

Endogenous Self Organ Repairing after Release of Unilateral Ureteral Obstruction (RUUO)

Dr. Shrikant L. Kulkarni*

Kulkarni Clinic, 175/1 Balwant Station Road, Near Post Office, Chinch wad Gaon Pune 411033, Maharashtra, India.

*Correspondence:

Dr. Shrikant L. Kulkarni, Kulkarni Clinic, 175/1 Balwant Station Road, Near Post Office, Chinch wad Gaon Pune 411033, Maharashtra, India.

Received: 16 August 2021; **Accepted:** 02 September 2021

Citation: Shrikant L. Kulkarni. Endogenous Self Organ Repairing after Release of Unilateral Ureteral Obstruction (RUUO). Stem Cells Regen Med. 2021; 4(4): 1-3.

Keywords

Kidney diseases, Stem cells, Regenerative medicine, Unilateral ureteral obstruction.

The increasing prevalence of chronic kidney disease in the absence of proper treatment technique has become a strong driver for innovation in nephrology. In-situ regeneration holds a great potential to provide new therapeutic options for functional tissue regeneration. In order for this approach to be successful stem cells need to be directed to the target site and guided to proliferate and differentiate into the cell type of interest by altering the toxic environment into a healthy microenvironment through elimination of renal fibrosis. The concept of endogenous stem cell regenerative medicine, based on the idea that native stem cells already reside at the site of injury in the mature tissue can be stimulated and functionally enhanced to repopulate, repair or regenerate. Human body possesses an enormous astonishing and persistent capacity to heal itself. A disease generally occurs when we abuse our bodies or deprive them of basic requirements to keep them healthy over a long period.

Unilateral ureteral obstruction (UUO)) is a well established experimental model to evaluate renal interstitial fibrosis [1]. Because of blockage of urine flow there are anatomical and biochemical changes in renal tissues. The effect of release of unilateral ureteral obstruction (RUUO) on the damaged kidney is recovery of function, reduced macrophage infiltration and decrease in proline and collagen content in the renal tissues [2]. Numerous studies show an after effect of UUO which leads to renal fibrosis but less is known about the inherent mechanism that promotes tissue modeling and regeneration i.e. the cortical parenchyma restored after RUUO due to decompression of the

kidney and continuous drainage of urine flow. There are several interconnected mechanisms involved in progressing the renal fibrosis in chronic kidney disease (ckd) including haemodynamic and non-haemodynamic changes. Fibrosis is part of the normal repairing process that is triggered after injury and deregulation of this process leads to replacement of parenchymal tissue by Extracellular Matrix (ECM) which are proteins mainly collagens. Accumulation of excessive ECM alters the tissue mechanism properties, which alters the organ function and often leads to organ failure. There is an urgent need to improve our understanding of the early mechanism of ckd which will enable early therapeutic intervention and delay ckd or even reverse the renal fibrosis.

Renal fibrosis formed by UUO and in-case of ckd due to other etiological factors are the same. Patho-physiological changes taking place in UUO is a very fast process of a few days and ends with ckd if the obstruction is not removed. But in case ckd is formed due to other etiological factors it takes a longer period, few months to even years to form renal fibrosis. This slow process provides additional time for early detection of the disease and early intervention to treat renal fibrosis. Researchers have found that the murine model kidney begins to repair at a fast pace after removal of obstruction (RUUO). They identified the "Precursor Cells", present during development of the kidney are the key players in the process of kidney repair [3]. These precursor cells may utilise to repair damaged kidneys in children and adults by waking them in the early stage of disease. A mouse model of UUO and RUUO that developed renal fibrosis and loss of renal parenchyma followed by resolution of renal injury and regeneration of renal parenchyma i.e renal function recovery was established by Cochrane et al. [8]. UUO is associated with progressive renal fibrosis and scarring with decline in renal function RUUO is the

variable of renal function recovery and structural repair of renal parenchyma.

The identified “Precursor Cells” are nothing but seeds of regeneration, which is the evidence within many of our tissues and organs in small numbers that can repair or replace parts or organs damaged by injury or diseases. These cells are the remnants of embryonic development, play an essential role called “Homeostatic Maintenance” keeping the organ in good health through renewal. How do the cells know when to kick start action to repair damaged tissues and organs?. Survival and behavior of each organism depends on interaction with the environment or niche in the ecosystem. The niche normally keeps stem cells in a balanced state of self renewal, perhaps the splitting of specialised cells in regular intervals by an internal “Clock”.

Development of the kidney in early postnatal may give us clues of how to push the precursor cells or to wake up these cells in adulthood to regenerate and maintain the kidney function in damaged kidneys. The preterm kidney can not be simply considered as a small kidney in size as compared to adults. The major difference is in the architecture and cell components between the two. At cellular level the preterm infant kidney has a huge amount of stem cells/precursor cells. The multiple stem cell niches present in preterm kidneys include the capsule sub capsular lesion nephrogenic zone ureteric bud cortical and medullary area. Subcapsular area represents the major stem cell niches in the preterm kidney which is defined as “Blue Strip” [3]. This morphological data analysis of preterm kidneys appears quite different that is typically utilized in kidney biopsies from adults. Better knowledge of molecular biology of blue strip stem cells/precursor cells could be the basis of new endogenous regenerative medicine. The bluestrip represents the nephron's progenitor renal cells of the preterm kidney which are capable of giving the segments new nephrons. All these data taken together may represent the basis for the new original approach to Physiological Regenerative Medicine. The huge number of active stem cells at perinatal period represents a new window for preventing and treating the chronic kidney disease in adults as well in children [4] The main innovative factors in treatment of ckd are predominantly based on endogenous stem cells which are physiologically present in huge amounts in the preterm kidney.

Unilateral ureteral obstruction causes subacute renal injury characterized by tubular cell injury interstitial inflammation and fibrosis. It serves as a model of both ir-reversible acute kidney injury and the events taking place during human chronic kidney disease. Apoptosis, inflammation and fibrosis, all three key processes in kidney injury of any kind provide information beyond obstruction [5]. There is no difference in the patho-physiological changes that take place in ckd and following obstructive nephropathy induced by UO. There is more data available regarding the formation of renal fibrosis after UO but less is known about the regeneration and repair of damaged renal tissues and improved renal function after RUO [6].

In UO, what happens to renal fibrosis? How is it eliminated and the process of regeneration starts?. The biological system in our body is so complex that there is no one answer. As we know, there are plenty of precursor cells present in the capsule and in the subcapsular area which are the seeds present from the embryo and have the power to form the segments of new nephrons [7]. But this regenerative power has lost because of renal fibrosis, which has produced a toxic microenvironment and constriction of blood vessels creating hypoxia. Ureteral obstruction for a long period leads to significant renal tissue loss as well as renal function. Tubular rarefaction of renal vasculature and reduced blood flow, ultimately leads to ckd if the obstruction is not removed. Persistent ureteric obstruction leads to the increase in the retrograde hydrostatic pressure which leads to elimination of renal fibrosis and is replaced by accumulation of urine and the kidney represents as a big cyst-like organ. High hydrostatic pressure has the potential to disrupt the structure of ECM through protein denaturation, it is highly critical to have suitable pressure conditions and mechanisms. This high hydrostatic pressure will not affect the stem cells in the capsular or even subcapsular region but they can not regenerate the nephrons because of the hypoxia and toxic microenvironment. But when the blockage at pelvi ureteric junction (PUJ) is released i.e. RUO results in striking regeneration of renal tubules dilation of arterioles which causes increased blood flow to ischemic renal tissues. Regeneration of vasculature is the key in the case of damaged organs or tissues.

What happens when the release of obstruction? There is change in the microenvironment due to reduction of retrograde hydrostatic pressure due to which the compressed vessels open and supply to the renal tissues like stem cell niches in capsule and subcapsular region. The environment impacts tissue repair via mechanical factors. Mechanical stress plays an important role in the process of constructing and modifying organs and tissues. Hydrostatic pressure inhibits collagen matrix production and suppresses fibroblast into myofibroblast. Ultimately they start the formation of new segments of nephrons and repair damaged renal tissues and start the renal function. Lastly, it can be emphasized that if we wait for every question to be answered, novel treatment based on self organ regeneration into human health is impossible.

This article may be the explanation how after RUO the regeneration and function of the renal tissue is restarted. The mechanism involved in kidney repair and regeneration post relief obstruction has potential therapeutic implications for infants, children and growing numbers of adults suffering from ckd. Even with the human data available in the children due to congenital ureteral obstruction, hydrostatic pressure increases and causes the renal parenchymal damage to the kidney causing it to form like a big cyst. With less than 10% of renal functionality remaining, if obstruction is removed the kidney function restarts in the same manner as we have discussed above. This is not just in the treatment of congenital nephropathy but in the treatment of all forms of kidney diseases. In biological systems we observe the sequences of events in a systematic manner and obtain positive result. Fibrosis

is a natural healing tissue in our body so it should be treated as natural as possible. Hydrostatic pressure is the most fundamental and common mechanical stimuli in the body playing a critical role in haemostasis of all organs systems. The high hydrostatic pressure is used as an antifibrotic agent to eliminate renal fibrosis to create a healthy microenvironment for regeneration of damaged renal tissue instead of antifibrotic drugs. There is no difference in the pathophysiological changes taking place in chronic kidney disease and the following obstructive nephropathy induced by UUU. The normal kidney when blocked develops renal fibrosis but when this block is removed renal function restarts i.e. if the cause is removed, regeneration of damaged renal tissue is possible by repairing the microenvironment. The effective antifibrotic strategy is still lacking because collagen degradation does not keep pace with collagen production resulting in accumulation of fibrosis which, once established cannot be reversed.

In an already fibrotic kidney the quickest way to go into fibrosis is through a direct antifibrotic action, where high retrograde hydrostatic pressure is applied by blocking urine flow. This will eliminate fibrosis and repair to regenerate damaged tissue in both children and adult ckd patients to get back normal renal function.

References

1. Martínez-Klimova E, Aparicio-Trejo OE, Tapia E, et al. Unilateral Ureteral Obstruction as a Model to Investigate Fibrosis-Attenuating Treatments. *Biomolecules*. 2019; 9: 141.
2. Park HC, Yasuda K, Ratliff B, et al. Postobstructive regeneration of kidney is derailed when surge in renal stem cells during course of unilateral ureteral obstruction is halted. *Am J Physiol Renal Physiol*. 2010; 298: F357-64.
3. Fanni D, Sanna A, Gerosa C, et al. Each niche has an actor: multiple stem cell niches in the preterm kidney. *Ital J Pediatr*. 2015; 41: 78.
4. Fanos V, Gerosa C, Loddo C, et al. State of the Art on Kidney Development: How Nephron Endowment at Birth Can Shape Our Susceptibility to Renal Dysfunction Later in Life. *Am J Perinatol*. 2019; 36(S02): S33-S36.
5. Ucero AC, Benito-Martin A, Izquierdo MC, et al. Unilateral ureteral obstruction: beyond obstruction. *Int Urol Nephrol*. 2014; 46: 765-776.
6. Chevalier, Robert & Forbes, Michael & Thornhill, Barbara. Ureteral obstruction as a model of renal interstitial fibrosis and obstructive nephropathy. *Kidney international*. 2009; 75: 1145-52.
7. Nogueira A, Pires MJ, Oliveira PA. Pathophysiological Mechanisms of Renal Fibrosis: A Review of Animal Models and Therapeutic Strategies. *In Vivo*. 2017; 31: 1-22.
8. Anita L. Cochrane, Michelle M. Kett, Chrishan S. Samuel, et al. Ricardo “Renal Structural and Functional Repair in a Mouse Model of Reversal of Ureteral Obstruction”, *JASN*. 2005; 16: 3623-3630.