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Editorial

Umbilical Vein as Urethral and Ureteral Replacement in Human the Only Reported Cases

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Story with umbilical vein

In the year 1982 while I was senior house officer in Urology at Johannes Gutenberg University in Mainz/Germany, a PhD thesis of my consultant professor K.F. Klippel attracted me. The topic was interesting; animal study on the use of umbilical vein as transplant to ureter and renal pelvis. So, I decided to do PhD after finishing my German Board in urology. This was approved by our Godfather Professor Hohenfellner the president of the German society of urology and the director of our urology clinic and polyclinic in Mainz the top urology center in Europe at that time. I studied the umbilical vein thoroughly for its capacity to deliver stem cells. Stem cells are thought to have great therapeutic and biotechnological potential. This will not only to replace damaged or dysfunctional cells, but also rescue them and/or deliver therapeutic proteins after they have been engineered to do so. Currently, ethical and scientific issues surround both embryonic and fetal stem cells and hinder their widespread implementation. In contrast, stem cells recovered postnatally from the umbilical cord, including the umbilical cord blood cells, amnion/placenta, umbilical cord vein, or umbilical cord matrix cells, are a readily available and inexpensive source of cells that are capable of forming many different cell types (i.e., they are "multipotent") [1-4].

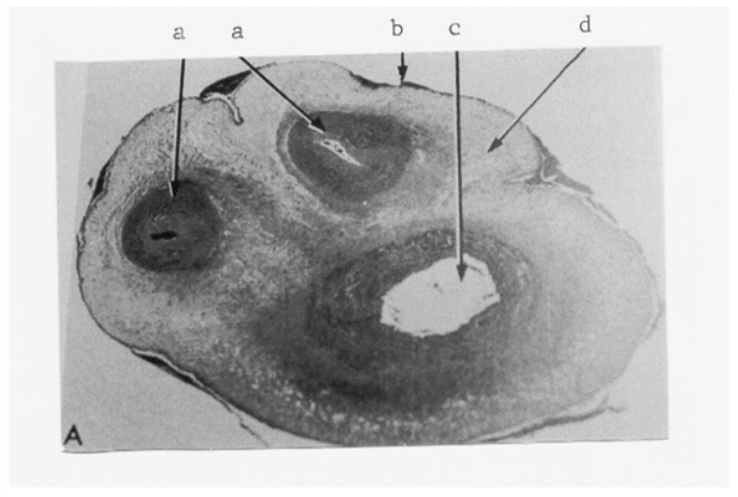

Figure 1: *Microscopic picture of the umbilical cord showing 2 arteries(a) and one vein(c) surrounded by Warton-jelly (d), stem cell manufacturer X4 magnification. Al-Naieb PhD Thesis, 1985.*

The covering of the vein contains Wharton's jelly. Wharton`s jelly-derived mesenchymal stem cells (WJ-MSCs), have a high proliferation valency and they do not produce teratogen or carcinogen after subsequent transplantation. They are known as regenerative multipotent graft. They can replace the damaged urinary tract when the vein and its outer shell are transplanted to human. The umbilical vein present during fetal development that carries oxygenated blood from the placenta into the growing fetus. The umbilical vein provides convenient access to the central circulation of a neonate for restoration of blood volume and for administration of glucose and drugs. The important characteristics to consider it good replacement to urethra and ureter are:

1. Has no vasa vasorum so it is easily to clear all donner antigenic leukocytes.
2. It supplies itself in first 6 weeks by diffusion until the growth of the urothelial mucosa starts and proliferate.so it acts as scaphoid for building layers of ureter and the urethra.
3. Water/urine resistant preventing extravasation of urine and subsequent damage of the implanted graft. Adding to it preventing electrolyte disturbances as with ileal or colonic transplant.
4. Economic [4].

The urethra and ureter

The capacity of the ureter and urethra to heal and regenerate is good when its continuity is maintained even by a narrow strip of ureteral wall. However, because of secondary strictures damage or injuries, the need for urinary diversion, ureteral and urethral replacement, or nephrectomy may confront the urologist. in situations when there is only one functioning kidney or disease in the other. Effective ureteral substitution is the only alternative to permanent nephrostomy or pyelostomy. Ureteral and urethral substitutes may be classified as (1) synthetic prostheses, (2) free grafts and (3) pedicle grafts. The first two are still in the experimental stage, although sporadic reports of success in human subjects have appeared. The degree and nature of the ureteral loss often determine the type of operative repair. In the early 1890s, Van Hook first used a bladder flap to bridge a lower ureteral defect. In cases of injury or disease in the distal third of the ureter, a bladder flap, or more recently, psoas-hitch with ureteroneocystostomy, has proven to be the treatment of choice. Transureteroureterostomy (Figure 2), has also been used successfully in carefully selected cases. Synthetic Prostheses Boari, in 1895, was the first to use a synthetic prosthesis (glass tube) in animals. Various other synthetic materials have been used, but practically all have failed because of anastomotic leaks, stone formation, reflux, hydronephrosis, or migration of the prosthesis. These experiments have included the use of Vitallium, tantalum, polyethylene, dimethylpolysiloxane, silver, Ivalon, polyvinyl, Teflon, Dacron and silicone rubber. Synthetic materials usually interfere with normal peristalsis and thus make poor substitutes for the ureter. Nevertheless, these disappointing results to date. There is promise that newer types of synthetic tubes may be used successfully in the future. Synthetic devices such as stents or templates have been more successful. Studies have shown that even extensive defects heal if the ureteral ends are bridged with a narrow strip of the wall. However, stricture not infrequently occurs in such cases. Regeneration of the circular muscle has been demonstrated, although it is uncertain whether longitudinal muscle regenerates. This phenomenon is the basis of the intubated ureterotomy of Davis. Most of such defects fail to heal unless a portion of Free Grafts Free autologous or homologous grafts have been used to replace portions of the ureter. Hovnanian reported one successful case using bladder mucosal grafts fashioned into a tube over a stent [4,19]. They found regeneration of longitudinal and circular fibers, but because of disruption of normal peristalsis, hydronephrosis developed. The ideal free graft for ureteral replacement has yet to be found. Pedicle Grafts Melnikoff [26] in 1912 and Schein [14] in 1956 used the fallopian tube and appendix on pedicles as substitutes for the ureter. The proximal ureter has been replaced by a flap of renal capsule. The method is useful to correct extensive ureteropelvic obstructions but has not proved applicable for ureteral replacement. Thus, the pedicle grafts that have been most successful in replacing the ureter are the Boari bladder flap and the intestine (ileal ureter). Bladder Flap (Boari-Ockerblad) and Psoas-Hitch the Boari bladder flap [12], is an effective method of replacing the distal ureter when ureteral reimplantation is not feasible. However, recently the psoas-bladder-hitch described by Harrow [4] and others [15,20] has largely replaced the need for the Boari flap in bridging defects of the lower one-third of the ureter. This procedure involves suturing the posterior bladder wall to the psoas muscle after mobilizing the bladder (and particularly the contralateral vascular pedicle). Ureteral reimplantation can then be performed without ten-

sion. If greater length is required, a Boari flap in conjunction with the psoas-hitch may be done. The use of a submucosal tunnel of ureter cystostomy minimizes the likelihood of reflux [22]. Up to 12 cm of bladder tube can be obtained from the normal bladder in this fashion. Transureteroureterostomy In cases in which direct ureteroplasty or the Boari-Ockerblad flap are not feasible for defects in the lower half of the ureter, the trans-uretero-ureteral anastomosis (TUU) is a highly successful surgical option. Ehrlich and Skinner have collected several cases illustrating complications of the procedure, but still endorse the technique as a· practical method of ureteral replacement [27]. The technique of TUU is shown in Figure1. The injured ureter is approached transperineally and freed to a point where it can be anastomosed without tension in an end-to-side fashion to the normal ureter. The ureter is passed over the aorta and vena cava behind the posterior peritoneum. The distal end of the ureter is spatulated and sutured to a linear incision in the normal ureter with interrupted or continuous sutures of fine chromic catgut.

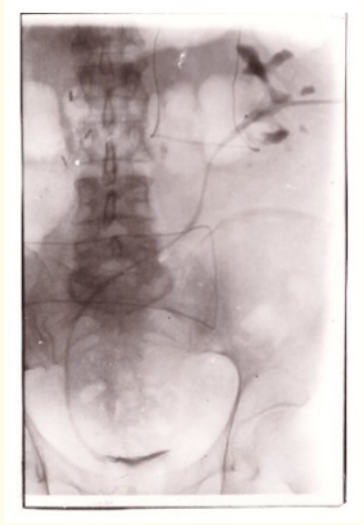

Figure 2: *Transureteroureterostomy with covering the renal pelvic gap with umbilical vein. Al-Naieb, 1983 Celle Germany. PhD thesis.*

The small intestine and the colon used to replace the ureter with good operative success, but the electrolytes disturbances reduce its modality but when no other option available it can be taken as ultimatum. The appendix is used but for a small lower and short segment with good success. But not everybody still having their appendix in place.

The colon beside its electrolytes disturbances we have poor blood supply and fistulae and stricture are most encountered sequelae. bilharzial infestation in endemic countries like Iraq, Iran, Egypt and India render boari flap and reimplantation problematic [4].

Prosthesis is also used experimentally and in few reported cases with very bad results and the same applied to xenogeneic tissue with intense rejection reaction and fistulas. Veins were used to bridge the urethra and ureter, but the main problem is extravasation of urine due to the presence of Vasa Vasorum.

Coming to the urethra transurethral visual urethrotomy is the golden standard in handling urethral stricture but frequent recurrences, very long stricture reduces the success rate significantly.

What we do in such cases is open urethrotomy penile or scrotal approach. also, the use of scrotal flap and skin flaps is not free of complications of ischemia, hair building and recurrent infections.

Good results achieved from the use of buccal mucosa, but very long strictures are problematic plus the discomfort in the mouth [4].

The ideal substitute

The search for Ideal substitute tissue for ureter and urethra depends on the following criteria:

1. Urine resistant.
2. No electrolytes loss.
3. Interference free anastomosis.
4. Enough elasticity.
5. Perfect organ integration.
6. Low antigenicity.
7. not carcinogenic.
8. Availability.
9. Possible peristaltic movement.
10. Economic

For the above-mentioned points, the Umbilical vein fulfill all the criteria for the ideal substitute for the ureter and urethra [4,2,10].

Preparation of the vein for transplantation

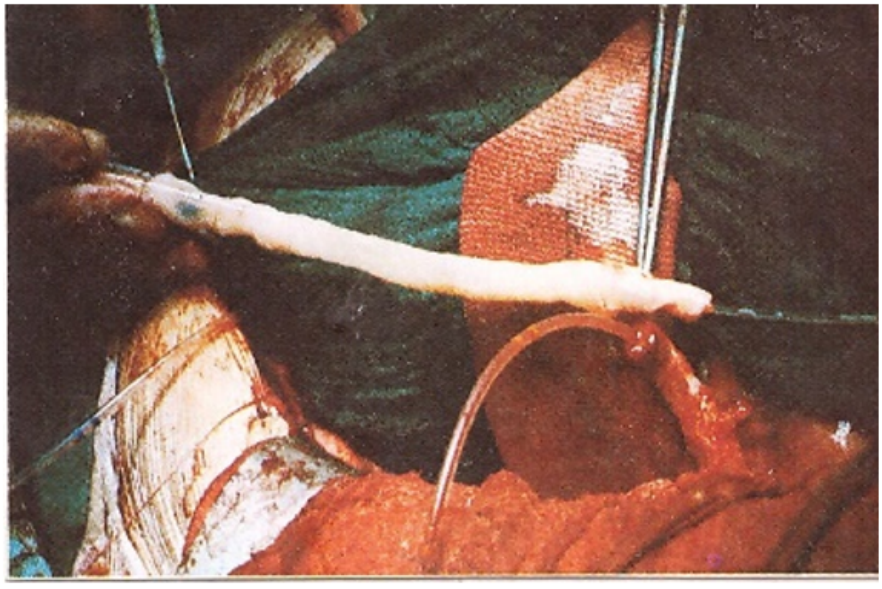

Figure 3

The umbilical cord is delivered fresh from the obstetric department. The cord blood group is ABO compatible with the recipient.

The umbilical veins have no valves, approximately 50 mm long in the umbilical cor and their diameter is about 4 mm. It can tolerate pressure of 300 mmHg. To prepare the vein first it is removed from cord the dissection is carried out carefully to include the Wharton's jelly with the wall. The vein is washed first with Cisplatin cytotoxic 20 mg in 20 ml normal saline for 45 min to kill all donner leukocytes. Next it is put in 160 mg Gentamycin for 30 min. then washed with 0.9%Nacl and it is ready for transplantation [4].

The demand for ideal ureteral and urethral replacement tissue is thus given by the umbilical cord veins. Histological and functional survival in xenogeneic systems could be demonstrated in animal experiments and in our patients selected for the study.

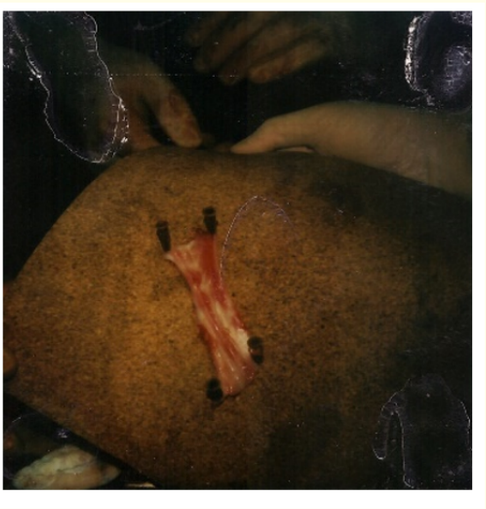

Figure 4

With suitable indications and after all autologous reconstruction tests, the implantation of a blood-group and tissue-compatible human umbilical cord could be discussed as standard ureters and urethral transplantation opportunity [4].

Before we illustrate the advantages of the umbilical vein I would like to mention an interesting point. So many people argued the use of the umbilical vein this issue irritated professor K.F. Klippel and he implanted and Umbilical vein in his upper left thigh for 6 months. After 6 months I removed the tissue which was healthy and not necrotic and well vascularized. No antigenic markers detected that might indicate possibility of rejection [4].

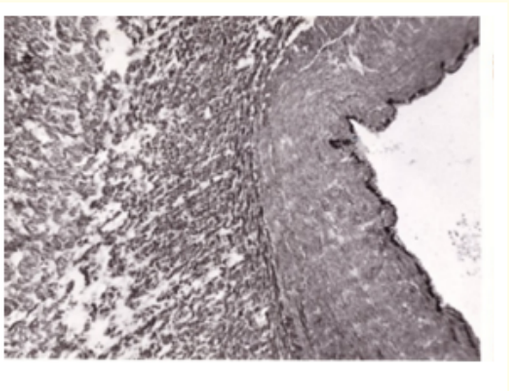

Figure 5

Why the umbilical vein is a good choice and worth further study?

This can be answered simply by the following points: The umbilical vein has very unique criteria that can distinguish it from other veins and arteries in human body.

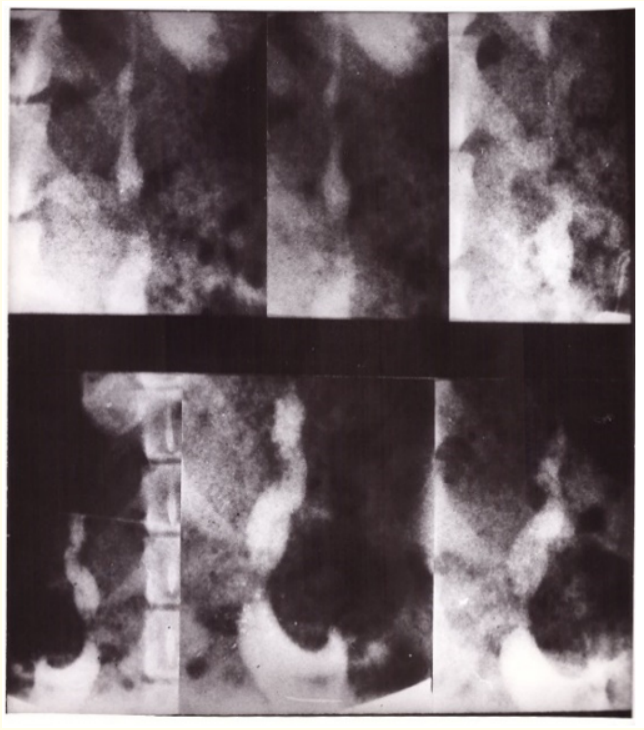

Figure 6: *The intravenous pyelography of the implanted dog. Mild hydronephrosis with elements of peristalsis after.*

These can be summarized in the following points:

1. Has no valves.
2. Very low antigenic reaction.
3. No vasa vasorum the caliber is like the original ureter.
4. Unlimited availability. Very good muscular layer.
5. No possibility of sclerosis.
6. Uniform caliber.
7. Cost free.

In 1979, Klippel and Hohenfellner studied the umbilical vein as replacement to ureter on animals. In 13 dogs the middle one-third of the ureter and in four dogs the entire ureter was replaced by fresh Rhesus monkey or human umbilical cord vein. They demonstrated success rate 60%; one dog revealed an excellent intravenous pyelogram; the typical roentgenographic appearance of the kidney was a slight

hydronephrosis. Animals surviving for more than 1 year were nephrectomies on the contralateral side. One dog is still alive at 36 months. Histologically, they found that the, typical structure of the umbilical vein remained unchanged after 2 years, but endothelium was replaced by urothelium. They concluded that the umbilical vein seems to be an embryonic tissue of extremely low antigenicity and therefore suitable for transplantation [4,11,20].

BASTARDHUNDE ——— HUMANNABELSCHNUR

Nr.	Wochen	Röntgenbefund
4 6 75	1	Pyonephrose
7 75	11	NBKS-Ektasie
8 75	6	o B
9 75	3	Hydronephrose
5 0 75	14	" " " "
1 75	7	Kaliektasie
2 75	7	" " "
3 75	6	kein Röntgen
4 75	3	" " "
5 75	3	" " "
6 75	5	" " "

Figure 7: *Klippel Hohenfellner, 1979, animal study on Dogs and Monkeys.*

Al-Naieb, Klippel studied 25 humans 15 urethral strictures 5 damaged ureter at proximal part and 5 damaged renal pelvises. Among the 15 urethral stricture one of them is 3 years old baby with distal recurrent hypospadius. This baby developed total failure with rejection of the umbilical vein. The upper ureter replacement showed mild dilation of renal pelvis. Patients with mid-ureteral stricture who was on ureterostomy for many years, showed complete recovery and the umbilical vein was incorporated totally with the ureter. The below figure 7, demonstrate the successful flow of urine to the bladder after transplantation of umbilical vein and anastomosing the upper ureter and lower ureter with umbilical vein [4].

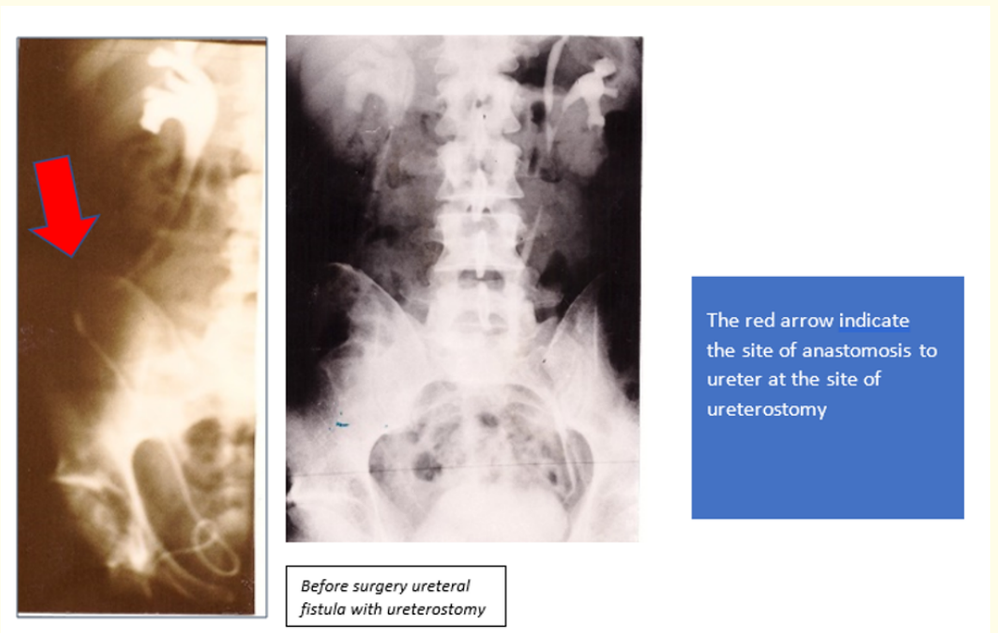

Figure 8

Urethral transplantation

The most fascinating application of the umbilical vein with part of Wharton's jelly cover is the urethra we achieved failure rate of 6.7% only which indicate that the urethra is ideal site for transplantation. I will present 2 cases only the first one is the posterior urethral rupture by Motorcycle accident with rupture of membranous urethra floating bladder and massive extravasation of dye given by urethro-cystography as seen in photo right [4].

Surgery was performed with orthopedic team in Germany. after removing pubic ramus the bladder mobilized down word as much as possible. The gap was bridged with umbilical vein after fixation of bladder to prostatic urethra and distal urethra.

Figure 9

6 months after surgery micturating cystourethrography showed excellent result ad flow. Cystoscopy revealed total incorporation of the umbilical vein with urethra and replacement of mucosa by transitional cell. Biopsy was taken and studied with scanning electron microscope with magnification X20000.

The second case was anterior urethra stricture with recurrent recurrences and multiple optical visual urethrotomy.

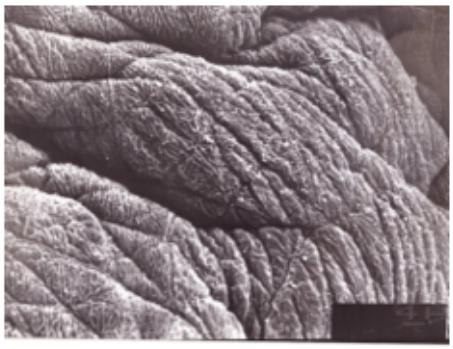

Figure 10: *Scanning electron microscope, SEM photo x20000. New-ureter 15 month after transplantation. No differentiation of the thick epithelium Transitional replaced by transitional epithelium. Al-Naieb, 2019.*

The results after 6 months were highly successful.

The first photo is how the vein with thin layer of the Wharton's Jelly after treatment with CIS platinum and gentamycin treatment delivered to operation field.

Figure 11

The second photo is the X-ray (urethrocystogram), showing multiple anterior urethral strictures.

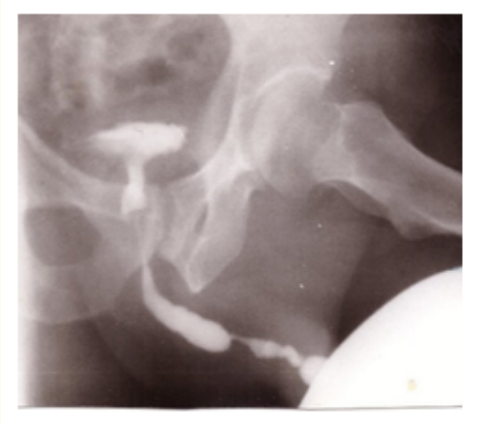

Figure 12

The last one after removing the stricture segment and the gap is replaced by the umbilical vein. 6 months after successful surgery with good flow demonstrated by micturating cystourethrography.

The unfortunate child with recurrent hypospadius and rejection, the results could be attributed to the anastomosis of the umbilical vein tissue to ectoderm. This fact cannot be proved from one surgery and need more intensive studies to detect the only rejection was mucocutaneous junction anastomosis.

No rejection was noticed on mucosal anastomosis in our groups of patients in ureter, urethra away from the meatus and renal pelvis.

The umbilical vein need more histo-immunological studies to consider it as an alternative to other modalities and tissues in replacing the ureter and the urethra.

In conclusion, I would love to say that the umbilical vein is an excellent choice in replacing urethra ureter

And renal pelvis. It can be replaced as tube or as a flap.

Its low antigenicity resistance to water and urine no vasa vasorum, nourish itself by diffusion, handy and economical put it in first line in urological reconstructive surgery [4].

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