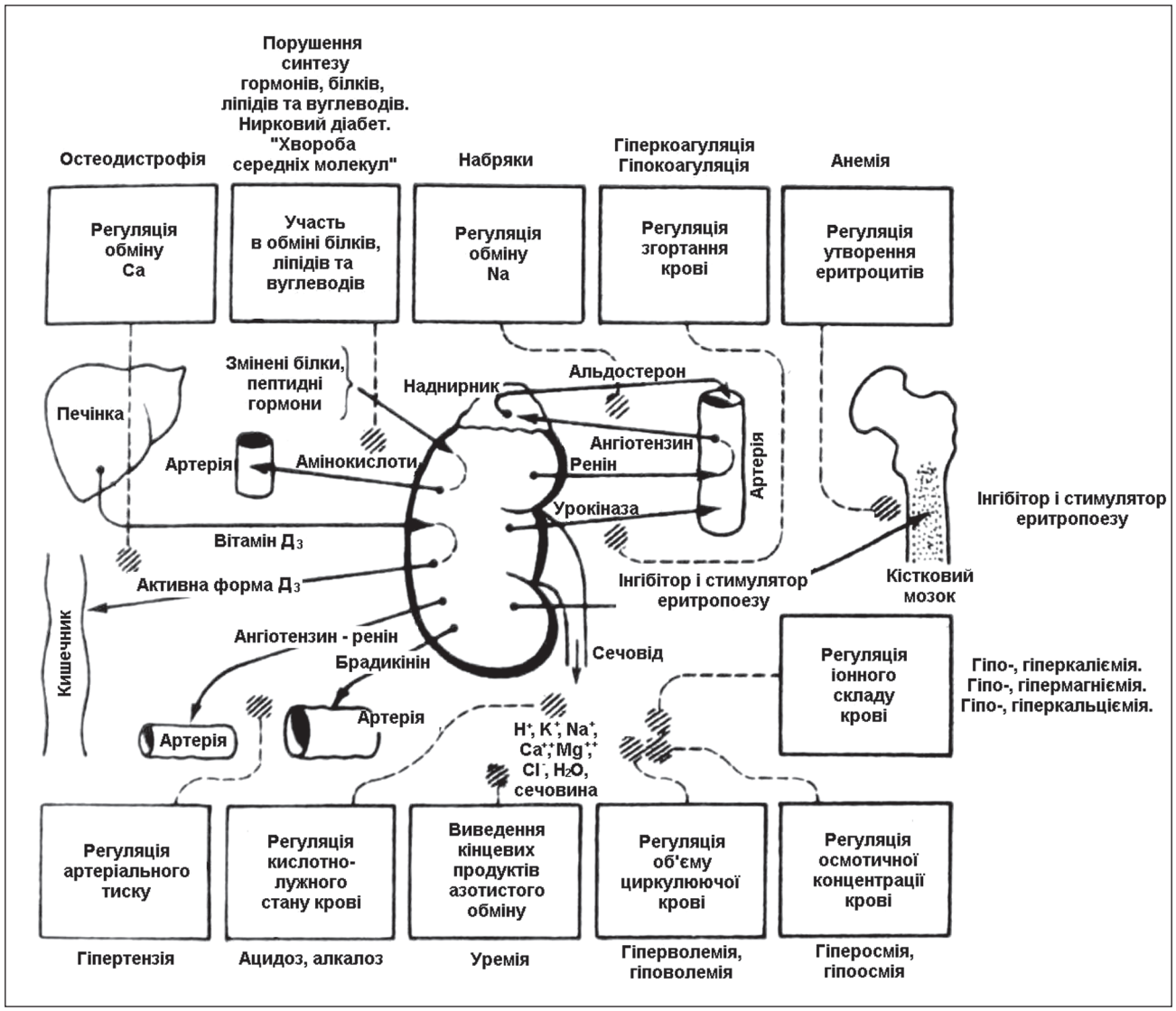

Рисунок 1. Нирки як ефективний гомеостатичний орган

Симптоматична АГ при ГН характеризується задовільною суб'єктивною переносимістю; для неї характерні високий рівень АТ упродовж доби і порушення добового ритму з недостатнім зниженням його вночі й нічною гіпертензією. Порушення добового ритму посилюється зі збільшенням ступеня АГ [40]. Результати дослідження О.Я. Підмурняк (2021) [41], присвяченого особливостям циркадіанних ритмів діяльності ССС, свідчать, що в школярів із нефрологічною патологією відсутні вірогідні зв'язки частоти серцевих скорочень з показниками АТ і наявна значна залежність діастолічного артеріального тиску (ДАТ) від парасимпатичної регуляції з найвищим корелятивним коефіцієнтом між ними — $R = –0,74$; $p < 0,05$. Також встановлено, що в дітей із нефрологічною патологією спектр корелятивних зв'язків між показниками добового моніторування артеріального тиску містить значно меншу кількість вірогідних асоціацій, ніж у дітей з іншими причинами АГ. Денний систолічний артеріальний тиск (САТ) мав вірогідні кореляції із нічною варіабельністю САТ і ДАТ ($R = 0,84$ і $R = 0,81$ відповідно, $p < 0,05$). Привертає увагу показник нічного зниження АТ, що корелює тільки з варіабельністю денного ДАТ ($R = 0,81$; $p < 0,05$).

Кожній системі організму людини притаманні як свої особливості біоритмів, так і умови їх порушення — десинхроноз (часова дискоординація функцій і ослаблення процесів із певним неузгодженням біоритмологічних проявів). Десинхроноз — це вид хронопатології, він є патофізіологічною основою певних хворобливих станів, провісником цілої низки функціональних розладів і супроводжує перебіг багатьох захворювань [40, 42–44], зокрема, у видільній системі (нирок), що регулює велику кількість циркадних процесів, спостерігається висока частота десинхронозів. Так, звичне сечоутворення залежить від часу доби, концентрації в крові гормонів тощо; максимальна активність сечового міхура спостерігається о 15–17-й годині, а нирок – пізніше, о 17–19 год виділення з організму фосфатних солей і білка помітно зменшується в ранкові й денні години; концентрація іонів калію в сечі максимальна вранці й прогресивно знижується у вечірній час, тоді як екскреція іонів натрію досягає пікового значення ополудні. Акрофаза діурезу, екскреції іонів натрію припадає на проміжок від 15-ї до 23-ї години, а клубочкової фільтрації — на більш ранній час, близько 11-ї год. Отже, практично будь-яке захворювання нирок виникає в результаті десинхронозу з порушенням добового ритму сечоутворення, при якому зсувається акрофаза [13]. Можливим практичним засобом для збереження наявних функцій та їх профілактики є нормалізація/відновлення кровопостачання нефрону, що виконується за допомогою інгібіторів ренін-ангіотензин-альдостеронової системи та, останнім часом, інгібіторів натрій-глюкозного котранспортера 2-го типу.

Висновки

Переважна більшість наукових досліджень зосереджена на вивченні первинної артеріальної гіпертензії, у той час як ранні зміни в біоритмах діяльності видільної системи (нирки) лежать в основі вторинної артеріальної гіпертензії.

Наявні результати клінічних досліджень вказують на суттєвий вплив хронобіологічних факторів і хронотипів людини на формування порушень з боку видільної системи (нирки) та наявність взаємообтяжуючих патофізіологічних чинників з боку ССС та ендокринної системи. У той же час немає достатньо переконливих даних щодо ефективних методів діагностики десинхронозів видільної системи (нирки), встановлення їх особливостей в осіб різних вікових категорій, особливо дитячого віку, і застосування засобів корекції на стадії виявлення ранніх порушень з боку видільної системи. Єдиним практичним заходом на сьогодні є призначення більшої дози антигіпертензивних препаратів на ніч для запобігання реалізації кардіоваскулярних ризиків при хворобах нирок.

Конфлікт інтересів. Автори заявляють про відсутність конфлікту інтересів і власної фінансової зацікавленості при підготовці даної статті.

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Chronobiological aspects of the excretory system (review)

Abstract. The paper examines the issues of circadian rhythms functioning and their significance in the regulation of physiological processes of the excretory system. The article deals with the issue of desynchronosis, its causes and effects on the physiological processes of the excretory system in children. The practical significance of chronobiological aspects, their dependence on both individual and population factors, the dynamism of such disturbances and their relevance in the age aspect are shown. The value of chronobiological aspects in the functioning of the excretory system and the expediency of continuing scientific and practical research in this direction of medical science were emphasized.

Keywords: circadian rhythms; desynchronosis; excretory system; children

Огляд

Review

НИРКИ KIDNEYS

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Регуляторні механізми підтримки гомеостазу іонів натрію

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Резюме. *За загальним науковим визнанням, уміст іонів натрію в організмі здорової людини є досить постійним, серед багатогранних біологічних функцій цього електроліту участь у підтримці водно-сольового гомеостазу є найважливішою. Відхилення від нормального рівня іонів натрію в плазмі крові є найбільш поширеними порушеннями електролітного балансу в клінічній медицині, однак дизіонії ще залишаються актуальним предметом досліджень, зокрема їх патогенетичні аспекти та можливості фармакологічної корекції. Натрій, як електроліт, є основним для об'єму позаклітинної рідини, уміст якого зворотним чином пов'язаний із сечовою екскрецією іонів натрію. Гомеостаз натрію жорстко регулюється. У реакціях забезпечення натрієвого балансу в організмі провідну роль відіграють нирки, зміни функціонального стану яких опосередковуються через дію базисних нейрогуморальних регуляторних систем. Головні ниркові гомеостатичні процеси — клубочкова фільтрація, канальцева реабсорбція та секреція мають вирішальне значення для виведення надлишку іонів натрію чи його збереження в організмі. Водночас встановлено, що також є і екстраренальні механізми, які ще продовжують вивчатися. Більше того, завдяки низці досліджень існує припущення, що іони натрію можуть зберігатися в тканинах організму без відповідної затримки води для буферизації електроліту. Беручи до уваги участь нирок у підтримці функціонально-метаболічних взаємозв'язків у нормі і в розвитку поєднаних з іншими органами патологічних синдромів, можна передбачити кореляцію активності встановлених і нових маркерів позаниркових механізмів із редукторами водно-електролітного обміну, кінцеві ефекти яких опосередковуються через зміни функціонального стану нирок. Оцінка додаткових натрійрегулювальних систем є перспективним актуальним напрямом для розширення уявлень про механізми сталості електролітів та води.*

Ключові слова: *гомеостаз іонів натрію; нирки; механізми регуляції*

За загальним науковим визнанням, уміст іонів натрію в організмі здорової людини є досить постійним. Натрій є основним позаклітинним катіоном, що визначає осмолярність плазми та підтримує об'єм внутрішньосудинної рідини, бере участь у регуляції водно-електролітного балансу, кислотно-лужної рівноваги, збудливості м'язових і нервових клітин, у транспорті поживних речовин і субстратів через плазматичні мембрани клітин, регуляції артеріального тиску.

Відповідно до своєї фізіологічної ролі підвищений уміст іонів натрію в організмі провокує патологічні процеси, перш за все артеріальну гіпертензію в більшості людей. Недостатня екскреція іонів натрію нирками призводить до збільшення об'єму позаклітинної рідини при споживанні великої кількості солі та подальшого підвищення артеріального тиску через збільшення серцевого викиду та адаптивне збільшення периферичного опору [1, 2]. Гіпернатріємія (ви-

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значається як плазмова концентрація іонів натрію вище від 145 мекв/л) індукує утворення прозапальних цитокінів, що може призвести до запалення судин та нирок, зсуву співвідношення тиск/натрійурез, розвитку нефропатії та гіпертонії [3]. Унаслідок надмірного споживання іонів натрію модифікується мікробіота кишечника, відповідно, збільшується системне запальне середовище, що також притаманне пацієнтам із серцево-судинною патологією, зокрема з артеріальною гіпертензією [4, 5].

Іони натрію беруть участь в імуномодулюючих функціях клітин [6]. Дослідження показали [7], що у хворих на розсіяний склероз збільшується вміст іонів натрію в головному мозку. Накопичення іонів натрію в церебральній тканині при цьому автоімунному захворюванні, виявлене при магнітно-резонансній томографії, свідчить про те, що імунні процеси тісно пов'язані з концентрацією цього електроліту.

Стійка гіпернатріємія індукує апоптоз, може спричинити необоротне пошкодження клітин/органів, ріст пухлин і високу смертність [8, 9].

Відхилення від нормального рівня іонів натрію в плазмі є найбільш поширеним порушенням електролітного балансу в клінічній медицині, однак дизіонії ще залишаються актуальним предметом досліджень, зокрема їх патогенетичні аспекти та можливості фармакологічної корекції [10–12].

Натрій, як електроліт, є основним для об'єму позаклітинної рідини, зміни якого зворотним чином пов'язані з екскрецією іонів натрію з сечею. Коли збільшується сироватковий натрій, збільшується і осмолярність плазми, що активує реакції на спрагу і синтез в гіпоталамусі антидіуретичного гормону (АДГ) чи аргінін-вазопресину для збереження води в організмі. За умов гіпернатріємії/гіповолемії АДГ виділяється із задньої частки гіпофіза і зв'язується з рецептором вазопресину 2-го типу в клітинах кінцевого відділу дистальних звивистих канальців і збірних трубочках нирок, що запускає внутрішньоклітинний шлях цАМФ, фосфорилювання аквапорину-2 (AQP2). Через водний канал AQP2 апікальної мембрани тубулоцитів вода пасивно переміщується в клітину під дією осмотичного градієнта, створюваного NaCl і сечовиною, залишає клітину на базолатеральній стороні через водні канали AQP3 і AQP4 і таким чином реабсорбується в нирках. Результатом цього процесу є утворення концентрованої чи гіперосмотичної сечі і, зрештою, досягнення водно-електролітного балансу [13].

Дія АДГ урівноважується низкою біологічних чинників, таких як простагландин (PG) E2, брадикінін, дофамін, ендотелін-1, ацетилхолін, епідермальний фактор росту та пурини. Водночас механізмом нормалізації об'єму циркулюючої крові як основного регуляторного параметра у відповідь на гіпернатріємію є первинне збільшення екскреції іонів натрію переважно за рахунок пригнічення його реабсорбції в канальцях, залежної від активності альдостерону. АДГ часто вивільняється одночасно з альдостероном. Мінералокортикоїдний гормон альдостерон, який є ключовим регулятором багатофакторної регуляції натрієвого обміну, виробляється в клубочковій зоні кори надниркових залоз. Крім впливу на нирки, альдостерон модулює транспорт іонів калію та натрію в слині, поті, епітелії дихальних шляхів та рідині товстої кишки. Основна функція альдостерону полягає в дії на кінцеві дистальні канальці та збірні трубочки нефронів, що сприяє реабсорбції іонів натрію та води, екскреції іонів калію, а також кислотно-лужному балансу. Для виконання завдання щодо підтримки натрієвого гомеостазу альдостерон впливає на апікальні епітеліальні натрієві канали (ENaC), насоси натрій-калієвого обміну, зокрема Na^+/K^+-АТФазу базолатеральної мембрани, викликаючи загальне збільшення трансепітеліальної реабсорбції іонів натрію [14]. Регулюючи градієнт іонів натрію в нефроні, альдостерон збільшує/зменшує реабсорбцію води, тим самим робить свій внесок у регуляцію об'єму позаклітинної рідини, підтримку артеріального тиску [15].

Серед інших регуляторів реабсорбції іонів натрію та підтримки водного балансу варто назвати ренін-ангіотензинову систему (РАС). Крім добре відомої системної РАС, наявність локальних РАС було зареєстровано в багатьох тканинах, включаючи нирки [16]. В умовах, коли РАС надмірно активована, її натрійзатримувальна дія опосередкована внутрішньонирковими й позанирковими механізмами. Ангіотензин II (Анг II), який значною мірою продукується в проксимальних канальцях, чинить стимулюючу дію на транспорт іонів натрію в багатьох сегментах нефрона шляхом зв'язування з рецепторами Анг II 1-го типу (АТ 1) плазматичної мембрани. У кортикальних збірних трубочках через рецептори АТ 1 збільшується транспорт електроліту через апікальні натрієві канали; у внутрішній мозковій речовині Анг II посилює транспорт сечовини, сприяючи збільшенню реабсорбції іонів натрію та води. Це свідчить про те, що активація рецепторів АТ 1 у ниркових канальцях є захисним механізмом для збільшення реабсорбції іонів натрію, коли об'єм позаклітинної рідини знаходиться під загрозою. Спектр внутрішньониркової дії Анг II включає також потужну констрикторну дію на еферентні артеріоли, завдяки якій збільшується канальцева реабсорбція за рахунок гемодинамічних змін у перитубулярних капілярах. Констрикторна дія Анг II на еферентні артеріоли також відіграє важливу роль у стабілізації швидкості клубочкової фільтрації (ШКФ) і, отже, впливає на елімінацію нирками речовин, екскреція яких залежить від рівня ШКФ [17].

Первинним позанирковим ефектом Анг II, як регулятора трансканальцевого транспорту іонів натрію, є стимуляція секреції альдостерону. Сучасні дані свідчать, що загальна ниркова дія Анг II кількісно важливіша для затримки іонів натрію, ніж опосередковані змінами секреції альдостерону ефекти. Однак комбінована внутрішньо- та позаниркова дія Анг II на реабсорбцію іонів натрію є найпотужнішою системою зворотного зв'язку для регулювання об'єму солей, рідини та артеріального тиску.

На відміну від Анг II, основними гормонами — інгібіторами транспорту іонів натрію в проксимальних канальцях нефрону є натрійуретичні пептиди (НП). Підвищений рівень НП у плазмі крові стимулює екскрецію іонів натрію з сечею при підвищенні об'єму позаклітинної рідини. Як система гормонів із натрійуретичним ефектом, що переважно виробляються тканинами серця, мозку та нирок у відповідь на збільшення об'єму позаклітинної рідини, також включає НП хондроцитів, ендотелію і клітин крові [18, 19]. Ця родина пептидів забезпечує натрійурез, діурез, вазодилатацію тощо на противагу ефектам РАС, альдостерону й симпатичної нервової системи.

До потенційних механізмів регуляції функцій нирок належить система оксиду азоту (NO). Вплив NO на канальцевий транспорт іонів натрію залежить від інших регуляторів, зокрема від активності ренін-ангіотензин-альдостеронової системи. Зазвичай вважається, що NO пригнічує канальцеву реабсорбцію іонів натрію вздовж нефрона. Відомо, що в проксимальних канальцях нейрональна NO-синтаза (nNOS) та ендотеліальна NO-синтаза (eNOS) інгібують базолатеральну Na^+/K^+-АТФазу та апікальний обмінник натрію/водню 3, а також модулюють активність базолатерального Na^+/HCO_3 котранспортеру. У товстій висхідній частині петлі Генле NO, який походить із eNOS, інгібує Na^+/H^+ обмінник (NHE3), а також може пригнічувати Na^+K^+-$2Cl^-$ котранспортер (NKCC2) апікальної мембрани і в клітинах macula densa. У клітинах збірних трубочок NO, отриманий із nNOS, може пригнічувати ENaC [20].

Проте визнання того, що натрійурез (і діурез) значною мірою залежить від об'єму позаклітинної рідини, контролююча функція якого полягає в підтримці водно-сольової рівноваги завдяки змінам ниркових процесів, не завадило визнанню значущості ще одного чинника регуляції екскреції іонів натрію. Основним нирковим механізмом при надлишку позаклітинної рідини є збільшення ШКФ під впливом передсердного найтрійуретичного гормону, який виділяється у відповідь на збільшення об'єму крові, що надходить до серця і спричинює розтягування стінок передсердь. Відповідно до кількості утвореного ультрафільтрату зменшується канальцева реабсорбція, внаслідок чого іони натрію в складі сечі виводяться з організму. Підтвердженням існування ще одного, ниркового регулятора натрійурезу слугували отримані докази того, що передсердний натрійуретичний пептид і натрійуретичний інгібітор транспортних систем ниркового епітелію, який залежний від Na^+/K^+-АТФази, є двома зовсім різними системами. Це так званий на початкових етапах отримання наукових доказів і переосмислення механізмів натрійурезу третій фактор модуляції натрієвого балансу, дія якого не залежить як від ШКФ, так і від рівня стимулятора канальцевої реабсорбції альдостерону. Через твердження, що його натрійуретична дія є результатом інгібування натрій-калієвої помпи, цей регулятор водно-сольового обміну позиціонується як ендогенний уабаїноподібний або дигіталісподібний фактор [21]. Відомо, що секреція ендогенного уабаїну опосередковується Анг II через вплив на АТ 2 рецептори в корі наднирників [22]. Відкриття ендогенного дигіталісподібного фактора/факторів та розкриття його фізіологічної і патофізіологічної ролі слугувало поштовхом для дослідження безпосередніх ренальних механізмів натрійурезу за відсутності змін ниркової гемодинаміки при підвищеному об'ємі рідини [23].

Протягом десятиліть Na^+/K^+-АТФаза визначається однією з мішеней ниркової регуляції солей в організмі. Сигнальна функція натрій-калієвої помпи, яка може регулюватися лігандами Na^+/K^+-АТФази (кардіотонічними стероїдами та активними формами кисню), зараз отримала широке підтвердження та забезпечує базове розуміння регуляції натрієвого обміну процесами в проксимальних канальцях нирок [24]. Варто відзначити, що пріоритет у дослідженнях уабаїнових ниркових механізмів належить професору Б.А. Пахмурному, завідувачу кафедри патологічної фізіології Чернівецького медичного інституту, при вивченні характеру і механізму дії серцевих глікозидів — строфантину і конвалятоксину на діяльність нирок і водно-сольовий обмін [25]. Так, ним було встановлено, що при експериментальній недостатності кровообігу немає кореляції між зменшенням виділення нирками іонів натрію, води і підвищенням тиску в порожній вені чи правому передсерді. Цей факт виключає переважну роль мозкового і передсердного натрійуретичних гормонів у реакції нирок на водно-сольові навантаження при недостатності кровообігу. Водночас під впливом глікозидів діурез і натрійурез підвищувались без змін тиску в порожній вені і правому передсерді, а також ниркового кровообігу та ШКФ. Екстракардіальна дія серцевих глікозидів була пов'язана зі зменшенням канальцевої реабсобції, супроводжувалась зниженням активності мембранної АТФази, тканинного дихання і окиснювального фосфорилювання в нирках і зберігалась незалежно від змодельованої активності нейрогуморальних регуляторів водно-сольової рівноваги за умов денервації нирки, гіпофізектомії та видалення наднирників.

Беручи до уваги встановлену сигнальну функцію Na^+/K^+-АТФази, внутрішньониркові механізми натрійурезу та маркери їх порушень продовжують цікавити дослідників. Споживання солі та внутрішньоклітинна концентрація іонів натрію є основними регуляторами синтезу та вивільнення ниркового дофаміну. У проксимальних канальцях нефрона і в товстій висхідній частині петлі Генле при зв'язуванні дофаміну з D1-рецепторами також зменшується трансканальцевий транспорт іонів натрію внаслідок інгібування натрій-водневого обмінника апікального епітелію і базальної Na^+/K^+-АТФази [26]. Цей подвійний вплив, разом із збільшеною під впливом дофаміну ШКФ, забезпечує відповідну до потреб організму регуляцію позаклітинного об'єму.

Присутність в сечі таких натрійуретичних пептидів, як урогуанілін та гуанілін, передбачила те, що ці

пептиди також можуть походити з ниркової тканини. Отримані дані щодо взаємодії між нирковим урогуаніліном та D1-рецепторами дозволяють припустити, що існує їх синергізм для збільшення екскреції натрію. Аберантна взаємодія між нирковим урогуаніліном та D1-подібними рецепторами може відігравати роль у порушеннях водо- та іонорегулювальної функції нирок і патогенезі артеріальної гіпертензії [27].

Порушений зв'язок між екскрецією іонів натрію та 20-гідроксіейкозатетраєновою кислотою (20-HETE) уперше було виявлено у хворих із сільчутливою артеріальною гіпертензією, що призводить до залежності екскреції солей від артеріального тиску [28]. Метаболіт цитохрому P450 арахідонової кислоти — 20-HETE викликає вазоконстрикцію та інгібування транспорту іонів натрію в ниркових канальцях. Автори дійшли висновку, що чутливість артеріального тиску до споживання солі при есенціальній гіпертензії може бути результатом порушення натрійуретичного механізму, що залежить від 20-HETE. Такі ейкозаноїди, як PGE 2, PGI 2, PGF 2α, тромбоксан A2, виконують свою регуляторну роль у нирках через рецептори, що експресуються практично в усіх відділах нефрона, завдяки підтримці ниркової гемодинаміки, канальцевого транспорту, регуляції секреції реніну, зменшенню фіброзу та запалення. Антидіуретичний гормон, крім збільшення реабсорбції води, стимулює утворення ниркових PG, і це підтримує клубочкову фільтрацію. Дослідження показали, що PG беруть участь у безлічі фізіологічних ниркових функцій, які забезпечують збалансовану екскрецію води та іонів натрію [29].

Таким чином, теорія сталості позаклітинних рідин організму тісно пов'язана з метаболізмом іонів натрію. Прийнято вважати, що відповідне до кількості споживання солі виведення іонів натрію нирками запобігатиме будь-яким змінам його інтерстиціального і плазмового вмісту. Водночас у низці висвітлених нещодавніх досліджень показано [30], що велика кількість іонів натрію зберігається в м'язах та шкірі без пропорційної затримки води. Крім того, довготривалі дослідження натрієвого балансу в людей вказують на наявність ендогенних годинників, які генерують тижневу та місячну інфрадіанну ритмічність накопичення іонів натрію незалежно від споживання солі [31]. Експерименти на тваринах дозволили припустити, що рідини в інтерстиції шкіри є гіпертонічними порівняно з плазмою крові і що інтерстиціальний осмотичний стрес індукує локальні позаниркові імунні клітини та лімфатичні капіляри для кліренсу електролітів та підтримки внутрішнього середовища.

Отже, натрієвий баланс підтримується й екстраренальними механізмами, які ще продовжують вивчатися. Іони натрію беруть участь у багатьох фізіологічних і патологічних процесах і є важливим електролітом для фізіології здоров'я в цілому, тому його нормальний рівень жорстко регулюється й підтримується багатьма ендогенними регуляторами. Вивчення натрійзалежних механізмів ще залишається актуальним для розкриття патогенезу багатьох захворювань і встановлення нових мішеней їх фармакологічної корекції. Гомеостаз натрію забезпечується нирковими і позанирковими регуляторними механізмами, останнє твердження не є принципово новим, а лише поповнюється новими науковими даними. Беручи до уваги найважливішу роль нирок у підтримці функціонально-метаболічних взаємозв'язків у нормі і розвитку поєднаних з іншими органами патологічних процесів — синдромів [32], таких як кардіо-, церебро-, гепаторенальний синдром, можна передбачити кореляцію активності встановлених і нових маркерів позаниркових механізмів із редукторами водно-електролітного обміну, кінцеві ефекти яких опосередковуються через зміни функціонального стану нирок. За такої умови оцінка додаткових натрійрегулювальних систем є перспективним напрямом, що, безумовно, розширить уявлення про механізми сталості електролітів та води. Встановлення нових механізмів непохитне, швидше за все, підтвердить пріоритетну роль ниркових процесів у гомеостазі іонів натрію.

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Regulatory mechanisms for maintaining homeostasis of sodium ions

Abstract. According to general scientific recognition, the content of sodium ions in the body of a healthy person is quite constant, and among the multifaceted biological functions of this electrolyte, participation in maintaining water-salt homeostasis is the most important. Deviations from the normal level of concentration of sodium ions in the blood plasma are the most common electrolyte balance disorders in clinical medicine; however, dysionias still remain a relevant subject of research, in particular, their pathogenetic aspects and the possibilities of pharmacological correction. Sodium as an electrolyte is essential for the volume of extracellular fluid the content of which is inversely related to the urinary excretion of sodium ions. Sodium homeostasis is tightly regulated. In the reactions of ensuring the sodium balance in the body, the kidneys play a leading role, and the changes in their functional state are mediated through the action of the basic neurohumoral regulatory systems. The main renal homeostatic processes — glomerular filtration, tubular reabsorption and secretion — are of decisive importance for the removal of excess ions of sodium or its retention in the body. At the same time, it was found that there are also extrarenal mechanisms that are still being studied. Moreover, a number of studies have suggested that sodium ions can be stored in body tissues without adequate retention of water to buffer the electrolyte. Given the participation of the kidneys in maintaining normal functional and metabolic relationships and in pathological syndromes related to other organs, it is possible to predict the correlation of the activity of established and new markers of extrarenal mechanisms with reducers of water-electrolyte exchange the final effects of which are mediated through changes in the functional state of the kidneys. Evaluation of additional sodium-regulatory systems is a promising current direction for expanding ideas about mechanisms of stability of electrolytes and water.

Keywords: homeostasis of sodium ions; kidneys; mechanisms of regulation

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Spontaneous retrograde urolithiasis migration in a woman: a case report and possible mechanism

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Abstract. *Urolithiasis is a condition which is commonly encountered in practice, however retrograde migration of a calculus within the ureter has only recently been documented with few cases reported in the literature. We present the case of a 47-year-old woman presenting with symptomatic urolithiasis confirmed by CT who recovered from her symptoms only for it to be discovered that the calculus had undergone retrograde migration into the renal calyx on a follow up CT examination. We theorise that retrograde urolithiasis migration may be an innate safety mechanism that evolved to prevent complications and/or death from urolithiasis impaction by attempting to return a migrated lithiasis to the renal calyx.*
Keywords: *urolithiasis; retrograde migration; calculus; ureteric calculus*

Introduction

Urolithiasis affects 1 of 11 people in the USA, having a slightly higher prevalence in men [1]. The typical presentation is colicky flank pain alongside nausea, vomiting and fever [1]. Most calculi will pass spontaneously though, the likelihood of this occurring decreases with calculus size [1]. However, despite the relatively high prevalence of urolithiasis, few cases of retrograde migration have been reported. We present a rare case of retrograde urolithiasis migration.

Case report

A 47-year-old woman presented with left flank pain to the radiology department following a referral from her general practitioner to exclude urolithiasis. The patient had presented with similar symptoms two years previous, at which point a single non-obstructive kidney stone of 2 mm was found within the left renal calyx during a CT (Computed Tomography) examination (Figure 1).

Upon this occasion, the pain had fluctuated since its first appearance four days prior and was coupled with white blood cells and red blood cells in the urine. A CT-examination demonstrated a 3 mm calculus located in the left proximal ureter with mild hydronephrosis, and no calculus within the kidney (Figure 2).

The patient was treated conservatively before subsequently presenting 11 days later for a follow up CT-exam to verify that the calculus had been eliminated, the pain having subsided in the meantime, leading the clinician to suspect that natural elimination had occurred. Surprisingly, the 3 mm calculus was once again observed, in the inferior renal calyx, with concomitant resolution of the hydronephrosis (Figure 3). We therefore hypothesize upward migration.

An abdominal x-ray was performed three days later, finding that the calculus was radiopaque and remained in the renal calyx.

Discussion

One could hypothesise that the migrating calculus seen in the lumbar ureter had been eliminated and that a second calculus, which had appeared in the meantime, was seen on the follow-up CT examination in the left inferior calix. This would raise two possibilities: first, that we would have missed a 3 mm calculus in the kidney on the first CT examination, or second that a new calculus had formed within the intervening 11 days.

It is improbable that there was a second, missed, kidney stone on the initial CT-exam given that CT technique has a reported sensitivity of up to 99 % with regards to the detection of kidney stones [2]. It is also improbable that a new 3 mm calculus formed within 11 days, as the average recurrence time for new symptomatic urolithiasis is over a year [3]. Furthermore, we know that in this patient the calculus took 2 years to grow from 2 to 3 mm in diameter, making the novel calculus hypothesis yet more improbable [3]. These

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facts make us confident that there was only a single kidney stone in this patient. Due to the improbability of both abovementioned hypotheses, we therefore postulate that the calculus seen in the lumbar ureter had migrated upwards.

Although urolithiasis is a relatively common occurrence, fewer than 10 cases of retrograde urolithiasis migration have been documented once it has entered the ureter. The first documented case in English literature dates from 2015 in Bahrain, with a few cases in the Middle East and India documented afterwards [4–7]. Of the previously reported cases, only Fatallah et al reported relatively little distal migration of the urolithiasis before it was subsequently found to have migrated back into the calyx, whereas the other reports detail the calculus having migrated to the vesicoureteral junction before beginning its retrograde migration [4–7]. The previous papers report intervals of 3 days to around 2 weeks between the onset of pain and its subsequent resolution, at which point it was assumed that the calculus had been spontaneously passed, as was the case in our patient, before it was discovered to have migrated to kidney [4–7].

Previous studies have shown that, once the calculus is within the ureter, the normal anterograde peristalsis of the ureter is disturbed [8]. Interestingly, the peristalsis becomes retrograde in the majority of cases when the calculus is in the proximal ureter, followed by a majority of uncoordinated waves once the calculus is in the distal ureter [8]. Retrograde peristalsis has also been observed in pig models after prolonged stenting, suggesting that foreign bodies, such as an impacted calculus, may be the inducing factor [9]. This theory is backed by evidence from Davenport et al who found that stretch and irritation from calculi resulted in abnormal peristalsis, thus building on a 1973 study which demonstrated abnormal peristalsis following acute or chronic obstruction [10, 11]. Furthermore, retrograde migration of urolithiases have also been recorded in both cats and dogs, lending

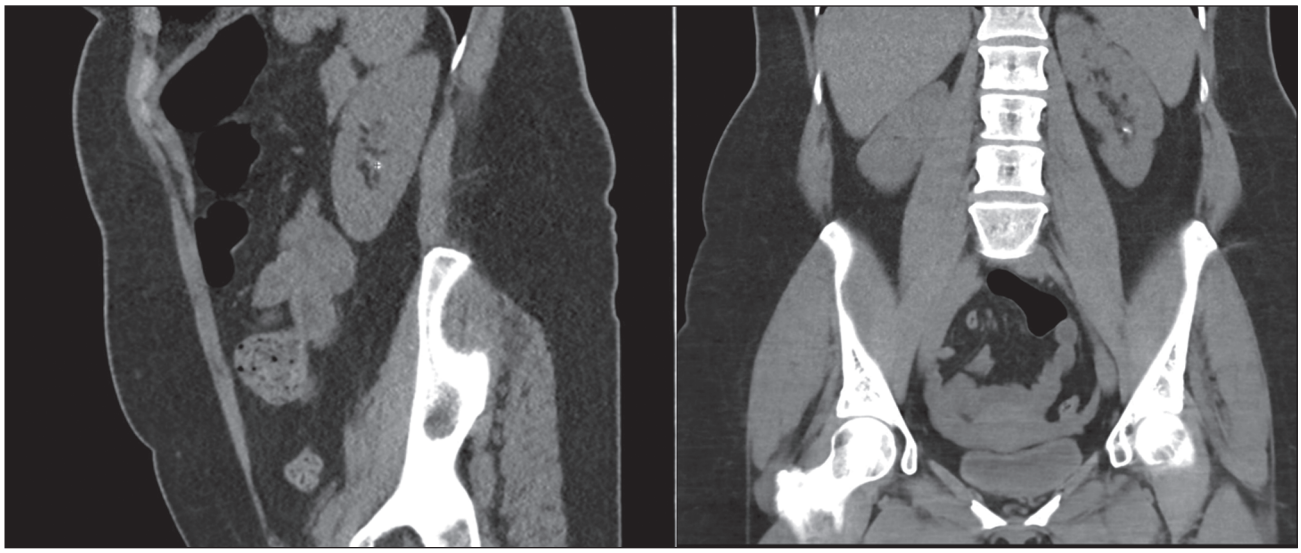

Figure 1. Images obtained 2 years prior showing a single non-obstructive intra-caliceal calculus

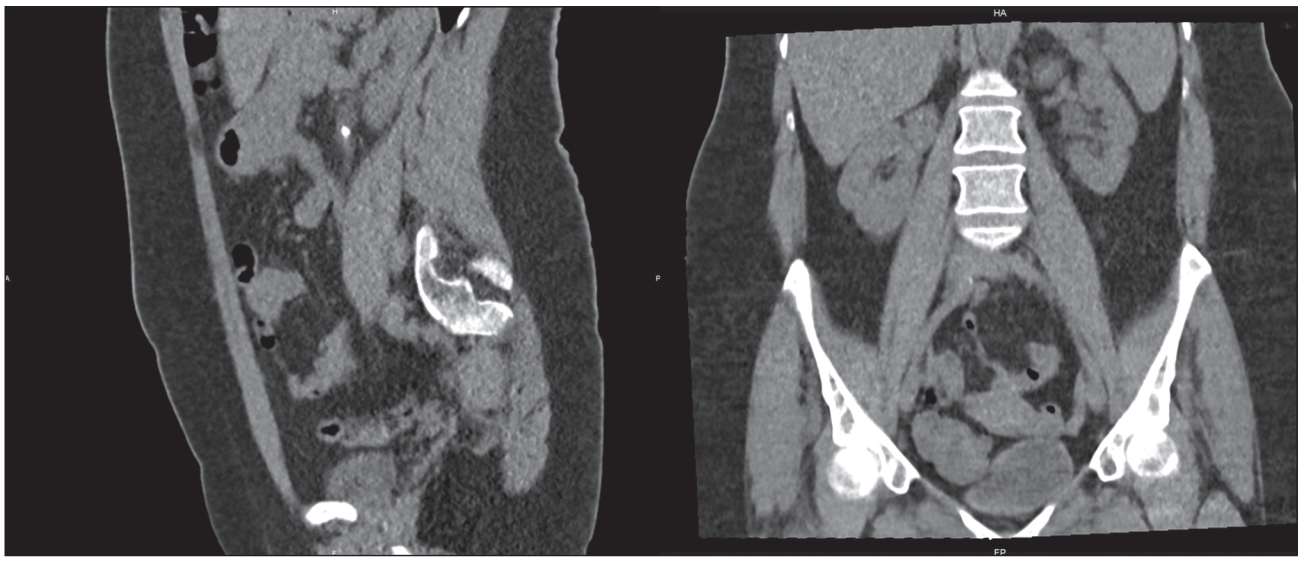

Figure 2. Images obtained during current presentation reconstructed in 5 mm MIP, showing the proximal ureteric calculus

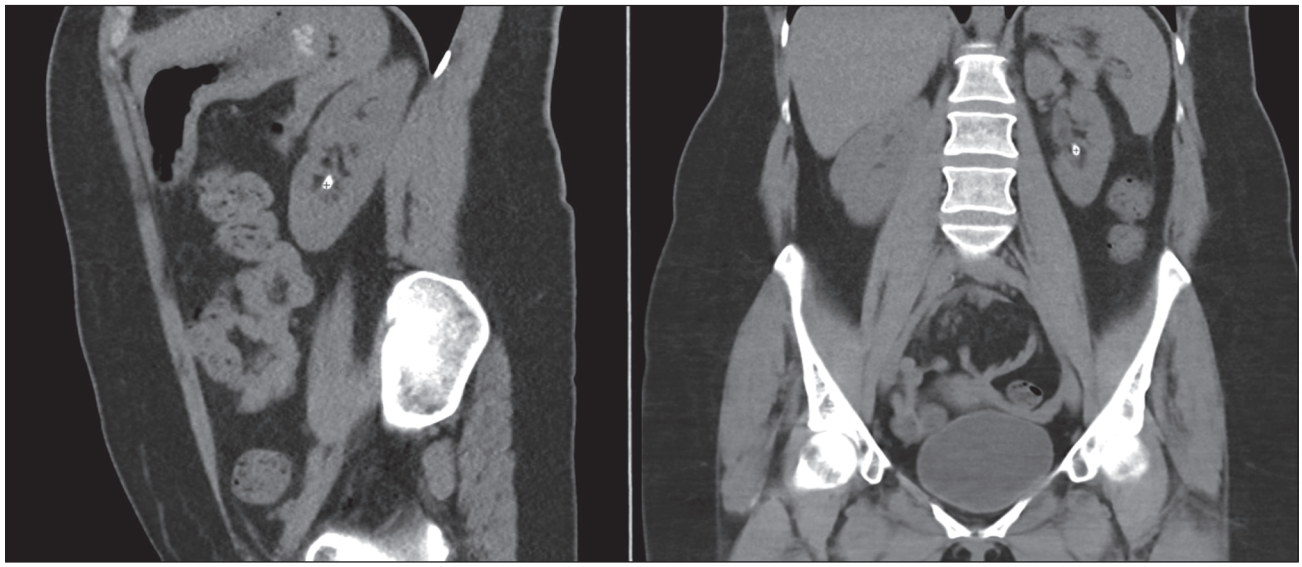

Figure 3. Images obtained 11 days post initial exam, after retrograde migration, showing the intra-caliceal calculus

further credence to the supposition that this is a natural phenomenon present across multiple species [12].

To summarise, there are many reports in the literature of ureter peristalsis being disturbed by a foreign object, with a propensity for retrograde peristalsis if the object is in the proximal ureter. Additionally, the retrograde peristalsis has been documented multiple times in vivo in both human and animal models. It therefore seems highly likely that, since the in vivo observations correlate with the expected outcome of the laboratory findings, that retrograde urolithiasis migration is due to a coordinated physiological response and not merely coincidence.

With regard to the evolutionary reason for the development of such a physiological response, one could theorise that, given the resultant morbidity and mortality in untreated urolithiasis cases, this mechanism might exist to move the calculi back into the kidney where they can remain asymptomatic [13, 14]. However, in the absence of further evidence to prove the evolutionary pressure for this to develop, this remains merely conjecture.

Given the relatively high incidence of urolithiasis it therefore seems unlikely that retrograde migration is so rare, even though it has only been documented a handful of times. We therefore speculate that ureteric calculi, which subsequently spontaneously undergoes retrograde migration, may be an explanation for relatively short-lived flank pain in patients who are found to have nephrolithiasis later but who did not undergo immediate imaging during the painful episode, resulting in the phenomenon going undocumented.

Conclusion

Retrograde urolithiasis migration as in this case is a rare, but probably underreported, phenomenon where a calculus that has begun its migration within the ureter undergoes retropulsion back into the renal calyx. Building on the previous reports and studies, we suggest that this may be a natural phenomenon aiming to protect the patient from potentially deadly impaction of the urolithiasis by returning it to the relative safety of the renal calyx.

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Спонтанна ретроградна міграція ниркового каменя в жінки: опис випадку і можливий механізм

Резюме. Сечокам'яна хвороба є станом, що часто зустрічається на практиці, однак ретроградна міграція конкрементів у сечоводі була задокументована лише нещодавно, у літературі описано кілька випадків. Ми наводимо випадок симптоматичної сечокам'яної хвороби в 47-річної жінки, що була підтверджена комп'ютерною томографією (КТ). Пацієнтка одужала лише після того, як конкремент зазнав ретроградної міграції в ниркову чашечку, що було виявлено під час подальшого КТ-обстеження. Ми припускаємо, що ретроградна міграція при сечокам'яній хворобі може бути вродженим механізмом безпеки, який розвинувся для запобігання ускладненням і/або смерті від уролітіазу шляхом спроби повернути камінь, що мігрував, до ниркової чашечки.

Ключові слова: сечокам'яна хвороба; ретроградна міграція; конкремент; камінь у сечоводі