SIRKKU MUSTONEN

Effect of Acute Urinary Retention on Renal Function

Clinical Studies in Men

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ACADEMIC DISSERTATION

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for public discussion in the small auditorium of Building K,
Medical School of the University of Tampere,
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University of Tampere
Tampere 2001

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ACADEMIC DISSERTATION
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LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals I-V.

I. Mustonen S, Ala-Houhala I and Tammela TLJ (1999). Proteinuria and renal function during and after acute urinary retention. J Urol 161: 1781-1785.

II. Mustonen S, Ala-Houhala IO, Turjanmaa V and Tammela TLJ. Effect of acute urinary retention on glomerular filtration rate. Clin Nephrol (in press).

III. Mustonen S, Ala-Houhala IO, Vehkalahti P, Laippala P and Tammela TLJ (2001). Kidney ultrasound and Doppler ultrasound during and after acute urinary retention. Eur J Ultrasound 12/3: 189-196.

IV. Mustonen S, Ala-Houhala IO and Tammela TLJ (2001). Characteristics of protein excretion in patients with acute urinary retention. BJU Int 87: 187-191.

V. Mustonen S, Ala-Houhala IO and Tammela TLJ (2001). Long-term renal dysfunction in patients with acute urinary retention. Scand J Urol Nephrol 35: 44-48.

In addition, this thesis includes unpublished data.

ABBREVIATIONS

ACE	angiotensin converting enzyme
AUR	acute urinary retention
α_1M	alpha$_1$-microglobulin
BPE	benign prostatic enlargement
BOO	bladder outlet obstruction
β_2M	beta$_2$-microglobulin
^{51}Cr-EDTA	^{51}chromium ethylene diamine tetra-acetic acid
GFR	glomerular filtration rate
HMW	high-molecular-weight
i.v.	intravenous
IgG	immunoglobulin G
IgG4	immunoglobulin G4
kd	kilodalton
LMW	low-molecular-weight
MW	molecular weight
pI	isoelectric point
RI	resistive index
TUIP	transurethral incision of the prostate
TURP	transurethral resection of the prostate
TRUS	transrectal ultrasound

INTRODUCTION

Since 1912 renal function has been studied mainly by determining glomerular filtration rate (Brochner-Mortensen 1978); since the 1950s changes in renal blood flow, glomerular filtration rate, acidifying ability and tubular secretive and reabsorptive functions during and after the relief of ureteral obstruction have been examined (Stecker and Gillenwater 1971).

Obstructive uropathy is a problem commonly encountered in urological practice. From the pathophysiological standpoint it is best characterized as an ischemic injury mediated through a number of well-defined vasoactive hormones (McDougal and Kerr Jr. 1999). It has been clearly demonstrated that obstruction initiates the events of apoptosis seen most dramatically in the distal tubule (Kennedy II et al. 1997). Tubulointerstitial injury may play a significant role in limiting the return of renal function after the relief of obstruction (Pimentel et al. 1995). It has also been suggested that the infiltration of inflammatory cells into the interstitium in the tubulus may be the primary event initiating interstitial fibrosis (Shappell et al. 1998).

The bulk of renal function likely to return does so by 2 weeks after relief of obstruction. The renal damage may become irreversible when the obstruction is left untreated for more than 3 months (Takeda et al. 1998). When renal function is not restored to the level clinically predicted, interstitial fibrosis should be suspected (Coroneos et al. 1997).

Benign prostatic enlargement is an extraordinary common disease of older men (Meigs and Barry 1996). As long ago as the 1940s it was concluded that pathological evidence of this disease appears in men between 40 and 50 years old (Swyer 1944). Voiding symptoms are most often caused by benign prostatic enlargement and this is the most common cause of acute urinary retention (AUR) (Nielsen et al. 1994). Though prostatic symptoms are known to occur in up to 40% of men over 65 years, the prevalence of renal failure due to prostatic disease is essentially unknown (Sacks et al. 1989). AUR causes bilateral obstruction, which may lead to obstructive nephropathy and finally to renal dysfunction (Wilson 1992).

The present work was designed to study the effect of AUR on renal function. Changes in serum renal function parameters, renal arterial blood flow, glomerular filtration rate and proteinuria were studied as well as the long-term effects of AUR on these functions.

REVIEW OF THE LITERATURE

1. NORMAL VOIDING

The urinary bladder is a hollow organ whose function is to store urine during the continence phase and to expel it through the urethra during micturation. During the storage phase the bladder accommodates increasing urine volumes with only a modest increase in pressure, while the bladder wall is distended. This distension results in afferent pelvis discharge, and after the synapse in the pudendal nucleus, efferent somatic pudendal nerve impulses result in contraction of the external sphincter (Blaivas 1982) and continence is guaranteed.

During micturation, the afferent pelvic nerve impulses ascend in the spinal cord and synapse in the pontine micturation center, and, if the cortex centers permit it, the descending efferent pathways inhibit both pudendal somatic impulses, which relaxes the external sphincter, and sympathetic impulses which opens the bladder neck and urethra. At the same time, increased parasympathetic impulses cause detrusor contraction and micturation ensues (Blaivas 1982, Tanagho and Miller 1970).

2. URINARY RETENTION

Acute urinary retention (AUR) is a condition characterized by a sudden inability to micturate which is almost always extremely painful (Choong and Emberton 2000) as urine gathers in the bladder. Many patients with AUR have preceding urinary symptoms (Birkhoff et al. 1976), but its occurrence is often unpredictable among men who are not clearly symptomatic (Jacobsen et al. 1997). Postoperative urinary retention is not uncommon especially among older men (Tammela et al. 1986). Chronic obstruction with increasing volumes of residual urine may lead to overflow incontinence and AUR (Graversen et al. 1989). In dogs the bladder over-distension caused by AUR has been found to lead to an increase in sympathetic activity, which at first resulted in a rise in intravesical pressure but subsequently relaxation in the bladder wall and closure of the external sphincter (Lawson and Tomlinson 1951). In addition, AUR causes a complete bilateral obstruction of the upper urinary tract, which results in a rise in intraluminal pelvi-ureteric pressure (Rodgers et al. 1992). In experimental studies this pressure rise has been

found to be subsequently transmitted to the individual nephrons, leading to increased intratubular pressure and reduced filtration pressure, and to reduced blood flow (Pope IV et al. 1994). If the obstruction is not relieved, hydronephrosis develops and the affected kidney will evince impaired urinary concentrating ability; if tubular and glomerular damage is allowed to progress, renal functional deterioration will eventually ensue (Lawson and Tomlinson 1951, Graversen et al. 1989, Pope IV et al. 1994).

2.1 *Prevalence and incidence*

In an actuarial analysis of 123 patients with varying degrees of prostatism followed for 7 years, approximately 10 per cent were expected to develop acute retention (Craigen et al. 1969). In a recent 4-year study AUR developed in 7% of patients with moderate to severe lower urinary tract symptoms (McConnell et al. 1998). Nonetheless the degree of prostatism does not predict the occurrence of AUR (Birkhoff et al. 1976). Reports suggest that the 10-year cumulative incidence rates of AUR are 4-73% (Meigs and Barry 1996), but many of these estimates come from single-center case series and cannot therefore be generalized. In a population-based Minnesota study of 2115 men the cumulative incidence of AUR increased with age so that a 60-year-old man would have 23% probability of experiencing AUR if he were to reach the age of 80 (Jacobsen et al. 1997).

2.2 *Etiology*

Broadly speaking, the causes of AUR can be classified into three categories. The first relates to any event which increases resistance to the flow of urine. This can be either a simple mechanical obstruction (prostatic enlargement, urethral stricture) or a dynamic obstruction resulting from an increase in muscle tone (bladder neck obstruction) (Powell et al. 1980, Emberton and Anson 1999). Secondly, AUR may result from an interruption of either the sensory innervation of the bladder wall or the motor supply of the detrusor muscle (Choong and Emberton 2000). The third category relates to any situation which permits the bladder to over-distend (spinal anesthesia, drugs) (Tammela et al. 1986, Jacobsen et al. 1995). A provocative factor is often involved, alcohol consumption, constipation, urinary tract infection, cold, bed rest and anal surgery being among the most frequently implicated (O'Flynn

1969, Anderson and Grant 1991). As the incidence of benign prostatic enlargement (BPE) increases with age (Birkhoff 1983, Ekman 1989), age as such constitutes the most conspicious source of risk in AUR etiology. Prostatic infarction has also been held to play some role in the development of AUR in BPE patients, as this injury has been revealed histologically in 85% of patients operated on for AUR, as against only 3% of those with BPE without retention (Baird et al. 1950, Spiro et al. 1974).

Etiology of AUR (according to Choong and Emberton 2000)

Etiology	Proportion
BPE	53.0
Constipation	7.5
Carcinoma of the prostate	7.0
Urethral stricture	3.5
Clot retention	3.0
Neurological disorders	2.0
Postoperative	2.0
Calculus	2.0
Drugs	2.0
Infection	2.0
Miscellaneous/unknown	16.0

2.3 *Treatment*

Most often AUR is treated by mechanical bladder emptying, whereafter the patient is discharged. Although not all patients presenting with AUR require prostatectomy, careful follow-up is recommended (Murray et al. 1984). A man with AUR can safely be catheterized and sent home to await elective prostatectomy within the matter of few weeks, provided he is not uremic, septic, ill or dehydrated (Pickard et al. 1998). However, retention has been reported to recur in 70% of AUR patients within a week, and 90% of them require definitive treatment within one year (Breum et al. 1982). Voiding was unaffected in only 16% of all AUR patients during 5 years' observation (Breum et al. 1982). Only a small difference in voiding between different durations of catheterization: 'in-and-out', 2 and 7 days, was found in AUR patients, but patients with

retention volumes >1300 ml benefited most from prolonged catheterization (Djavan et al. 1998). In addition, AUR patients unfit for surgical procedure may benefit from bioabsorbable urethral stenting combined with finasteride therapy (Isotalo et al. 2000).

2.4 *Benign prostatic enlargement*

BPE, common among older men, is the main cause of bladder outlet obstruction, and it can be progressive, with a risk of urinary retention and renal failure (Girman et al. 1994). About 40% of men over 60 years have symptomatic disease (Berry et al. 1984). About 17% of subjects between 50 and 59 years old, 27% of those between 60 and 69 years, and 35% of those between 70 and 79 years will need some form of treatment (Jacobsen et al. 1995). Many men with mild-to-moderate symptoms do well without therapy whereas others have gradually asseverating symptoms and require medical therapy or surgery (McConnell et al. 1998). Of the male population 50% will have pathological BPE when they are 51 to 60 years old and by the age of 85, 90% will have this condition (Berry et al. 1984, Oesterling 1996). About 75% of men over 50 years suffer from some symptoms associated with BPE (Da Silva 1997). Autopsy studies show histological evidence of BPE in about 70% of men aged over 70 years (Donovan et al. 1997), and also the number of men requiring an operation for prostatic obstruction increases progressively in the eighth decade (Lytton et al. 1968). In addition, severe obstruction may occur without prostatic symptoms (Sacks et al. 1989). Bladder outlet obstruction (BOO) usually causes mild to moderate urinary problems and in this respect the case history is therefore not reliable (Choong and Emberton 2000).

BPE is still the most common cause of AUR (Breum et al. 1982, Murray et al. 1984, Nielsen et al 1994), and chronic BOO may predispose to bladder over-distension in special circumstances and thus precede AUR. AUR is the indication for surgery in 25 to 30% of patients undergoing transurethral resection of the prostate (TURP) (Fowler at al. 1988, Mebust et al. 1989). Indeed, prostatectomy is the recommended treatment for any healthy man with BPE and AUR (Graversen et al. 1989). It has been estimated that the lifetime incidence of surgical or medical intervention for BPE is 35% in 50-year-old man (Oesterling 1996). However, mortality after prostatic surgery is significantly higher in patients with than without AUR (Higgins et al. 1990, Pickard et al. 1998).

TURP has been the gold standard in the treatment of BPE, but numerous alternative therapies have been introduced in recent years. Criteria for treatment generally include symptom severity, development of complications secondary to BPE for example urinary retention, azotemia, bladder stone formation and older age (Kaplan et al. 1995).

Transurethral incision of the prostate (TUIP) may be of greater efficacy and cause fewer complications than TURP (Turner-Warwick et al. 1973, Kletscher and Oesterling 1992), and is recommended for patients with obstructive symptoms secondary to a prostate weighing less than 30 g (Hellström et al. 1986). Other modes of treatment frequently adopted include prostate stent (Thomas et al. 1993), transurethral microwave thermotherapy (Devonec et al. 1991), transurethral needle ablation (Schulman et al. 1993), laser surgery (Kabalin et al. 1997) and pharmacotherapy (alpha-blockers and 5-alpha-reductase inhibitor) (Kaplan et al. 1995, McConnell et al. 1998).

In addition, urinary obstruction caused by an enlarged prostate may induce progressive kidney dysfunction, leading to irreversible renal failure (Sarmina and Resnick 1989), especially in men with high voiding pressure and chronic retention (George et al. 1986). It is estimated that urinary obstruction due to prostatic disease in men is responsible for at least 5 per cent of new cases of end-stage renal disease among patients over the age of 65 (Coroneos et al. 1997). The presence of urinary tract infection with AUR increases the risk of renal function impairment in BPE patients (Ogbonna et al. 1997).

2.5 *Bladder neck obstruction*

The normal urinary bladder neck, an arrangement of the lower fibres of the detrusor and trigonal musculature, is an important sphincter (Turner-Warwick et al. 1973). BOO due to bladder neck obstruction and dyssynergia is found exclusively in young and middle-aged men (Dawson and Whitfield 1996). The definitive treatment is bladder neck incision but in some cases alpha-adrenergic blockers have been used (Turner-Warwick et al. 1973, Dawson and Whitfield 1996).

2.6 *Urethral stricture*

AUR may be attributable to urethral stricture (Kleist 1992) once it becomes impassable (Andrich and Mundy 2000). In most instances the stricture is a narrowing of the calibre of the urethra caused by the presence of a scar consequent on infection or injury (Steenkamp and De Kock 1994, Andrich and Mundy 2000). Serious complications include chronic renal failure (Steenkamp and De Kock 1994). Initial treatment is by urethral dilatation or direct-vision urethrotomy (Sachse 1974), although complex or recurrent cases may require urethroplasty (Dawson and Whitfield 1996).

3. KIDNEY ANATOMY AND FUNCTION

The functional unit of the kidney is the nephron and each human kidney is estimated to contain about 1,300,000 nephrons (Tischer and Madsen 1986). The essential components of the nephron are the glomerulus, the proximal and distal tubulus, the loop of Henle and the collecting duct (Figure 1).

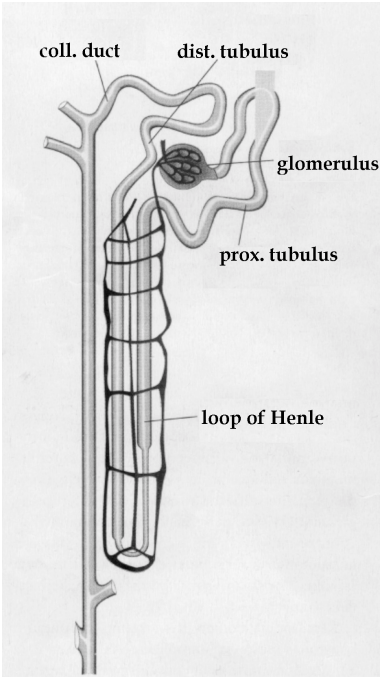

Figure 1. The nephron and the collecting duct. Modified from Jalanko and Holmberg 1998.

Urine production begins with the formation of an ultrafiltrate of plasma by the glomerulus (Wright 1982) (Figure 2). The process of glomerular filtration depends on a difference in hydraulic pressure across a permeable glomerular capillary wall between the capillary lumen and Bowman's space, the most proximal portion of the tubule system (Wright 1982, Levey et al. 1988). The glomerular filtration rate (GFR) also depends on the rate of flow at which blood enters the glomerular capillary (Wright 1982). In addition, urine production may be affected by bladder distension. It has been shown that acute distension of the urinary bladder causes a reduction in urine production in humans (Hvarness et al. 1999).

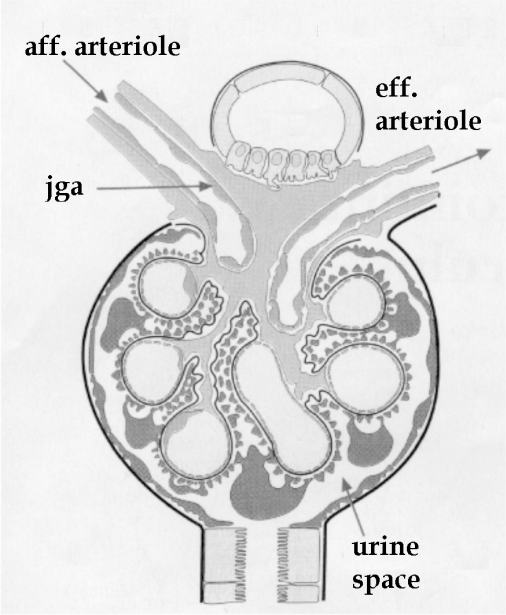

Figure 2. Glomerulus with afferent and efferent arterioles (jga = juxtaglomerular apparatus). Modified from Jalanko and Holmberg 1998).

The glomerular capillary wall is a porous molecular membrane capable of permitting an essentially free filter of water and small plasma solutes and restricting the passage of larger molecules, including plasma proteins (Brenner et al. 1986). The glomerular mesangium consists of mesangial cells and matrix containing collagen and glycoprotein, and is separated from the capillary lumen by the epithelium (Raij et al. 1979, Tischer and

Madsen 1986). The mesangium is essential to the regulation of the flow of macromolecules in the glomerulus (Takahashi et al. 1999). Macromolecules move into the mesangium by way of the endothelial fenestra and this mesangial uptake is dependent on the type, size and blood level of the macromolecule (Raij et al. 1979).

Under normal conditions there is a blood-urine barrier in the kidney, which is characterized by a major portion of restrictive pores of identical radius and a minor portion of large non-discriminatory pores, which behave as a shunt pathway through the barrier. Proteins cross this barrier as a result of three factors: pressure gradient, protein charge and protein size (Deckert et al. 1988, Di Mario et al. 1990). It would appear that large proteins can pass through this shunt pathway, and an increase in this large-pore area causes proteinuria (Gall et al. 1994). Such an increase is preceded by loss of anionic charge in the glomerular basement membrane (Deckert et al. 1988). Changes in the size- and charge-selectivity of the glomerular filter have been reported in diabetic nephropathy and in different primary glomerulopathies (Ala-Houhala and Pasternack 1987).

The major functions of the proximal and distal tubules are the reabsorption of filtered substances such as proteins, electrolytes and water (endocytosis), the secretion of these substances (exocytosis) and the concentration of urine (Tischer and Madsen 1986). The processes of transport of different molecules include diffusion, convection and mediated transport (Molony and Andreoli 1983). Most of the proteins are reabsorbed along the proximal tubule by merit of several mechanisms, among them their charge (Myers et al. 1982, Morano et al. 1988). The tubular lumen contains the filtered proteins and peptides. These latter are split by exopeptidases situated on the brush border membrane of the proximal tubule and then reabsorbed as amino acids or dipeptides. Proteins of higher molecular weight, which are normally not filtered by the glomerulus, are reabsorbed through coatpit vesicles which merge with primary lysosomes to form secondary lysosomes, where the proteins are digested to amino acids (Guder and Hofmann 1992). Normally cationic proteins will bind to the negative charges at the tubulus membrane, this causing restriction of the passage of other cationic proteins but also possibly helping anionic proteins to reach the endocytic site (Mueller et al. 1997). Since total proteinuria usually consists in an increase in anionic protein excretion, and since low-molecular-weight (LMW) proteins are cationic, massive glomerular damage can exist without a significant increase in the excretion of LMW proteins in humans (Mueller et al. 1997); the ratio of high-molecular-weight (HMW) to LMW protein excretion thus gives a valuable indication of the presence of glomerular and/or tubular damage (Mueller et al. 1997). The

proximal tubule, where the metabolic activity is high, is found to be particularly vulnerable to ischemia (Nouwen and De Broe 1994).

The normal kidney controls the volume and composition of extracellular fluid by regulating the amounts of water and electrolytes excreted in the urine in the nephron (Bricker et al. 1957). In certain forms of intrinsic renal disease and after relief of urinary retention, inordinate urinary conservation of salt and water may occur (Bricker et al. 1957).

3.1 *Serum renal function parameters*

3.1.1. Creatinine

One of the product of the liver is creatine phosphate, which is converted to creatinine during muscle metabolism (Brochner-Mortensen 1978, Bloor et al. 1996, Swan 1997). Serum creatinine is freely filtered in the glomerulus and there is normally 10-40% excretion in the tubulus (Levey et al. 1988). In daily clinical practice the serum concentration of creatinine is the parameter most widely employed to assess renal function (Brochner-Mortensen 1978, Levey et al. 1988). During glomerular dysfunction the serum creatinine value is elevated, and has been found to be accurate enough to measure renal function (Parkin et al. 1989, Robert et al. 1993); however, it is also known to be a poor index of the glomerular filtration rate (Levey et al. 1988, Garwood and Hines 1996, Swan 1997). Also when GFR is reduced, extrarenal elimination of creatinine in stool and sweat is increased (Levey et al. 1988), this due to the nonlinear relation between concentrations of creatinine in the blood and GFR; even a 50% decline in GFR shows normal serum creatinine (Flynn 1990). Serum creatinine is also affected by age, body weight, exercise and meat-containing food (Flynn 1990, Levey et al. 1988).

3.1.2. Urea

Urea develops in the course of nitrogen metabolism. Serum urea is freely filtered in the glomerulus and thereafter reabsorbed or secreted in the renal tubule, which is independent of the state of hydration (Brochner-Mortensen 1978). The extent of the reabsorption and excretion is determined by the net reabsorption of water (Larson and Jamison 1983). Serum urea increases when glomerulus function is reduced to 20-40% from normal. It is nevertheless more sensitive parameter of glomerulus function than serum creatinine (Brochner-Mortensen 1978).

3.1.3. Urate (Uric acid)

Urate develops during the process of purine metabolism. Serum urate is freely filtered through the glomerulus and totally reabsorbed in the proximal tubulus; usually the secretion of urate in the tubulus is minimal (Weinman 1983). Elevated serum urate values are often associated with gout or decreased reabsorption in the tubulus.

3.1.4. Phosphate (Phosphorus)

Phosphate is a bone mineral. Phosphate is freely filtered through the glomerulus and reabsorbed in the proximal tubulus, but excess amounts are actively secreted to the urine (Wilson 1992). The phosphate concentration in serum increases in renal insufficiency due to intestinal overabsorption of phosphate and decreased secretion in the tubulus (Corry et al. 1983). Hypophosphatemia is found during tubulus malfunction due to excess loss in the urine (Dennis 1983).

3.1.5. Albumin

Albumin maintains the osmotic pressure in the plasma. It is not normally filtered in the glomerulus, but if filtration occurs, almost all is reabsorbed in the proximal tubulus (Jensen et al. 1995). Lowered serum albumin values are associated with excess loss of albumin in the glomerulus, e.g. in malnutrition. Serum albumin levels do not reflect renal function.

3.1.6. β_2-Microglobulin

β_2-microglobulin (β_2M) is a LMW protein which provides an extremely sensitive test for both glomerular and tubular function (Garwood and Hines 1996). It is filtered through the glomerulus (95%) and reabsorbed almost totally (99.9%) and hydrolyzed in the tubulus (Garwood and Hines 1996). Elevated serum values are associated with diminished tubulus function and serum β_2M may be used to determine GFR, as an inverse correlation obtains between serum β_2M and GFR (Garwood and Hines 1996).

3.1.7. Lysozyme

Lysozyme is a small molecular lysozymal enzyme. It is extensively filtered through the glomerulus, reabsorbed in the tubulus and released back into the circulation either as intact molecules or as catabolic products (amino acids and polypeptides) (Maack 1975, Johnson and Maack 1983). Elevated serum values are associated with uremia.

3.2. *Urinary renal function parameters*

3.2.1. Urate (Uric acid)

Urinary urate excretion is elevated in conditions of decreased reabsorption in the proximal tubulus and when the serum urate level is abnormally high. The small amount of urate secreted in the tubulus is subsequently reabsorbed in the tubulus (Weinman 1983).

3.2.2. Phosphate (Phosphorus)

Urinary phosphate excretion depends on tubular function and elevated values reflect a defect in reabsorption (Dennis 1983, Wilson 1992, Eriksson et al. 1995).

3.2.3. Citrate

Urinary citrate excretion is likewise dependent on tubular function, as citrate is normally filtered in the glomerulus and reabsorbted in the proximal tubulus (Eriksson et al. 1995). Hypocitruria is associated with distal renal tubular acidosis (Eriksson et al. 1995).

3.3 *Proteinuria markers*

Albumin, β_2-microglobulin (β_2M), α_1-microglobulin (α_1M), total immunoglobulin G (IgG) and its subclass immunoglobulin G4 (IgG4) are endogenous plasma proteins differing in size and electric charge (Deckert et al. 1988). Plasma proteins are handled in the kidneys by both glomerular filtration and tubular reabsorption (Jensen et al. 1995), and dysfunction in either may thus be a cause of proteinuria (Guder and

Hofmann 1992). Although the pathogenesis of proteinuria has not yet been fully elucidated, it is now widely accepted that hemodynamic alterations, the size and charge selectivities of the glomerular capillary filtration barrier and tubular reabsorption are implicated (Chiba et al. 1991, Ishibashi 1993, Gall et al. 1994). If the amount of filtered protein increases, the kidney can adapt by increasing tubular reabsorption up to a saturation point, beyond which overflow proteinuria occurs (Myers et al. 1982, Guder and Hofmann 1992).

Albumin is used to test the ability of the glomerulus to appropriately restrict the filtration of HMW proteins, in particular those with negative charges, and if tubular protein reabsorption is normal, albuminuria is an early marker of glomerular disease (Schmitz et al. 1989, Mueller et al. 1997). Tubular damage usually precedes glomerular damage of postrenal origins such as obstruction, which renders evaluation of proximal tubular function markers important in the identification of proteinuria (Kristjansson et al. 1995). In addition, the renal tubules may be affected by diseases, drugs or poisons independent of glomerular function, so that increased proteinuria may appear in spite of normal glomerular filtration. In progressive glomerular disease dysfunction of glomerular filtration and tubular reabsorption are found together, giving rise to so-called tubulo-glomerular proteinuria (Guder and Hofmann 1992). Diurnal (circadian) variation in the excretion of albumin, α_1M, β_2M, IgG and IgG4 has been seen manifested (Di Mario et al. 1990, Jung 1994, Hansen et al. 1995). Provided reliable reference limits are used, that is, different limits for day and night excretion, circadian change in excretion of proteins does not affect results (Jung 1994). Also, exercise increases the glomerular permeability of proteins by influencing renal hemodynamics but does not disturb tubular protein reabsorption (Ala-Houhala 1990).

3.3.1 Albumin

Albumin is an electrostatically negative-charged protein (molecular weight [MW] 69 kilodaltons [kd], isoelectric point [pI] 4.7-5.5) and a reliable parameter for monitoring early glomerular damage in different stages of nephropathy (Morano et al. 1987, Deckert at al. 1988). Even a small increase in the urinary level of albumin points to glomerular dysfunction of clinical significance (Levitt et al. 1992, Mpofu and Mann 1992, Recker et al. 1992, Nergelius et al. 1997). With its relatively small molecular weight it in fact tends to pass through the kidney filter in many common conditions such as physical exercise and urinary infection (Morano et al. 1987); normally, however, 90% is reabsorbed in the

proximal tubule (Guder and Hofmann 1992). Microalbuminuria in diabetes appears to be a result of both an increase in the glomerular passage of albumin and an eventual decrease in the protein reabsorptive capacity of the tubules (Nouwen and De Broe 1994). Hypertension is associated with increased urinary excretion of albumin, and angiotensin-converting enzyme (ACE) inhibitors and antihypertensive drugs like diuretics and β-blockers are known to reduce urinary albumin excretion in diabetic and primary hypertensive patients (Parving and Smidt 1986, Hansen et al. 1995b, Siewert-Delle et al. 1996). As glomerular membrane damage results in an elevation of the urinary excretion of albumin, there is a negative correlation between albuminuria and GFR in patients with chronic pyelonephritis (Jacobson et al. 1987, Yoshiara et al. 1993).

3.3.2 β_2-Microglobulin

β_2-microglobulin is a LMW plasma protein (MW 11 kd, pI 5.8) (Deckert at al. 1988), which is freely filtered in the glomerulus and normally more or less completely reabsorbed by the proximal tubule (Garwood and Hines 1996). Disease states producing a dysfunction of the proximal tubules will be accompanied by reduced tubular reabsorption and increased urinary excretion of β_2M (Flynn 1990, Garwood and Hines 1996). Increased excretion of β_2M has also been found to precede a fall in GFR (Garwood and Hines 1996). Measurement of β_2M is difficult by reason of its instability in room temperature and in low pH, which necessitates alkalinization and rapid storage of urine at appropriate temperatures (Garwood and Hines 1996).

3.3.3. α_1-Microglobulin

α_1-microglobulin, a LMW protein (MW 20 kd) which is almost freely filtered through the glomerulus membrane and more or less completely reabsorbed in the proximal tubulus, is relatively stable in urine (Ayatse and Kwan 1991, Tsukahara et al. 1993). Hence it affords a clinically useful index of proximal tubular damage (Flynn 1990).

3.3.4 Immunoglobulin G and G4

Positively charged total immunoglobulin G (IgG) (MW 156 kd, pI 5.8-7.3) and its subclass, negatively charged immunoglobulin G4 (IgG4) (MW 156 kd, pI 5.5-6.0) (Deckert et al. 1988), are HMW proteins of identical size. IgG4 is more anionic than IgG and concentration in plasma and urine is only 3-4% of the total IgG concentration (Deckert et al. 1988). Since proteins of higher molecular weight are not normally filtered by the glomerulus, increased urinary excretion of IgG reflects glomerular proteinuria (Guder and Hofmann 1995, Nergelius et al. 1997), indicating a defect in the glomerular filtration barrier allowing the passage of large and anionic macromolecules into the urine (Hemmelder et al. 1997). In normal subjects anionic immunoglobulins (IgG4) have been found to be excreted in a ratio of about one to ten in comparison with cationic immunoglobulins (IgG), which suggests that the positively charged proteins easily reach the glomerular basement membrane, where they are reabsorbed (Di Mario et al. 1990).

Since total IgG is electrically neutral, increased excretion may indicate increased pore size in the glomerular filtration barrier (Myers et al. 1982, Hemmelder et al. 1997). Also, as the IgG4 subclass is more anionic but of the same size and configuration as total IgG, increased excretion of IgG4 may be explained by reduced amounts of retropulsive anionic components in the glomerular filter (Jensen et al. 1995). Further, an altered tubular charge may influence the excretion level of IgG and IgG4 (Hansen et al. 1995), as 90% of both IgG and IgG4 is under normal conditions reabsorbed in the tubules (Gall et al. 1994).

3.4 *Glomerular filtration rate*

The use of determination of the renal plasma clearance (the ratio between urinary excretion rate and plasma concentration) of different substances to assess GFR has been important in the management of patients with nephro-urological disorders and other conditions affecting renal function (Brochner-Mortensen 1978).

GFR is generally considered the best measure of renal function (Brochner-Mortensen 1978, Swan 1997, Herget-Rosenthal et al. 1999). For the clearance of a substance to provide a reliable measure of GFR, it must be freely filtered at the glomerulus, be neither reabsorbed nor secreted by the renal tubule, undergo no extrarenal elimination, be constant in level in the plasma during the period of urine collection and reliably measurable in plasma and urine (Flynn 1990, Swan 1997).

Several factors are known to influence GFR in the normal state, namely age, sex and diet (Davies and Schock 1950, Levey et al. 1988). Moreover, a positive correlation has been found between GRF and renal size (Andersen and Mogensen 1973).

Many drugs, especially those acting on the renal microvascular circulation, exert an effect on GFR. Use of prostaglandin synthesis inhibitor may result in a significant reduction in GFR in hypertensive patients (Marin et al. 1992). Angiotensin II raises blood pressure by vasoconstriction and renal actions, and plays a significant role in hypertension and the pathophysiology of vascular damage in hypertensive conditions (Fyhrquist et al. 1995). ACE inhibitor therapy may result in markedly reduced absolute reabsorption in both distal and proximal tubules in renovascular hypertension patients, predominantly due to a fall in GFR (Pedersen et al. 1989). In patients with prostaglandin-dependent renal function, non-steroidal anti-inflammatory drug administration constantly reduces GFR by removing the modulatory action of prostaglandins on vasoconstrictor agents (Pugliese and Cinotti 1997). In contrast, antihypertensive treatment with calcium antagonists has been found to prevent the decrease in GFR in nephrotic patients (Herlitz 1992), and antihypertensive treatment with β-blockers, hydralazine and diuretics in mild to moderate primary hypertension have been found to protect the kidney from decline in GFR (Mogensen et al. 1993, Siewert-Delle et al. 1996). In general, effective treatment of hypertension protects the kidney from impairment of GFR.

3.4.1 Inulin clearance

Although inulin clearance is generally regarded as the gold standard measure of GFR (Lindgårdh 1972, Flynn 1990), its assessment is too complex (Chantler and Barratt 1972) and time-consuming for routine use (Askergren et al. 1981). The clearance of inulin has only been used to a minor extent in routine clinical work as the method calls for i.v. infusion and complete urine collections, and the chemical analysis of inulin is cumbersome and subject to interference from other substances, e.g. glucose (Brochner-Mortensen 1978, Levey et al. 1988, Flynn 1990). Also, simultaneous measurements of renal and plasma clearance of inulin during constant infusion are significantly related, although the plasma clearance has been shown to be greater than the renal owing to the lack of complete equilibration of inulin in body fluids (Sambataro et al. 1996). Furthermore, inulin single injection clearance has been found accurate in determining GFR in young children (Müeller-Suur et al. 1983).

3.4.2 Creatinine clearance

The clearance of endogenous creatinine has been used as a measure of GFR since the 1940s (Brochner-Mortensen 1978, Garwood and Hines 1996), but its use poses problems in that creatinine is actively secreted by the renal tubules and the plasma creatinine concentration may rise during the period of urine collection if cooked meat is consumed or strenuous exercise is undertaken (Payne 1986, Flynn 1990). Tubular secretion of creatinine varies not only within an individual but also between individuals (Swan 1997). Also, as glomerular function deteriorates, the rate of filtrations tends to be increasingly overestimated as tubular secretion and metabolic breakdown of creatinine increase (Shemesh et al. 1985, Bloor et al. 1996). In addition, creatinine clearance measurement entails timed urine collections, which are time-consuming and impractical in routine use (Swan 1997). Moreover, creatinine clearance tends to decline with age and a diurnal variation in creatinine clearance has been demonstrated, with a higher value in the afternoon than in the morning (Garwood and Hines 1996). Several substances can interfere with laboratory measurements of creatinine. Glucose, uric acid, ketones, plasma proteins and cephalosporines may lead to falsely high creatinine when the Jaffe colorimetric method is used (Swan 1997), but this can be avoided by using the enzymatic method in measuring creatinine concentrations.

For the above reasons, some investigators do not recommend the use of creatinine clearance alone when studying glomerulopathies (Shemesh et al. 1985), while others consider creatinine clearance an inaccurate and imprecise measure of GFR (Payne 1986). Nevertheless, in clinical practise creatinine clearance is still the most frequently used method in measuring GFR.

The 24-h period of urine collection being, as noted, a time-consuming procedure, 24-h creatinine clearance may be impractical for day-to-day monitoring of renal function. Shorter periods of urine collection (two hours) have been found sufficiently valid for measuring renal function (Herget-Rosenthal et al. 1999).

In addition, it is possible to calculate creatinine clearance with sufficient accuracy, provided serum creatinine and the patient's weight and age are known, by the Cockroft-Gault equation as follows: crea clearance = (140 - age [yr] x (patient's weight [kg]) / 72 x (serum creatinine [mg/dl]), correcting serum creatinine to 1 mg/dl (85 μmol/l) (Cockcroft and Gault 1976, McLigeyo 1993, Robert et al. 1993, Bloor et al. 1996, Herget-Rosenthal et al. 1999).

3.4.3 ^{51}Cr-EDTA clearance

Clearance of the radionuclide marker ^{51}chromium ethylene diamine tetra-acetic acid (^{51}Cr-EDTA) has been used as a reliable measure of GFR especially in patients with slightly or moderately reduced clearance levels (Granerus and Aurell 1981); the procedure is, however, costly, involves special specimen handling and requires radiation exposure (Flynn 1990, Swan 1997). Clearance of ^{51}Cr-EDTA has been found to be slightly less than that of inulin, probably because of a small difference in the excretion of the two substances in the kidney (Lindgårdh 1972). ^{51}Cr-EDTA is excreted solely by glomerular filtration (Traub et al. 1973). As ^{51}Cr-EDTA clearance decreases with increasing age, age-related reference values in ^{51}Cr-EDTA clearance have been reported in a few studies (Askergren et al. 1981, Granerus and Aurell 1981) but they are not in general use. No male/female difference in ^{51}Cr-EDTA clearance has been found when the GFR is corrected for 1.73 m^2 body surface area (Granerus and Aurell 1981). ^{51}Cr-EDTA clearance >70 ml/min/1.73m^2 has been considered the limit of relatively good glomerular function (Chan et al. 1992).

Technical factors such as sample timing or dehydration of the patient can interfere with ^{51}Cr-EDTA measurement. The advantage in this approach is that a bolus injection of ^{51}Cr-EDTA suffices to provide an accurate measurement of GFR in both normal and diabetic subjects and children (Chantler and Barratt 1972, Traub et al. 1973, Sambataro et al. 1996). In addition, the need for timed urine collections is eliminated as the clearance of ^{51}Cr-EDTA is measured from blood samples (Chantler and Barratt 1972).

4. ULTRASOUND EXAMINATION

4.1 *Conventional ultrasound*

Ultrasonography of the kidney and renal vessels has been used to measure the kidney, to search for cystic and mass lesions and investigate the collecting systems and the vasculatory (Kuijpers et al. 1993, Garwood and Hines 1996, Koch et al. 1996). Kidney length has traditionally been used to predict kidney size and volume, which correlates well with the amount of nephrons (Levitt et al. 1992, Thakur et al. 1997). Normal renal length pole to pole, as assessed by ultrasound,

varies between 8 and 13 cm (average 11-12 cm) and the left kidney is larger than the right (Brandt et al. 1982). Length alone is not in fact a reliable predictor of kidney volume or the number of functioning nephrons (Thakur et al. 1997), a limitation also noted in animal studies (Ferrer et al. 1997).

Increased cortical echogenicity has been shown to correlate with renal diseases of many etiologies but is generally considered nonspecific (Duel et al. 1998).

Sonography has also become a method of choice for the diagnosis of urinary obstruction (De Toledo et al. 1996). The method achieves 98% sensitivity in detecting hydronephrosis, but only 78% specificity (McDougal and Kerr Jr 1999) because the occurrence of false negatives due to the absence of hydronephrosis is not uncommon (De Toledo et al. 1996).

4.2 *Doppler ultrasound*

Renal artery flow velocities are determined using Doppler ultrasound (Garwood and Hines 1996). To characterize intrarenal impedance in Doppler waveform, most investigators have used the resistive index (RI), an easily calculated parameter RI = [peak systolic shift – minimum diastolic shift] / peak systolic shift (Platt et al. 1991, Platt 1997). The renal vascular bed in a normal kidney is characterized by low impedance to blood flow, allowing a continuous forward flow in the diastole (Platt et al. 1989, Mostbeck et al. 1991, Platt 1992). Increases in downstream resistance result in a relative reduction in diastolic compared with systolic flow (Platt 1992). As renal vascular resistance increases, the diastolic flow diminishes, leading to an increase in the RI (Platt et al. 1989, Mostbeck et al. 1991). The RI is thus a sensitive indicator of changes in intrarenal vascular flow and renal arterial resistance (Pozniak et al. 1988, Platt 1992). Unfortunately, measurements of Doppler parameters are subject to substantial intrinsic variability, and caution and repeated measurement are thus essential both within a suspect kidney and between individuals (Keogan et al. 1996, Kliewer et al. 1997).

Definition of a normal RI range is difficult in that renal dysfunction can exist with nonspecific findings such as normal serum levels of creatinine. In a large series of normal native kidneys mean RI values were 0.58 (Platt et al. 1989) and 0.62 (Rodgers et al. 1992). However, from normal data, 0.70 has emerged as a reasonable upper limit for a normal mean intrarenal RI (Platt 1992), and application of this discriminatory RI value has yielded a sensitivity of 92%, a specificity of

88% and an overall accuracy of 90% in the diagnosis of significant obstruction (Platt et al. 1989).

Essential hypertension is associated with normal RI (Pozniak et al. 1988) and microalbuminuria with increased RI (Pontremoli et al. 1999). Conditions such as significant hypotension and a markedly decreased heart rate can elevate the index (Platt et al. 1991). It also has been shown that Doppler waveforms are likely to be age-dependent, particularly in children, who tend to have higher RIs than adults (Wong 1989, Scholbach 1996, Shokeir et al. 1996). The RI may also be affected by certain nonurologic renal diseases and oral hydration, as fasting elevates the level (Shokeir et al. 1996). Also the amount of edema in renal parenchymal disorders leads to an increase in RI (Mostbeck et al. 1991). RI elevation can also be caused by secondary compression either by an adjacent mass or by manual compression transmitted through the transducer by the sonographer (Pozniak et al. 1988). In addition, extracorporeal shock wave litotripsy has been observed to cause an immediate increase in resistive index levels especially among patients older than 60 years (Janetschek et al. 1997).

RI provides information regarding renal status not reflected by creatinine levels (Platt 1992). Only a weak positive correlation has been found between creatinine level and RI in acute renal failure patients (Platt 1992), but combining Doppler data with serum creatinine level has proved clinically most useful; if both are elevated, renal failure is quite obvious (Platt et al. 1997b). In diabetic patients a correlation has been found between RI and serum creatinine and in cirrhosis patients an inverse correlation between RI and creatinine clearance, probably attributable to reduced blood flow (Wong 1989, Kim et al. 1992, Sacerdoti et al. 1993).

5. OBSTRUCTION OF THE URINARY TRACT

Obstruction of the urinary tract is a common cause of loss of renal function and is potentially reversible with treatment. The incidence of urinary tract obstruction increases after the age of 60 in males, in whom it may be due to prostatic enlargement (Baker and Whitfield 1992).

Obstruction to the flow of urine causes functional and pathologic changes in the kidney. The severity of renal impairment and the degree of recovery of function after relief of obstruction depends on whether the obstruction is uni- or bilateral, acute or chronic, or partial or complete

(Sacks et al. 1989, Baker and Whitfield 1992, Wilson 1992). Bilateral obstruction is a greater threat to the patient than unilateral.

Obstructive nephropathy is characterized by significant changes in the renal tubular handling of electrolytes and water excretion, and the major site of injury would appear to lie in the distal nephron (Yarger and Buerkert 1982). Ureteral occlusion also induces alterations in mesangial uptake and egress of macromolecules, which may be mediated in part by the hemodynamic changes accompaning ureteral obstruction (Raij et al. 1979, Takahashi et al. 1999).

Doppler ultrasound is useful in evaluating the consequences of obstruction on renal function in man (De Toledo et al. 1996). In state of significant renal obstruction hemodynamic changes occur: in the first 1-2 hrs after obstruction a transient rise in renal blood flow and prostaglandin-mediated vasodilatation is characteristic; subsequently elevated postglomerular renal vascular resistance due to the secretion of a potent vasoconstrictor, thromboxane A_2 (Platt 1992, De Toledo et al. 1996), decreased renal blood flow and elevated ureteral pressures are found. After 5 hrs of obstruction normalized ureteral pressures and elevated preglomerular resistance are noted, and a marked elevation in renal vascular resistance and hence elevated RI are to be expected (Platt 1992). If obstruction is relieved within 5 hrs, there should be a rapid return to normal renal vascular resistance and hence normal RI. If obstruction persists for at least 18-24 hrs, the normalization of RI may not be immediate and may take days or even weeks to return to baseline levels (Platt 1992).

Kidneys obstructed for a somewhat longer period of time (12-36 hours) have been found not to have significantly higher RIs than those with shorter duration (less than 12 hours) of obstruction (Platt et al. 1993). In conditions of incomplete obstruction normal RI may be found (De Toledo et al. 1996). Clinically significant partial obstruction is almost always a chronic condition, and if the obstruction is of a certain degree, changes similar to those seen in complete obstruction can occur (Platt 1997).

Unrelieved obstruction finally induces severe tubular atrophy, diffuse interstitial fibrosis, interstitial inflammation and progressive glomerular damage, leading to chronic renal failure, whereafter no recovery of the renal function will take place (Coroneos et al. 1997). Microscopic examination of obstructed kidneys shows tubular dilatation and atrophy with chronic interstitial inflammatory changes and fibrosis, which are more severe than glomerular changes. When both kidneys are affected by lower urinary obstruction, the pathologic changes are usually asymmetric (Wilson 1992). In addition, histopatologic, biochemical and genetic

studies have demonstrated that the renal atrophy associated with hydronephrosis is related to the onset of programmed cell death or apoptosis, primarily in the distal tubular epithelium, this process being consequent upon cessation of the production of epidermal growth factors (Kennedy II et al. 1997). Subcutaneous injection of epidermal growth factor into unilaterally obstructed rats has been seen to promote renal cell epithelial cell regeneration and to prevent cells from undergoing apoptosis (Kennedy II et al. 1997).

Urinary tract infection is a common and potentially serious accompaniment of obstruction and frequently concomitant with the presence of obstruction to bladder flow and increasing volumes of residual urine (Wilson 1992).

Hypertension in obstructive nephropathy may result from fluid and salt retention, increased renin secretion or decreased synthesis of renal medullary vasodepressor substances such as prostaglandins (Wilson 1992). Volume-dependent hypertension may improve as fluid retention is corrected after relief of bilateral obstruction (Klahr and Bander 1983). Hypertension in unilateral ureteral obstruction has been found to be associated with elevated renin concentrations in the renal vein from the obstructed kidney; after relief of obstruction the hypertension disappears and the renin level returns to normal (Belman et al. 1968). Several studies of patients with chronic hydronephrosis have revealed that the values of perirenal renin are usually normal or low, which suggests that hypertension in this setting is not due to increased renin secretion but to the lack of release of vasodepressant substances by the kidney (Klahr and Bander 1983).

5.1. *Findings in renal function tests during obstruction*

5.1.1 Experimental studies

It has been shown that a number of experimentally induced and clinically occurring varieties of acute renal failure are characterized by alterations in intrarenal hemodynamics which induce marked changes in renal excretory function (Jaenike 1972). An increase in ureteral and intraluminar pelvic pressure is transmitted to the tubule and peritubular capillaries, and chronic elevations in ureteral pressure cause a decrease in renal blood flow and GFR (Stecker and Gillenwater 1971, Rodgers et al. 1992). After unilateral ureteral obstruction the tubules are collapsed with depressed intraluminar pressure, while after bilateral obstruction they are

dilated with elevated intraluminar pressure (Jaenike 1972). These observations indicate that the intrarenal hemodynamic response to bilateral obstruction differs fundamentally from that to unilateral obstruction (Jaenike 1972). If the obstruction is not relieved, hydronephrosis develops.

After one day from unilateral ureteric obstruction increased weight due to edema, reduction in blood flow and severely reduced GFR in the obstructed kidney has been observed in rats (Lyrdal and Olin 1975). It would also appear that the glomerular and tubular function in the contralateral kidney increases as a consequence of compensatory hypertrophy probably due to vasodilatating substances (Stecker and Gillenwater 1971, Lyrdal and Olin 1975, Wright 1982). In dogs, the ipsilateral renal blood flow increases after unilateral ureteral obstruction up to 5 hrs and then falls, and upon release of the obstruction increases again, with a subsequent fall to normal (Vaughan et al. 1968). Also in dogs unilateral ureteral obstruction has been shown to cause a significant depression of GFR and impairment of tubular secretive and reabsorptive functions (Vaughan et al. 1968, Stecker and Gillenwater 1971). In rats, GFR is markedly reduced after 1-2 hrs of complete unilateral or bilateral ureteral obstruction, and GFR is 20-30% of normal after 24 hrs duration of uni- or bilateral ureteral obstruction (Wright 1982, Wilson 1992). Similar observations have been recorded in rabbits (Lyrdal and Olin 1975).

The vasodilatation which occurs in the obstructed kidney after 1-2 hrs of unilateral ureteral obstruction appears to be caused by local release of prostaglandins (Wright 1982). The vasoconstriction that appears in the postobstructive kidney after relief of complete unilateral ureteral obstruction, is possibly due to angiotensin, as ACE inhibitors increase GFR after release of 24 hr unilateral ureteral obstruction (Yarger et al. 1980, Wright 1982). In bilateral ureteral obstruction there is less vasoconstriction before relief and GFR is less sustained than in unilateral ureteral obstruction (Wright 1982).

5.1.2 Studies in humans

Little information is available as to the effects of urinary tract obstruction on GFR in man. However, ureteric obstruction is known to result in a marked fall in GFR, and bilateral incomplete obstruction leads to the development of progressive renal failure (Baker and Whitfield 1992). In chronic obstruction a reduction in GFR has been found (Olbrich et al. 1957). In man the relationship between duration of obstruction and extent of recovery of renal function after its reversal is unknown, but some

studies indicate that GFR either remains the same or increases (Baker and Whitfield 1992). In newborns and infants renal function returns to normal within 14 days from resolution of obstructive uropathy (Kallerhoff et al. 1992).

Renal ultrasound has been the most useful and convenient tool in determining clinical obstructive uropathy. A significant correlation prevails between elevated serum creatinine values and hydronephrosis detected by ultrasound in BOO patients (Koch et al. 1996). By reason, however, of the limitation of this approach in depicting which kidneys are significantly obstructed, the use of Doppler ultrasound has increased in recent years (El-Azad et al. 1966, Bude et al. 1991, Gilbert et al. 1993). In the acutely obstructed kidney De Toledo and group found mean RI to be 0.71 compared to the contralateral nonobstructed kidney, with a mean RI of 0.62 (De Toledo et al. 1996). The longer the obstruction had lasted and the more proximal the obstruction was, the higher were the mean RI values (De Toledo et al. 1996). Partial obstruction, on the other hand, may be accompanied by a normal RI (Platt 1992).

5.2 *Renal function after relief of obstruction*

Recovery of renal function is frequently observed after obstruction of less than 2-3 weeks' duration (Stecker and Gillenwater 1971, Wilson 1992). The extent of recovery depends upon whether the obstruction is partial or complete, the duration of obstruction and the presence of infection (Baker and Whitfield 1992, Wilson 1992).

Marked and prolonged diuresis may follow the relief of severe obstruction of both kidneys, and this is characterized by massive losses of water, sodium and other solutes (Wilson 1992). Mechanisms underlying this postobstructive diuresis include excretion of excess salt and water retained during obstruction, osmotic diuresis due to retained urea, inappropriate losses of sodium and water due to defective tubular reabsorption, inappropriate losses of water due to impaired renal concentration area and recovery of glomerular filtration (Bricker et al. 1957, Yarger and Buerkert 1982, Jones and Nandra 1983). Also hypophosphatemia due to inappropriately high urinary excretion of phosphate has been reported during diuresis after resolution of bilateral obstruction in humans and animals (Wilson 1992).

Renal blood flow increases after relief of obstruction, and in man GFR either remains the same or increases (Baker and Whitfield 1992). In contrast, an impairment of GFR, renal blood flow and concentration ability has been shown after relief of unilateral hydronephrosis

(Gillenwater et al. 1975). Also, relief of 24-hour unilateral ureteral obstruction in rats is followed by severe renal vasoconstriction in the postobstructive kidney, apparently mediated by angiotensins and thromboxanes (Yarger et al. 1980).

Impairment of GFR and diuresis have been observed in the rat after release of bilateral obstruction, and identical findings have been described in patients after relief of urinary obstruction (Bricker et al. 1957, Luton and Dietrich 1967, Jones and Nandra 1983). The impairment of GFR in the postobstructive state results from an intrarenal hemodynamic abnormality and the GFR is better maintained in superficial than in deep-lying nephrons (Jaenike 1972). The reduction in GFR is more severe following the relief of unilateral than bilateral ureteral obstruction (Yarger and Buerkert 1982).

AIMS OF THE STUDY

The overall purpose of the present study was to evaluate renal function subsequently to acute urinary retention caused by a benign disease. The detailed aims were:

1) to explore abnormalities in renal function and proteinuria during and after an episode of urinary retention by monitoring serum and urinary biochemical markers (I).

2) to investigate the effect of AUR on creatinine and ^{51}Cr-EDTA clearances (II).

3) to evaluate changes and correlations in kidney ultrasound and Doppler ultrasound images subsequent to AUR and during follow-up (III).

4) to ascertain the size and charge selectivity properties of the glomerular filtration barrier and the tubular reabsorption of proteins during and after AUR (IV).

5) to establish whether there is any recovery of glomerular and tubular function and to study the long-term prognosis in the patients with renal dysfunction after treatment of AUR (V).

PATIENTS AND METHODS

PATIENTS

1.1 *Subjects (I, II, III and IV)*

Twenty-five consecutive male patients attending the emergency department of the hospital for their first AUR, confirmed by mechanical emptying of at least 400 ml, participated in the study. Their median age was 67 yrs (mean 69 yrs), range 50-87, median retention time 24 hrs (mean 31 hrs), range 7-96, and median retention volume 1000 ml (mean 1135 ml), range 400-3080. A provoking factor was found in 13 patients: alcohol consumption (5), urinary tract infection (3), medical examination (2), minor trauma (1), obstipation (1) and use of furosemide (1). Previous diseases included arteriosclerosis (7), hypertension (8), atrial fibrillation (4), asthma (1), gout (1) and dementia (1). None of patients had previous renal dysfunction, renal artery stenosis, liver disease or diabetes, but many had a history of lower urinary tract symptoms. All were in good general health. Clinical data on the study patients are listed in Table 1. One patient was lost from the six months' follow-up due to death of heart infarction two months after AUR, and this patient was also excluded from study IV because of lacking measurements of IgG and IgG4 excretions during AUR. Thus, in study IV the mean age of the patients was 68 years (range 50-87), mean retention time 31 hours (range 7-96) and mean retention volume 1140 ml (range 400-3080).

1.2 *Subjects (V)*

At the six months' follow-up visit 15 of the above 25 patients still suffered from renal dysfunction, manifested as albuminuria or elevated excretion of urinary α_1M, and an additional follow-up visit was arranged 18 months after AUR. As noted, one patient was lost to this follow-up.

In the remaining 14 patients (mean age 71 years, range 50-87) the mean urinary retention time was 31 hours (range 9-96) and mean retention volume 1130 ml (range 400-3080). Of these patients five had arteriosclerosis, three hypertension, two atrial fibrillation and one gout. All were in good general health. Hypertension was treated with β-blockers in two cases and with ramipril in one.

1.3 *Ethical aspects*

All studies were conducted according to good clinical practice and the principles of the Declaration of Helsinki. All subjects gave written informed consent and the study was approved by the ethics committee of Tampere University Hospital.

2. METHODS

On admission to the hospital AUR was relieved by insertion of a suprapubic catheter and the volume of retention was measured. Patients were hospitalized for urine collections and usually discharged the following day with the catheter kept open to guarantee free bladder drainage until the 1-month follow-up visit.

During the 1-month visit the cause of urinary retention was clarified as BPE in 21 cases, bladder neck obstruction in 2 and urethral stricture in 2. All but two patients underwent surgery after this visit to release the infravesical obstruction, whereafter all started to void normally. Two patients with BPE needed no surgical procedure, as was verified at the 6-month follow-up visit

2.1 *Serum renal function parameters*

Blood samples were drawn during each attendance: immediately the patient arrived in the hospital before AUR was relieved and at the one, six and 18 months' visits. The following parameters were analyzed: s-creatinine, s-urea, s-urate, s-phosphate, s-albumin, s-β_2-microglobulin and s-lysozyme.

Serum creatinine, urea and lysozyme were measured by conventional quality-controlled methods and serum urate by an enzymatic method. Serum phosphate and albumin were assessed using colorimetric endpoint measurement and serum β_2M was measured by radioimmunoassay (Pharmacia, Uppsala, Sweden).

2.2 *Urinary renal function parameters*

After the relief of AUR urine collection was initiated for 8 hours. During the one-, six- and 18-month visits the patients brought in an 8-hour

overnight collection with the precise time of collection documented. After each collection another urine sample was provided to analyze β_2-microglobulin and pH from a separate sample. The following parameters were analyzed in the urine: osmolality, albumin, α_1-microglobulin, β_2-microglobulin, creatinine, phosphate, urate, citrate, total immunoglobulin G and immunoglobulin G4. As β_2M is rapidly destroyed in an acid medium, tubes containing sodium carbonate were used.

Urine samples were stored at -70 C until assayed. Urinary albumin and α_1M were measured from urine using a Behring Nephelometer (Behringwerke AG, Marburg, Germany) and β_2M by radioimmunoassay (Pharmacia, Uppsala, Sweden). Urinary creatinine, urate and citrate were measured by conventional methods and urinary phosphate using colorimetric endpoint assay. Urinary concentrations of total IgG and IgG4 were measured by enzyme-linked immunosorbent assay (ELISA).

2.3 *Glomerular filtration rate*

Creatinine and 51-chromium ethylene diamine tetra-acetic acid (^{51}Cr-EDTA) clearances were measured during each hospital visit. Creatinine clearance was measured subsequently after relief of AUR but ^{51}Cr-EDTA clearance for technical reasons approximately 39 hrs after relief of AUR. During follow-up visits one and six months after AUR both clearances were measured simultaneously. During the 18-month visit creatinine clearance was measured from serum creatinine using the Cockroft-Gault equation (Herget-Rosenthal et al. 1999).

Creatinine clearance was calculated from serum and urinary creatinine and corrected to 1.73 m^2 body surface area. Clearance of ^{51}Cr-EDTA was measured and calculated from plasma samples at 1½ and 3 hrs and corrected to 1.73 m^2 body surface area. The Cockroft-Gault equation was calculated as follows: crea clearance = (140- age [yr] x (patient's weight [kg]) / 72 x (serum creatinine [mg/dL]), correcting serum creatinine to 1 mg/dL (85 μmol/L).

2.4 *Ultrasound examination*

A sonography of both kidneys was obtained with a 3.5 MHz sector transducer and Doppler examination performed with a 3.5 MHz sector transducer (Acuson 128XP10 Mountain View). The Doppler signal was taken in the area of the arcuate arteries. Conventional kidney ultrasound

was applied in all cases to measure kidney length and cortical echogenicity during AUR, and after one and six months. Kidney Doppler ultrasound examination was made in 19 cases to calculate the RI simultaneously with conventional ultrasound. The time interval between the relief of AUR and the ultrasound examination was on the average 21 hours (range 0-96 hrs).

RI was calculated according to the following formula: RI = (peak systolic shift - minimum diastolic shift) / peak systolic shift. Each result was the mean of three measurements in different parts of each kidney.

2.5 *Transrectal ultrasound, uroflowmetry, residual urine and blood pressure*

Transrectal ultrasound of the prostate was applied to all except one of the patients during the one-month visit to measure the size of the prostate. Brüel & Kjaer ultrasound scanner type 1846 with 7 MHz transducer was used. Uroflowmetry and residual urine were measured in patients who were able to void during one- and six-month visits. Dantec Urodyn 1000 was used for uroflowmetry and Bladder Scan BVi 3000 with 2 MHz transducer for residual urine measurement.

Blood pressure was measured on admission to the hospital and at the one-month visit.

2.6 *Statistical methods*

Values are given as mean $\pm$ SD or median with range. For statistical analysis Wilcoxon´s non-parametic test and Student´s t-test for paired comparisons were used, with a probability <0.05 accepted as significant. The correlation analysis was based on the Pearson correlation coefficient, its value supported by the respective p-values. The level of significance equals 0.05.

Table 1. Clinical data on study patients (I-V)

Pt. No.	Age yrs.	Retention hrs.	Retention L	Retention cause	TRUS mL	Diseases	Medication
1.	64	72	3.1	BPE	51	ASO	salisylic acid
2.	76	96	1.2	BPE	24	ASO	salisylic acid, sotalol, nitroglycerin
3.	76	24	0.9	BPE	54	none	none
4.	60	24	1.0	BPE	32	HT	metoprolol
5.	69	24	1.0	BPE	52	none	none
6.	71	24	0.6	BPE	54	ASO, HT	amiloride, digoxin, diltiazem, salisylic acid
7.	64	48	1.4	BPE	41	HT	atenolol
8.	56	24	1.1	BPE	31	none	none
9.	74	72	1.7	BPE	27	dementia	melperonihydrochloride
10.	59	72	1.0	BNO	17	HT	pindolol, diltiazem
11.	58	24	0.8	BPE	64	HT	amiloride
12.	66	24	1.3	BPE	77	none	none
13.	83	24	1.4	BPE	71	none	none
14.	67	48	1.0	BPE	21	asthma	salmeterol, salbutamol, ipratropium. bromide
15.	74	12	1.0	BPE	40	ASO, HT	warfarin, amiodarone, iso-sorb.mononitrate, ramipril
16.	54	10	1.3	BPE	56	fibrill.	none
17.	80	12	0.9	BPE	25	ASO,AF	salisylic acid
18.	75	24	1.1	BPE	99	ASO, HT	isosorb.m-nitrate,atenolol furosemide, nifedipine, salisylic acid
19.	67	7	0.8	US	NA	none	none
20.	50	10	0.4	US	20	none	none
21.	65	11	1.3	BPE	54	none	none
22.	87	9	0.8	BNO	15	gout	allopurinol
23.	73	24	1.1	BPE	88	AF	sotalol
24.	65	24	1.0	BPE	43	none	none
25.	82	24	1.4	BPE	37	ASO, HT	metoprolol,salisylic acid

BPE= benign prostatic enlargement HT= hypertension
BNO= bladder neck obstruction AF= atrial fibrillation
US= urethral stricture ASO= arteriosclerosis
TRUS= transrectal ultrasound (size of the prostate)

RESULTS

1. POLYURIA AND ACIDIFICATION OF THE URINE (I)

After retention was relieved 5 patients evinced polyuria (20%) exceeding 1000-1750 ml within 8 hours. The average pH of the urine was mildly acidic (pH = 6.2) and osmolality 1.02 (normal > 1.015) during and after AUR (unpublished data).

2. SERUM RENAL FUNCTION PARAMETERS (I)

During retention average serum creatinine was slightly elevated. It became normal during follow-up but the improvement was not statistically significant. Average serum urea, urate, phosphate, albumin, β_2-microglobulin and lysozyme values were within normal limits during retention and follow-up. The difference during retention and follow-up was statistically significant only for urea (Table 2).

3. URINARY RENAL FUNCTION PARAMETERS (I)

Average urinary excretion of urate and citrate was within the normal range during acute retention and follow-up. There was a statistically significant difference in average urinary phosphate excretion during retention and after 6 months, although the excretions were within the normal range (Table 2).

Although mean urinary urate excretion was normal, abnormally low urate excretion was noted during retention in 29% of the patients, after 1 month in 56% and after 6 months in 46%, but the proportions of elevated excretion was 8%, 4% and 13%, respectively (Table 3).

4. GLOMERULAR AND TUBULAR PROTEINURIA (I, IV)

Urinary excretion of albumin, total IgG and IgG4 were elevated during AUR. Albuminuria and excretion of total IgG and IgG4 improved during follow-up, but the median excretion of albumin remained somewhat increased at the 6-month follow-up. Albumin clearance diminished during the follow-up period, the median value being within normal limits

at the 6-month visit (Table 4). Albuminuria persisted in 54% of the patients after AUR was relieved. Proportions of urinary total IgG and IgG4 excretion decreased significantly during follow-up (Table 3).

Excretion of α_1-microglobulin was elevated while that of β_2-microglobulin was normal during AUR. Median α_1M excretion remained increased 6 months after relief. In collected and separate urine samples median β_2M excretion was normal during acute retention and 6 months later but higher in the separate specimen (Table 4). There was a difference in the proportion of abnormal values in β_2M excretion between collected and separate urine specimens at the 6-month follow-up (9 and 21%, respectively); 58% of patients still had elevated α_1M excretion 6 months after relief of AUR (Table 3).

5. CREATININE AND ^{51}CR-EDTA CLEARANCE (II)

Average and median creatinine clearances were diminished during retention but became normal during follow-up. There was a statistically significant difference in both average and median creatinine clearance during retention and after 6 months (Table 2 and 4). Lowered values were noted during AUR, after one and six months in 65%, 48% and 42% of the patients, respectively (Table 3).

Median ^{51}Cr-EDTA was 86 ml/min/1.73m^2 during AUR and remained at the same level throughout follow-up (Table 4). The ^{51}Cr-EDTA values tended to remain at the same level in each patient. According to age-related reference values ^{51}Cr-EDTA clearance was decreased in three patients during AUR, in one after 1 month and in two after 6 months. Changes in ^{51}Cr-EDTA clearance during follow-up were not statistically significant.

6. ULTRASOUND FINDINGS (III)

A total of 50 kidneys were studied by ultrasound during the period of acute urinary retention and after one and six months. During retention ultrasound showed hydronephrosis in three patients, including one with hydroureters, but renal parenchyma and kidney size were normal in all. The average kidney length was 10.9 cm on the right and 11.2 cm on the left during AUR. Kidney length decreased non-significantly at follow-up. Only one of our study patients had enlarged kidneys during retention, the

right kidney being 14 cm and the left 14.5 cm; this normalized during follow-up.

RI was calculated for 38 kidneys. During retention the average resistive index (normal less than 0.70) was elevated in both kidneys, being 0.71 in the right and 0.70 in the left. It improved slightly during follow-up and was more or less within normal limits at the 6-month follow-up, 0.69 right and 0.68 left. The changes were not statistically significant. During retention, after one month and after six months the proportions of normal RI in both kidneys were 42%, 53% and 64%, respectively. RI differences between right and left kidney in any given patient were minimal.

An inverse correlation emerged between age and RI ($r = -0.465$, $p = 0.045$) and between retention volume and RI ($r = -0.4996$, $p = 0.029$) during retention, but none between these parameters at follow-up. There was a positive correlation between the time interval before relief of retention and resistive index values ($r = 0.4881$, $p = 0.034$). No correlation was noted between RI and serum creatinine, or between RI and creatinine clearance during retention and at the one-month follow-up; at six months, however, there was an inverse correlation between RI and creatinine clearance ($r = -0.5996$, $p = 0.007$).

7. TRANSRECTAL ULTRASOUND, UROFLOWMETRY, RESIDUAL URINE AND BLOOD PRESSURE

The average size of the prostate measured by transrectal ultrasound in BPE and urethral stricture patients was 49 ml, and in bladder neck obstruction patients 16 ml. After one and six months from retention the voided volume in uroflowmetry was 263 ml and 259 ml, the maximum peak flow 12.1 ml/s and 18.5 ml/s and residual urine 69 ml and 65 ml, respectively (unpublished data).

The mean systolic and diastolic blood pressure was 159/89 (ranges 205-115/120-79) during retention and 142/84 (ranges 176-120/100-65) after one month. The blood pressure reduction was statistically significant in systolic ($p < 0.012$) but not in diastolic pressure ($p < 0.24$).

8. LONG-TERM RENAL FUNCTION (V)

During retention and follow-up median serum creatinine and serum urea were normal. Serum urea was elevated in patients with elevated serum

creatinine. Median serum phosphate and albumin were in most cases within normal limits during retention and at follow-up. Median creatinine clearance was 1.4 ml/s/1.73m^2 during retention which was normal, and it deteriorated slightly to 1.2 ml/s/1.73m^2 during follow-up.

During retention and after one month and six months median urinary albumin excretion was 234 μg/min, 12 μg/min and 8 μg/min (normal < 11 μg/min), respectively. Median daily protein excretion was measured at the long-term visit only and was found to be elevated 0.15 g (normal 0.02-0.08 g).

During retention all patients had albuminuria, but this diminished to 29% during follow-up. During retention almost half of the patients (42%) evinced elevated excretion of α_1M and the number of such patients increased during follow-up, up to 100% at 18 months after AUR. The proportion of patients with abnormal creatinine clearance likewise increased from 46% during AUR to 71% during follow-up.

Table 2. Serum and urinary renal function parameters (average ± SD) during and after AUR

	During AUR	1 month	6 months
s- creatinine (normal < 115 μmol/l)	128 ± 102	97 ± 25	98 ± 19
s- urea (normal 3-8.5 mmol/l)	8.6 ± 4.8	5.9 ± 1.7*	6.3 ± 1.6*
s- urate (normal 0.16-0.45 mmol/l)	0.3 ± 0.08	0.3 ± 0.08	0.3 ± 0.06
s- phosphate (normal 0.8-1.4 mmol/l)	1 ± 0.4	1 ± 0.2	0.9 ± 0.1
s- albumin (normal 36.1-47.5 g/l)	42.4 ± 6.4	42.2 ± 8.3	41.8 ± 3.9
s- β_2-microglobulin (normal 1-2.5 μg/l)	2.0 ± 0.6	2.1 ± 0.8	2.2 ± 0.7
s- lysozyme (normal 0.9-2.1 mg/l)	1.5 ± 0.5	1.5 ± 0.6	1.4 ± 0.3
cu-urate excretion (normal 2-4.1 μmol/min)	2.7 ± 1.8	2.1 ± 0.8	2.4 ± 1.4
cu-phosphate excretion (normal 14-35 μmol/min)	24 ± 9.9	24 ± 9.4	30 ± 17.1*
cu-citrate excretion (normal > 1.0 μmol/min)	1.7 ± 1	1.6 ± 1	2.2 ± 1.8
creatinine clearance (normal > 1.4 ml/s/1.73m^2)	1.2 ± 0.5	1.4 ± 0.5	1.7 ± 0.6*
c- pH	6.2 ± 0.7	6.3 ± 0.7	6.2 ± 0.9

* t test $p < 0.05$

Table 3. Proportion (%) of abnormal serum and urinary values during and after AUR

	During AUR	After relief of AUR 1 Month	6 Months
s-creatinine	28	12	13
s-urea	36	4	8
s-urate	4	0	0
s-phosphate	24	12	8
s-albumin	16	16	4
s-lysozyme	4	4	8
cu-uric acid	8	4	13
cu- phosphate	14	8	13
cu-citrate	24	28	17
cu-albumin	100	92	54
cu-IgG	79	58	40
cu-IgG4	67	42	20
cu-α_1M	54	39	58
cu-β_2M	17	19	9
cu-β_2M*	21	18	21
creatinine clearance	65	48	42

*separate sample

Table 4. Proteinuria and GFR (median and range) during and after AUR

	During AUR	1 month	6 months
cu- albumin excretion (normal < 11 μg/min)	**238** (12-7292)	**72 *** (4-1746)	**12 *** (2-135)
cu- IgG excretion (normal < 2.5 μg/min	**13.07** (1.0-2741.7)	**7.83*** (0.3-179.6)	**2.15•** (0.04-91.8)
cu- IgG4 excretion (normal < 0.1 μg/min)	**0.49** (0.02-125.42)	**0.04*** (0-3.03)	**0.01•** (0-7.98)
albumin clearance (normal < 0.33 ml/min)	**5.4** (0.3-39.6)	**1.9•** (0.1-39.9)	**0.3•** (0.03-2.9)
cu-α_1-M excretion (normal < 7 μg/min)	**7.7** (2-175)	**6.4** (1-43)	**9.8** (2-47)
cu-β_2-M excretion (normal < 400 μg/l)	**154** (100-19000)	**135** (100-2000)	**126** (28-800)
u-β_2-microglobulin⊗ (normal < 400 μg/l)	**225** (100-12200)	**238** (100-2000)	**211** (28-1363)
creatinine clearance (normal > 1.4 ml/s/1.73m^2)	**1.1** (0.3-2.0)	**1.4** (0.7-2.4)	**1.7 *** (0.4-2.7)
^{51}Cr-EDTA clearance (ml/min/1.73m^2)	**86** (28-129)	**85** (44-128)	**81** (45-128)

*****Wilcoxon's signed rank test p<0.01
•Wilcoxon's signed rank test p<0.001
⊗ Separate sample

DISCUSSION

1. TREATMENT OF ACUTE URINARY RETENTION

During prolonged urinary tract obstruction the urine may escape across the walls of the collecting system or be reabsorbted directly across the walls of the renal pelvis through the lymphatics or renal venous system in order to prevent damage to the kidney (Wilson 1992). This may explain, at least partly, the relatively small average retained urine volume 1135 ml in the present patients although the average duration of retention was 31 hours.

Because most patients with acute retention have chronic obstruction, a suprapubic catheter was left indwelling for one month in our patients to guarantee free drainage before obstruction relieving surgery, permitting the recovery of renal function. None of our patients had macroscopic hematuria after the suprapubic catheter was inserted and urinary collections were not started until after bladder emptying. At one and six months of follow-up there was no hematuria. It would thus seem unlikely that suprapubic insertion, an indwelling catheter or the subsequent surgical procedure contributed significantly to urinary collection findings. AUR is considered a powerful indication for definitive treatment in prostatic disorders, simple mechanical emptying of the bladder being inadequate without subsequent observation (Breum et al. 1982). Among the present patients all but two needed surgery to normalize voiding. Since they voided normally at follow-up, as seen in uroflowmetry results, obstruction could not have hampered recovery of renal function.

2. POLYURIA AFTER THE RELIEF OF AUR

Marked and prolonged diuresis may follow the relief of severe obstruction of both kidneys. This condition is characterized by massive losses of water, sodium, and other solutes (Wilson 1992), and urine osmolality may be reduced due to tubular dysfunction. Another predictable consequence of obstructive uropathy is impaired ability to secrete an acid load and to excrete potassium; thus, urinary pH measurements will be inappropriately high during chronic uni- or bilateral obstruction (Klahr and Brander 1983). Only five of the present patients had polyuria and the urine osmolality was normal following

drainage of the bladder. Also the average pH was acidic during and after AUR and only three patients had urinary tract infections preceding AUR. These observations all suggest the acute nature of the retention in these subjects.

3. CHANGES IN SERUM AND URINARY RENAL FUNCTION PARAMETERS

Renal function is most commonly monitored by serum creatinine. Many studies indicate that this is a sufficiently precise mode of measurement (Parkin et al. 1989, Robert et al. 1993). In this study there were six patients with elevated serum creatinine during AUR although all had albuminuria. Thus serum creatinine did not predict proteinuria. Serum urea was elevated in the patients with elevated serum creatinine. In serum uric acid, phosphate, albumin, β_2-microglobulin and lysozyme values there were random low and high values during AUR and follow-up. These parameters seemed to give no information regarding possible renal dysfunction in AUR patients, although the proportion of abnormal serum values of these parameters decreased during the observation period. Hypocitraturia and excessive excretion of phosphate and urate in postobstructive diuresis have been described in some previous reports (Wilson 1992), but such findings could not be confirmed in the present study. In contrast, urate excretion was decreased in many of our patients during retention and at follow-up, probably because most of our patients did not have postobstructive polyuria. In only two cases were all urinary renal function parameters normal six months after acute urinary retention was relieved.

Some diseases such as hypertension and diabetes, and drugs such as antibiotics, diuretics, ACE inhibitors and non-steroidal anti-inflammatory analgetics may cause renal damage. However, in the present study was noted no difference in serum or urinary renal function parameters in the 8 patients with hypertension, or in the 4 on diuretics or angiotensin converting enzyme inhibitor compared with the others.

4. PROTEINURIA

Since plasma proteins are handled in the kidneys by both glomerular filtration and tubular reabsorption (Jensen et al. 1995), dysfunction in either may be a cause of proteinuria (Guder and Hofmann 1992). It is

widely accepted that hemodynamic alterations, the size and charge selectivities of the glomerular capillary filtration barrier and tubular reabsorption are implicated in the pathogenesis of proteinuria (Deckert et al. 1988, Chiba et al. 1991, Jensen et al. 1995). Proteins of higher molecular weight are not normally filtered by the glomerulus, and increased urinary excretion of IgG reflects glomerular proteinuria (Guder and Hofmann 1992). Increased excretion of total IgG may indicate increased pore size in the glomerular filtration barrier. Also, as the IgG4 subclass is more anionic but of the same size and configuration as total IgG, an increased excretion of IgG4 may be explained by reduced amounts of retropulsive anionic components in the glomerular filter (Jensen et al. 1995). In addition, an altered tubular charge may influence the excretion level of urinary albumin, IgG and IgG4 (Hansen et al. 1995).

Proteinuria was a common finding in this material. We noted albuminuria and increased excretion of total IgG and IgG4 immediately following relief of acute urinary retention, this reflecting increased glomerular permeability. During follow-up albuminuria and excretion of both IgG and IgG4 diminished. In healthy subjects the mean excretion of total IgG has been reported to be 2.3 μg/min and IgG4 0.14 μg/min, and a significant difference has been found in the excretion of albumin, total IgG and IgG4 between normal and diabetic subjects with nephropathy (Gall et al. 1994). With this in mind, we used an excretion level < 2.5 μg/min for total IgG and < 0.1 μg/min for IgG4 as the limit of normal excretion. The proportions of elevated excretion of IgG and IgG4 thus diminished significantly during follow-up, reflecting recovery of glomerular filtration. As excretion of both IgG and IgG4 increased during retention and resolved during follow-up, it would appear that the charge of the glomerular basement membrane is not altered during retention; the cause is either increased pore size or impaired tubular reabsorption or both in combination. Increased glomerular permeability due to AUR and manifested as elevated excretion of IgG and IgG4 seemed to recover rapidly.

Patients with albuminuria also evinced elevated α_1-microglobulin and β_2-microglobulin excretion. During the follow-up excretion of α_1M persisted. Although measurement of β_2M is difficult by reason of its instability, it was used in this study together with α_1M to provide more reliable data on tubular function. Urinary β_2M excretion was elevated in only few patients with elevated urinary α_1M excretion, and there was a difference in urinary β_2M excretion at one and six months, as measured in collected and separate urine specimens. This finding confirms the

conception that β_2M is unstable in the urinary bladder and is not a reliable parameter of tubular dysfunction.

Immediately after AUR both glomerular and tubular renal function was impaired but partly recovered during the first month of free bladder drainage. Glomerular damage seen as albuminuria and tubular damage seen as increased α_1M excretion also persisted at the 6 month follow-up visit in about half of the patients. It would seem that a major site of injury resulting from obstructive nephropathy lies in the distal nephron (Yarger and Buerkert 1982). Bilateral ureteral obstruction reduces reabsorption either by prolonged increased intratubular pressure or by changes in renal blood flow (Yarger and Buerkert 1982). Since slight albuminuria and increased α_1M excretion persisted in the majority of our patients after 6 months from relief of AUR, tubular reabsorptive function would seem to be permanently disturbed by the episode, a conception also confirmed in the long-term study (V). This may of course be due partly to previous chronic obstruction, which could not be evaluated in present context.

Although hypertension and diabetes and drugs such as diuretics and ACE inhibitor may have an influence on proteinuria, we noted no difference in proteinuria in the 8 patients with hypertension or in 4 patients on diuretics or ACE inhibitor compared with the rest. The three patients with urinary tract infection during AUR likewise showed no difference in proteinuria findings compared to the others and had prophylactic antibiotic treatment concomitant with the use of a catheter. During the 1-month visit urinary infection was found in four patients with a suprapubic catheter, but their proteinuria findings were nonetheless similar to those without infection.

5. CREATININE AND ^{51}CR-EDTA CLEARANCE

The clearance of endogenous creatinine has long been used to provide a measure of the GFR (Flynn 1990). Creatinine clearance as a marker in fact overestimates the rate in renal insufficiency (Shemesh et al. 1985), because creatinine is actively secreted in the tubulus and secretion increases as the GFR decreases (Bloor et al. 1996). In addition, creatinine clearance tends to decline with age (Garwood and Hines 1996). Several substances can, moreover, interfere with laboratory measurements of creatinine. In the present case, however, serum and urinary creatinine concentrations were measured by the enzymatic method, which is considered to be reliable. The average creatinine clearance was dimished

in 65% of our patients during retention but improved significantly during follow-up, a reflecting recovery of filtration after relief of AUR.

Clearance of radionuclide marker ^{51}Cr-EDTA has been used as a reliable measure of GFR but is costly, involves special specimen handling and requires radiation exposure (Swan 1997). Also, ^{51}Cr-EDTA clearance decreases as age increases (Askergren et al. 1981, Granerus and Aurell 1981). In addition, technical factors such as sample timing or dehydration of the patient can interfere with ^{51}Cr-EDTA measurement. In our patients technical sources were standardized to eliminate errors in measurements.

^{51}Cr-EDTA clearance is the method of choice for detecting changes in glomerular function in patients with slightly or moderately reduced clearance levels (Granerus and Aurell 1981). It has been shown in animal studies that ^{51}Cr-EDTA clearance decreases after one day of ureteral obstruction (Lyrdal and Olin 1975). As GFR declines with age, it is important to use reliable reference values. Age-related reference values have been reported in a few studies (Askergren et al. 1981, Granerus and Aurell 1981) but they are not in general use. ^{51}Cr-EDTA clearance >70 ml/min/1.73m^2 has been considered a limit of relatively good glomerular function (Chan et al. 1992). In our patients the median values of ^{51}Cr-EDTA clearance during AUR and follow-up were above 80 ml/min/1.73m^2. Applying age-related reference values according to Askergren and associates (1981), ^{51}Cr-EDTA clearance were found to be decreased in three patients during AUR, one patient after one month and two patients after six months. ^{51}Cr-EDTA clearance tended to remain at the same level in each patient. Changes in ^{51}Cr-EDTA clearance during follow-up were not statistically significant.

Here creatinine clearance was measured immediately after the retention was relieved whereas ^{51}Cr-EDTA clearance for technical reasons was assessed approximately 39 hours after relief, which is most probably the reason for the high number of patients with normal ^{51}Cr-EDTA clearance values during AUR. Creatinine clearance was measured at such an early stage after retention that glomerular dysfunction was present. Dysfunction seemed to recover rapidly. Although it was not possible to measure ^{51}Cr-EDTA earlier, measurement of creatinine clearance simultaneously with ^{51}Cr-EDTA might have given more information of the recovery of glomerular function after relieving AUR. At one and 6 months after AUR both creatinine clearance and ^{51}Cr-EDTA were normal in most of the patients.

Many drugs, especially those acting on the renal microvascular circulation, have an effect on the GFR. Use of prostaglandin synthesis inhibitor or ACE inhibitors may result in a lowered rate (Pedersen et al.

1989, Marin et al. 1992). In the patients with prostaglandin-dependent renal function, non-steroidal anti-inflammatory drug administration constantly reduces GFR (Pugliese and Cinotti 1997). Among our patients none used prostaglandin synthesis inhibitors. Only one used ACE inhibitor and his GFR was normal during AUR and follow-up. Six used salicylic acid at low dosages, eight β–blockers and three diuretics, but there was no difference in fitration rates in this group compared with other study patients. Other medication used is not known to have any effect on the GFR. Eight of our patients had hypertension and three urinary tract infection during AUR, but their GFR did not differ from that in other study patients

6. CONVENTIONAL AND DOPPLER ULTRASOUND

Ultrasound showed hydronephrosis in three of the present patients during retention, one of them with hydroureters, but renal parenchyma was normal in all, this reflecting the acute nature of the retention. At follow-up the ultrasound image was normal in all cases. The average kidney length was within normal limits (Brandt et al. 1982) during retention and at follow-up in all except one patient who had hydronephrosis during retention.

The renal vascular bed in a normal kidney is characterized by low impedance to blood flow, resulting in a continuous forward flow in the diastole (Mostbeck et al. 1991). From normal data, 0.70 has emerged as a reasonable upper limit for a normal mean intrarenal RI (Platt 1992) and this was therefore adopted in the present series. Hemodynamic changes occur in a state of significant renal obstruction. After 5 hrs of obstruction elevated RI is to be expected and if obstruction persists for at least 18-24 hrs, the normalization of RI may not be immediate; it may take days or even weeks to return to baseline levels (Platt 1992). In our patients the retention time ranged from 7 to 96 hrs, mean 31 hrs, and in most of them RI was not normal at Doppler ultrasound examination, which took place on an average 21 hrs after the release of AUR. Our RI findings therefore most probably fairly accurately present the situation at the time of AUR.

In the acutely obstructed kidney the mean RI has been found to be 0.71 compared to the contralateral nonobstructed kidney with a mean RI of 0.62 (De Toledo et al. 1996). The longer the obstruction had lasted and the more proximally it was located, the higher were the mean RI values (De Toledo et al. 1996). However, partial obstruction may be accompanied by a normal RI (Platt 1992). Clinically significant partial

obstruction is almost always a chronic disease, and if the obstruction is of a certain degree, changes similar to those in complete obstruction may occur. Prediction regarding which instances of partial obstruction are significant and will lead to renal atrophy and functional loss is an open question. Although no data were available on RI values in our patients prior to retention, improvement in both mean RI and a proportion of patients with normal RI did occur during follow-up. In spite of this, previous chronic obstruction may have caused structural changes in the kidneys and deteriorated renal blood flow, a possibility which could not be evaluated in this study. In addition, RI differences between right and left kidney were not significant in our patients. Thus, urinary retention caused complete bilateral ureteral obstruction and both kidneys experienced the same increase in intrapelvic pressure. This is in contrast to previous findings where the obstruction has been unilateral and differences have been found between obstructed and nonobstructed kidney in the same individual (Rodgers et al. 1992, De Toledo et al. 1996). It has been noted in animal studies that in cases of unilateral ureteral obstruction the nonobstructed kidney compensates renal function and renal blood flow of the obstructed kidney probably by means of circulating vasodilatating agents (Wright 1982). However, since in AUR both kidneys are equally obstructed, no compensation can occur. AUR thus constitutes a potential overall threat to renal function. In our patients there was a positive correlation between the time interval before relief of obstruction and RI, which further stresses the importance of rapid treatment of AUR.

Essential hypertension is associated with a normal resistive index (Pozniak et al. 1988) and RI increases with age in these patients (Pontremoli et al. 1999). Patients without evidence of renal disease, diabetes mellitus or hypertension show an increase in RI with increasing age (Platt 1992, Mostbeck et al. 1991). Nonetheless 0.70 is considered the upper limit of normal RI even at ages over 70 years (Platt 1992). In our patients an inverse correlation was found between RI and age during retention, while none was found between these parameters during follow-up. This can only be explained by the disturbing effects of urinary retention on RI. It probably also explains the inverse correlation between retention volume and RI. The RI can also be affected by certain nonurologic renal diseases and oral hydration (Shokeir et al. 1996). However, none of our study patients was suffering from renal or liver disease or diabetes. We found no difference in resistive index or kidney ultrasound images in our eight patients with essential hypertension treated with β-blockers, diuretics or ACE inhibitor as compared to other subjects. Moreover, since ultrasound was performed approximately 21

hours after relief of retention, our patients were in a state of normal hydration during the examination.

RI provides information regarding renal status not reflected by creatinine levels (Platt 1992). Only a weak positive correlation has been found between creatinine level and RI in acute renal failure patients (Platt 1992). A significant correlation prevails between elevated serum creatinine values and hydronephrosis in BOO patients (Koch et al. 1996). In diabetic patients a correlation has been found between RI and serum creatinine and in cirrhosis patients an inverse correlation between RI and creatinine clearance (Kim et al. 1992, Sacerdoti et al. 1993). Here we found no correlation between RI and serum creatinine during retention and follow-up, nor was any correlation found between RI and creatinine clearance during retention and at the one-month follow-up, while a significant inverse correlation emerged between these parameters at the six-month follow-up. This confirms the conception that renal blood flow, as well as glomerular filtration rate, was affected by urinary retention, and both partly recovered after relief of retention, but recovery was not instant.

7. BLOOD PRESSURE CHANGES

Hypertension in obstructive nephropathy may result from fluid and salt retention, increased renin secretion or decreased synthesis of renal medullary vasodepressor substances such as prostaglandins (Wilson 1992). The elevation of systolic blood pressure at the time of urinary retention in our patients was most probably caused by the pain due to bladder distension, because only 5 of our patients had polyuria following the relief of AUR. However, increased renin secretion or decreased prostaglandin synthesis might have played some role in the elevation of systolic blood pressure, an aspect which could not be evaluated in this study. The renal function findings during retention in the patients with systolic blood pressure over 140 were no different from those in the other study patients. Because urinary collection did not commence until the bladder was emptied, we assume that the systolic blood pressure returned to normal level after the relief of retention, and thus probably had no effect on the proteinuria findings.

8. LONG-TERM RENAL FUNCTION

In the long-term renal function study serum renal function parameters proved inaccurate as indicators of renal function, since they failed in most cases to detect mild renal tubular dysfunction. In our patients median serum creatinine was normal during retention and at follow-up, but 64% still had albuminuria at the 6-month visit. Serum urea, serum phosphate or serum albumin also yielded no information on renal dysfunction during retention or at follow-up.

Although the changes in creatinine clearance in our patients were mild, clearance did decline and the number of patients with abnormal creatinine clearance values increased during the follow-up of 18 months. Creatinine clearance overestimates the GFR (Shemesh et al. 1985); creatinine is actively secreted in the tubulus and the secretion increases as the GFR decreases (Bloor et al. 1996). In addition, creatinine clearance tends to decline with age (Garwood and Hines 1996). In the present case, however, the observation period was not long enough for aging to have caused a decline in GFR. Since the number of patients with impaired creatinine clearance increased during follow-up, it seems likely that renal function partly deteriorated even after urinary obstruction was relieved and despite normal median serum creatinine. On the other hand, all patients had albuminuria during retention; this diminished, however, during the observation period of 18 months, indicating partial recovery of glomerular permeability. The discrepancy between results by these two methods is probably explained by the fact that albumin is more predominantly an indicator of glomerular damage whereas creatinine clearance also reflects tubular dysfunction. This is supported by the finding that total protein excretion, which measures both glomerular and tubular proteinuria, was elevated in 69% of our patients during 18 months' follow-up. In addition, albumin tends to pass through the kidney filter in many common conditions such as physical exercise and urinary infection (Morano et al. 1987). In all, AUR caused no any significant impairment of glomerular permeability in the long term.

One important finding was that excretion of α_1M, a sensitive and reliable marker of proximal tubular function (Baker and Whitfield 1992), increased up to the 18-month follow-up, when all patients had abnormally high α_1M excretion values. It has been suggested that obstruction disturbs tubular more severely than glomerular function (Yarger and Buerkert 1982), and it is possibly the diminished blood flow which induces histopathological changes in the tubule, that is, chronic tubulointerstitial nephritis, which continues to progress even after the

obstruction is relieved (Coroneos et al. 1997). Although in most of our cases the increase in α_1M excretion was mild it, nonetheless, showed that AUR interfered with tubular function and this did not recover after relief of retention but continued to worsen.

We found no difference in serum and urinary renal function parameters between the three patients with hypertension treated with β–blockers or ACE inhibitor compared to the remainder. There was likewise no difference in these parameters between the patient with urinary tract infection and the other participants.

CONCLUSIONS

The major findings and conclusions were the following:

1. AUR had an effect on both glomerular and tubular renal function and after the release of AUR increased glomerular permeability and tubular damage persisted in the majority of patients. Serum renal function parameters did not predict possible renal dysfunction in AUR patients.

2. Although lowered creatinine clearance immediately subsequent to AUR suggested impairment of the GFR in some cases, the ^{51}Cr-EDTA clearance, which we consider the most accurate method of measuring the GFR was normal in almost all of our patients measured approximately 1½ days, one month and 6 months after relieving AUR. This suggests that short-term acute urinary retention does not cause irreversible glomerular failure.

3. The resistive index measured by Doppler ultrasound was elevated following AUR, which may be interpreted as manifesting diminished renal blood flow or increased arterial resistance. RI was still elevated in one third of the patients six months after AUR, suggesting previous chronic obstruction which had hampered renal function before the onset of AUR. A significant inverse correlation emerged between RI and creatinine clearance at the six-month follow-up. This confirms the conception that renal blood flow as well as the glomerular filtration rate were affected by urinary retention, and both partly recovered after relief but the recovery was not instant.

4. AUR caused disturbances in both glomerular filtration and tubular reabsorption of proteins. Albuminuria and increased excretion of the HMW proteins IgG and IgG4 and the LMW protein α_1M were evinced in the majority of our patients during AUR. After relief of retention, excretion of IgG and IgG4 diminished significantly while that of albumin and α_1M persisted, indicating slightly increased glomerular permeability and a permanent disability of the proximal tubulus to reabsorb proteins.

5. Patients suffering from albuminuria or elevated α_1M excretion six months after relief of AUR had persistent renal dysfunction in the long term in spite of adequate treatment of BOO. Especially tubular function was permanently impaired, whereas glomerular permeability partially recovered.

SUMMARY

The aim of the present study was to assess the effect of acute urinary retention on renal function by measuring changes in serum and urinary renal function parameters, renal arterial blood flow, glomerular filtration rate and proteinuria as well as long-term effects of AUR on these functions. The renal arterial blood flow was measured by determining RI by Doppler ultrasound and the GFR by creatinine and ^{51}Cr-EDTA clearances.

Serum and urinary renal function parameters as well as GFR and RI were measured in 25 male patients, and glomerular and tubular proteinuria in 24 male patients subsequently and one and six months after their first acute urinary retention was relieved by a suprapubic catheter. All but two of them underwent surgery to normalize voiding after one month from AUR. Long-term effects of AUR on renal function were studied in 14 of these 25 patients.

Immediately after AUR both glomerular and tubular renal function were impaired but partly recovered during the first month of free bladder drainage. Glomerular damage seen as albuminuria, and tubular damage seen as increased α_1-microglobulin excretion also persisted at the 6-month follow-up visit in about half of the patients. Renal arterial blood flow was also diminished during retention and partly normalized during follow-up. At the 18-month follow-up all patients still evinced abnormally high α_1M excretion, showing persistent impairment in tubular function, whereas glomerular permeability had recovered. The increase in α_1M excretion was in most cases mild and may in part be explained by previous chronic obstruction. These findings stress the importance of early recognition and prompt treatment of AUR, since the degree of irreversible renal damage resulting from obstruction is related to its duration as well as to its severity. There is nonetheless a need for further studies on larger numbers of patients and with longer follow-up to confirm our findings.

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