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HISTORY AND BACKGROUND OF KIDNEY TRANSPLANTATION IN UZBEKISTAN

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This paper presents a brief outline of the history of transplantation service in the Republic of Uzbekistan, which originated at the country's Center for Kidney Transplantation. The role played by outstanding scientists in Uzbekistan, their works and efforts towards the creation of a separate area of clinical and scientific medicine in Uzbekistan, are highlighted. Achievements by the research school of U.A. Aripov, Academician of the Academy of Sciences of the Republic of Uzbekistan, who performed the first successful kidney transplantation in 1972, are shown. The ups and downs of national transplantation nephrology, as well as the birth of a national school of kidney transplantation, domiciled at the Vakhidov Republican Specialized Scientific and Practical Medical Center of Surgery, headed by academician F.G. Nazirov, and giving a stimulus to the "second breath" of the national school of transplantology, is reflected. Separate attention is devoted to the actual problems of national transplantology, moral, ethical and regulatory issues that inevitably accompany this scientific and clinical direction are reflected. Kidney transplant outcomes in Uzbekistan are given, the prospects for further scientific and clinical directions are indicated.

Keywords: kidney transplantation, kidney transplant history, living related donors, immunosuppressive therapy.

Kidney transplantation (KTx) is known to be the only radical way to help patients suffering from chronic progressive kidney disease. According to WHO, the number of patients today suffering from end-stage kidney disease in the world is above 4 million; meanwhile, the number of surgical interventions to replace an organ that has lost its functions is steadily growing. With improvement in surgical technique, as well as a more detailed understanding of the mechanisms of immunosuppression, KTx allows to achieve 5- and 10-year survival rates of 90% and 74%, respectively (according to UNOS, USA) [1].

At the same time, the incidence of chronic progressive kidney disease, leading to chronic kidney disease (CKD) in its later stages, does not tend to decrease. In addition, due to the constantly expanding nosological range of diseases requiring KTx, donor organ shortage is still an acute problem. In connection with the above, the use of renal transplants from living related donors has acquired special relevance. Immediate restoration of transplanted kidney function and rare rejection crises in native transplantation, in addition to better immediate results, certainly make it possible to predict a higher long-term graft and patient survival rate than in cadaveric organ transplantation. This is associated not only with a higher degree of donor-recipient immunological compatibility, but also largely determined by reduced cold ischemia time and, accordingly, lower severity of reperfusion injuries [2].

The history of kidney transplantation in Uzbekistan is closely connected with the name, Uktam Aripovich Aripov, Academician of the Academy of Sciences of the Republic of Uzbekistan. In 1964, Aripov, having become the First Deputy Minister of Health of Uzbekistan, made great efforts to develop specialized medical services and train highly qualified scientific and pedagogical personnel to meet the country's needs. Being a polyvalent surgeon who performed the most complicated surgeries, he created all conditions for a comprehensive study of the pressing issues in abdominal surgery and transplantology. From 1971 to 1984, Aripov, being the rector of Tashkent State Medical University, organized a problematic research laboratory on overcoming tissue incompatibility in transplanted organs and tissues, he was also appointed to head the first kidney transplant center in Central Asia with a hemodialysis laboratory. At this center, he formed a team of young and talented like-minded scientists, uniting doctors of various specialties. Here, the problems of transplantation immunity, development of home-made immunosuppressants, clinical transplantology and treatment of CKD patients were developed. So, the first kidney transplant was performed in Uzbekistan on September 14, 1972, for end-stage CKD [3].

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Fig. 1. Academician U.A. Aripov

In 1974, Uktam Aripov was elected an Academician of the Academy of Sciences of the Republic of Uzbekistan and in 1978 he was elected an honorary doctor at the research-led medical Semmelweis University in Budapest. In 1983, Academician Aripov and a number of his coworkers were awarded the Beruni State Prize of Uzbekistan in Science and Technology for the development and introduction into clinical practice of new improved methods of treating CKD patients and for creation of domestic drugs [3].

So, in 1972, on the basis of the Problem Research Laboratory on overcoming tissue incompatibility in organ and tissue transplantation of the Tashkent Order of the Red Banner of Labor State Medical Institute, the Republican Center for Kidney Transplantation was organized. This center was a therapeutic, consultative, scientific, and educational center for the treatment of CKD patients [4].

The 40-bed kidney transplant center was located at the Clinical Hospital of the Uzbek SSR Ministry of Health. The work of the Center was headed by Academician of the Academy of Sciences of the Uzbek SSR, Uktam Aripov and professor N.P. Pak. Two senior and two junior researchers, and 11 residents worked at the Center. In addition, work at the Center was done in close cooperation with the Republican Nephrological Center [4].

The senior researcher and head of the clinical group on kidney transplantation of the Tashkent Kidney Transplantation Center was Pak Nikolay Petrovich, a laureate of the Beruni State Prize of Uzbekistan in Science and Technology, a medical doctor, a professor, an Academician of the International Academy of Sciences of Nature and Society, an Academician of the European Academy of Natural Sciences. Professor Pak was the chief specialist on hemodialysis and kidney transplantation at the Ministry of Health of the Republic of Uzbekistan for 19 years.

In addition, Uktam Aripov's initiative and scientific interest saw him forming his own scientific school and nurturing talented students. Such scientists as Academician M.S. Abdullakhojaeva, Professor R.N. Akalaev, Immunologist Professor F.Y. Garib, Dr. A.V. Barabash, Dr. K.G. Urazmetov, M.D. Urazmetova, Dr. B.F. Islamov and others worked under Uktam Aripov's leadership. In clinical and experimental studies, they showed that the drug gamma globulin, derived from a mixture of placental blood serum in contrast to similar drugs from venous (donor) blood, at 0.5–1.0 mg/mL, can inhibit the proliferative response of human lymphocytes to transplant antigens in mixed lymphocyte culture.

According to the results of the research activities of the above-mentioned scientists, there were formed and subsequently presented materials concerning kidney transplant complications in the clinic, results of studying the toxicity of "middle molecules" in CKD, experimental studies of the mechanisms of action of a number of drugs considered as potential immunomodulators.

A separate contribution to the development of the direction made by top doctor Evgenia Kholodova, who worked for more than 20 years as head of the department of hemodialysis and rehabilitation of transplant recipients in Republican Clinical Hospital No. 1 in Tashkent (formerly Kidney Transplant Center). For her excellent work as head of the Center, she was awarded the state Order of Mehnat Shukhrati award.

Some of Aripov's followers and students continued the program initiated by him. For example, Professor Dmitriy Arustamov, Honored Worker of Health of the Republic of Uzbekistan, laureate of the Abu Rayhan Beruyun Award, recipient of the Dustlik Order, was the director of the Republican Specialized Center for Urology. As head of the Department of Urology at the Tashkent State Medical Institute, he was the director of the Republican Specialized Center of Urology. Under his leadership, a number of scientific works, monographs, and methodological guidelines were written, author's

Fig. 2. Professor N.P. Pack

Fig. 3. E.G. Kholodova, Head of Department of Hemodialysis and Rehabilitation of Transplant Recipients.

certificates for inventions on organ and tissue transplantation were obtained.

The structure of the Nephrology Center as part of the organizational medical department included: a unit for kidney disease patients without renal failure, a unit for CKD patients, a unit for acute renal failure, a chronic dialysis unit, and a kidney transplant center.

The kidney transplant center itself included clinical groups: preoperative patient preparation, hemodialysis group, kidney harvesting and preservation group, postoperative patient management group, tissue typing and immunologic monitoring group.

The preoperative preparation group examined potential recipients, prepared them for kidney transplantation by conservative measures, and counseled patients in the units of the nephrology center and in other medical institutions.

The hemodialysis group was involved in hemodialysis programming and direct administration. The laboratory had a central dialysis fluid preparation station and 14 hemodialysis sites. During existence of the Center, the staff of the hemodialysis laboratory introduced such progressive and economic forms of treatment of patients as creation of various modifications of arterial-venous fistulas, transfer of some patients to outpatient hemodialysis, wide use of special methods of hemodialysis – diafiltration and hemosorption.

The kidney harvesting and preservation group had close ties with the intensive care, trauma and neurosurgical departments of city hospitals; it performed kidney harvesting and preservation for subsequent transplantation.

The postoperative management group was directly involved in nursing patients after surgical interventions, in issues of immunosuppressive therapy and in prevention of complications.

The patients spent their first post-kidney transplant month in wards of increased box sterility with a doctor, a nurse and a medical assistant, who were all on duty 24 hours a day.

The tissue typing and immunological control group conducted immunological study of potential recipients, dealt with selection of donor-recipient pairs, and carried out postoperative monitoring of the effectiveness of immunosuppressive therapy.

Hemodialysis units were opened in Samarkand, Fergana, Andijan, Bukhara, Almaty, Ashkhabad, Dushanbe, and Chimkent with the direct assistance and participation of the Center staff. The Center had a close connection with the Kidney Transplant Center of Almaty, with which donor kidneys and information about recipients was exchanged [4].

The Center provided consultative assistance in all regions of the country, as well as in the regions of neighboring Central Asian countries. Every year, the Center's staff attended to 200 calls by air ambulance.

Scientific research was conducted by the Center staff under a comprehensive plan to the assignment of the State Committee on Science and Technology under the USSR Council of Ministers, Uzbek SSR Ministry of Health and the All-Union Scientific Council for Transplantation and the Creation of Artificial Organs.

A search for and introduction of new immunosuppressive drugs into clinical practice was one of the problems of transplantology that required urgent attention. The accumulated experience allowed the native school of transplantology not only to study the effect of pharmaceutical drugs and their influence on the mechanisms of immunosuppression but also to synthesize their own drugs. So, in the 80s, the Institute of Bioorganic Chemistry of Uzbek SSR Academy of Sciences already had

Fig. 4. Prof. D.L. Arustamov

10 names of their own immunosuppressants in its arsenal. In turn, preparations batriden and megosyn were selected for clinical study, the first of which after clinical testing was approved for medical use as an immunosuppressant in kidney transplants and for clinical study in autoimmune diseases.

To solve the problems of prevention and treatment of immunosuppressive therapy complications in patients after KTx, the Kidney Transplant Center together with the Institute of Bioorganic Chemistry of Uzbek SSR Academy of Sciences and the Laboratory of Physical and Chemical Research Methods of the Central Research Laboratory, studied the metabolic pathways of immunosuppressants, target organs for aggressive metabolites of these drugs, search for possible protectors from adverse effects of immunosuppressors.

The accumulated experience also allowed to raise the scientific potential to an entirely new level; so by 1982, research workers at the Center defended two doctoral and nine phd dissertations, published two monographs and five methodical guidelines, published over 200 research papers; together with the tissue incompatibility problem laboratory, eight collections of scientific works were published.

The Tashkent Kidney Transplant Center hosted a meeting of experts of CMEA (Council for Mutual Economic Assistance) on KTx problems in 1977, and an All-Union Conference "Immunosuppression in allotransplantation" was held in 1979.

It should be noted separately the number of procedures performed; in 1972 the Center performed two KTx and 300 hemodialysis sessions, but by 1981 the number of kidney transplants had reached 227 (20–25 operations a year), and hemodialysis sessions had reached 25,500. The average 6-month survival rate was 65% [4].

The Center was frequently visited by foreign delegations and its staff had ties with the Semmelweis Medical University in Budapest (an agreement was signed on scientific cooperation with the renal transplant centers of the GDR, Poland, and Czechoslovakia). The Center's staff had frequent visits from foreign delegations to the Budapest Semmelweis Medical University (an agreement on scientific cooperation was signed), kidney transplantation centers in East Germany, Poland, and Czechoslovakia.

However, adoption of the Criminal Code of the Republic of Uzbekistan in its new version of 1994 had a significant impact on the entire kidney transplantation sector. The new law allowed the removal of organs from a corpse only with the permission of the relatives of the deceased or a consent given by the deceased while alive. This completely stopped kidney transplantation in our country.

During the existence of the Kidney Transplant Center, a total of 358 kidney transplants were performed. In 311 cases, cadaveric kidney transplants were performed, while 47 patients underwent kidney transplantation from a living related donor.

It was not until 2002 that the Ministry of Health issued an order authorizing kidney transplantation from a living related donor, which gave rise to a new program of living donation. The first such operation was performed at the Kidney Transplant Center (present-day Republican Clinical Hospital No. 1). However, 4 years later, this order was withdrawn, and such surgical interventions were stopped again. This situation, caused by lack of normative and legal support for the program, forced patients to seek help abroad.

Thus, as in other countries of the world, formation of organ and tissue transplantation service in Uzbekistan went through many difficult challenges in its development. The complicated logistical and political situation in post-Soviet countries at the end of the 1980s and beginning of the 1990s resulted in a complete loss of the previously created fundamental base and accumulated experience. Attempts to rehabilitate the transplantation service were faced with the lack of clearly formulated legislative acts, complicated moral and ethical background that excluded organ transplantation from brain-death donors.

Related transplantation remained the only available option for families with many children in Uzbekistan. Repeated attempts by academician Vasit Vakhidov, the director of the country's leading surgery center, to realize this direction were unsuccessful; more and more potential patients who needed this type of surgical treatment continued to go to foreign clinics. Only a decade later, his talented pupil, surgeon and organizer of health care, academician Feruz Nazirov managed to move this problem forward. At the cost of his enormous efforts, transplantology in Uzbekistan got a second wind. At the Vakhidov Republican Scientific and Practical Medical Center for Surgery (Vakhidov Center), the organ transplantation program was not only revived, but also took on completely new features.

Specialized departments were established, in particular, Department of Vascular Surgery and Kidney Trans-

Fig. 5. Academician V.V. Vakhidov

Fig. 6. Academician F.G. Nazyrov

plantation, headed until now by Professor Fazliddin Bahritdinov, and Department of Hemodialysis, headed by Ulugbek Yuldashev, presently head of Transplantology and Laboratory of the Republican Specialized Scientific and Practical Medical Center for Nephrology and Kidney Transplantation. Also there was a narrow profile transplantation commission, a material and technical base was strengthened, retraining of personnel was carried out in leading foreign clinics, indications for surgical intervention were expanded, a solid foundation for scientific work in an area which is very important for the country was created. All the above mentioned has seen some positive impacts not only by way of an increase in the number of interventions, but also in direct improvement in the quality of such interventions. Physicians started performing transplant surgeries in patients with diabetes mellitus and other comorbidities that previously did not allow one to count on a favorable outcome of the intervention.

Thus, since 2010, the Vakhidov Republican Specialized Scientific and Practical Medical Center of Surgery (Vakhidov Center) renewed kidney transplant surgeries, and in February 2018, after the publication of the draft law "on related kidney and liver lobe transplantation", academician F.G. Nazirov performed the first living related liver transplantation in the country. In addition, by the end of 2021, the number of kidney transplant operations performed at Vakhidov Center had reached 540.

At the same time, not only new areas of clinical transplantology were created, but also the already developed techniques were modified and improved. So, in 2015 the center performed the first kidney transplantation using laparoscopic donor nephrectomy.

The successes achieved at Vakhidov Center not only showed the safety, but also clearly demonstrated the need for further development of transplantology service in the country, being the impetus for further improvement of the legislative and regulatory framework. Thus, already in December 2019, amendments and additions were made to the draft law "on the order of related kidney and (or) liver lobe transplantation" significantly expanding the donor pool.

Currently, in Uzbekistan, surgical removal of organs for transplantation is possible only from living donors who are relatives of the recipient, and with their voluntary consent.

All patients with a transplanted kidney living in the Republic of Uzbekistan are registered at the department

Fig. 7. Staff at the Department of Vascular Surgery and Kidney Transplantation, headed by Prof. F.S. Bakhritdinov

of hemodialysis and rehabilitation of transplant recipients in the Republican Clinical Hospital No. 1 in Tashkent.

In addition, based on the results of scientific research at Vakhidov Center, two dissertations (PhD) have been defended and guidelines ("Optimization of tactical and technical aspects in kidney transplantation from a living related donor") developed. The proposed guidelines improved the efficiency of patient preparation for kidney transplantation and optimized the technical aspects of surgical intervention. A program for assessing the surgical risk of a kidney recipient was developed. Application of the proposed program with determination of 33 aggravating factors of the disease allows to estimate the surgical risk in the preoperative period and optimize the process of preparation for transplantation. The obtained scientific results have been implemented in the practical activity of public health service. For example, joint operations on kidney transplantation have been started in the regions (at the surgery department of Navoi Regional Multidisciplinary Medical Center and others). Implementation of the scientific research results allowed to reduce the incidence of complications in the early postoperative period from 29.5% to 11.2% and in the late period from 47.5% to 22.7% and overall mortality from 8.2% to 4.1%.

At the Vakhidov Center, teams of specialists of various fields also played a great role in the successful implementation of kidney transplants. They includes the department of General Resuscitation and Intensive Care under the leadership of Dr. Ibadov R.A., Department of Anesthesiology under the leadership of Dr. Nazirova L.A., Department of Hemodialysis under the leadership of Abdullaeva M.A., Department of Experimental Surgery under the leadership of Prof. Sadykov R.A., Department of Radioisotope Diagnostic Laboratory under the direction of Arifkhodjaev G.G., Biochemistry Department with a microbiology group under the leadership of Dr. Khaybullina Z.R., Functional Diagnostics Department under the leadership of Sharapov N.U., Department of Computed and Magnetic Resonance Imaging under the leadership of Dzhuraeva N.M., and Consultative and Diagnostic Department under the leadership of Ganihodjaev S.S.

In the development of transplantation of other organs, in particular, the liver, at the surgery center under the leadership of the director, academician F.G. Nazyrov, the chief researcher of the Department of Surgery of Portal Hypertension and Pancreatoduodenal Zone Dr. A.V. Devyatov, head of the Department of Liver and Bile Duct Surgery Dr. M.M. Akbarov and other employees of the departments contributed their share. In 2018 and 2019, 10 liver transplant surgeries were successfully performed.

Meanwhile, the work done has opened up additional opportunities in terms of development in this direction; so, in the future, the possibility of performing heart, cardiothoracic, pancreatic and lung transplantation surgeries is being considered.

In addition, organ and tissue transplantation is now being performed at several treatment and prevention centers in the country. For instance, a kidney transplantation program has been implemented at the Vakhidov Center since 2018 thanks to efforts by Khadzhibaev A.M.; achievements by the collective center correspond to those of leading international clinics.

At the same time, despite the successes achieved in the field of transplantology, there are still a number of unresolved issues in the country. Among these, issues with acute shortage of highly skilled specialists in the field of transplantology play a special role. It is known that transplantation service is not built only on transplant surgeons; for successful realization of the program, it is necessary to have morphologists, immunologists, specialists in the field of interventional interventions and many others. Thus, in spite of the work done, the development of this direction of clinical medicine undoubtedly requires even greater efforts aimed at creating and strengthening the solid material and technical base of specialized departments, improving its own scientific and clinical school. That said, one of the priority tasks can be considered the creation of a national transplantation center, allowing not only to unite specialists of different profiles specializing in clinical transplantology, but also allowing to significantly consolidate the efforts aimed at development of the national transplantology service.

Thus, related kidney transplantation, which opened the era of clinical transplantation of vital organs in the last century, has now acquired a new lease on life. Prospects for kidney transplantation in Uzbekistan in the 21st century are related to overcoming ethical problems of organ transplantation, improving tactical and technical aspects of KTx, opening new transplantation centers and centers for rehabilitation of organ recipients with all modern capabilities for examining and treating severe patients.

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