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Voiding cystourethrography in the renal pre-transplantation workup: an essential investigation?

By Zelia Sofianos

Registrar enrolled in the degree FC Rad Diag (SA) MMed,

Student number 344951

In the faculty of Health Sciences,

The University of Witwatersrand, Department of Radiology,

Johannesburg, South Africa.

In the fulfilment of the requirements for the degree of Master of Medicine in the Clinical Disciplines.

Supervised by

Dr Leisha Rajkumar

MBChB (UCT), FC Rad (Diag) SA, MMed (RadD)(Wits)

Consultant in Radiology, Helen Joseph Hospital, Johannesburg, South Africa.

Email: leishar@gmail.com

Dr Susan Lucas

MBChB (Pret), FC Rad (Diag) SA, MMed (RadD)(Wits)

Consultant in Radiology, Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa.

Email: sulucas.radiology@gmail.com

Declaration by candidate:

I hereby declare that this research paper is my own original work and has not been submitted before to any other institution for assessment purposes.

I have acknowledged all sources and cited these in the reference section.

There are no conflicts of interest in creating this research paper.

This paper was prepared in a "submissible" format in line with the guidelines of the South African Journal of Radiology.

Signed on this day 18th of October 2022,



Dr Zelia Sofianos

Declaration by Supervisors:

The following people contributed as supervisors to the work undertaken by the candidate, Zelia Sofianos, 344951, as part of their research paper entitled "**Voiding cystourethrography in the renal pre-transplantation workup: a necessary investigation?**" in fulfilment of the requirements for the degree of FC Rad Diag (SA) MMed.

Details of Candidate and Supervisors (including percentage contributions):

- Candidate: Zelia Sofianos (60%)
- Supervisor 1: Leisha Rajkumar (20%)
- Supervisor 2: Susan Lucas (20%) etc

Contribution of work by supervisors and candidate for the above-mentioned research paper:

- The research paper is the original work of the candidate, Zelia Sofianos, who drafted the protocol and final research paper for this study.
- Supervisors reviewed draft manuscripts of the protocol and the final research paper and provided guidance regarding research methodology, improvements to content, general conduct, and conceptual ideas.
- This proposal and the research paper were submitted to Turnitin concerning plagiarism. The plagiarism certificates were checked and are satisfactory.

Signed on this day 18th of October 2022,

Dr L Rajkumar

Dr S Lucas

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To my friend and colleague Dr Sheree Gray for always being in my corner and being an amazing source of support.

Dedication

To Megan, who has been by my side from the beginning.

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These guidelines are taken from the South African Journal of Radiology (SAJR) (1)

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Acknowledgements

The acknowledgement section follows the conclusions section and addresses formal, required statements of gratitude, and required disclosures. It includes listing those who contributed to the work but did not meet authorship criteria, with the corresponding description of the contribution. Acknowledge anyone who provided intellectual assistance, technical help (including with writing and editing), or special equipment and/or materials. Authors are responsible for ensuring that anyone named in the Acknowledgements agrees to be named.

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• Author contributions

• Funding information

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Competing interests

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Voiding cystourethrography in the renal pre-transplantation workup: a necessary investigation?

Abstract

INTRODUCTION: Due to resource constraints in the South African public healthcare sector, patients with End-Stage Renal Disease (ESRD) are eligible for renal replacement therapy only if they are also found to be eligible for renal transplant.

AIM: The aim of this study is to document Voiding Cystourethrogram (VCUG) findings in potential renal transplant candidates to assess the contribution of the VCUG as a standard investigation in the renal transplant workup.

METHODS: Of the patients who underwent VCUG in Klerksdorp/Tshepong Hospital Complex (North West province, South Africa) from 1 January 2019 to 31 March 2020, 85 patients were included in the study and their VCUG findings retrospectively analysed.

RESULTS: The mean age was 40.0 years (range 21-62 years), with males constituting 57.7% of patients and females 42.3%. Lower urinary tract abnormalities were identified in 24.7% of patients, some of whom had more than one abnormality. Of the total abnormalities, VUR (vesicoureteral reflux) accounted for 15.3%, bladder diverticula for 5.9%, urethral strictures for 3.5% and a significant post-void residual volume for 4.7%. No comorbidities were found to have a statistically significant association with the presence of VCUG abnormalities.

CONCLUSIONS: To ensure that patients with End-Stage Renal Disease are adequately prepared for renal dialysis and potential renal transplant, and that their comorbidities and lower urinary tract are optimised should abnormalities be identified on VCUG, the VCUG remains an essential investigation in the renal transplant workup.

Introduction

Epidemiology of CKD in South Africa

Despite the growing number of people afflicted by CKD and ESRD in South Africa, access to renal replacement therapy (RRT) remains at levels similar to or even less than those in 1994 (2, 3). Based on the data supplied by the South African Renal Registry 2017 Report, the treatment rate in the public sector is only 66 per million population (pmp) (2). According to the Organ Donor Foundation of South Africa, there were only 234 adult kidney transplants in 2016, while there were 10744 patients on RRT in 2017 (2, 4).

This lack of access is due to resource constraints and the lack of infrastructure (5). The South African Guidelines for Chronic Renal Dialysis state that, in order to ration the provision of health resources in the public sector, a patient must be eligible for transplant before addition to the chronic dialysis programme (6). Determination of eligibility for RRT and transplant depends on the results of several investigations and the absence of exclusion criteria– these will be detailed below.

Exclusion criteria for potential renal transplant candidates

The national guidelines for chronic dialysis were devised in 2009 and list the exclusion criteria (6):

1. "Medical" exclusion criteria
    a. Active, uncontrollable malignancy or with short life expectancy
    b. Advanced, irreversible progressive disease of vital organs such as:
        i. cardiac, cerebrovascular or vascular disease
        ii. advanced cirrhosis and liver disease
        iii. medically or surgically irreversible coronary artery disease
        iv. lung disease
        v. unresponsive infections e.g, HPV, Hepatitis B and C
    c. HIV and AIDS are not medical exclusion criteria provided the patient has access to a comprehensive AIDS treatment plan including antiretroviral treatment, has been stable for at least six months on HAART and the above exclusion factors are absent. Furthermore, the CD4 count should be >200cells/mcl, the viral load undetectable, and there should be no current opportunistic infections or the history of prior HIV-related conditions e.g. progressive multifocal leukoencephalopathy, EBV or HHV-8-associated lymphoproliferative disorders.

    d. Age (provided above exclusion factors are absent) is not a contraindication for chronic renal dialysis. In the UK the median age of starting renal replacement therapy is 63 years and the median age of the population is 54 years.
2. Psychological Exclusion Criteria
    a. Any form of mental illness that has resulted in diminished capacity for patients to take responsibility to their actions.
    b. Active substance abuse or dependency including tobacco use.
    c. Obesity
3. Compliance
    a. Patients with proven habitual non-compliance with dialysis treatment and lifestyle modification will be excluded or removed from chronic renal dialysis programme" (7, 8)

Investigations required before dialysis/transplant

Transplant workup is not a linear process, and bookings for the various investigations are often done simultaneously in the interests of expediting patient workup. If at any point a comorbidity/result is identified which would preclude the patient from dialysis (and therefore transplant) further investigations can be cancelled. Frequently, however, a patient will undergo several investigations before returning to their managing clinician for assessment of the results, and a preclusive factor will only be identified at this stage.

The investigations required by the renal unit at Klerksdorp/Tshepong Hospital Complex are based on the guidelines used at the Dumisani Mzamane Institute of Kidney Diseases at Chris Hani Baragwanath Academic Hospital, and these are based on the guidelines provided by the South African Department of Health (as listed above) (6). The required medical investigations are:

1. Electrocardiogram, echocardiogram and carotid doppler (to exclude advanced, irreversible progressive disease of the cardiac, cerebrovascular and vascular systems; to detect medically or surgically irreversible coronary artery disease),
2. VCUG (to detect potentially correctable and irreversible lower urinary tract abnormalities),
3. Abdominal ultrasound (to detect active, uncontrolled malignancy, and to image the upper urinary tract),
4. Pap smear (also for the detection of malignancy),
5. G-scope (to assess for the presence of Helicobacter pylori and ulceration and/or gastritis,

as these would need to be addressed prior to starting immunosuppressive therapy and steroids),

6. Dental check-up (good dental hygiene is a necessity prior to starting immunosuppressive therapy to ameliorate the potential of dental infection),
7. Blood tests: HIV ELISA (including CD4 and viral load), hepatitis B and C, Cytomegalovirus, Syphilis, blood group and HLA typing. It is important to screen for infection in the recipient to ensure that effective treatment can be given prior to transplantation (9). Screening for latent infections like syphilis allows prompt treatment before transplantation, as the use of immunosuppressive treatments post-transplant may lead to reactivation of the latent virus, and preventable morbidity and mortality (9).

The guideline checklist used at Klerksdorp/Tshepong Hospital Complex is included in Figure 1 below.

K/T HOSPITAL COMPLEX DEP OF INTERNAL MEDICINE DIVISION OF NEPHROLOGY

Transplant workup sheet **KH 856**

PT information	Hospital number	Date of start transplant w up

Diagnosis	
Cause of R. Failure	

WORKUP	BOOKED DATE	RESULTS	COMMENT
ECG			
ECHO			
VCU			
Abd U/S			
Pap smear			
G scope			
Dental check up			
Carotid Doppler			
Others			

Blood Test

Test	date	date	date	date	date
HIV					
CD4/VL	/	/	/	/	/
HBV					
HCV					
CMV					
VDR/PRP					
Blood group& HLA					

Final assessment

Pt eligible	comment	Date and DR signature
YES		
NO		

Figure 1. Klerksdorp/Tshepong Hospital Transplant Workup Sheet

While the presence of HIV itself is not an absolute contraindication for the provision of renal replacement therapy or renal transplantation, the infection should be well-controlled and the

patient compliant on anti-retroviral therapy (ART). The CD4 count and viral load are used as markers of compliance and disease control. The CD4 count must be greater than 200cells/mm^3 while the viral load must be lower than the detectable limit for the patient to be accepted for RRT and potential renal transplant. Should the CD4 count be lower than this limit (and/or the viral load detectable), the prospective RRT recipient will be required to be compliant on ART for 6 months at which point the CD4 count and viral load are re-tested.

Urological evaluation in the renal pre-transplantation workup

A VCUG is a dynamic study that images the bladder and urethra during filling of the bladder and during voiding, assessing both the maximum capacity of the bladder and the volume of urine which remains after voiding. Images of the ureters and kidneys might also be obtained in the presence of VUR. In order to increase the chance of survival of the renal allograft post transplantation, pre-transplantation identification of genitourinary abnormalities is essential (10-12).

The abnormal findings which would exclude a patient from RRT include bladder capacity <200mL or >600mL, residual urine volume of >50mL, any urethral abnormalities and VUR of Grade IV or higher (13). Should these abnormalities be correctable, referral to the urology team is recommended and surgical correction may be undertaken before the patient is referred back to the renal unit for repeat VCUG.

The purpose of the VCUG is to image the lower urinary tract (bladder and urethra) and the upper urinary tract (ureters and kidneys) in the presence of VUR; these images are obtained during both filling and emptying of the urinary bladder. A normal bladder can store urine at a low pressure, is of adequate capacity, is sterile and empties to leave a small residual volume of urine. It is important that such an environment is present prior to renal transplant (14).

Methods

Study Design

This was a retrospective cross-sectional study entailing a record review of VCUG results. The data was collected from the Radiology and Renal Departments of Klerksdorp/Tshepong Hospital Complex in the North West Province, South Africa. A total of 109 VCUGs done in individuals aged 18-65 for the purpose of renal transplant workup were identified from 1 January 2019 to 31 March 2020, and their VCUG reports were analysed. Patients who were excluded from the study were those whose data was incomplete or whose VCUG was not completed for any reason. Of the 109 patients identified, 4 were excluded because of inability to perform the VCUG secondary to unsuccessful catheterisation. A further 20 were excluded due to incomplete data with regards to the presence of comorbidities.

Data Analysis

The clinical data captured included patient age and gender, comorbid conditions, whether the patient was already receiving RRT at the time of VCUG, and presence of lower urinary tract abnormalities. VCUG data comprised VUR, urethral or bladder outlet obstruction, bladder diverticula and small bladder capacity/significant residual volume.

The data extracted from the reports was appraised using the statistical software SPSS (SPSS Inc., Chicago, Ill) for Mac. Findings were expressed as percentages and frequencies, and a standard 95% confidence interval was used. Pearson's chi-squared (X^2) test was used to test for significant relationships between the presence of comorbidities and abnormal findings in the VCUG.

Ethics

Unconditional ethics approval for this study was granted by the Wits Human Research Ethics Council (HREC). Ethics clearance certificate number: M200607 (Appendix A).

Results

Study Population

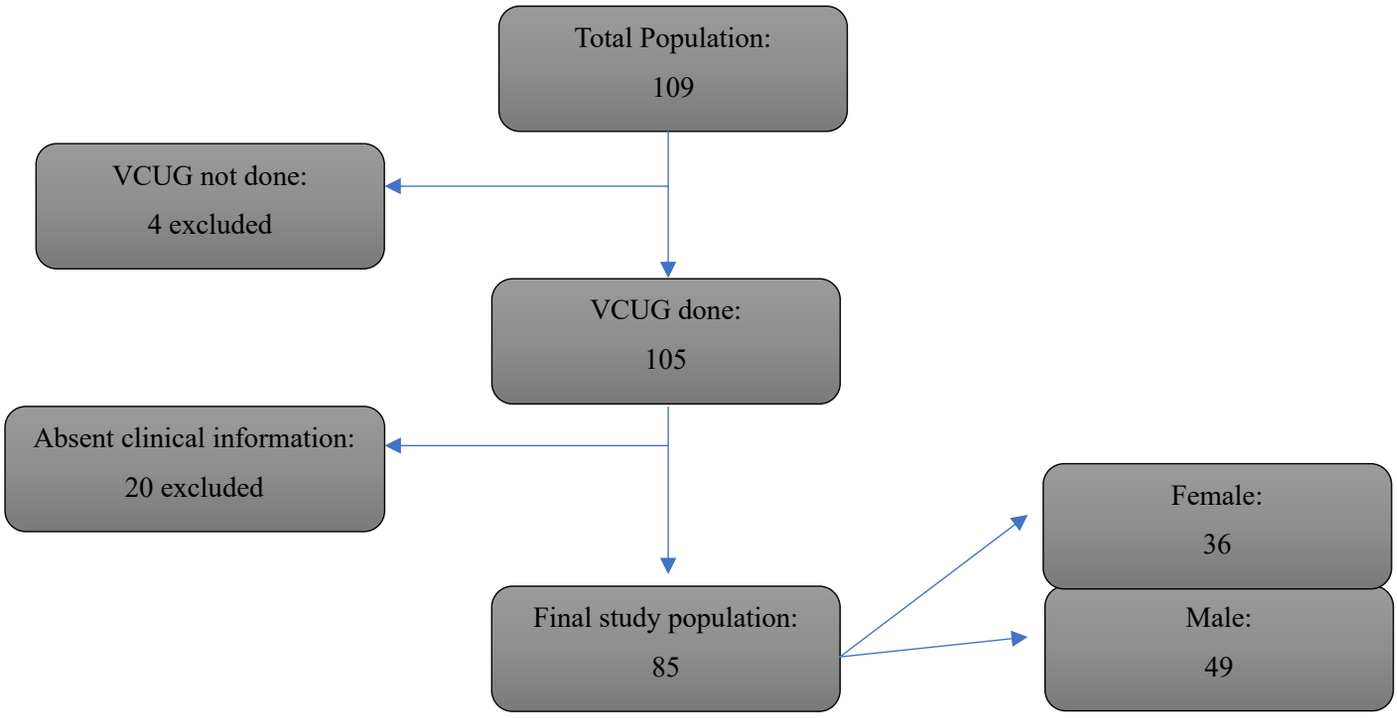


Figure 2. Flow diagram of the constitution of final study population

A total of 85 patients who underwent VCUG in the process of renal pre-transplantation workup were included in this study. The mean age was 39.8 years (range 21-62 years), with males constituting 57.7% of patients and females the other 42.3%.

Comorbidities

The majority of patients had at least one comorbidity, as shown in table 1. Only 1.2% (1 of 85) had no identifiable pre-existing comorbidity.

Table 1. Presence of comorbidities in study population

COMORBIDITY	NUMBER OF PATIENTS (N = 85) N (%)
HYPERTENSION	73 (85.9%)
DIABETES MELLITUS	5 (5.9%)
URINARY TRACT OBSTRUCTION	5 (5.9%)
HIV	24 (32.9%)
OTHER	10 (11.8%)

Note: percentages don't add up to 100%, as some patients had more than one comorbidity.

Table 1 lists the presence of comorbidities in the study population. Hypertension was the most common comorbidity, present in 85.9% (73 of 85) of patients. Urinary tract obstruction (including both upper and lower urinary tracts) had been identified prior to the VCUG in 5 patients: two had a urethral stricture which was detected clinically, and had a suprapubic catheter inserted, one had acute urinary retention, while another two were found to have UPJ (ureteropelvic junction) obstruction complicated by hydronephrosis. Of the 85 patients included in the study, the HIV status was available and known in 73. Of these, 67.1% (49 of 85) had a negative result and 32.9% (24 of 85) had a positive result. In those patients identified as HIV positive, four had biopsy-proven HIVAN (HIV-associated Nephropathy) and one biopsy-proven HIVICK (HIV-associated Immune Complex Kidney Disease). The presence of HIV was not found to have a statistically significant association to the presence of abnormalities detected on VCUG (p=0.268).

Identified comorbidities not including hypertension, diabetes mellitus and obstruction (upper or lower urinary tract) were grouped together in the "Other" category, as demonstrated in Table 2.

Table 2. Identified comorbidities classified as "Other"

COMORBIDITY	NUMBER OF PATIENTS (N = 85) N (%)
GLOMERULONEPHRITIS	2 (2.4%)
HYPOTHYROIDISM	2 (2.4%)
LUPUS NEPHRITIS	2 (2.4%)
EPILEPSY	2 (2.4%)
TUBEROUS SCLEROSIS, BILATERAL NEPHRECTOMY	1 (1.2%)
POLYCYSTIC KIDNEY DISEASE	1 (1.2%)

VCUG findings

Lower urinary tract abnormalities were identified in 24.7% (21 of 85) of patients. Of these abnormalities, VUR accounted for 15.3% (grading as per the International Reflux Study Committee Scale (15)): 5.9% of patients (5 of 85) had unilateral low-grade reflux (grades 1-2), 3.5% had bilateral low-grade reflux, 4.7% had moderate-grade unilateral reflux (grade 3), and 1 patient had bilateral moderate-grade reflux (1.2%). High-grade (grades 4-5) reflux was not documented in any of the patients. Further abnormalities detected were bladder diverticula in 5.9% (5 of 85), urethral strictures in 3.5% (3 of 85) and a significant post-void residual volume in 4.7% (4 of 85), as shown in Table 3. Post-void residual volume ranged from 60ml to 150ml.

Table 3. VCUG findings

FINDING	NUMBER OF PATIENTS (N = 85) N (%)
NO ABNORMALITY	36 (42.4%)
SMALL BLADDER VOLUME	28 (32.9%)
BLADDER DIVERTICULA	5 (5.9%)
VESICOURETERAL REFLUX	13 (15.3%)
URETHRAL STRICTURE/BLADDER OUTLET OBSTRUCTION	3 (3.5%)
SIGNIFICANT RESIDUAL VOLUME	4 (4.7%)

Note: percentages do not add up to 100%, as some patients had more than one abnormality.

Of note is that bladder volume is closely related to dialysis status. Of the 85 included participants, there were 28 with a small bladder volume (irrespective of the presence of other

accompanying VCUG abnormalities). Of these 28 patients, 92.9% (26) were already on dialysis at the time of VCUG. There is thus a strong correlation between being on dialysis and having a small bladder volume (p=0.000236). The longer a patient has been on dialysis, the smaller the bladder capacity (16).

There was no statistically significant association between the presence of hypertension, diabetes mellitus, or "other" comorbidities (as demonstrated in Table 4) and the presence of abnormalities on the VCUG. The odds ratio of having a VCUG-detected abnormality in the presence of hypertension (p=0.397), diabetes mellitus (p=0.801) or "other" comorbidities (p=0.337) was not found to be statistically significant.

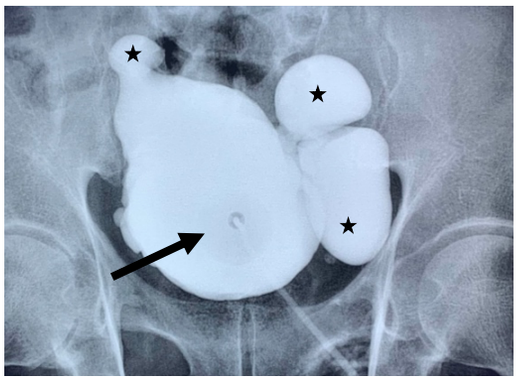
A prior history of upper or lower urinary tract obstruction did not have a statistically significant association with the presence of abnormal findings on VCUG. The odds ratio of having a VCUG-detected abnormality in the setting of a history of urinary tract obstruction is not statistically significant (p=0.059). The above findings are reflected in Table 4.

Table 4. Correlation between comorbidity and abnormality

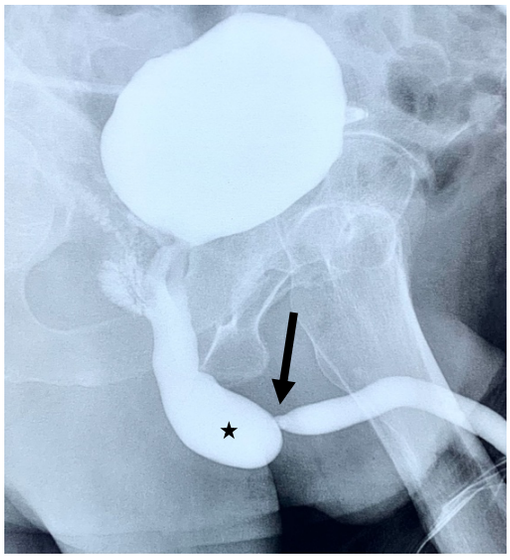
	NO ABNORMALITY	VUR	SIGNIFICANT RESIDUAL	DIVERTICULA/ STRICTURES
HYPERTENSION	53	11	4	6
DIABETES MELLITUS	4	0	1	0
URINARY TRACT OBSTRUCTION	2	1	0	2
OTHER	7	3	0	0

NOTE: Some patients had more than one abnormality on VCUG.

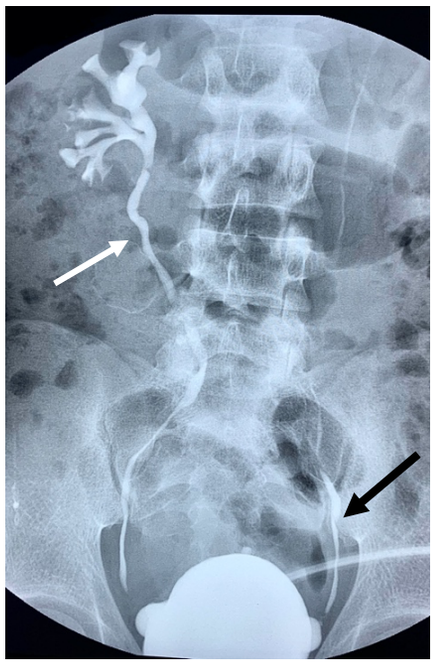
Typical VCUG abnormalities are shown in the fluoroscopic images below in Figure 3.



a. Multiple large urinary bladder diverticula *(stars)* secondary to urethral stricture. Suprapubic catheter in situ *(black arrow)*.



b. Dilatation of the posterior urethra *(star)* due to stricture at the junction of the bulbar and penile urethra *(black arrow).*



c. Bilateral vesicoureteral reflux: Grade 2 VUR on the right *(white arrow)* and Grade 1 VUR on the left *(filled black arrow).*

Figure 3. Examples of abnormal VCUG findings during renal transplantation workup

Discussion

History of abnormalities

The detection of abnormalities is important in the pre-transplantation period and their presence can sometimes be ascertained through thorough history-taking. In the setting of a patient with anuria/oliguria and a defunctionalised bladder due to long-term renal dialysis, however, symptoms of lower urinary tract dysfunction may be obscured and investigation becomes necessary (17).

The studies by Yang et al. and Shandera et al. recommended that VCUG be done in all patients with a history of diabetes mellitus due to the possible presence of a neurogenic bladder (13, 18). In the present study, the odds ratio of having an abnormality on VCUG in the presence of diabetes mellitus was not statistically significant (p=0.801). Similarly, the odds ratio of abnormalities in the presence of hypertension and "other" comorbidities was p=0.397 and p=0.337, respectively.

As per the South African guidelines for chronic renal dialysis, patients should be eligible for transplantation – and must therefore have undergone all the necessary work-up, including the VCUG – before being started on renal dialysis. The finding that 65.9% of the current study participants were already on dialysis at the time of VCUG is not in keeping with national guidelines.

A history of urinary tract obstruction had no statistically significant correlation with VCUG-detected abnormality (p=0.059). There were 5 patients who were identified as having either upper or lower urinary tract obstruction before undergoing VCUG: two had UPJ obstruction, two had a urethral stricture, and one had acute urinary retention. Of these, only three had abnormalities detected on VCUG: one had VUR, and two had a combination of bladder diverticula and urethral stricture. There was one patient who did not have a history of bladder outlet obstruction before undergoing VCUG, but a urethral stricture was identified during the imaging investigation.

The presence of HIV was not found to have a statistically significant association to the presence of abnormalities detected on VCUG (p=0.276). HIV is an important comorbidity to include in a country such as South Africa, where the 2021 mid-year population estimates showed a 13.7% HIV prevalence in the general population (19). Naicker et al. found that CKD occurs in 3.5 –

48.5% of HIV positive individuals, as a result of several factors including the HIV infection itself and its treatment (20). Of the individuals included in the study, five had documented HIVAN or HIVICK; none of these five patients had abnormalities detected on VCUG. 20.8% of the HIV positive individuals identified had documented, biopsy-proven renal involvement by the HIV infection.

VCUG Findings

The most common abnormality detected in the current study was VUR (15.3%) – of these, 9.4% represented low-grade (grade 1-2) reflux, either unilateral or bilateral, and the remaining 5.9% represented grade 3 reflux (unilateral or bilateral). Several studies have showed that pre-transplant VUR (grade 3 or higher) into the native kidney increases the risk of post-transplant urinary tract infection (UTI), and that the majority of post-transplant UTIs occurred in patients with persistent VUR (21-23). Other studies, however, showed no statistically significant correlation between the presence of VUR and the development of post-transplantation UTI (15, 24-26).

UTI is the commonest post-transplant infection, with up to 75.1% of patients developing UTI and 18.7% developing acute pyelonephritis post-transplantation (27). The majority of UTIs (74%) developed in the first year post-transplantation (28). If these percentages are applied to the current study, it would be expected that approximately 63 of the 85 patients would develop a UTI after receiving a transplant, while only 21 patients had an abnormality detected on VCUG – at least 42 of the patients who develop a post-transplant UTI will have had no abnormality at all.

The detection of a small bladder in patients on RRT is not necessarily a preclusive factor for renal transplantation, and may reflect a defunctionalised bladder which will likely return to normal post-transplantation (29, 30). The longer the duration of dialysis, the smaller the bladder capacity (16, 31). In our study, 92.9% of the patients who had a small bladder capacity were on dialysis at the time of the VCUG; there was a significant association between being on dialysis and having a small bladder volume ($p=0.000236$).

There is some controversy regarding the risk of post-transplant urinary complications in those with atrophic bladders when compared to those with normal bladder volume before transplantation. Chun, *et al* compared patients with pre-transplant bladder capacity of <100mL and those with a capacity of >100mL and assessed clinical outcomes post renal transplant. The

study found no difference between the two groups with regards to surgical complications, the development of UTI requiring admission, serum creatinine levels or graft survival at 5 years (32).

A larger study done by Hotta, *et al* demonstrated that those with a small bladder volume (defined in the study as <50mL) had an increased risk of developing post-transplant urinary complications compared to those with a normal bladder capacity. The urinary complications studied included VUR, leakage and development of urethral stricture (33).

In our study, 4.7% of patients (4 of 85) had a significant post-void residual volume ranging between 60-150mL. Of these 4 patients, none had an obstructive cause of ESRD. 3 patients (3.5%) were found to have bladder outlet obstruction on VCUG. Any cause of bladder outlet obstruction (e.g. benign prostatic hypertrophy) has the potential of increasing the risk of developing post-transplant urinary tract complications, including progressive worsening of renal allograft function (34, 35). In our setting, the presence of bladder outlet obstruction (either on history or as an abnormal finding during VCUG or ultrasound investigation) necessitated referral to urology for intervention before the patients would be considered for dialysis or transplant.

Pre-transplantation interventions in an abnormal lower urinary tract

Evaluation of the lower urinary tract through urodynamic studies (including VCUG) allows for the identification of abnormalities which are potentially correctable in order to optimise renal transplant graft survival and minimise post-transplant complications (36). Surgical intervention may need to be undertaken before they can be considered eligible for renal transplant (37), or planned for during or after renal transplantation (38).

VUR is defined as retrograde flow of urine from the bladder into the ureter due to dysfunction of the vesicoureteric junction (39), with different grades of severity according to the International Reflux Study Committee (40). VUR, an atrophic bladder (33), bladder with poor compliance, an overactive detrusor muscle (37), and bladder outlet obstruction in the form of prostatic enlargement or urethral strictures (41) may increase the risk of developing UTI post-transplant (36).

The detection of VUR necessitates the exclusion of a causative factor such as bladder obstruction or non-compliant urinary bladder, as these patients would benefit from bladder

augmentation prior to transplant (36). Additionally, the presence of prostatomegaly in men may have a deleterious effect on the function of the renal allograft post renal transplantation, and independently increases the risk of post-transplant acute urinary retention, UTI, and graft loss (42). However, transurethral resection of the prostate (TURP) need not be done prior to the transplant, but can be planned for the post-transplantation period (43).

The detection of a small bladder in patients on RRT is not necessarily a preclusive factor for renal transplantation, and may reflect a defunctionalised bladder which will likely return to normal post-transplantation (29, 30). In fact, the longer the duration of dialysis, the smaller the bladder capacity (16, 31). Another potential complication in the presence of a small bladder is the technical difficulty faced by the surgeons when they need to implant the donor ureter into the bladder (32), as well as the significant association between a small bladder capacity and VUR (31). It was demonstrated in the study by Chun *et al*, however, that the success rate for ureteroneocystostomy was not affected by the presence of a pre-operative small bladder, that increasing the capacity of the urinary bladder pre-transplant is not necessary, and that there was no significant negative impact on graft survival post transplantation into a small bladder (32).

The presence of a non-compliant bladder with high intravesical pressure could pose a danger to the renal allograft, by predisposing to VUR. A detrusor leak point pressure (DLPP) of >40cmH_2O or bladder compliance of <9ml/cmH_2O were found to be risk factors for renal allograft damage through dilation of the upper urinary tract (44).

In the study done by Sullivan *et al* renal allograft failure post transplantation was shown to be secondary to biopsy-confirmed rejection (in the majority) and, in those where there was no evidence of rejection, the cause was found to be inadequate bladder emptying – demonstrated as a significant post-void residual volume – or bladders which generate high pressures, and frequent urinary tract infections (UTIs) (29).

In cases where conservative treatment of small, high pressure bladders fails, augmentation cystoplasty may be necessary (37). Augmentation cystoplasty aims to create a urinary reservoir of low pressure and high volume (45). As with any surgical procedure there may be post-operative complications, including stomal incontinence and stenosis, and the need for life-long intermittent catheterisation (37, 45).

The effect that VUR has on graft function has been a topic of much study, with differences seen when there is reflux into the native kidneys versus the transplanted kidney. VUR into the native kidneys was found to significantly increase the risk of recurrent UTI (21). VUR into the transplanted kidney was also found to increase the risk of pyelonephritis and renal scarring (37).

Erturk *et al* showed that there was a lower incidence of UTI in patients who underwent ureteral reimplantation prior to renal transplantation in the treatment of VUR, but that there was no statistically significant difference in the incidence of UTI in patients who underwent bilateral nephrectomy versus those with persistent reflux pre-transplantation (23). In this study, pre-transplantation endoscopic correction of VUR was favoured rather than nephrectomy, which would be indicated in patients with persistent hypertension post-transplant (23, 46).

Pre-transplant VUR (grade 3 or higher) into the native kidney has been shown to increase the risk of post-transplant UTI (21, 22). Bouchot *et al* demonstrated no difference in the incidence of post-transplant UTI in patients with grades 1-2 reflux when compared to those with either treated VUR or no VUR into the native kidney; however, the presence of higher grade reflux (grades 3-4) was shown to increase both the incidence and severity of post-transplantation UTI episodes and that this would need to be addressed prior to transplantation (22).

In contrast, several studies have demonstrated that, in the long-term, there was no statistically significant difference in graft survival rates and UTI incidence between patients with post-transplant VUR when compared to those without VUR (24-26, 47). Jung et al. showed in their short-term study that even grades 3 and 4 of VUR were not significantly associated with an increased risk of graft failure or UTI, and that observation rather than early surgical intervention was preferable (48).

Studies by both Chuang *et al* and Erturk *et al* demonstrated an increased risk for the development of post-transplantation UTI in patients with VUR pre-transplant (21, 23). Yaziki *et al* also showed that the presence of VUR increased the risk of UTI, but that there was neither graft nor patient loss secondary to UTI during the course of the study period (49).

In contrast, in a more recent study by Olenski *et al* – published in 2019 – pre-transplant risk factors for the development of post-transplant UTI included only female gender and age, and no statistically significant increased risk was found in the presence of a pre-existing history of

UTI or urogenital abnormality (50). Other articles list further risk factors for the development of UTI including female gender, advanced age, haemodialysis for long duration, immunosuppression and cadaveric donor, among others (21, 28).

Crowe *et al* demonstrated that patients with a normal bladder function, whether or not there was VUR, had a post-transplant survival rate of 100% at 1 year and 93% at 5 years (14). The study by Adams *et al* showed slightly lower, but still significant, 5-year post-transplant survival rates in patients with VUR (78.5% survival rate) (51).

Numerous studies have demonstrated that VUR, an atrophic bladder, bladder with poor compliance, an overactive detrusor muscle, and bladder outlet obstruction in the form of prostatic enlargement or urethral strictures may increase the risk of developing UTI post-transplant (33, 36, 37, 41). The presence of UTI itself may increase the risk of morbidity and mortality independent of graft function (21, 28). UTI symptoms are often not clinically apparent in patients who have received a renal allograft as they take immunosuppressive treatment post-transplantation, and there is ureteral and renal denervation in the allograft.

The use of routine perioperative antibiotics post-transplantation is also a much-debated topic. While the study by Crowe *et al* showed the use of prophylactic antibiotics for the first six months post operatively, a more recent study opposes this due to the possibility of the development of antimicrobial-resistant strains of bacteria (14, 52).

VCUG – necessary or not

The VCUG is a type of fluoroscopic investigation which is used to image the various components of the lower urinary tract: in a normal system, the urethra and the urinary bladder will be imaged; in a refluxing system, the ureters and kidneys can also be imaged. It involves the transurethral or suprapubic catheterisation of the patient, and the instillation of a radiological contrast medium into the urinary bladder (53, 54). The VCUG demonstrates the anatomy of the lower urinary tract, can detect the presence of VUR, posterior urethral valves (PUV) and urethral strictures, and can also assess the post-micturition residual bladder volume (36, 54).

The need for VCUG in all potential renal transplant recipients has been a topic of much debate, with some authors saying that VCUG should be performed on all pre-transplant patients (55), and other authors saying that only those patients with features of lower urinary tract dysfunction should undergo VCUG (10, 11, 18, 56-58). The VCUG can detect the presence of VUR, PUV

and urethral strictures, and can assess the post-void residual urine (36).

A study published in the journal Transplantation in 1996 showed that, of the 13 patients who had abnormal VCUG findings during the renal pre-transplantation workup, all of them had a prior history of urological abnormality (57) . The prospective study by Yang, *et al* (59) claimed that, if VCUG was not conducted in patients without diabetes mellitus or urological symptoms (or a history thereof), costs in the renal pre-transplantation workup could be reduced significantly without increasing the risk of missing significant abnormalities, as no VCUG abnormalities were detected in patients who were non-diabetic or had no prior history of UTI or voiding symptoms (13).

Studies conducted in the USA and Europe show the detection of lower urinary tract abnormalities when VCUG is done on all patients with ESRD is 2.5–15%, while this percentage increases to 45% when patients with a history of lower urinary tract abnormality are specifically selected (57, 60). Modi showed that the yield of abnormalities detected on VCUG is too low for it to be used as a routine investigation, and that the incidence of having a urinary tract abnormality in the absence of a suggestive history is low; only 5% of the adult population with ESRD has urologic abnormalities (61).

On the other hand, the study by Sarier *et al* showed abnormalities in 19.2% of patients, and this was taken to be significant enough to require routine VCUG in all patients with ESRD regardless of comorbidities or aetiological factors (54). In the current study, the percentage of patients with abnormalities on VCUG done non-selectively was 24.7% (21 of the 85 patients included in the study had an abnormality detected on VCUG).

Should pre-existing urological disease be present in the CKD patient being worked up for dialysis and transplant, referral to a urologist should occur and VCUG, urodynamic studies and other targeted investigations will be required (11, 36, 62).

Our study supports the necessity for routine VCUG in **all** patients being considered for transplant, as there were no statistically significant associations between the presence of a specific comorbidity and abnormal findings. Comorbidities assessed were hypertension, diabetes mellitus, urinary tract obstruction, HIV and “other” comorbidities, such as glomerulonephritis, hypothyroidism, lupus nephritis, epilepsy, tuberous sclerosis and polycystic kidney disease.

It can thus be seen that the presence of comorbidities cannot be used to select patients for VCUG. If only those patients with a history of upper/lower urinary tract obstruction or diabetes mellitus had been selected for VCUG – as recommended by several studies (13, 17, 18, 57) – only 4 of the 21 abnormal VCUGs would have been performed: 81% of patients with abnormalities would have been missed.

The standard practice of the University of the Witwatersrand hospitals is that patients with urethral strictures/bladder outlet obstruction (3.5% of the study population) required referral to the Urology Department for correction of their abnormalities before being included in the chronic dialysis programme or being placed on the renal transplant list. Three patients were identified as having a urethral stricture on VCUG: two were known with urethral stricture, and one was newly diagnosed. If only the history of urethral stricture was used to select patients for VCUG, the patient with the newly diagnosed stricture would have been missed. Similarly, the four patients with significant residual volume would need to be referred for urological assessment and intervention before they could be considered for transplantation.

The presence of the other detected abnormalities (VUR, diverticula, small bladder volume, did not affect patient inclusion in the dialysis/transplant programme, but knowledge of the presence of VUR would allow for surgical planning with regards to ureteral reimplantation in cases of moderate and severe VUR (grade 3-5); in the present study, this would include 5.9% of patients.

Table 5. Comparison table – necessity of routine VCUG in the pretransplant workup

Study	**Glazier (12)**	**Yang (6)**	**Shandera (14)**	**Errando (21)**	**Sarier (19)**	**Sofianos**
Year	1996	1993	1996	2000	2020	2021
Imaging Modality	VCUG	VCUG, Ultrasound, urinalysis and urine culture	VCUG	Urodynamic studies	VCUG	VCUG
Age (average)	41 years	43 years		40 years	42.3 years	40.0 years
Age range	16-65 years	20-68 years		12-66 years		21-62 years
No. of patients included in study	562	100	439	33	1265	85
Percentage of patients with abnormalities on VCUG	2.5%	26%	15%	45%	19.2%	24.7%
Use of routine VCUG in all patients	No – only in patients with prior urological history.	No – selective use of VCUG in patients with history of diabetes mellitus, UTI or voiding symptoms.	No – selective use of VCUG in patients with history of UTI, pyelonephritis, diabetic nephropathy, reflux nephropathy, paediatric patients.	No – selective use of VCUG in patients with lower urinary tract symptoms, defunctionalised bladder, complex urologic history.	Yes	Yes

Conclusion

The VCUG is currently an essential investigation in the renal transplantation workup in South Africa. While this study attempted to determine whether the VCUG could be used as a selective investigation rather than a routine one, the results obtained did not allow for the identification of a statistically significant means of selecting patients. There would be significant risks and costs associated with the missing of an abnormality severe enough to require pre-transplant correction, or severe enough to preclude a patient from the transplant list altogether. In the absence of a reliable way of predicting the probability of a lower urinary tract abnormality, we thus recommend that all patients undergo a VCUG as an essential part of their renal transplant workup.

Limitations of the current study

The study was based on retrospective reports. It was based on the patient population at a hospital in the North West province, which may not be representative of national demographic data. Additionally, there is no follow-up data with regards to how many of the included patients went on to receive a renal transplant, treatment undertaken prior to renal transplant, nor their eventual outcome.

Conflicting Interests

The author does not have any financial or personal conflicting interests which could have influenced her in the writing of this article.

Data Availability

The data which forms the basis of this study is not openly available in a public forum as it contains personal patient information and details. The data is available from author Z.S. upon reasonable request.

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Appendix 1: Tables with legends

Table 1. Presence of comorbidities in study population

COMORBIDITY	NUMBER OF PATIENTS (N = 85) N (%)
HYPERTENSION	73 (85.9%)
DIABETES MELLITUS	5 (5.9%)
URINARY TRACT OBSTRUCTION	5 (5.9%)
HIV	24 (32.9%)
OTHER	10 (11.8%)

COMORBIDITY	Number of patients (N = 85) n (%)
HYPERTENSION	73 (85.9%)
DIABETES MELLITUS	5 (5.9%)
URINARY TRACT OBSTRUCTION	5 (5.9%)
HIV	24 (32.9%)
OTHER	10 (11.8%)

Note: percentages don't add up to 100%, as some patients had more than one comorbidity.

Source: Authors' own work

Table 2. Identified comorbidities classified as "Other"

COMORBIDITY	NUMBER OF PATIENTS (N = 85) N (%)

GLOMERULONEPHRITIS	2 (2.4%)
HYPOTHYROIDISM	2 (2.4%)
LUPUS NEPHRITIS	2 (2.4%)
EPILEPSY	2 (2.4%)
TUBEROUS SCLEROSIS, BILATERAL NEPHRECTOMY	1 (1.2%)
POLYCYSTIC KIDNEY DISEASE	1 (1.2%)

Table 3. VCUG findings

FINDING	NUMBER OF PATIENTS (N = 85) N (%)
NO ABNORMALITY	36 (42.4%)
SMALL BLADDER VOLUME	28 (32.9%)
BLADDER DIVERTICULA	5 (5.9%)
VESICOURETERAL REFLUX	13 (15.3%)
URETHRAL STRICTURE/BLADDER OUTLET OBSTRUCTION	3 (3.5%)
SIGNIFICANT RESIDUAL VOLUME	4 (4.7%)

Note: percentages don't add up to 100%, as some patients had more than one abnormality.

Table 4. Correlation between comorbidity and abnormality

	NO ABNORMALITY	VUR	SIGNIFICANT RESIDUAL	DIVERTICULA/ STRICTURES
HYPERTENSION	53	11	4	6
DIABETES MELLITUS	4	0	1	0
URINARY TRACT OBSTRUCTION	2	1	0	2
OTHER	7	3	0	0

NOTE: Some patients had more than one abnormality on VCUG.

Table 5. Comparison table – necessity of routine VCUG in the pretransplant workup

Study	**Glazier (12)**	**Yang (6)**	**Shandera (14)**	**Errando (21)**	**Sarier (19)**	**Sofianos**
Year	1996	1993	1996	2000	2020	2021
Imaging Modality	VCUG	VCUG, Ultrasound, urinalysis and urine culture	VCUG	Urodynamic studies	VCUG	VCUG
Age (average)	41 years	43 years		40 years	42.3 years	40.0 years
Age range	16-65 years	20-68 years		12-66 years		21-62 years
No. of patients included in study	562	100	439	33	1265	85
Percentage of patients with abnormalities on VCUG	2.5%	26%	15%	45%	19.2%	24.7%
Use of routine VCUG in all patients	No – only in patients with prior urological history.	No – selective use of VCUG in patients with hx of diabetes mellitus, urinary tract infection or voiding symptoms.	No – selective use of VCUG in patients with hx of UTI, pyelonephritis, diabetic nephropathy, reflux nephropathy, paediatric patients.	No – selective use of VCUG in patients with lower urinary tract symptoms, defunctionalised bladder, complex urologic history.	Yes	Yes

Appendix 2: Figures with legends

K/T HOSPITAL COMPLEX DEP OF INTERNAL MEDICINE DIVISION OF NEPHROLOGY

Transplant workup sheet **KH 856**

PT information	Hospital number	Date of start transplant w up

Diagnosis	
Cause of R. Failure	

WORKUP	BOOKED DATE	RESULTS	COMMENT
ECG			
ECHO			
VCU			
Abd U/S			
Pap smear			
G scope			
Dental check up			
Carotid Doppler			
Others			

Blood Test

Test	date	date	date	date	date
HIV					
CD4/VL	/	/	/	/	/
HBV					
HCV					
CMV					
VDR/PRP					
Blood group& HLA					

Final assessment

Pt eligible	comment	Date and DR signature
YES		
NO		

Figure 1. Klerksdorp/Tshepong Hospital Transplant Workup Sheet

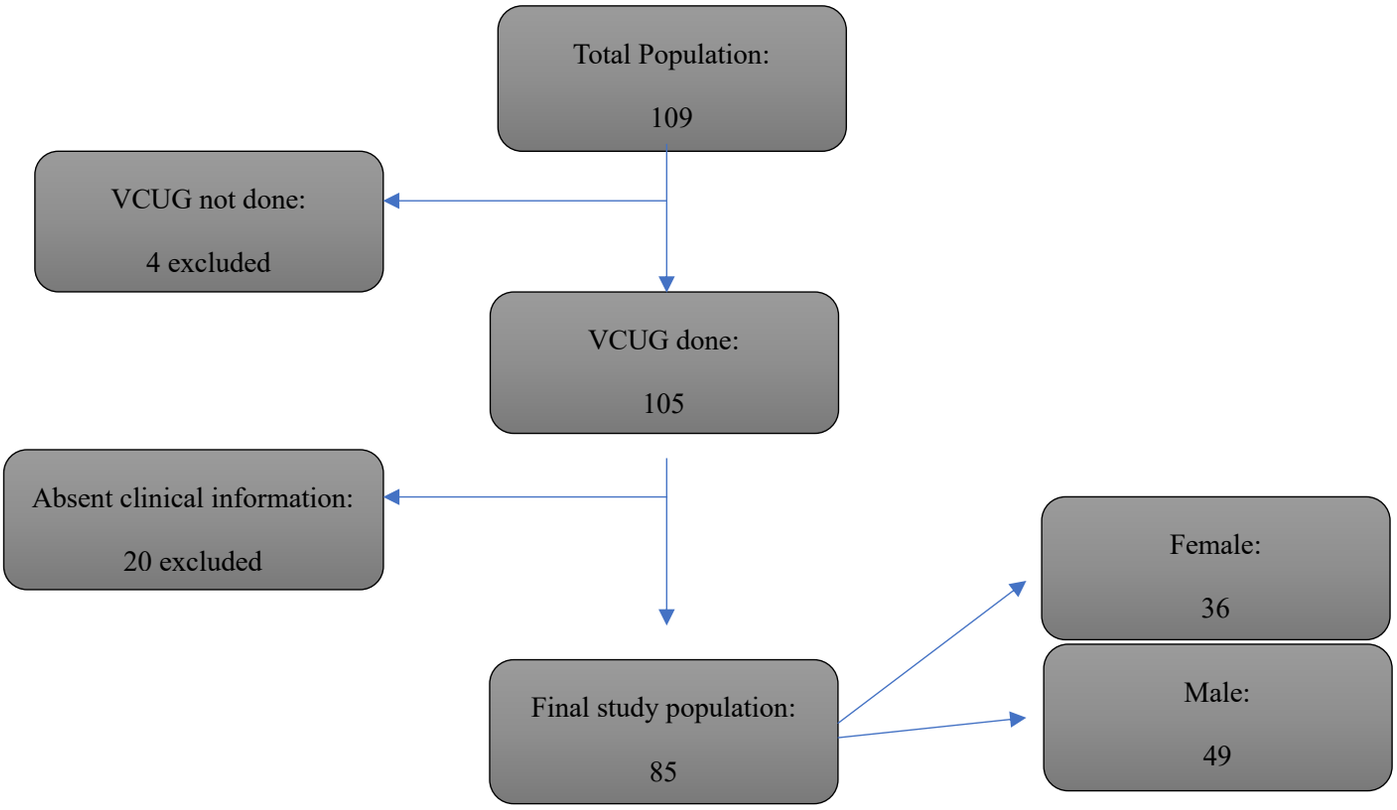
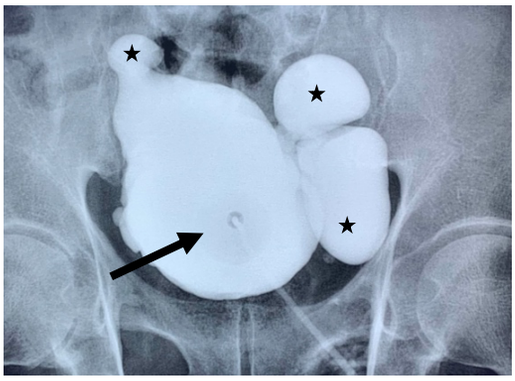
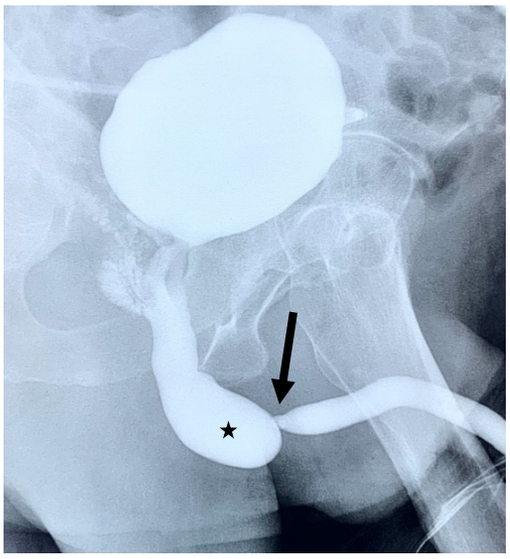


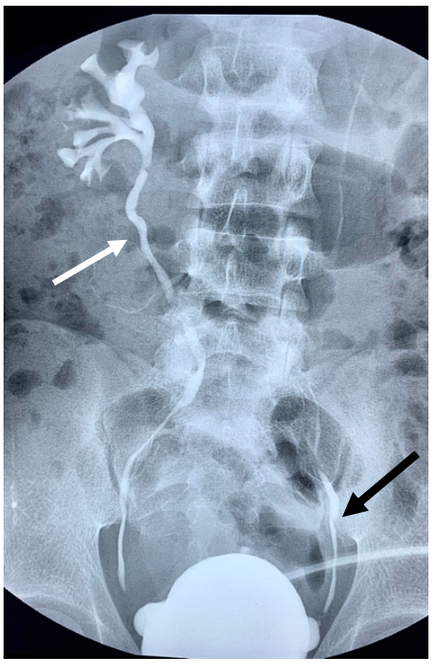
Figure 2. Flow diagram of the constitution of final study population



a. Multiple large urinary bladder diverticula *(stars)* secondary to urethral stricture. Suprapubic catheter in situ *(black arrow)*.



b. Dilatation of the posterior urethra *(star)* due to stricture at the junction of the bulbar and penile urethra *(black arrow)*.



c. Bilateral vesicoureteral reflux: Grade 2 VUR on the right *(white arrow)* and Grade 1 VUR on the left *(filled black arrow)*.

Figure 3. Examples of abnormal VCUG findings during renal transplantation workup

Appendix 3: Ethical clearance certificate

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WITWATERSRAND
JOHANNESBURG

R14/49 Dr Z Sofianos

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M200607

NAME: (Principal Investigator)	Dr Z Sofianos
DEPARTMENT:	School of Clinical Medicine Department of Radiation Sciences Division of Radiology Medical School University
PROJECT TITLE:	Voiding cystourethrography in the renal pre-transplantation workup: an essential investigation?
DATE CONSIDERED:	2020/06/26
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr L Rajkumar and S Lucas
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2020/07/21

This clearance certificate is valid for 5 years from the date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **June** and will therefore reports and re-certification will be due early in the month of **June** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

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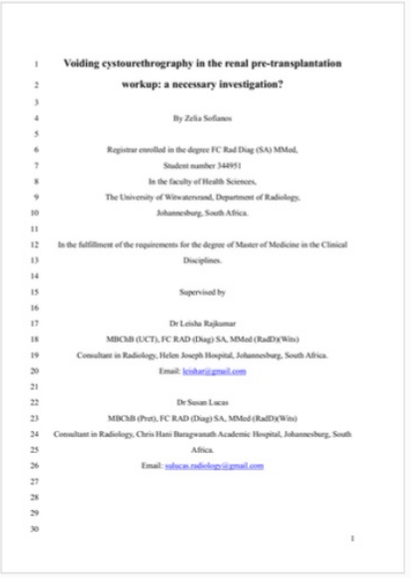
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Voiding cystourethrography in the renal pre-transplantation workup: a necessary investigation?

By Zelia Sofianos

Registrar enrolled in the degree FC Rad Diag (SA) MMed,
Student number 344951
In the faculty of Health Sciences,
The University of Witwatersrand, Department of Radiology,
Johannesburg, South Africa.

In the fulfillment of the requirements for the degree of Master of Medicine in the Clinical Disciplines.

Supervised by

Dr Leisha Rajkumar
MBChB (UCT), FC RAD (Diag) SA, MMed (RadD)(Wits)
Consultant in Radiology, Helen Joseph Hospital, Johannesburg, South Africa.
Email: leishar@gmail.com

Dr Susan Lucas
MBChB (Pret), FC RAD (Diag) SA, MMed (RadD)(Wits)
Consultant in Radiology, Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa.
Email: sslucas.radiology@gmail.com

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Appendix 5: Original protocol with updated literature review

Voiding cystourethrography in the renal pre-transplantation workup: a necessary investigation?

Zelia Sofianos

Student number: 344951

Course registered for: MMed (RadD)

Supervisors:

Dr Leisha Rajkumar MBChB (UCT), FC RAD (Diag) SA, MMed (RadD)(Wits)

Dr Susan Lucas MBChB(Pret) MMed(RadD)(Wits)

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Appendix A. **Error! Bookmark not defined.**

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1. Rationale

Klerksdorp/Tshepong Hospital Complex is a secondary governmental hospital in the North West Province. Here, End-Stage Renal Disease (ESRD) patients have numerous investigations performed in order to determine eligibility for renal transplantation. One of these routine investigations is the Voiding Cystourethrogram, an invasive radiological investigation aimed at identifying lower urinary tract abnormalities. There is a paucity of South African publications which look at the necessity of this investigation as a routine study, or whether it should be only be conducted on those patients with pre-existing lower urinary tract symptoms. By looking at data collected from Tshepong Hospital, the need of the voiding cystourethrogram (VCUG) as a routine renal pre-transplantation investigation can be determined.

2. Introduction

A patient's eligibility for renal transplant depends on several factors. At Tshepong Hospital, a VCUG performed on all patients with ESRD is a necessary part of the transplant workup. The VCUG "aims to image the urinary tract, including the urethra, bladder, ureters, and kidneys, during bladder filling and emptying." (1)

There is much debate globally as to the need for the VCUG in the standard transplant recipient workup (2-8). The VCUG is a radiological investigation which exposes patients to ionising radiation (9). The principle of ALARA (as low as reasonably achievable) should be applied in all radiology departments the world over in order to limit the risks from radiation exposure (10).

From an economic perspective, the VCUG is a costly imaging study, with a bottle of Urograffin costing R303.47 in 2016-2018 as per circular HP05-2016DI from the National Department of Health (11). In addition, if the images require printing due to the lack of a global PACS system (such as is lacking in Tshepong Hospital), the current cost of a 14 x 17 inch Fujifilm X-ray film is approximately R70 per sheet (R7015 per box of 100 sheets). Further disposable equipment which would be necessary for each VCUG includes Foley catheters (the size depends on the patient), syringes, infusion sets and KY gel. It is difficult to estimate the exact cost of these

resources but, considering the great number of patients who are being worked up for potential renal transplant, it can be surmised that this would result in a significant cost.

At Klerksdorp/Tshepong Hospital Complex, each patient with End-Stage Renal Disease (ESRD) has a checklist of investigations which must be completed as part of the pre-transplant workup; the Voiding Cystourethrogram (VCUG) is one of these investigations This checklist is included as Appendix B. Though the workup is done in the North West Province, the transplant itself is conducted in Johannesburg at either Charlotte Maxeke Academic Hospital or Wits Donald Gordon Medical Centre – where the expertise and resources are available to conduct the transplant (12).

A normal bladder is one which fills and stores urine at a low pressure, of adequate capacity, is sterile and empties to leave a small residual volume of urine. It is important that such an environment is present prior to renal transplant (13). Cairns, et al. (14) stated that – at the very least – all patients should have an abdominal ultrasound focusing on the lower urinary tract.

Urodynamic studies, which include the VCUG, are the gold standard for the assessment of lower urinary tract symptoms. They are, however, invasive and other, ultrasound-based investigations are being investigated (15). The use of ultrasound to determine bladder volume and residual capacity is highly sensitive and specific (90.24% and 100%, respectively) (16). In cases where the ultrasound-determined residual volume and uroflowmetry are normal, the VCUG may not be necessary.

2.1. Epidemiology of Chronic Kidney Disease (CKD) worldwide

CKD is a worldwide health issue – the global all-age prevalence is estimated to be 9.1% (697.5 million cases) (17).

2.2. Epidemiology of CKD in South Africa

End-Stage Renal Disease (ESRD) is defined as “advanced, irreversible, (CKD), which requires

the initiation of RRT" (18). The most commonly reported causes of ESRD include hypertensive renal disease, diabetic nephropathy, glomerular disease, polycystic kidney disease, obstruction and reflux (19), medications (20), as well as HIV infection (21, 22), tuberculosis (23), infectious glomerulonephritis, schistosomiasis and leishmaniasis (22).

A cross-sectional population study published by George et al. reported the overall prevalence of CKD as 10·7% (95% CI 9·9–11·7) within sub-Saharan Africa (24). Despite the growing number of people afflicted by CKD and ESRD in South Africa, access to renal replacement therapy (RRT) remains at levels similar to – or even less than – those in 1994 (18, 19). This lack of access is due to resource constraints and the lack of infrastructure (25).

A potential transplant candidate is a person with ESRD who has undergone all necessary workup investigations, with results that do not fit the exclusion criteria; furthermore, the potential candidate should not have any medical, socioeconomic or psychological factors which are part of the exclusion criteria (26, 27).

In the resource-limited South African public healthcare sector, only those patients who are deemed "transplantable" – i. e. they do not have any preclusive medical, socioeconomic or psychological factors, as laid out in the South African national guidelines (26, 27) – will be initiated on RRT (21, 25, 26), despite an estimated mortality rate of >95% if dialysis is not initiated (25). A systematic review of dialysis outcomes in sub-Saharan Africa showed that the average percent access of ESRD patients to dialysis was only 39.1%; a pooled incidence of 48% of adult ESRD patients required dialysis, but did not receive it (25). Of those who initiated dialysis, 59% discontinued dialysis even though it was indicated and necessary. Discontinuation was dependent on a number of factors, such as availability of funds for transport, female sex, and non-functioning dialysis facilities (25). Finally, the large proportion of patients who discontinue dialysis – according to this study – may be an indication of the high early mortality rate due to ESRD (25).

According to the Organ Donor Foundation of South Africa, there were only 234 adult kidney

transplants in 2016 (more recent data has not been provided on their website) (28), while there were 10744 patients on RRT (renal replacement therapy) in 2017 (18). A study by Moosa (12) further elucidates the discrepancy between the increasing number of people with ESRD and the decreasing number of renal transplants in the public sector. During the period of 1991-2015, the mean transplant rate in the public sector was 4.8 per million population (pmp). The 2017 annual report by the South African Renal Registry indicated a 66 pmp prevalence of RRT in the public sector, and a 4.6 pmp renal transplant rate – only approximately 7% of those on RRT went on to have a renal transplant (18).

2.3. Exclusion criteria for potential renal transplant candidates

At Klerksdorp/Tshepong Hospital Complex, there is a checklist of investigations to be done on every patient with CKD before they can be assessed as being eligible (or ineligible) for transplantation (Appendix B). The Voiding Cystourethrogram is one of these investigations, and is done on all CKD patients, not only those with urological issues. Other routine investigations are ECG, ECHO, abdominal ultrasound, pap smear, gastroscopy, dental checkup, carotid doppler, and various blood tests, including HIV status, hepatitis and syphilis serology. It is important to screen for infection in the recipient in order to ensure that effective treatment can be given prior to transplantation (29). Screening for latent infections like syphilis allows prompt treatment before transplantation, as the use of immunosuppressive treatments post-transplant may lead to reactivation of the latent virus, and preventable morbidity and mortality (29).

In 2009, the then Minister of Health – Barbara Hogan – approved guidelines for Chronic Renal Dialysis in South Africa (26). The Dumisani Mzamane African Institute of Kidney Diseases – based at Chris Hani Baragwanath Academic Hospital – still uses these guidelines when assessing patients for the RRT programme. The Western Cape guideline developed by Moosa, et al. (27) is almost identical to that previously approved by the then Minister of Health. The guidelines, as per the 2009 Minister of Health, list the following exclusion criteria:

4. ‘“Medical” exclusion criteria

a. Active, uncontrollable malignancy or with short life expectancy
b. Advanced, irreversible progressive disease of vital organs such as:
    i. cardiac, cerebrovascular or vascular disease
    ii. advanced cirrhosis and liver disease
    iii. medically or surgically irreversible coronary artery disease
    iv. lung disease
    v. unresponsive infections e.g, HPV, Hepatitis B and C
c. HIV and AIDS are not medical exclusion criteria provided the patient has access to a comprehensive AIDS treatment plan including antiretroviral treatment, has been stable for at least six months on HAART and the above exclusion factors are absent. Furthermore, the CD4 count should be >200cells/mcl, the viral load undetectable, and there should be no current opportunistic infections or the history of prior HIV-related conditions e.g. progressive multifocal leukoencephalopathy, EBV or HHV-8-associated lymphoproliferative disorders.
d. Age (provided above exclusion factors are absent) is not a contraindication for chronic renal dialysis. In the UK the median age of starting renal replacement therapy is 63 years and the median age of the population is 54 years.

5. Psychological Exclusion Criteria
    a. Any form of mental illness that has resulted in diminished capacity for patients to take responsibility to their actions.
    b. Active substance abuse or dependency including tobacco use.
    c. Obesity
6. Compliance
    a. Patients with proven habitual non-compliance with dialysis treatment and lifestyle modification will be excluded or removed from chronic renal dialysis programme' (26, 30)

Neither of the approved guidelines specifically mention abnormal imaging findings on VCUG as a contraindication to renal transplant or renal replacement therapy eligibility.

In Europe, a recent proposal regarding the workup of low-risk kidney transplant candidates has been made by the Developing Education Science and Care for Renal Transplantation in European States (DESCARTES) Working Group (31). This proposal recommends a small number of investigations for the low-risk patient: abdominal ultrasound, echocardiography, syphilis biochemistry, gynaecological consultation, and Duplex Doppler of the iliac vessels (31).

2.4. Urological evaluation in the renal pre-transplantation workup

The normal bladder "is a continent, sterile, low-pressure reservoir, which empties easily and completely" (14) . In order to increase the chance of survival of the renal allograft post transplantation, pre-transplantation identification of genitourinary abnormalities (bladder capacity <200ml or >600ml, residual urine volume of >50ml, any urethral abnormalities and vesicoureteral reflux of Grade IV or higher (32)) is essential (3, 6, 33). An abnormal lower urinary tract is no longer an absolute contraindication to the receipt of a renal transplant (34), as long as candidates are carefully selected (35).

The urological system should be evaluated using renal ultrasound in all patients with CKD being worked up for the transplant list. The need for VCUG in all potential renal transplant recipients has been a topic of much debate, with some authors saying that VCUG should be performed on all pre-transplant patients (2), and other authors saying that only those patients with features of lower urinary tract dysfunction should undergo VCUG (3-8). The VCUG can detect the presence of vesicoureteric reflux (VUR), posterior urethral valves (PUV) and urethral strictures, and can assess the post-void residual urine (34).

A study published in the journal Transplantation in 1996 showed that, of the 13 patients who had abnormal VCUG findings during the renal pre-transplantation workup, all of them had a prior history of urological abnormality (4) . The prospective study by Yang, et al. (32) claimed that, if VCUG was not conducted in patients without diabetes mellitus or urological symptoms

(or a history thereof) costs in the renal pre-transplantation workup could be reduced significantly, without increasing the risk of missing significant abnormalities.

Studies conducted in the USA and Europe show the detection of lower urinary tract abnormalities when VCUG is done on all patients with ESRD is 2.5–15%, while this percentage increases to 45% when patients with a history of lower urinary tract abnormality are specifically selected (4, 35).

Should pre-existing urological disease be present in the CKD patient being worked up for dialysis and transplant, referral to a urologist should occur and VCUG, urodynamic studies and other targeted investigations will be required (6, 14, 34). The detection of a small bladder in patients on RRT is not necessarily a preclusive factor for renal transplantation, and may reflect a defunctionalised bladder which will likely return to normal post-transplantation (36, 37).

2.5. Lower urinary tract abnormalities requiring intervention before transplant

For some patients in whom lower urinary tract abnormality is detected, surgical intervention may need to be undertaken before they can be considered eligible for renal transplant (38), or planned for after renal transplantation (39).

VUR is defined as retrograde flow of urine from the bladder into the ureter due to dysfunction of the vesicoureteric junction (40), with different grades of severity according to the International Reflux Study Committee (41). VUR, an atrophic bladder (42), bladder with poor compliance, an overactive detrusor muscle (38), and bladder outlet obstruction in the form of prostatic enlargement or urethral strictures (43) may increase the risk of developing urinary tract infections (UTI) post-transplant (34).

3. Aim

The aim of this study is to assess the prevalence of urinary tract abnormalities by the VCUG in the renal pre-transplantation workup, and determine whether this imaging study is necessary as a routine investigation in all patients undergoing workup for renal transplantation, or if there

is a way to determine which specific patients would benefit from this invasive investigation.

4. Specific Objectives

Primary objective

- To document the reported radiological imaging findings of VCUGs done on patients with ESRD who are being worked up for renal transplant.

Secondary objectives

- To identify the prevalence of abnormal VCUG findings in potential renal transplant candidates.
- To assess the contribution of the VCUG as a standard investigation in the renal pre-transplant workup.

5. Methods

5.1. Research paradigm

The research paradigm is a retrospective cross-sectional study entailing a record review of VCUG results. Detection of abnormalities (or the absence of abnormalities) in each patient's VCUG will be assessed and analysed. A systematic review and analysis of existing local and international guidelines for renal transplantation with reference to structural and functional renal tract assessment will be performed.

5.2. Sample

The data will be collected from the Radiology and Nephrology Departments of Klerksdorp/Tshepong Hospital Complex (public health care sector) in the North West Province. VCUGs conducted over a period of 6 months (01/10/2019 – 31/03/2020) in individuals aged 18-65 years, and for the purpose of renal transplant workup, will be included in the study.

5.2.1. Inclusion criteria

Inclusion criteria

- Presence of ESRD

- Age between 18-65 years
- Participation in a voiding cystourethrogram at the Tshepong Radiology Department
- Referral by the Renal Unit during the work-up for a renal transplant

5.2.2. Exclusion criteria

Patients who will be excluded from the study

- Those whose data is incomplete (lost file, or illegible documentation)
- Those whose VCUG was not completed for any reason e.g. patient discomfort

5.3. Materials and Methods

5.3.1. Materials

A Siemens AXIOM R200/R200 ND fluoroscopy system has been used in pulsed fluoroscopy mode using the standard VCUG protocol (kV and mAs), and intermittent screening used to capture images for the VCUG. Urografin 150 (active ingredients: sodium amidotrizoate and meglumine amidotrizoate) is the standard iodinated contrast medium in this institution. The VCUG studies have been conducted by radiology registrars (ranging from 1st to 4th year of study), or radiology medical officers.

Disposable equipment to be used includes Foley catheters (the size depends on the patient), syringes (2mL, 5mL, 10mL), KY gel, normal saline (200mL bags).

The American College of Radiology has published standard procedures for performing cystourethrography in adults. This practice parameter document assists radiologists in the performance of the VCUG, and ensures that the VCUG is of diagnostic quality (44).

The imaging sequence during a VCUG is standardised in order to ensure reproducibility, and is as follows: control image of the pelvis (prior to catheterisation and contrast administration), early bladder-filling views, full bladder views (anteroposterior, oblique and lateral views) (45). It is then necessary to remove the urinary catheter, and ask the patient to void in an oblique

position for the voiding views. Thereafter, a post-micturition image can be taken in order to assess the bladder residual volume. Throughout study, the presence and grade of vesicoureteric reflux is determined by imaging over the kidneys (44).

5.3.2. Method

Records of all VCUG studies done at Tshepong Hospital are filed and kept within the Department of Radiology. Upon completion of the study, a report is written by hand – by the radiologist who performed the study, after review with a senior consultant – in duplicate: one copy of the report is given to the patient, and the other is immediately filed on site in the records room of the department. While the electronic image archival system is limited by the lack of local hard drive storage space, every attempt will be made to locate these images.

Since this will be a retrospective study, radiology reports of VCUGs already done in the Tshepong Department of Radiology will be used. The hand-written reports which are stored at Tshepong Hospital will be accessed and analysed, and data extracted. Where these reports are unclear, an attempt will be made to access the corresponding image.

Should the reports not have adequate patient details with regards to age, gender comorbidities and whether or not the patient is on dialysis, the corresponding patient files detailing prior admissions and past and current treatment will be requested from the archives of Klerksdorp Hospital, where the Renal Unit is located.

The data from VCUGs done at Tshepong Hospital – a secondary hospital in the North West Province – over a period of six months (01/10/2019-31/03/2020) will be collected, and the number of studies with abnormal findings significant enough to preclude a patient from the transplant list will be noted. By determining the positive yield (presence of abnormal findings) of the VCUG, it can be determined whether this radiological study is a necessary routine investigation for all patients with ESRD, or if it should be used only for those patients with a pre-existing lower genitourinary tract abnormality. Further, it would be useful to determine

whether the detection of abnormalities during the imaging study immediately precluded the patient from the transplant list, or if surgical intervention was undertaken in order to correct the abnormality before considering transplant eligibility – it is hoped that each step of working an individual patient up for transplant eligibility has been documented and is available within the patient files kept in the Klerksdorp Hospital archives.

5.3.3 Data collection

The data extracted from the reports will be captured in an Excel Spreadsheet, and appraisal of this data will be done using the statistical software Stata/IC (StataCorp, College Station, Texas, USA) for Mac.

The data to be captured is (Appendix A):

1. Patient age
2. Patient gender
3. Comorbid conditions – diabetes mellitus, hypertension, obstructive uropathy or congenital lower urinary tract anomalies.
4. Whether or not the patient is already receiving renal replacement therapy
5. Presence of lower urinary tract abnormalities
    a. Vesicoureteric reflux, whether unilateral or bilateral, and the grade
    b. Urethral obstruction in the form of stenosis or stricture
    c. Bladder diverticulae and presence of leak
6. Bladder capacity

5.4. Reliability and validity

The standard imaging technique outlined above effects reliable findings in the reports which form our sample. However, there is a dynamic component to this investigation, the detection and analysis of which, is operator-dependent. Consequently, it is possible that subtle abnormalities (e.g. minor vesico-ureteric reflux) may have been overlooked. Having had each VCUG reviewed by the same senior consultant does contribute to the validity and reliability of the sample, likely limiting suboptimal imaging. The actual images from each VCUG will only

be reviewed if the resultant reports are unclear, due to the dynamic nature of the imaging study as well as the lack of a long-term fluoroscopic imaging archive at Klerksdorp/Tshepong Hospital Complex – senior consultant review of each case, should once again offset concerns regarding validity in this respect.

5.5. Bias

The patients included in the study are all from a single institution, and this may not be a population representative of the South African population on a larger scale. In addition, all VCUG investigations and reports were executed by Registrars and Medical Officers in the Department of Radiology and, despite the findings being reviewed by a senior Radiology consultant, it is possible that subtle abnormalities were missed, due to the dynamic nature of the investigation.

Official statistics with regards to the prevalence of RRT and numbers of renal transplants performed annually is outdated, with the latest South African Renal Registry Annual Report published on 27 November 2019 using statistics from 2017 (18).

6. Ethics

Application for ethics approval was made to Wits Human Research Ethics Committee (HREC) was made; unconditional approval was granted. Ethics clearance certificate number: M200607.

6.1. Consent forms

Consent for access to patient records in the form of radiological procedure reports and the corresponding images, as well as archived patient files (notes on prior hospital admissions and current treatment), was sought from – and granted by – the CEO of Klerksdorp/Tshepong Hospital Complex, and the Head of the Radiology Department at this institution.

6.2. Data safety

Patient names will not be included in the recorded data, and each patient will be assigned a random number. The order in which the data is captured will be random, so that it will not be

possible to determine the date of the imaging procedure. The raw data will be accessible only at the Klerksdorp/Tshepong Hospital Complex archives and Radiology Department, but only the primary investigator and supervisors will be aware of which patient data has been included. Data will be stored on a home-based personal computer of the primary investigator, with password protection. Access will thus not be possible for anyone else.

7. Data analysis and statistics

Findings will be expressed as percentages and frequencies. A standard 95% confidence interval will be used. Pearson's X^2 test will be used to test for significant relationships between the presence of comorbidities and abnormal findings in the VCUG. In order to test the strength of any associations found using Pearson's X^2 test, Cramer V will also be applied.

Content analysis of existing imaging guidelines outlined in the literature review will be done. Findings will then be reviewed in the context of the guidelines that have been analysed.

8. Timeline

Month	2020 Jan	Feb	Ma	April	May	June	July	Aug	Sept	Oct	Nov	Dec	2021 Jan	Feb	Mr	April	May
Literature search	S	C															
Reading literature		S	C														
Summarising literature		S	C														
Preparing Protocol			S				C										
Protocol Assessment				S						C							
Ethics Application						S	C										
Collecting Data										S	C						
Data Analysis										S		C					
Writing up thesis												S			C		
Submit: Marking			S	C											S	C	
Writing up paper			S		C										S		C

*Note: S = Start C= Complete

9. Budget:

Stationery (including printing and binding)	R1500
External Hard Drive	R1000
Travel costs to Klerksdorp for data collection (including fuel, accommodation)	R3000
TOTAL	R5500

This study will be self-funded, encompassing all above costs.

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Appendix A. Data collection sheet.

PATIENT NUMBER	GENDER	ON DIALYSIS (HD - 1, PD - 2)	COMORBIDITIES					VESICOURETERIC REFLUX (Grade 1 -5)			URETHRAL/BLADDER ABNORMALITY			BLADDER VOLUME			COMMENT	
	Male - Female		Hypertension	Diabetes Mellitus	Bladder Outlet Obstruction	HIV	Hepatitis, Syphilis	Unilateral	Bilateral		Diverticulae	Leak	Urethral stenosis/stricture	Small (<200ml)	Normal (200-600ml)	Large (>600ml)	Normal	Abnormal
									Left	Right								

Appendix B. Transplant workup sheet

K/T HOSPITAL COMPLEX DEP OF INTERNAL MEDICINE DIVISION OF NEPHROLOGY

Transplant workup sheet **KH 856**

PT information	Hospital number	Date of start transplant w up

Diagnosis	
Cause of R. Failure	

WORKUP	BOOKED DATE	RESULTS	COMMENT
ECG			
ECHO			
VCU			
Abd U/S			
Pap smear			
G scope			
Dental check up			
Carotid Doppler			
Others			

Blood Test

Test	date	date	date	date	date
HIV					
CD4/VL	/	/	/	/	/

HBV					
HCV					
CMV					
VDR/PRP					
Blood group & HLA					

Final assessment

Pt eligible	**comment**	**Date and DR signature**
YES		
NO		