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PRESIDENT WRITES

Dear Fellows and Members,

The topic of this issue is a problem commonly seen in all age groups and in different socioeconomic strata. In high socioeconomic strata the formation of stones occurs in the upper urinary system; and in lower economic strata it occurs in the lower urinary system.



In short, it enunciates that there is a likelihood of nutrition being involved as an etiological factor. A lot of work has gone into the etiology of urolithiasis, still more work is needed to be done towards unraveling the etiology of this disease; this will help in designing prevention strategies.

Our annual convention is taking place at Chandigarh. I am sure all of us will have a good meeting at Chandigarh.

K. Jagadeesan

Dr. K. Jagadeesan
President, IMSA

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All fellows and members of IMSA can have access to the site and get information about its objectives, benefits to the fellows/members, chapters and their activities including seminars, refresher courses, rural CME;s etc. and also IMSACON - a regular annual event of international standard; *application form for enrollment as fellow/member can also be downloaded. Fellows - members and even not fellows - members can have access to full text in the quarterly journal - jimsa from July - Sept. 2003 onwards by putting their E-mail address under 'user name' and using the password 'UserJimsa'.*



Dr. P. Narasimha Rao

Ex. President, IMSA World H.Q.

Dr. Pinnamaneni Narasimha Rao International Award

Appeal by Vice-President IMSA



Dr. R.R.Thukral

Vice President IMSA World H.Q.

Dear Fellows and Members

You are aware late Dr. P. Narasimha Rao, an international figure both in academic and teaching had been the President of this prestigious organization for more than a decade from 1990 to 2002. He was President of Medical Council of India and Vice Chancellor of various Universities. He had to his credit several outstanding contributions to the medical fraternity till his death. He had been in close association with IMSA since its very inception in 1981. The Academy has flourished tremendously during his tenure as President. Keeping in view his status, services rendered to the mankind and on the insistence of senior Fellows, the Academy has established an International Award in his honour named 'Dr. Pinnamaneni Narasimha Rao International Award', on the lines of Dr. B.C. Roy National Award. Substantial funds are needed for this prestigious award. Initially, the family of Dr. P. Narasimha Rao has contributed a fair amount of money and has also assured to contribute more.

I appeal to all our Fellows and Members to contribute generously for this noble cause in the memory of this dedicated acadamecian - Dr. P. Narasimha Rao. A separate account has been opened for this Award.

(R.R.Thukral)

IMSA Chapter Activities

Tamil Nadu Chapter

- 12.7.09 **Dr. Sivagadatcham:** Management of Congestive Cardiac Failure & Hypertension.
 9.8.09 **Prof. P. Sekar:** Diagnosis and Management of Pyrexia of Unknown Drigin.
 13.9.09 **Dr. R. Ramnarayan :** Recent Treants in the management of chronic pain.
 Sub Chapter Annamalaiinagar
 10.7.09 **Dr. Ms N. Amudhavalli:** Physical aspects of mammography and case demonstration.
 10.7.09 **Dr. Sethurjan:** Clinical aspects of mammography

Delhi Chapter

- 26.9.09 *Problem of adolescent girls symposia organized by Delhi Chapter of IMSA & Moolchand Medcity*
 Participants were:
 Dr.S. Mehra, Dr. M. Hotchandani
 Dr. Y. Juneja, Dr.I. Khatri,
 Dr. S. Kala,

Election of Fellows and Members (July-Sept 2009)

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(till these doctors complete their qualifications)
 Dr. Manoj Gaur , Delhi
 Dr. Kapil Dev Mohindra, UP

HONOUR

Dr. P.D. Gulati, FIMSA, has been awarded the "MASTER TEACHER 2009" award, by the Association of Physicians of India and Indian College of Physicians, in recognition of his Outstanding Teaching Capabilities.

Suggestions to Enhance Image of Medical Profession and Improve Doctor-Patient Relationship

President, Vice President and Trustees of IMSA have stressed that IMSA must engage itself in enhancing the image of Medical Profession by organizing seminars/conferences on various issues relating to medical profession, medico legal, patient — doctor relationship protocol of drug trials and research etc. It was also desired that suggestions be invited from all fellows and members, for improving relationship among doctors and patients. The Fellows and Members are, therefore, requested to send their suggestions & ways and means to IMSA World Headquarter at New Delhi, for enhancing image of medical profession and improving doctor — patient relationship.

Secretary General, IMSA

Change in Address

If the address of any Fellow/Member of IMSA has been changed , he may please intimate his latest address to IMSA, WHQ, New Delhi for future communication.

Dr.R.R.Thukral, Vice - President IMSA,WHQ



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FROM EDITOR'S DESK

Dear colleagues

The speciality of Urology has evolved into a less surgical and more cognitive discipline. Indeed, much of Urology that is practised today involves non-or mini-operative patient care. This is specially true of Urolithiasis which is a third common kidney disease encountered in clinical practice. Technological advancements have, perhaps, brought the biggest benefit to the field of Urology by way of prompt diagnosis, recognition of risk factors, early therapeutic intervention, effective preventive strategies and aggressive management wherever necessary. These have led to least morbidity in kidney stone disease. India has a high incidence of kidney stones, specially in states of Jammu & Kashmir, Punjab, Delhi, Rajasthan, Madhya Pradesh, Gujarat (*Stone belt*): data regarding prevalence in population are not available; however, in a tertiary care urological centre, renal stones account for more than 40% of all admissions.

This special issue on "**Urolithiasis: Current Perspective**" has been compiled and edited by **Prof. N.P.Singh** who is the head of Nephrology section at Maulana Azad Medical College, New Delhi. He deserves full appreciation and felicitation for an excellent planning, selecting experts for the topics and editing the various articles so as to make this issue into a comprehensive monogram. I, heartily, congratulate Dr.N.P.Singh for accomplishing this gigantic task. I am confident, the readers of JIMSA will benefit from this publication and will most certainly like to keep a copy for their personal reference. I take this opportunity to personally thank Prof.N.P.Singh and his team members for their valuable contributions.

I must acknowledge, with gratitude, the financial assistance provided by various pharmaceutical firms without which this publication would not have been possible.

P. D. Gulati

JIMSA BEST PUBLISHED ARTICLE AWARDS 2008 - Declared

The following articles have been selected for the "**JIMSA Best Published Article Award 2008**" as per ranking given below:

1st Best Article Award : "**Efficacy of Herbal Medication for Enhancing the Breast and Teats in Female Wistar Rats**" *R.Karunanidhi, V.Pugalendi, TMR Paniker, K.Jagadeesan, M.Paul Koraath.*

2nd Best Article Award : "**MRI Changes in Compressive Myelopathy in Fluorosis – Study of 18 cases from North West India**". *Ashok Panagariya, Ravindra Singh, Paresh Sukhani, Bhawna Sharma.*

3rd Best Article Award : "**Preoperative Evaluation of Colorectal Carcinoma by Computed Tomography**" *Rajul Rastogi, Satish Kumar Bhargava, Satish Kachhawa.*

Each award consists of a **medal, citation and cash prize**: the awardees will receive the award at the forthcoming IMSACON 2009 at Chandigarh on 24th & 25th October 2009 (contact urgently Dr.H.K.Chopra, Secretary General IMSAWHQ). In case he or she is unable to attend IMSACON 2009, he/she should intimate the editor JIMSA, accordingly.

Editor

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Dr. Narinder Pal Singh

Dr. Narinder Pal Singh is currently working as Professor of Medicine and In-charge of Nephrology at Maulana Azad Medical College & associated Lok Nayak Hospital, Delhi. He is an excellent clinician, researcher and postgraduate teacher and has over 120 publications, 20 chapters in different books, and has edited a book on poisoning (in press).

Prof. N.P.Singh has been the recipient of several awards and oration, notable amongst them are the State Award by Delhi Government 2007-08, API Searle Oration, Dr Wig Oration of API Delhi State Chapter, Shurvir Singh Visiting Professorship, WHO fellowship on epidemiology & biostatistics, Smt. Pawan Kumari Jain Oration. Considering his academic achievements, he has been awarded fellowships of the Indian College of Physicians of Indian Society of Nephrology, International Medical Science Academy and Indian Academy of Clinical Medicine. He has recently finished his MBA in Health Care from FMS, Delhi University. He has been involved in the scientific deliberations of APICONS, for several of earth and has been and on various committees of the APICON held at Delhi. He has been appointed peer reviewer for some of the national & International fames the American Journal of Kidney Diseases, Haemodialysis International, JAPI, JIACM and is presently on National Advisory Board of JAP & JIACM.

He hold important position in some of the prestigious Scientific bodies such as Governing Body member of API(2008-11), Executive Member Delhi Medical Council, Joint Editor JAPI, Secretary of Delhi Nephrology Society served as Joint Secretary of the API-Delhi chapter. Member of International Society of Nephrology and European Renal Association & is, President and Secretary of the Faculty Association & Secretary of the Ethics Committee of MAM College. Dr. N.P. Singh has been actively involved in the public awarness programmes; has been Organizing Kidney disease detection camps periodically, at the community level.

EDITORIAL

RENAL STONE DISEASE - AN INDIAN PERSPECTIVE

Nephrolithiasis (from Greek *nephros*, "kidney" and *lithos*, "stone") refers to the condition of having kidney stones. The existence of kidney stones has been recorded since the beginning of civilization, and lithotomy for the removal of stones is one of the earliest known surgical procedures. In 1901, a stone was discovered in the pelvis of an ancient Egyptian mummy, and was dated to 4,800 BC. Part of the Hippocratic oath contains an admonition about the dangers of operating on the bladder for stones.

Renal stone disease is third commonest disorder of urinary tract after urinary tract infection (UTI) and benign prostatic hyperplasia (BPH). It is more common in a region of India, called "stone belt", which runs in the north part of India. It is generally believed that risk of developing nephrolithiasis in normal adults is lower in Asia (1-5%) compared to the figures for Europe (5-9%) and United States (13%). According to estimates from Western cohorts, males are two to four times more likely to be afflicted with kidney stone disease than females¹. The incidence of kidney stones peaks around 40-60 years age in males and around late 20s in females². The studies assessing composition of renal stones suggest that renal stone disease in India is probably different from other nations. Whether this is related to our environmental and/or genetic factors will be interesting to see.

Renal calculi formation is a relatively complex process and involves an interplay of various physiochemical and anatomical factors. The predisposition to urolithiasis in all these conditions are also contributed by the intricate anatomical structure and complex development of the urogenital system. The article Mishra et al briefly describes the gross anatomical structure and the development of the urinary tract and various congenital anomalies which can lead to obstructive uropathy thereby leading to urinary stasis and higher chances of urolithiasis. Urinary organs develop from intermediate mesenchyme.

Kidney stones may form when the normal balance of water, salts, minerals, and other substances found in urine changes. There are several types of kidney stones based on the type of crystals of which they consist. The majority are calcium oxalate stones, followed by calcium phosphate stones³. One of the most common factors in the formation of kidney stones happens to be hereditary. Urinary tract infections, kidney diseases and metabolic disorders such as hyperparathyroidism are also known to increase the chances of a person developing a stone. Aggarwal SK in his article reviewed the various etiopathogenetic factors for development of nephrolithiasis.

Symptoms of kidney stones are many, the most obvious and often spoken about, is the severe sharp kidney pain in the flank or side that are accompanied with fever, nausea, and even mental confusion. Other people pass kidney stones and only find out when an x-ray or a urine specimen reveals them. Some experience microhematuria (microscopic blood in urine) gross hematuria, or even granular specks when urinating. Pain, infection, or hematuria is classical triad of symptoms reported by patients with renal stone disease⁴. Dramatic costovertebral angle tenderness is common; this pain can move to the upper or lower abdominal quadrant as a ureteral stone migrates distally

Radiological investigations play a key role in diagnostic work up of urolithiasis which has been discussed in detail by. Sapna Singh in her article. While conventional investigations like X ray KUB, USG and IVP are still considered essential for diagnosis, newer modalities like

CT Urography and MR Urography have increased the sensitivity and specificity of diagnostic work up.

Kalra OP et al highlighted the importance of medical management in treatment of urolithiasis. Variety of medical treatments can prevent recurrence of stones⁵ About 90% of stones 4 mm or less in size usually will pass spontaneously, however 99% of stones larger than 6 mm will require some form of intervention. There are various measures that can be used to encourage the passage of a stone. These can include increased hydration, medication for treating infection and reducing pain, and diuretics to encourage urine flow and prevent further stone formation. A detailed diagnostic work up is essential and prerequisite for medical management Dietary modifications like high fluid intake and Animal protein restriction are essential for any type of stone disease. Specific modalities like Potassium citrate, thiazide diuretics, allopurinol and treatment of infections might help in preventing recurrent stone disease in specific situations.

Surgery is necessary when the pain is persistent and severe, in renal failure and when there is a kidney infection. It may also be advisable if the stone fails to pass or move after 30 days. In most of these cases, non-invasive extracorporeal shock wave lithotripsy (ESWL) will be used. Otherwise some form of invasive procedure is required; with approaches including ureteroscopic fragmentation (or simple basket extraction if feasible) using laser, ultrasonic or mechanical (pneumatic, shock-wave) forms of energy to fragment the larger stones. In recent years, as clinical experience with ESWL revealed its limitations, the role of PCNL for treating urolithiasis was redefined. According to the literature reviewed by. Anil varshney and associates PCNL should be the first line treatment of large or multiple kidney stones, and stones in the inferior calyx.⁶ Furthermore, improvements in instruments (i.e. ureteroscopes) as well as lithotripsy technology (i.e. ultrasound / pneumatic devices, Holmium-YAG-Laser) increased the efficacy of percutaneous stone disintegration yielding stone free rates of >90%. Pediatric urolithiasis is endemic in developing countries including India. An underlying metabolic disorder is the cause in about half of children, infection being the cause in the other half. In Uttar Pradesh, parts of Gujrat and Maharashtra, vesical calculi are very frequent. The mean age of presentation is 6.9 years for girls and 5.2 years for boys. Infected stones generally present early before 4 years of age. Recurrence rates range from 3.6% to 68% and is the highest for children with metabolic risk factors.^{7,8} . Aggarwal et al have laid out more focussed approach for treatment of urolithiasis in paediatric age group.

Although Medical and surgical management constitutes the cornerstone of treatment of nephrolithiasis, in India, alternative and complimentary systems provide many opportunities and claims for cure for this recurring disease. Review of literature by Saxena et al highlights some of the important remedies in alternative system which many patients resort to escape surgery.

I would like to complement JIMSA for bringing out a dedicated issue on nephrolithiasis.

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EPIDEMIOLOGY OF KIDNEY STONES

N. P. Singh,*Vinay Saini

Professor of Medicine, *Research Associate, Maulana Azad Medical College,
Associated Lok Nayak & G.B. Pant Hospital, New Delhi-110002, India

Abstract : Urolithiasis is a common condition with significant morbidity and if not treated is one of the common causes of Chronic Kidney disease. Prevalence of this condition varies with geographical location and is showing a rising trend in past two decades. Male subjects in their 3-4th Decade are more likely to suffer more so during summer months due to loss of fluid from extra renal sources. Calcium oxalate stones are the commonest. Diet, inadequate fluid intake, genetic factors, systemic and metabolic factors like diabetes mellitus constitutes risk factors for kidney stones. Left untreated it can be of immense economic burden; hence prompt recognition and treatment is warranted.

BACKGROUND

Urinary tract stone disease is a common condition with significant morbidity. Depending on the location of calculus in the urinary tract there are three distinct subgroups of urolithiasis; nephrolithiasis, ureterolithiasis and vesicolithiasis. While incidence of bladder calculi is decreasing, primarily due to increasing living standards it is still a common entity in societies with low per capita income. Many tropical countries, including India, till recently featured prominently in the 'endemic bladder stone belt'. With changing dietary patterns and living standards there has been an increase in incidence of upper urinary tract stone disease including nephrolithiasis¹. Epidemiological studies on kidney stone disease can enable us to quantify the disease burden and to formulate strategies to lower its incidence. The present article discusses some epidemiological aspects of nephrolithiasis in adult population.

INCIDENCE AND PREVALENCE OF KIDNEY STONE DISEASE

There is no population based data on incidence and prevalence of kidney stones in India. However, it is generally believed that risk of developing nephrolithiasis in normal adults is lower in Asia (1-5%) compared to the figures for Europe (5-9%) and United States (13%)². In a large population based study in United States, subjects with Asian descent had an intermediate prevalence of kidney stone disease (3.42%), Caucasians (5.78%) and Afro-Americans (2.95%)³. There has been a global trend of increasing prevalence of kidney stone disease over the past few decades. Whether this represents an actual increase or improved detection of stones is debatable⁴. A hospital based study from North India analyzing the stone composition of urinary tract stones demonstrated that, over a 20 year period, the proportion of upper urinary tract stones increased from 69% to 91%⁵.

AGE AND SEX DIFFERENCE

According to estimates from Western cohorts, males are two to four times more likely to be afflicted with kidney stone disease than females⁶. The incidence of kidney stones peaks around 40-60 years in males and around late 20s in females⁴. The only hospital based study from India which comments on age and sex distribution of upper urinary tract stones however also included children in the study population and did not give an age group wise breakdown of stone incidence. Nevertheless, they found that the mean age for stone formers was around 30 years (range 3-78 years) and males were twice more likely to have stones than females⁷. The lower risk of stone formation in females is believed to be due to a protective effect

of estrogen. This is further corroborated by studies which have demonstrated that estrogen supplementation in post menopausal females could decrease stone incidence⁸. The only study from India evaluating the influence of sex (males vs. reproductive females vs. menopausal females) in risk of urolithiasis demonstrated similar results⁹.

SEASONAL VARIATION

It is now generally believed that subjects in hotter climates have a greater predisposition for kidney stone formation¹. Formation of a concentrated, acidic urine and increased vitamin D production are the two principal factors believed to be contributing to this observation. In a population based study in United States, southern states which were closer to equator had a higher prevalence of kidney stones than the cold northern states after adjusting for other covariates³. A study in slum population of Mumbai failed to demonstrate any seasonal variation in recurrent stone formers which were presumed to have an underlying metabolic problem¹⁰. This could be related to the absence of extreme temperature fluctuations in Mumbai climate or the preponderance of calcium stones as upper urinary tract stones. A study from Western Australia also did not demonstrate any seasonal variation in incidence of calcium stones though they did find significant seasonal differences in incidence of uric acid and infection stones¹¹. However, studies from Rajasthan demonstrated a higher prevalence of urinary calculus disease there as compared to other parts of India¹².

COMPOSITION OF KIDNEY STONES

Many hospital based studies have assessed composition of upper urinary tract stones in Indian population¹³⁻¹⁵. The latest study analyzed 1,050 upper urinary tract calculi (900 renal and 150 ureteric) by X ray diffraction⁷. Calcium oxalate (CaOx) constituted 93% of all stones; in 80% of these it was in the monohydrate form (COM, whewellite) and in remaining 20% in the dihydrate form (COD, weddellite). While calcium oxalate stones are the commonest stones even in the Western population, the distribution of COM and COD stones is almost even. This is in contrast to Indian subjects where majority of CaOx stones were COM. The next most common stone (2.76%) in North Indians was of mixed type containing varying proportions of CaOx, calcium phosphate (CaP, apatite), uric acid and magnesium ammonium phosphate (struvite). Pure CaP, struvite and uric acid stones were found in <2% each. About 20% of 900 renal stones were staghorn calculi with majority (90%) being composed primarily of CaOx and not struvite as they are in western population. Though cystine and insoluble drugs like indinavir can

precipitate as renal stones none of the existing studies have demonstrated these stones in adult Indian subjects. By comparison, in United States calcium containing stones (CaOx and CaP) constitute 75-80%, uric acid about 10%, struvite 3-5% and rest are cystine or mixed stones⁶.

RISK FACTORS FOR KIDNEY STONE FORMATION

Many prospective studies in Western populations have identified several key risk factors for kidney stones. However, prospective studies on this aspect are lacking for Indian population. Based on the data from western cohorts and where possible, corroborating evidence from Indian population enables one to identify risk factors for nephrolithiasis.

a) Diet: The composition of urine is influenced by the diet and several dietary factors are known to influence kidney stone formation. Since calcium stones are the commonest significant volume of literature has evaluated role of calcium in nephrolithiasis. Interestingly, a high dietary calcium intake protects against kidney stones¹⁶. Restricting calcium intake rather promotes lithiasis¹⁷. This is believed to be due to upregulation of oxalate absorption from gut in calcium deficient diet. Evidence also supports role of protein and salt restriction in preventing lithiasis⁴. While excessive protein intake lowers urine pH which favors crystallization of calcium salts, excess of sodium intake promotes calcium excretion. The role of dietary oxalate in stone formation has not been yet reliably evaluated. Though usually avoiding oxalate rich foods, like spinach, is advised for these patients there is no objective data to justify this. The prevailing notion is that stone formers have increased dietary oxalate absorption. Some researchers suggest a possible deficiency of oxalate degrading bacterium, *Oxalobacter formigenes*, in the gut as a reason for this. In a study in North India only 30% of CaOx stone formers had gut colonized by this bacterium and this decreased further to only 5.6% in those stone formers with 33 stone recurrences¹⁸. Magnesium complexes with oxalates and can lower absorption of oxalate from gut. However, whether magnesium supplementation has any role in preventing kidney stones is questionable. Vitamin C is also metabolized to oxalate in body and taking supplemental Vitamin C has been shown to increase risk of stone formation¹⁹. A diet low in potassium is also lithogenic²⁰. This is believed to be due to increased urine calcium excretion and lowered urinary citrate levels which is a lithogenesis inhibitor.

Only two studies from India have evaluated a possible role of dietary factors in lithiasis. In one study¹², stone formers independent of their affluence had a higher urinary excretion of calcium and oxalic acid besides also having higher urinary saturation. However none of the dietary nutrients influenced the urinary parameters and authors suggested that pathogenesis of lithiasis may be related to differences in *enteric absorption*. Another study²¹, though had a very small sample size, demonstrated a correlation between dietary calcium levels, higher protein intake and urinary calcium excretion in stone formers. They concluded that limitation of protein intake and normal calcium intakes could avoid renal stone formation.

b) Fluids: A urine output of <1L/d significantly increases risk of renal lithiasis⁴. Though drinking plenty of oral fluids is known to reduce risk of renal stones, there is no consensus on the volume

or preferred fluids. Some evidence suggests additional protection against lithiasis with drinking tea, coffee and wine²². Emerging evidence also suggests a role of trace elements in promoting lithiasis, especially fluorine. In a study in India, the prevalence of urolithiasis was nearly 5 times higher in fluoride endemic areas than non endemic areas²³.

- c) Genetics:** Every 1 in 4 persons with kidney stones has a family history of urolithiasis²⁴. Certain renal stone disorders like cystinuria, familial renal tubular acidosis and others have a clear hereditary pattern. These tend to present early in life. However, possibility of a polygenic inheritance is being evaluated to explain familial tendency for stone formation, especially CaOx stones. Polymorphisms in Vitamin D receptor (VDR) genes are also under study considering the importance of Vitamin D in maintaining in vivo calcium homeostasis. Preliminary results from a study from North India suggest that allelic variations in VDR gene may be associated with varied calcium excretion in nephrolithiasis subjects²⁵.
- d) Systemic disorders:** Certain systemic disorders like primary hyperparathyroidism, gout and Crohn's disease have well known associations with kidney stones. Increasingly, however many non-communicable disease risk factors have also been linked with nephrolithiasis. Increased BMI or waist circumference are now known to increased risk of lithiasis, especially in women²⁶. In the two studies from India assessing influence of diet on renal lithiasis, stone forming subjects had a higher caloric intake than their healthy counterparts^{12,21}. In fact one group of authors²¹, suggested a possible role of hyperphagy and obesity in renal stone formation in Indian subjects. Diabetes mellitus has also been associated with renal stones. In a prospective study in Caucasians, women with type 2 DM had a 30-50% higher risk of having renal stones²⁷. Similarly, subjects with hypertension are more likely to have renal stones²⁸. In a cross sectional study in United States, presence of 32 traits of metabolic syndrome significantly associated with a self reported history of kidney stones²⁹. More so, uric acid stones are now being speculated to be a manifestation of metabolic syndrome³⁰.
- e) Metabolic factors:** Subjects with lithiasis have varied metabolic abnormalities. Hypercalciuria, hyperoxaluria, hyperuricosuria and hypocitraturia are some of the common metabolic abnormalities⁶. However, it is very difficult to establish a definite cut-off value above which the concentration of these substances can be regarded as abnormal in urine. Many subjects may have these abnormalities in urine but remain stone free. This can be understood by fact that stone formation is not just a function of concentration but also crystal solubility and saturation which in turn depends on many other factors like urine pH, volume and presence of crystallization inhibitors like citrates, pyrophosphates and glycosaminoglycans³¹. In a study on 181 stone formers in India only 50 (27.6%) had hypercalciuria, hyperoxaluria or both¹². Several other studies from India have demonstrated a decreased excretion of crystallization inhibitors in stone formers as compared to normal subjects^{32,33}.

MORBIDITY AND MORTALITY

Nephrolithiasis is a more of a nuisance. There is significant morbidity associated with this condition. This is primarily due to stone

recurrence. For idiopathic calcium stones, recurrence rate is 40-50% at 5 years and 50-60% by 10 years³¹. The recurrence rates for those with underlying metabolic abnormality are probably higher. Significant efforts have been focused over predicting the risk of recurrence in renal lithiasis patients. Though several risk indices have been devised in past none provides a reliable estimate of recurrence. Crystalluria appear to be a promising indicator of stone disease but its use is limited by practical difficulties³⁴. Mortality from renal stones is rare but some forms of renal lithiasis associated with systemic disorders can cause renal insufficiency³⁵.

ECONOMIC BURDEN OF KIDNEY STONES

The annual health care budget of India is about 4% of its GDP. Within this amount all activities related to health sector need to be sustained. This warrants a cost effectiveness analysis of kidney stone management. Unfortunately such an assessment is lacking in Indian scenario. It will however be useful to gather some primers from similar analysis done in other countries. In United States, a person with nephrolithiasis claimed \$3,500 more in medical expenses than his/her normal counterpart. There was a mean loss of 19 work hours per year due to renal lithiasis. A cost effectiveness study of medical management strategies for nephrolithiasis showed that dietary modification alone was the most cost effective approach, followed by empiric therapy. Comprehensive evaluation and targeted medical therapy were the least cost effective ways of management³⁶. Though direct extrapolation to Indian scenario from these studies will be inaccurate but it should serve the purpose of enabling physicians to let the patients make an informed decision.

CONCLUSIONS

Though limited data is available on epidemiological aspects of nephrolithiasis in India, it is clear that it is a significant cause of morbidity. Its likely that prevalence of renal lithiasis is lower in India than many other Western nations, but it is difficult to say it with certainty in view of lack of studies. The studies assessing composition of renal stones suggest that renal stone disease in India is probably different from other nations. Whether this is related to our environmental and/or genetic factors will be interesting to see. Finally, cost effectiveness of conservative measures deserves a thorough assessment in the Indian scenario where significant portion of population cannot afford medical management. Finally, evidence from across the globe can enable Indian physicians to more effectively practise evidence based management of renal lithiasis.

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ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH

The need for uniform ethical guidelines for research on human subjects is universally recognised. It has acquired a new sense of urgency as the critical issues in the area of biogenetic research involving human subjects have become acute. Apart from the mandatory clinical trials on new drugs, a number of diagnostic procedures, therapeutic interventions and prevention measures including the use of vaccines, are being introduced which involve human subjects. Further the advent of new medical devices and radio-active materials and therapeutic benefits of recombinant DNA products have added a new dimension to the ethical issues that need to be considered before evaluating these for their efficacy, utility and safety.

Any research using the human beings as subjects shall bear in

mind the following principles of : (i) essentiality, (ii) voluntariness, informed consent, (iii) non exploitation, (iv) privacy and confidentiality, (v) precaution and risk minimisation, (vi) professional competence, (vii) accountability & transparency, (viii) maximisation of public interest and distributive justice (ix) institutional arrangements (x) public domain (xi) totality of responsibility and (xii) compliance.

Recent advances in the field of Assisted Reproductive technologies, organ transplantation, Human genome analysis and gene therapy promise unquestionable benefits to mankind. At the same time, they raise many questions of law and ethics, stimulating public interest and concern.

(Source : ICMRT Publication 2000)

UROGENITAL ANATOMY- HOW IT IS PRONE FOR UROLITHIASIS ?

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Abstract: Most recent studies report that the incidence of kidney and ureteral stones has increased significantly in both adults and children. According to the literature, renal calculi formation is a relatively complex process and involves an interplay of various physiochemical and anatomical factors. Almost 50% of the pediatric cases of urolithiasis are idiopathic and the rest due to hypercalciuria (30%) and hyperoxaluria (20%), or rarely due to hyperuricosuria, xanthinuria or hypocitruria in addition metabolic disorders are also a contributing factor. The predisposition to urolithiasis in all these conditions are also contributed by the intricate anatomical structure and complex development of the urogenital system. The article briefly describes the gross anatomical structure and the development of the urinary tract. Urinary organs develop from intermediate mesenchyme. The intermediate mesenchyme is found longitudinally placed in the trunk, sub-adjacent to somites, at the junction between splanchnopleuric mesoderm and somatopleuric mesoderm. In brief, the ureteral bud developing from the mesonephric duct dilates to form the ampulla which induces the surrounding mesenchymatous tissue i.e. metanephros resulting in the differentiation of mesenchymal agglomerates and their organization in concentrates. The condensate then epithelizes and forms vesicles, which fuse with the ampulla to form a nephron. The various congenital anomalies which can lead to an obstructive uropathy due to hydronephrotic changes causing urinary stasis and, subsequently become a major predisposing factor for urolithiasis. All these have been discussed from an anatomical perspective.

Urolithiasis is a problem that is generally increasing in the tropics as well as in most of the Western countries. There are 2 main types of the urolithiasis the bladder stones in children, and upper urinary tract stones in adults. The former has been decreasing in most developed countries with gradual improvement in levels of nutrition. Reno-ureteral calculosis typical of adult age is more frequent in economically developed countries, with a prevalence rate between 4% and 20%. On the contrary "primitive" vesical calculosis is fairly widespread in Asia, due to malnutrition in the very early years of life. However, the concurrence of a genetic predisposition seems to be crucial for stone formation¹.

Congenital anomalies and anatomical variations in the urogenital tract can be a major contributing factor in stone formation. It is well known that renal calculi formation is a relatively complex process and involves an interplay of various physiochemical and anatomical factors. Literature shows that almost 50% of the pediatric cases of urolithiasis are idiopathic and the rest due to hypercalciuria (30%) and hyperoxaluria (20%), or rarely due to hyperuricosuria, xanthinuria or hypocitruria. Hypocitruria has been quoted as the most important risk factor in the development of idiopathic calcium stones in children. Male children suffer more frequently with urolithiasis². The urinary concentration of stone-forming ions like calcium and oxalate is vital, especially in combination with a deficiency of inhibitors of crystallization-like citrate. In addition, abnormal urinary pH can contribute significantly to stone formation by affecting ion solubility and thereby promoting their crystallization. Metabolic disorders are uncommon etiopathological factors for urolithiasis³. Other known predisposing factors for urolithiasis are obstructive uropathy, ureterovesicular reflux, neurogenic bladder, renal foreign body, renal papillary necrosis and UTI. Neonatal renal calculus formation can be subsequent to maternal conditions like hyperparathyroidism, Vitamin D intoxication and diuretic therapy, or due to neonatal diseases like hyperparathyroidism, hypothyroidism, idiopathic hypercalciuria, renal tubular acidosis, inborn errors of metabolism and steroid or diuretic therapy⁴.

In a recent analysis of McKusick's On-line Mendelian Inheritance in Man (OMIM) database, NL was found to be a component of more than 30 genetic disorders, namely familial idiopathic hypercalciuria,

(autosomal dominant) Dent's disease (X-linked recessive), adenine phosphoribosyl-transferase deficiency (autosomal dominant), idiopathic calcium oxalate nephrolithiasis (autosomal dominant/polygenic) and several others, which are either autosomal recessive or X-linked³ autosomal recessive. The pathogenesis of urolithiasis in these conditions is not well understood. Some of these disorders, especially those inherited via an autosomal recessive or X-linked autosomal recessive pattern, can result in end-stage renal disease. The emphasis on genetic counseling and the possibility of early prenatal diagnosis of congenital malformation have stimulated interest in fetal anatomy⁵.

The question arises-Is the anatomy of the urinary system such that it could lead to calculi formation?

Most recent studies report that the incidence of kidney and ureteral stones has increased significantly in both adults and children. Hence to understand the possibility of calculi formation it is necessary to briefly understand the gross structure and development of the urogenital system.

UROGENITAL SYSTEM

Gross Anatomy

The urogenital system comprises of the urinary tract and the reproductive system. The kidneys are essentially regulatory organs which maintain the volume and composition of body fluid by filtration of the blood and selective re absorption or secretion of filtered solutes, the kidneys are retroperitoneal organs (ie located behind the peritoneum) situated on the posterior wall of the abdomen on each side of the vertebral column, at about the level of the twelfth rib. The left kidney is slightly higher in the abdomen than the right, due to the presence of the liver pushing the right kidney down.

The kidneys derive their blood supply directly from the aorta via the renal arteries; blood is returned to the inferior vena cava via the renal veins. Urine (the filtered product containing waste materials and water) excreted from the kidneys passes down the fibromuscular ureters and collects in the bladder. The bladder muscle (the detrusor muscle) is capable of distending to accept urine without increasing the pressure inside; this means that large volumes can be collected (700-1000ml) without high-pressure damage to the renal system.

When urine is passed, the urethral sphincter at the base of the bladder (trigone) relaxes, the detrusor contracts, and urine is voided via the urethra.

The male urethra is longer and comprises of 4 parts, the preprostatic, prostatic, membranous and spongy part and the lumen are small slits while the female urethra is shorter and has a length of 4cm. The structural difference between male and female urethra makes males more prone to obstructive uropathies and urolithiasis².

On sectioning, the kidney has a pale outer region- the cortex- and a darker inner region- the medulla. The medulla is divided into 8-18 conical regions, called the renal pyramids; the base of each pyramid starts at the corticomedullary border, and the apex ends in the renal papilla which merges to form the renal pelvis and then on to form the ureter. In humans, the renal pelvis is divided into two or three spaces -the major calyces- which in turn divide into further minor calyces. The walls of the calyces, pelvis and ureters are lined with smooth muscle that can contract to force urine towards the bladder by peristalsis. The cortex and the medulla are made up of nephrons; these are the functional units of the kidney, and each kidney contains about 1.3 million nephrons and it is the unit of the kidney responsible for ultrafiltration of the blood and reabsorption or excretion of products in the subsequent filtrate. Each nephron is made up of: glomerulus filtering unit) 125ml/min of filtrate is formed by the kidneys as blood is filtered through this sieve-like structure. This filtration is uncontrolled. In the proximal convoluted tubule-controlled absorption of glucose, sodium, and other solutes occur. The loop of Henele is responsible for concentration and dilution of urine by utilising a counter-current multiplying mechanism- basically, it is water-impermeable but can pump sodium out, which in turn affects the osmolarity of the surrounding tissues and will affect the subsequent movement of water in or out of the water-permeable collecting duct. The distal convoluted tubule is this region responsible, along with the collecting duct that it joins, for absorbing water back into the body, therefore the kidney filters 125ml of urine every minute and 99% of the water is reabsorbed, leaving a highly concentrated urine to flow into the collecting duct and then into the renal pelvis⁶. It would be interesting to understand the development of this complex anatomical structure

DEVELOPMENT OF KIDNEY

Urinary organs develop from intermediate mesenchyme. The intermediate mesenchyme is found longitudinally placed in the trunk, sub-adjacent to somites, at the junction between splanchnopleuric mesoderm and somatopleuric mesoderm. Development progresses cranio-caudally⁷. Glomeruli are specific arrangements of capillaries and overlying coelomic epithelium and arise from the ventral wall of nephrocele (internal glomeruli) or the roof of coelom adjacent to peritoneal funnels (external glomeruli), or in both situations. It has been customary to regard renal excretory system as three organs- pronephros, mesonephros and metanephros succeeding each other in time and space. Last to develop is retained as permanent kidney. Both pronephros and mesonephros has a craniocaudal arrangement, so results in production of hypotonic urine. The tubular arrangement in metanephric kidney in the form of loops of Henle allows differential concentration of urine to form hypertonic urine. Metanephric kidney develops from three sources: an evagination of mesonephric duct, the ureteric bud and a local condensation of mesenchyme termed metanephric blastema form the nephric structure, while angiogenic mesenchyme migrates into metanephric blastema to form glomeruli and vasa recta. The angiogenic mesenchyme migrates into metanephric blastema to form glomeruli and vasa recta^{6,7,8,9,14,15,17}.

In brief, the ureteral bud developing from the mesonephric duct dilates to form the ampulla which induces the surrounding mesenchymatous tissue i.e. metanephros resulting in the differentiation of mesenchymal agglomerates and their organization in concentrates. The condensate then epithelizes and forms vesicles, which fuses with the ampulla to form a nephron. First vesicle is formed at the end of 7th week in relation to 6th division of ureteric bud. Cells at the proximal pole of the vesicles organize to form C-shaped or comma shaped body followed by cellular reorganization of tubular cells at distal end to form a S-shaped body or S-body. In the cleft of the S-body at the distal pole, formation of extra cellular matrix and penetration by capillaries targets at formation of future mesangial region. The proximal limb of the S-body organizes to form distal convoluted tubule while the intermediate limb enlarges to form loop of Henle and the proximal convoluted tubule resulting in entire development of a nephron. Many such nephrons are present in the fetal kidney due to multiple branching of the ampullary bud and induction of various mesenchymatous condensates to form nephron arcades. This process of renal development begins at deeper regions and reaches the peripheral part of the cortex with the advancement of ampulla in that region and terminates during the last month of gestation with subsequent interstitial growth^{8,10,14}. The metanephric kidney is initially

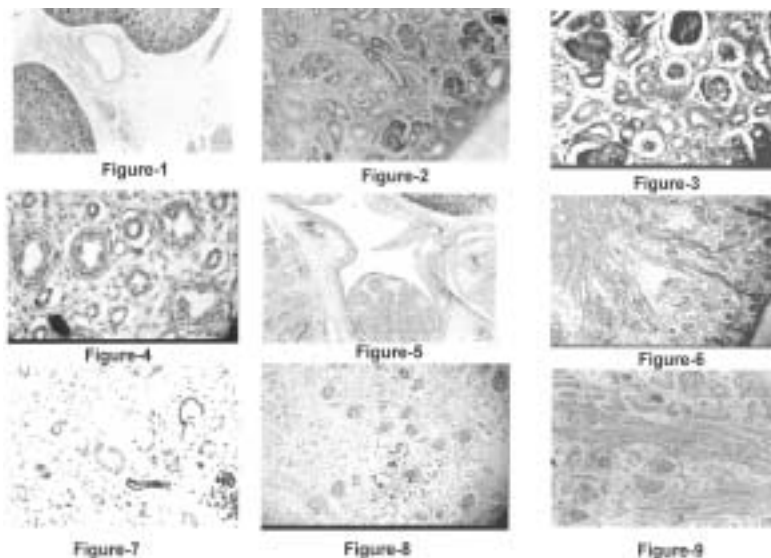


Photo micrographs of developing human kidney (Mishra et al 2006)

Fig 1. Metanephric blastema 2 lobules with intervening future pelvis at 14 weeks, 10x

Fig 2 Developing tubules in cortex at 14 weeks. Mag 40x

Fig 3 . Metanephric blastema cap over the ampulla at 14 weeks Mag 40x

Fig 4. Stratification of tubules at 18 weeks Mag 40x

Fig 5 Successive generation of ampulla at renal pelvis 20 weeks Mag 10x

Fig 6 Well defined glomeruli and tubules seen at 24 weeks Massons trichrome stain Mag 10x

Fig 7 differentiation of 2 sets of tubules eosinophilic and baophilic at 22 weeks of gestation Mag 40x

Fig 8. Well defined glomeruli and tubules seen at 24th weeks of gestation. Magnification 10x. Massons Trichrome stain.

Fig 9 well defined cortex and medulla at 28 weeks of gestation.

Collecting ducts converging towards the excretory system Mag 10x

sacral and as the ureter lengthens, it ascends upto the level of 2nd lumbar vertebrae. Kidney size is presumably influenced both by genetic and environmental factors. (figure1to11). The number of glomeruli at birth is presumably genetically determined. The size of kidneys is dependent on the number and size of nephrons^{8,11,12,13,17,18}. The total filtration surface area depends on the glomerular density and the glomerular surface area, any variation in these factors alters the total filtration area which is a useful indicator of renal development.

The manifestation of renal disorders is directly related to developmental anatomy of kidney including both morphological and

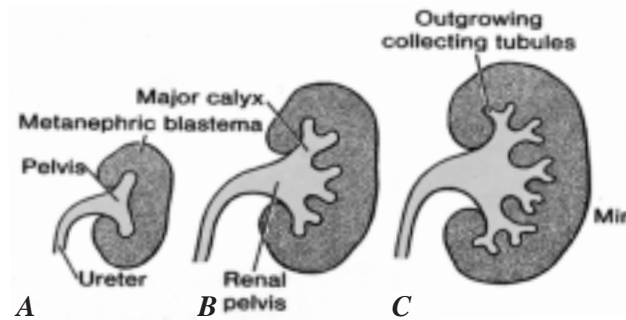
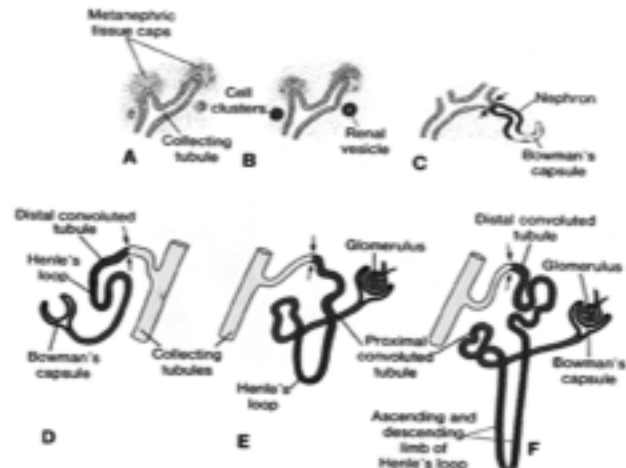


Fig 10. Formation of the calyceal system. Development of urogenital system Sadler T W , Langman;s medical embryology



Schematic representations of the formation of the nephron in sequence Fig 11. Sadler T W , Langman;s medical embryology

stereological parameters^{14,15,16,18,19}. The incidence of renal anomalies is about 20-30%. Thus, in utero detection of anomalies prevents delay in postnatal diagnosis and enables early surgical repair of significant lesions⁵.

Development of Urinary bladder is from the ventral part of the cloaca. The cloaca is divided into three parts, the cranial vesico urethral part continuous with the urachus, middle pelvic part and the deep phallic part. The ureter and mesonephric duct open separately into the vesico urethral part. The pelvic and phallic part the narrowest region forms the urogenital sinus. Hence the urinary bladder develops from ventral endodermal cloaca (most of urinary bladder except trigone) and the absorbed mesonephrous (trigone).Fig 12

Though there is not much literature on the correlation of urolithiasis and congenital anomalies, it would be interesting to analyse the

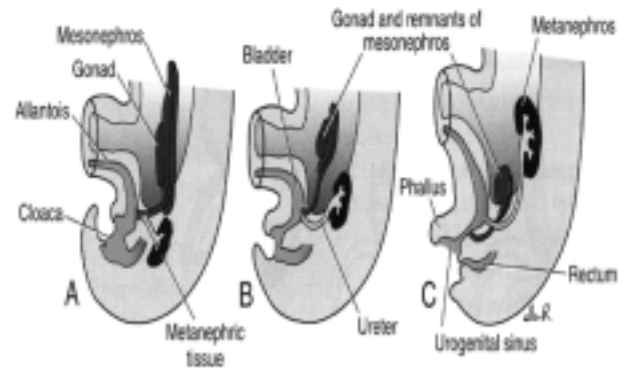


Fig12. Development of urogenital system Sadler T W , Langman;s clinical embryology

incidence of some of the anomalies which cause an obstructive uropathy, lead to back pressure and hydronephrosis an important predisposing factor for urolithiasis.

CONGENITAL ANOMALIES OF KIDNEY

The congenital anomalies of kidney can be described as follows.

Horseshoe kidney, the most common fusion anomaly, occurs when renal parenchyma on each side of the vertebral column is joined at the corresponding (usually lower) poles; an isthmus of renal parenchyma or fibrous tissue joins at the midline. The ureters course medially and anteriorly over this isthmus and generally drain well. Obstruction, if present, is usually secondary to insertion of the ureters

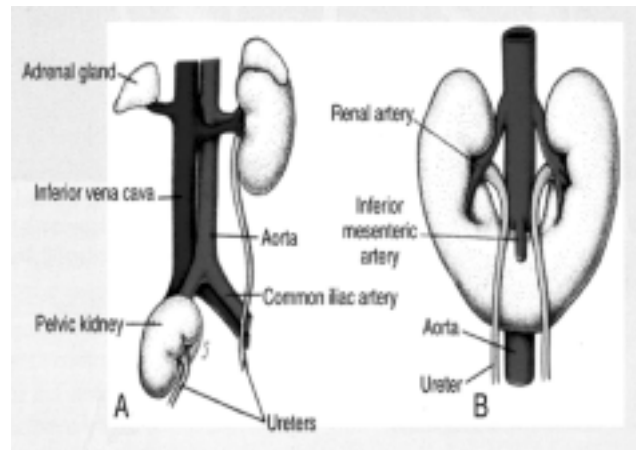


Fig 13. Pelvic kidney and horse shoe kidney Sadler T W , Langman;s medical embryology

high in the renal pelvis. Stone disease is thought to be due to the associated hydronephrosis or ureteropelvic junction obstruction PUJ obstruction that causes urinary stasis, which hinders stone passage.(Fig 13)

Crossed fused renal ectopia is the 2nd most common fusion anomaly. The renal parenchyma (representing both kidneys) is on one side of the vertebral column. One of the ureters crosses the midline and enters the bladder on the side opposite the kidneys. When ureteropelvic junction obstruction is present, pyeloplasty is the treatment of choice.

Fused pelvic kidney (pancake kidney) is much less common. A single pelvic kidney is served by 2 collecting systems and ureters.

Malrotation is usually of little clinical significance. There is an axis shift in the collecting system anatomy.

Multicystic dysplastic kidney: In this condition, a nonfunctioning renal

unit consists of noncommunicating cysts with intervening solid tissue composed of fibrosis, primitive tubules, and foci of cartilage. Usually, ureteral atresia is also present. Uncommonly, the kidney develops tumors or infection, and hypertension may develop.

Renal dysplasia: In renal dysplasia - a histologic diagnosis, the renal vasculature, tubules, collecting ducts, or drainage apparatus develops abnormally.

Renal ectopia: Renal ectopia, abnormal renal location, usually results when a kidney fails to ascend from its origin in the true pelvis; a rare exception occurs with a superiorly ascended (thoracic) kidney. **Pelvic ectopia** increases the incidence of ureteropelvic junction obstruction, vesicoureteral reflux, and multicystic renal dysplasia.

Renal hypoplasia: Hypoplasia usually occurs because inadequate ureteral bud branching causes an underdeveloped, small kidney with histologically normal nephrons^{20,21,22}.

CONGENITAL URETERE ANOMALIES

The ureter drains urine from the kidney into the bladder. Not simply a tube, the ureter is an active organ that propels urine forward by muscular action. It has a valve at its lower end that prevents urine from flowing backward into the kidney. Normally there is one ureter on each side of the body for each kidney. Ureters may also be malformed in a variety of ways—which can cause have severe manifestations, and some go unnoticed in life.

Double ureter: However, among the many abnormalities of ureteral development, duplication is quite common

Retrocaval ureter: A ureter can be perfectly normal but have an abnormal position, such as behind the vena cava (retrocaval ureter), the large vein in the middle of the abdomen. In this case the ureter may be pinched by the vena cava so that flow is hindered. Other abnormal locations may also lead to compression and impaired flow, leading to hydronephrosis. Urethral anomalies which can be associated with obstructive uropathies, can be enumerated as phimosi, paraphimosis, hypospadias, malformation of penis, ureteral reflux..

Hence one can conclude though the etiology of urolithiasis is multifactorial and is strongly related to dietary lifestyle habits and practices a defective

anatomy could be a major contributing factor. Insight into the etiology would help in proper management of the condition.

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LITERATURE REVIEW

Factors other than glomerular filtration rate affect serum cystatin C levels Lesley A Stevens, Christopher H Schmid, Tom Greene, et al. Kidney Int. 2009, 25, 652-660

Cystatin C is an endogenous glomerular filtration marker hence its serum level is affected by the glomerular filtration rate (GFR). To study what other factors might affect it blood level we performed a cross-sectional analysis of 3418 patients which included a pooled dataset of clinical trial participants and a clinical population with chronic kidney disease. The serum cystatin C and creatinine levels were related to clinical and biochemical parameters and errors-in-variables models were used to account for errors in GFR measurements. The GFR was measured as the urinary clearance of ¹²⁵I-iothalamate and ⁵¹Cr-EDTA. Cystatin C was determined at a single laboratory while creatinine was standardized to reference methods and these were 2.1+/-1.1 mg/dL and 1.8+/-0.8 mg/L, respectively. After adjustment for GFR, cystatin C was 4.3% lower for every 20 years of age, 9.2% lower for female gender but only 1.9% lower in blacks. Diabetes was associated with 8.5% higher levels of cystatin C and 3.9% lower levels of creatinine. Higher C-reactive protein and white blood cell count and lower serum albumin were associated with higher levels of cystatin C and lower levels of creatinine. Adjustment for age, gender and race had a greater effect on the association of factors with creatinine than cystatin C. Hence, we found that cystatin C is affected by factors other than GFR which should be considered when the GFR is estimated using serum levels of cystatin C.

NOBEL PRIZE IN CHEMISTRY

Dr. Venkataraman Ramakrishnan – a scientist of Indian origin, working at MRC laboratory of Molecular Biology at Cambridge, England has been awarded this Noble Prize in Chemistry for year 2009, for his work on **ribosomes** which began way back in 1978. A ribosome is a collection of several DNA molecules and some protein molecules. Dr.Venkataraman's work has wide ranging applications from designing more effective antibodies to complex biotechnological processes.

(Source TOI October 8th 2009)

ETIOPATHOGENESIS OF RENAL STONE DISEASE

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Abstract: Renal lithiasis is a common condition encountered specially in 'Stone belt' in India. Majority of stones in India and all over the globe consist of calcium stones. Nucleation is an important mechanism, which increases the tendency of stone formation. In addition to concentration of solutes, stone inhibitors are also important components; decreased concentration of which leads to calculus formation. There are two types of stone inhibitors; organic and inorganic. hypercalcuria, hyper-oxaluria, hyperuricosuria and hypocitraturia are primary metabolic abnormalities in more than 95%. Renal stone disease is of multifactorial etiology but the basic defect is relative concentration of solvent and solutes along with disturbance of urinary inhibitors. In the background of some genetic abnormality in a risk prone person, dietary and environmental changes lead to renal stone formation.

EPIDEMIOLOGY

Renal stone disease (RSD) is third commonest disorder of urinary tract after urinary tract infection (UTI) and benign prostatic hyperplasia (BPH). It is more common in a region of India, called "stone belt", which runs in the north part of India. Peak incidence of RSD is in thirties and new stone formation goes on decreasing with age. RSD has tendency to recur with average 50% recurrence rate in 10-year time.

True prevalence in India is not known, as there are no good population based studies. It is estimated that prevalence is 7% in men and 3% in women. In a hospital-based study from AIIMS, Agarwal et al have shown that of the 14,456 new patients who attended renal outpatient department, 6.6% patient had RSD¹. Of these new patients 60% were male. Of these patients, 72.3% presented as RSD, 15% as chronic kidney disease (CKD), 5% as obstructive uropathy and 7.7% with other miscellaneous presentations. Further, Agarwal et al in a community based study, while studying prevalence of CKD in Delhi, showed that at least 4.4% adult population in community had self reported renal stone disease out of 5000 approximate population screened².

The **common types of stone** found in clinical practice are:

- | | |
|---------------------|------|
| 1. Calcium stone | 80% |
| 2. Struvite stones | 12% |
| 3. Uric acid stones | 6% |
| 4. Cystein stones | 1.5% |
| 5. Others | 0.5% |

ETIOPATHOGENESIS OF RENAL STONE DISEASE³

Urine is a liquid, which as in any liquid has solvent and solutes. It is primarily imbalance of solvent and solutes relative concentration, which leads to tendency of precipitation of solutes which leads to stone formation. In addition to solvent and solute concentration, there are some crystal inhibitor substances, which prevent renal stone formation.

Depending upon concentration of solute, the state of urine as a fluid is classified into different stages of saturation of solute. *First stage* is **under-saturation**; in which majority of crystal of solute remains dissolved and very few crystals remain in solution.

Next stage is called **saturation** in which majority of crystals remain in solution and though there is little new crystal nucleation, previous **crystal aggregation does increase in size**. Once the concentration of

solute increases further, it reaches to *Third stage* of **super-saturation**. In this stage there is new crystal nucleation and further aggregation of previous nucleated crystals.

Nucleation is an important mechanism, which increases the tendency of stone formation. Nucleation is of two types: **homogenous nucleation**, in which nucleation material is same as of the stone itself. This type of nucleation is basically due to over excretion of a particular type of solute. Another type of nucleation is called heterogeneous nucleation; in which nucleation is due to substance other than stone material itself; this tendency is also called '**nidus formation**'. The few examples of heterogeneous nucleation are uric acid for calcium oxalate stone, infection in urinary tract and hypovitaminosis-A causing changes in epithelium, which act as a nidus.



Figure 1: Renal Stone: Basic Pathogenesis

STONE INHIBITORS

In addition to concentration of solutes, stone inhibitors are also important components; decreased concentration of which leads to RSD. There are *two types* of stone inhibitors; *organic and inorganic*.

I. Inorganic Stone Inhibitors

1. Citrate

Hypocitraturia is defined as urinary citrate excretion of <250 mg in 24 hours. Urinary citrate forms a soluble complex with calcium that inhibits the formation and propagation of crystals. It is a common correctable cause of recurrent pure calcium phosphate or brushite stones. Women excrete more citrate and have lower incidence of stone formation than men. Urinary citrate is mainly derived endogenously through the tricarboxylic acid cycle and is excreted by renal tubular

cells. Intracellular acidosis, acidic diets (diets rich in animal proteins), and hypokalemia decrease urinary citrate excretion. Fruits such as oranges and grapefruits are the main exogenous sources of urinary citrate. *Hormonal replacement therapy* in postmenopausal women results in higher urinary calcium excretion, but it also increases urinary excretion of citrate and leads to net inhibition of crystal precipitation, thereby decreasing the risk of calcium stones.

2. Magnesium

There are usually no major differences reported in magnesium (Mg) excretion between stone formers and normal subjects. Low urinary Mg excretion is only observed in patients with disturbed intestinal function and malabsorption. The inhibitory properties of Mg are mainly related to the growth of calcium phosphate crystals. In terms of calcium oxalate reduced magnesium excretion slightly increases the ion-activity product of the salt. Mg also reduces the rate of conversion of amorphous calcium phosphate (ACP) to octacalcium phosphate (OCP) and HAP.

3. Pyrophosphate

Inorganic pyrophosphate is a potent inhibitor which appears to affect calcium phosphate more than calcium oxalate crystals.

II. Organic Stone Inhibitors

1. Nephrocalcium

It is a strongly acidic glycoprotein present in normal urine, which inhibits calcium oxalate crystal growth and has been isolated from urinary stone matrix

2. Tamm-Horsfall (TH) Protein

THP is a glycoprotein produced by the thick ascending limb of the loop of Henle of mammalian kidney. While the monomeric molecule has a MW of approximately 68 kD, it is physiologically present in a highly aggregated state in urine. When this protein is concentrated at low pH, it forms a gel. Tamm-Horsfall protein is the most abundant protein in mammalian urine. It is the matrix of urinary casts derived from the secretion of renal tubular cells. Tamm-Horsfall protein is part of the matrix in renal calculi but its role in kidney stone formation remains debatable.

3. Glycosaminoglycans

The glycosaminoglycans excreted in urine are chondroitin sulfate, heparan sulfate, and hyaluronic acid, but the major glycosaminoglycans in stones are heparan sulfate and hyaluronic acid. Glycosaminoglycans inhibit calcium oxalate crystal growth and crystal aggregation, but their definite role in stone formation is not known and there are usually no differences in the total excretion of glycosaminoglycans between stone formers and normal subjects.

4. Osteopontin

A negatively charged extracellular matrix protein that plays a role in the regulation of bone metabolism and a variety of other biological functions. Its decrease is responsible in some cases for tendency to stone formation

ETIOLOGY

Renal stone are formed due to primary metabolic abnormality in more than 95% cases and systemic disease is responsible in less than 5% cases. Basic *metabolic abnormalities* are:

1. Hypercalciuria
2. Hyper-oxaluria
3. Hyperuricosuria
4. Hypocitraturia

I. HYPERCALCIURIA

Urine calcium excretion more than 4 mg/Kg/day is classified as hypercalciuria. Common *systemic diseases* associated with

hypercalciuria are as follows:

1. Hyperparathyroidism
2. Hyper-vitaminosis-D
3. Sarcoidosis
4. Renal Tubular Acidosis
5. Prolong immobilization
6. Paget Disease
7. Hyperthyroidism

Other than small number of patients in whom renal stone disease is because of above systemic abnormality, majority is caused by idiopathic hypercalciuria. There are four types of **idiopathic hypercalciuria**.

A. Type-I idiopathic Hypercalciuria

In type-I hypercalciuria, there is *excess absorption of Ca from the diet*. It is similar to type-II Idiopathic hypercalciuria but the degree of Ca absorption is significantly high in type-I than in type-II. Majority of studies of type-I and II Idiopathic hypercalciuria has shown that 1,25(OH)₂ Vit-D concentrations in serum are high as compared to normal individuals. This may be the cause of excess Ca absorption from diet, but the cause of excess Vit-D is not known in these patients. There is some suggestion of candidate genes related to this phenomenon but exact cause is still not clear. Candidate genes shown in some studies are type-2 Na-PO₄ cotransporter, Ca sensing receptor, chloride channel, vitamin-D receptors etc.

B. Type-II idiopathic Hypercalciuria

Type-II Idiopathic hypercalciuria is *very similar to Type-I* except that the degree in type-II is less than Type-I.

C. Type-III idiopathic Hypercalciuria

In Type-III Idiopathic hypercalciuria, there is *excess absorption of Ca from kidney*.

D. Renal leak hypercalciuria

In renal leak Idiopathic hypercalciuria, there is *leak of PO₄ from the kidney*, which leads to hypo-PO₄ in blood. This hypo-PO₄ leads to stimulation of 1,25(OH) hydroxylase enzyme in kidney which in-turn leads to excess conversion of 25(OH) to 1,25(OH)₂ in kidney tubules, which causes excess absorption of Ca from intestine. This causes hypercalcemia and hypercalciuria.

In all the above types of hypercalciuria, increasing salt in diet will increase hypercalciuria. Excess salt can cause volume expansion and will decrease the absorption of solutes including calcium from the proximal tubules and thus can lead to hypercalciuria and increases tendency to stone formation. Further, increasing Ca in diet obviously increases hypercalciuria. Increasing dietary protein has also shown in the studies increase in hypercalciuria. Thus, patients with calcium stone tendency should be advisable to decrease salt, calcium and protein in diet to moderate degree.

II. HYPER-OXALURIA

Urinary oxalate excretion in excess of 40 mg /day is taken as hyperoxaluria. Hyperoxaluria is **classified** as **dietary, enteric** and **genetic**.

Dietary hyperoxaluria is usually a mild type of hyperoxaluria, where urinary excretion of oxalates is 40-60 mg/day. 50% of urinary oxalate is contributed by dietary oxalate. Thus, dietary hyperoxaluria is common. 80% patients of dietary hyperoxaluria have some membrane abnormality causing excess absorption of oxalate from diet. Some of these patients also have *oxalobacter formigines deficiency*. Oxalobacter formigines are normal flora in intestine upto 1st year of life. They degrade oxalates using oxalate dehydrogenase enzymes and thus decrease absorption of oxalate from intestine. However, its role in recurrent oxalate stone formation is not clearly known. The

substances, which are rich in oxalate, are beets, spinach, rhubarb, tea, chocolate and peanuts. Their excess use is linked with dietary hyperoxaluria.

Enteric hyperoxaluria is little more severe than dietary hyperoxaluria, in the sense that urinary oxalate excretion is usually more than 60 mg/day. Normally bile acid is absorbed in proximal intestine. If for any reason, its absorption in proximal intestine is decreased, then it reaches to distal intestine. In distal intestine bile acid binds with Ca and decreases free Ca in bowel. Once free Ca decreases in bowel, it leaves more oxalate, which can be absorbed as normally Ca binds to oxalate and decreases its absorption. This ultimately leads to hyperoxaluria. This can also be understood from some studies in which *low Ca intake in diet* has been associated with increased oxalate absorption from intestine and hyperoxaluria. Enteric hyperoxaluria is seen in patients with Crohn's disease, particularly following intestinal resection, with jejunio-ileal bypass for obesity, or with any other condition associated with fat and bile acid malabsorption such as pancreatic insufficiency. It has, moreover, been suggested that bile acids, which are present at high concentrations throughout the intestinal tract because of the malabsorption, increase the permeability of the colon. This mechanism might thus further augment the intestinal absorption of oxalate. The importance of the colon for oxalate absorption is further supported by the fact that patients with an ileostomy usually form uric acid and not calcium oxalate stones.

Genetic hyperoxaluria, the most serious abnormality of the metabolism of oxalate occurs in two different forms: Type 1 and Type 2; the 24-h excretion in these patients is usually greater than 100 mg/day. Patients with Type 1 hyperoxaluria have a deficiency of alanine-glyoxylate aminotransferase (AGT), which is a pyridoxal phosphate-dependent enzyme. This enzyme is responsible for the conversion of glyoxylate to glycine. The deficiency or insufficient synthesis of AGT results in an increased supply of glyoxylate. In this way increased amounts of oxalate are synthesized from glyoxalate by the action of peroxisomal glyoxylate oxidase (XO) and cytosolic lactate dehydrogenase (LD). The enzyme AGT is synthesized in the liver where it is localized to the peroxisomes. It is encoded by the AGXT gene on the 2q 37.3 chromosome. Several mutations have been identified. The analytical findings in patients with primary hyperoxaluria Type 1 are increased urinary excretion of *oxalate* and *glycolate*. The stones are in most cases composed of COM. Liver biopsy and assessment of the AGT activity is required for a reliable diagnosis. A definite cure for these patients cannot be obtained unless liver transplantation is carried out.

The abnormality behind primary hyperoxaluria Type 2 is a deficient production of GR. This enzyme is responsible for conversion of glyoxylate to glycolate. A deficient function of GR leads to an accumulation of glyoxylate with an increased conversion to oxalate. Inasmuch as GR also is responsible for conversion of hydroxypyruvate to d-glycerate, surplus amounts of hydroxypyruvate give an excessive production of l-glycerate by the action of LD. The genetic defect has been localized to chromosome 9q11. Primary hyperoxaluria Type 2 usually has a milder clinical course than hyperoxaluria Type 1 and renal failure is less commonly seen in patients with the Type 2 disease. Clinically, these patients have an increased urinary excretion of *oxalate* and *l-glycerate* and it has been stated that stone formation is a more typical entity in hyperoxaluria Type 2 than is nephrocalcinosis.

III. HYPERURICOSURIA

Urate has no direct influence on the ion-activity products of calcium

phosphate or calcium oxalate and its role in calcium stone formation has been a matter of debate for decades. It has been suggested that sodium urate might serve as a nidus for calcium oxalate precipitation, that colloidal urate might interfere with the activity of crystallization inhibitors, or that calcium oxalate is precipitated as a result of a salting-out effect. Of these alternatives the last one presently appears most plausible. Coe and coworkers described a *uricosuric calcium oxalate stone syndrome*, but there is no information available on how common this syndrome is. Geographical and dietary factors might explain the variability by means of which hyperoxaluria calcium oxalate stone formation obviously occurs in different populations of the world. In some groups of stone-formers urinary urate is increased compared with normal subjects, in others it is not. It is noteworthy that an increased excretion of urate usually accompanies several of the other changes in urine composition that are associated with excessive dietary habits.

There is significant effect of urinary pH on dissolution of uric acid. As the pH decreases towards acidic side, undissociated uric acid concentration increases and chances of uric acid crystallization increases. Dietary protein also is another factor, which increases urinary uric acid excretion.

IV. HYPOCITIURIA

Normal excretion of citrate in urine is more than 325 mg/day. It is a stone inhibitor as it complexes Ca and decreases Ca oxalate crystallization. More than 30% of calcium stone formers have hypocitraturia. Hypocitraturia can be idiopathic or it can be caused by systemic acidosis and hypokalemia. In a small study after oral citrate therapy tendency of recurrent stone formation had decreased significantly.

Comparative significance of various abnormalities is shown in figure-2.

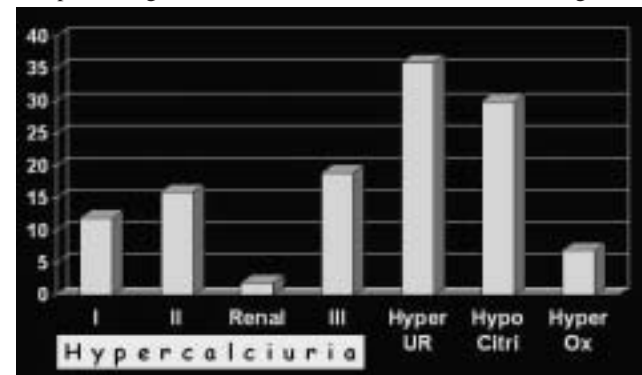


Figure 2: Renal Stone: Comparative Primary Abnormality

CONCLUSION

Renal stone disease is of multifactorial in etiology but the basic defect is relative concentration of solvent and solutes along with disturbance of urinary inhibitors. In the background of some genetic abnormality in a risk prone person, dietary and environmental changes lead to renal stone formation.

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UROLITHIASIS - CLINICAL FEATURES AND DIAGNOSIS

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Abstract : Urinary tract stone disease has been an important part of the human disease for millennia. Pain, infection, or hematuria are classical triad of symptoms reported by patients with renal stone disease. While acute obstruction may produce a classic renal colic, long standing obstruction may be asymptomatic and may present with symptoms of renal failure; costovertebral angle tenderness is common; this pain can move to the upper or lower abdominal quadrant as a ureteral stone migrates distally. Peritoneal signs are usually absent—an important consideration in distinguishing renal colic from other sources of flank or abdominal pain. A detailed radiological investigation and metabolic profile are essential for the diagnosis for renal stone disease.

Urinary tract stone disease has been a part of the human condition for millennia; in fact, bladder and kidney stones have even been found in Egyptian mummies. Some of the earliest recorded medical texts and figures depict the treatment of urinary tract stone disease. The overall lifetime rate of kidney stones in the general population is approximately 12% for men and 4% for women. Having a family member with a history of stones doubles these rates. Approximately 30 million people are at risk in the United States. No such data available for the Indian population. Peak incidence occurs in people aged 35-45 years, but the disease can affect anyone at any age.

HISTORY

- Patients with urinary calculi may report *pain, infection, or hematuria*. Small nonobstructing stones in the kidneys only occasionally cause symptoms. If present, symptoms are usually moderate and easily controlled.
- The passage of stones into the ureter with subsequent acute obstruction, proximal urinary tract dilation, and spasm is associated with classic renal colic.
 - Renal colic is characterized by undulating cramps and severe pain and is often associated with nausea and vomiting.
 - As the stone travels through the ureter, the pain moves from the flank to the upper abdomen, then to the lower abdomen, down to the groin, and eventually to the scrotal or labial areas.
 - Associated bladder irritative symptoms are common when the stone is located in the distal or intramural ureter.
- Patients with large renal stones known as staghorn calculi are often relatively asymptomatic.
 - Staghorn refers to the presence of a branched kidney stone occupying the renal pelvis and at least one calyceal system. Such calculi usually manifest as infection and hematuria rather than as acute pain.
 - Asymptomatic bilateral obstruction, which is uncommon, manifests as symptoms of renal failure.
- Important historical features are as follows:
 - Duration, characteristics, and location of pain

- History of urinary calculi
- Prior complications related to stone manipulation
- Urinary tract infections
- Loss of renal function
- Family history of calculi
- Solitary or transplanted kidney

A few important words about the pathophysiology of renal colic.

RENAL COLIC PAIN

The colicky-type pain known as renal colic usually begins in the upper lateral mid back over the costovertebral angle and occasionally subcostally. It radiates inferiorly and anteriorly toward the groin. The pain generated by renal colic is primarily caused by the dilatation, stretching, and spasm caused by the acute ureteral obstruction. (When a severe but chronic obstruction develops, as in some types of cancer, it is usually painless.)

Colic is a misnomer because renal colic pain tends to remain constant, whereas intestinal or biliary colic is usually somewhat intermittent and often comes in waves. The pattern of the pain depends on the individual's pain threshold and perception and on the speed and degree of the changes in hydrostatic pressure within the proximal ureter and renal pelvis. Ureteral peristalsis, stone migration, and tilting or twisting of the stone with subsequent intermittent obstructions may cause exacerbation or renewal of the renal colic pain. The severity of the pain depends on the degree and site of the obstruction, not on the size of the stone. A patient can often point to the site of maximum tenderness, which is likely to be the site of the ureteral obstruction. A stone moving down the ureter and causing only intermittent obstruction actually may be more painful than a stone that is motionless. A constant obstruction, even if high grade, allows for various autoregulatory mechanisms and reflexes, interstitial renal edema, and pyelolymphatic and pyelovenous backflow to help diminish the renal pelvic hydrostatic pressure, which gradually helps reduce the pain. The interstitial renal edema produced, stretches the renal capsule, enlarges the kidney (ie, nephromegaly), and increases renal lymphatic drainage. (Increased capillary permeability facilitates this edema.) It may also reduce the radiographic density of the affected kidney's parenchyma when viewed on a noncontrast CT scan. Distension of the renal pelvis initially stimulates ureteral hyperperistalsis, but this diminishes after 24 hours, as does renal blood flow. Peak hydrostatic renal pelvis pressure is attained within

2-5 hours after a complete obstruction. Within the first 90 minutes of a complete ureteral obstruction, afferent preglomerular arteriolar vasodilation occurs, which temporarily increases renal blood flow. Between 90 minutes and 5 hours after the obstruction, renal blood flow starts to decrease while intraureteral pressure continues to rise. By 5 hours after a complete obstruction, both renal blood flow and intraluminal ureteral pressure decrease on the affected side. Renal blood flow decreases to approximately 50% of normal baseline levels after 72 hours, to 30% after 1 week, to 20% after 2 weeks, and to 12% after 8 weeks. By this point, intraureteral pressures have returned to normal, but the proximal ureteral dilation remains and ureteral peristalsis is minimal.

Interstitial edema of the affected kidney actually enhances fluid reabsorption, which helps to increase the renal lymphatic drainage to establish a new, relatively stable, equilibrium. At the same time, renal blood flow increases in the contralateral kidney as renal function decreases in the obstructed unit.

In summary, by 24 hours after a complete ureteral obstruction, the renal pelvic hydrostatic pressure has dropped because of (1) a reduction in ureteral peristalsis; (2) decreased renal arterial vascular flow, which causes a corresponding drop in urine production on the affected side; and (3) interstitial renal edema, which leads to a marked increase in renal lymphatic drainage. Additionally, as the ureter proximal to the stone distends, some urine can sometimes flow around the obstruction, relieving the proximal hydrostatic pressure and establishing a stable, relatively painless equilibrium. These factors explain why severe renal colic pain typically lasts less than 24 hours in the absence of any infection or stone movement.

Experimental studies in animals have suggested that renal damage may begin within 24 hours of a complete obstruction and permanent kidney deterioration starts within 5-14 days. While some practitioners wait several months for a stone to pass in an asymptomatic patient, others argue that permanent damage is occurring as long as intervention is delayed. Based on personal experience and anecdotal cases, the author recommends waiting no longer than 4 weeks for a stone to pass spontaneously before considering intervention. Convincing asymptomatic patients of the need for surgical intervention may be difficult in the absence of a clear consensus in the urological community about the length of time to wait before surgical stone removal, fragmentation, or bypass.

If only a partial obstruction is present, the same changes occur, but to a lesser degree and over a longer period. Proximal ureteric and renal pelvic hydrostatic pressures tend to remain elevated longer, and ureteral peristalsis does not diminish as quickly. If the increased pressure is sufficient to establish a reasonable flow beyond the obstructing stone, glomerular filtration and renal blood flow approximates reference range baseline levels, although pain may be ongoing.

PHASES OF THE ACUTE RENAL COLIC ATTACK

The actual pain attack tends to occur in somewhat predictable phases, with the pain reaching its peak in most patients within 2 hours of onset. The pain roughly follows the dermatomes of T-10 to S-4. The entire process typically lasts 3-18 hours. Renal colic has been described as having 3 clinical phases.

Acute, or onset, phase

The typical attack starts early in the morning or at night, waking the patient from sleep. When it begins during the day, patients most commonly describe the attack as starting slowly and insidiously. The pain is usually steady, increasingly severe, and continuous; some patients experience intermittent paroxysms of even more excruciating

pain. The pain level may increase to maximum intensity in as little as 30 minutes after initial onset or more slowly, taking up to 6 hours or longer to peak. The typical patient reaches maximum pain 1-2 hours after the start of the renal colic attack.

Constant phase

Once the pain reaches maximum intensity, it tends to remain constant until it is either treated or allowed to diminish spontaneously. The period of sustained maximal pain is called the constant phase of the renal colic attack. This phase usually lasts 1-4 hours but can persist longer than 12 hours in some cases. Most patients arrive in the ED during this phase of the attack.

Abatement or relief phase

During this final phase, the pain diminishes fairly quickly, and patients finally feel relief. Relief can occur spontaneously at any time after the initial onset of the colic. Patients may fall asleep, especially if they have been administered strong analgesic medication. Upon awakening, the patient notices that the pain has disappeared. This final phase of the attack most commonly lasts 1.5-3 hours.

Pain in renal colic

Renal pain fibers are primarily preganglionic sympathetic nerves that reach spinal cord levels T-11 to L-2 through the dorsal nerve roots. Aortorenal, celiac, and inferior mesenteric ganglia are also involved. Spinal transmission of renal pain signals occurs primarily through the ascending spinothalamic tracts. In the lower ureter, pain signals are also distributed through the genitofemoral and ilioinguinal nerves. The nervi erigentes, which innervates the intramural ureter and bladder, is responsible for some of the bladder symptoms that often accompany an intramural ureteral calculus.

- *Upper ureter and renal pelvis:* Pain from upper ureteral stones tends to radiate to the flank and lumbar areas. On the right side, this can be confused with cholecystitis or cholelithiasis; on the left, the differential diagnoses include acute pancreatitis, peptic ulcer disease, and gastritis.
- *Middle ureter:* Midureteral calculi cause pain that radiates anteriorly and caudally. This midureteral pain in particular can easily mimic appendicitis on the right or acute diverticulitis on the left.
- *Distal ureter:* Distal ureteral stones cause pain that tends to radiate into the groin or testicle in the male or labia majora in the female because the pain is referred from the ilioinguinal or genitofemoral nerves. If a stone is lodged in the intramural ureter, symptoms may appear similar to cystitis or urethritis. These symptoms include suprapubic pain, urinary frequency, urgency, dysuria, stranguria, pain at the tip of the penis, and sometimes various bowel symptoms, such as diarrhea and tenesmus. These symptoms can be confused with pelvic inflammatory disease, ovarian cyst rupture, or torsion and menstrual pain in women.

Most of the pain receptors of the upper urinary tract responsible for the perception of renal colic are located submucosally in the renal pelvis, calices, renal capsule, and upper ureter. Acute distention seems to be more important in the development of the pain of acute renal colic than spasm, local irritation, or ureteral hyperperistalsis. Stimulation of the peripelvic renal capsule causes flank pain, while stimulation of the renal pelvis and calices causes typical renal colic. Mucosal irritation can be sensed in the renal pelvis to some degree by chemoreceptors, but this irritation is thought to play only a minor role in the perception of renal or ureteral colic.

In the ureter, an increase in proximal peristalsis through activation

of intrinsic ureteral pacemakers may contribute to the perception of pain. Muscle spasm, increased proximal peristalsis, local inflammation, irritation, and edema at the site of obstruction may contribute to the development of pain through chemoreceptor activation and stretching of submucosal free nerve endings.

Nausea and vomiting are often associated with acute renal colic and occur in at least 50% of patients. Nausea is caused by the common innervation pathway of the renal pelvis, stomach, and intestines through the celiac axis and vagal nerve afferents. This is often compounded by the effects of narcotic analgesics, which often induce nausea and vomiting through a direct effect on GI motility and through an indirect effect on the chemoreceptor trigger zone in the medulla oblongata. Nonsteroidal anti-inflammatory drugs (NSAIDs) can often cause gastric irritation and GI upset.

The presence of a renal or ureteral calculus is not a guarantee that the patient does not have some other, unrelated medical problem causing the GI symptoms.

Acute onset of severe flank pain radiating to the groin, gross or microscopic hematuria, nausea, and vomiting not associated with an acute abdomen are symptoms that most likely indicate renal colic caused by an acute ureteral or renal pelvic obstruction from a calculus. Renal colic pain rarely, if ever, occurs without obstruction.

In some cases, a stone may pass before the definitive imaging procedure has been completed. In these cases, residual inflammation and edema still may cause some transient or diminishing obstruction and pain even without any stone being positively identified.

NERVE BLOCK & RENAL COLIC

Nerve blocks have been used successfully in both the diagnosis and treatment of renal colic, although they are more helpful in chronic than in acute cases. Intercostal nerve blocks can be used to differentiate pain from chondritis, neuromas, and radiculitis from true renal pain. This is achieved by injecting an anesthetic agent, such as lidocaine, around the 11th or 12th intercostal nerve proximal to the site of the pain at a time when the patient is experiencing pain. If the injection causes abolition of the pain, a peripheral nerve or musculoskeletal etiology is suggested. Subsequent injections of various agents to produce neurolysis (eg, 10% phenol or 100% absolute alcohol) have been tried but often result in an intolerable denervation-related discomfort.

In the mid 1950s, a study was reported in which 51 patients with documented renal colic were successfully treated for pain using only a unilateral posterior splanchnic nerve block. Complete relief from pain, nausea, and vomiting was reported in all 51 patients treated.

PHYSICAL EXAMINATION

- Dramatic costovertebral angle tenderness is common; this pain can move to the upper or lower abdominal quadrant as a ureteral stone migrates distally.
- Peritoneal signs are usually absent—an important consideration in distinguishing renal colic from other sources of flank or abdominal pain.
- Findings should correlate with the reports of pain, so that complicating factors (eg, urinary extravasation, abscess formation) can be detected.
- Beyond this, the specific location of tenderness infrequently correlates with the exact location of the stone, although the calculus is often in the general area of maximum discomfort

LABORATORY STUDIES

- Urinalysis

- Evaluation of the urine for evidence of hematuria and infection. Approximately 85% of patients with urinary calculi exhibit hematuria.
- An absence of hematuria does not rule out urinary calculi; in fact, approximately 15% of patients with urinary stones do not exhibit hematuria.
- Complete blood cell count. In the context of nephrolithiasis, an elevated white blood cell count suggests renal or systemic infection.
- A depressed red blood cell count suggests a chronic disease state or severe ongoing hematuria.
- Serum electrolytes, creatinine, calcium, uric acid, parathyroid hormone (PTH), and phosphorus studies
- These are needed to assess a patient's current renal function and to begin the assessment of metabolic risk for future stone formation.
- A high serum uric acid level may indicate gouty diathesis or hyperuricosuria, while hypercalcemia suggests either renal-leak hypercalciuria or hyperparathyroidism.
- If the serum calcium level is elevated, serum PTH levels are usually obtained.
- Twenty-four-hour urine collection for levels of pH, calcium, oxalate, uric acid, sodium, phosphorus, citrate, magnesium, creatinine, and total volume

Metabolic Evaluation

- This is designed to provide more information about the exact nature of the chemical problem that caused the stone. This information is useful not only to allow more specific and effective therapy for stone prevention but also to identify patients with renal calculi who might have other significant health problems. The following are the objective **indications for a metabolic evaluation** with a 24-hour urinalysis:

- Residual calculi after surgical treatment;
- Initial presentation with multiple calculi;
- Initial presentation before age 30 years;
- Renal failure;
- Solitary kidney (including renal transplant);
- Family history of calculi;
- More than one stone in the past year;
- Bilateral calculi.

An important consideration in determining whether to perform a 24-hour urine study is the patient's interest. If a patient is strongly motivated to follow a protracted stone-prevention treatment plan (involving diet, supplements, medications, or a combination), obtain the study. If a patient is unlikely or unwilling to follow a long-term treatment plan, a metabolic evaluation is probably unwarranted. Patients have to understand that stone disease is a chronic disease. If they do not commit to helping themselves in behavior modification, dietary changes, or medical compliance, they are prone to frequent and possible symptomatic calculi.

Calcium, oxalate, and uric acid Elevation of the 24-hour excretion rate of any of these 3 components indicates a predisposition to form calculi.

- **Hypercalciuria** can be subdivided into *absorptive*, *resorptive*, and *renal-leak* categories based on the results of blood tests and 24-hour urinalysis on both regular and calcium-restricted diets.
- Depending on the specific subtype, the treatment of *absorptive* hypercalciuria may include dietary calcium restriction, thiazide diuretics, oral calcium binders, or phosphate supplementation. Resorptive hypercalciuria occurs in primary

hyperparathyroidism and requires *parathyroidectomy*.

- **Renal-leak** hypercalciuria, which is relatively uncommon, is usually associated with secondary hyperparathyroidism and is best managed with thiazide diuretics.
- Another clinical approach to hypercalciuria, once hyperparathyroidism has been excluded with appropriate blood tests, is to avoid excessive dietary calcium (usual recommendation, 600-800 mg/d) and to use thiazides. If thiazide therapy fails, additional workup (eg, calcium-loading test, more thorough evaluation) may be needed.
- **Hyperoxaluria** may be primary (a rare genetic disease), enteric (due to malabsorption and associated with chronic diarrhea or short-bowel syndrome), or idiopathic. Oxalate restriction and vitamin B-6 supplementation are somewhat helpful in patients with idiopathic hyperoxaluria. Enteric hyperoxaluria is the type that is most amenable to treatment; dietary calcium supplementation often produces dramatic results. Calcium citrate is the recommended supplement because citrate tends to further reduce stone formation. Calcium carbonate supplementation is less expensive but does not provide citrate's added benefit. Calcium therapy works as an oxalate binder, reducing oxalate absorption from the intestinal tract. Calcium should be administered with meals, especially those that contain high oxalate levels. The supplement should not contain added vitamin D because this increases calcium absorption, leaving less in the intestinal tract to bind to oxalate.
- **Hyperuricosuria** predisposes to the formation of calcium-containing calculi because sodium urate can produce malabsorption of macromolecular inhibitors or can serve as a nidus for the heterogeneous growth of calcium oxalate crystals. Gouty diathesis, a condition of increased stone production associated with high serum uric acid levels, is also possible. Therapy involves potassium citrate supplementation, allopurinol, or both. In general, patients with pure uric acid stones and hyperuricemia are treated with allopurinol, and those with hyperuricosuric calcium stones are treated with citrate supplementation.

Sodium and Phosphorus

- Excess sodium excretion can contribute to hypercalciuria by a phenomenon known as solute drag. Elevated urinary sodium levels are almost always associated with dietary indiscretions. Decreasing the oral sodium intake can decrease calcium excretion, thereby decreasing calcium saturation.
- An elevated phosphorus level is useful as a marker for a subtype of absorptive hypercalciuria known as renal phosphate leak (absorptive hypercalciuria type III).
- Renal phosphate leak is identified by high urinary phosphate levels, low serum phosphate levels, high serum 1,25 vitamin D-3 (calcitriol) levels, and hypercalciuria. This type of hypercalciuria is uncommon and does not respond well to standard therapies. The above laboratory tests are confirmatory, but they are performed only if the index of clinical suspicion is high. Any patient with hypercalciuria who has a low serum phosphorus level and a high-normal or high urinary phosphorus level may have this condition. Phosphate supplements are used to correct the low serum phosphate level, which then decreases the inappropriate activation of vitamin D originally caused by the hypophosphatemia.

Citrate and Magnesium

- Magnesium and, especially, citrate are important chemical inhibitors of stone formation. Hypocitraturia is one of the most common metabolic defects that predispose to stone formation, and some authorities have recommended citrate therapy as primary or adjunctive therapy to almost all patients who have formed recurrent calcium-containing stones.
- Liquid or powder pharmacologic citrate preparations are recommended when absorption is a problem or in cases involving chronic diarrhea. Sustained-release tablets are available and may be more convenient for some patients. Concentrates of lemon juice provide an excellent source of citrate, or, alternatively, large quantities of lemonade can be ingested, which, of course, has the added benefit of providing increased fluid intake.
- Potassium citrate is the preferred type of pharmacologic citrate supplement, although a potassium/magnesium preparation is under investigation.
- Magnesium is a more recently recognized inhibitor of stone formation, and the clinical role of magnesium replacement therapy is less defined than that of citrate.

Creatinine

- Creatinine is the control that allows verification of a true 24-hour sample. Most individuals excrete 1-1.5 g of creatinine daily.
- Values at either extreme that are not explained by estimates of lean body weight should prompt consideration that the sample is inaccurate.
- Patients in whom stones form should strive to achieve a urine output of more than 2 L daily in order to reduce the risk of stone formation.
- Patients with cystine stones or those with resistant cases may need a daily urinary output of 3 L for adequate prophylaxis.

pH: Some stones, such as those composed of uric acid or cystine, are pH-dependent, meaning that they can form only in acidic or basic conditions. Although the other parameters in the 24-hour urine usually identify patients at risk of forming these stones, pH studies can be important in monitoring these patients or in identifying occult stone disease in some patients.

IMAGING STUDIES

These have been detailed elsewhere in this Journal; and are discussed in brief :-

Plain abdominal radiography (also known as a flat plate or kidney, ureter, and bladder [KUB] radiography) (a) may suffice for assessing total stone burden, as well as the size, shape, and location of urinary calculi in some patients. (b) Calcium-containing stones (approximately 85% of all upper urinary tract calculi) are radiopaque, but pure uric acid, indinavir-induced, and cystine calculi are relatively radiolucent on plain radiography. (c) When used with other imaging studies, such as a *renal sonography* or, particularly, *CT scanning*, the plain film helps provide a better understanding of the size, shape, location, and even composition of urinary stones

Renal ultrasonography

(a) Renal sonography by itself is frequently adequate to determine the presence of a renal stone. The study is mainly used in combination with plain abdominal radiography to determine hydronephrosis or

ureteral dilation associated with an abnormal radiographic density believed to be a urinary tract calculus. (b) A stone easily identified with renal ultrasonography but not visible on the plain radiograph may be a uric acid or cystine stone, which is potentially dissolvable with urinary alkalinization therapy. (c) Ureteral calculi, especially in the distal ureter, and stones smaller than 5 mm are not easily observed with ultrasonography.

Intravenous urography

(a) An intravenous urography (IVU) test, also known as an intravenous pyelography (IVP), is the standard for determining the size and location of urinary calculi. IVU provides anatomical and functional information. A replacement imaging technique is being sought because IVU is a labor-intensive imaging study. (b) Up to 6 hours may be required to complete the study in the presence of severe obstruction; for optimal results, IVU requires a bowel preparation; It involves intravenous injection of potentially allergic and mildly nephrotoxic contrast material. (c) Although some authorities have advocated substituting plain abdominal radiography plus renal ultrasonography for IVU, a helical CT scan without contrast material is currently believed to be the best radiographic examination for acute renal colic. (d) The so-called delayed nephrogram on the IVU is one of the hallmark signs of acute urinary obstruction. The relative delay in penetration of intravenous contrast passing through an obstructed kidney elicits this sign. The kidney appears to develop a whitish color, and contrast appearance within the collecting system of the affected renal unit is significantly delayed. (e) The IVU is helpful in identifying the specific problematic stone among numerous pelvic calcifications and for establishing that the other kidney is functional. These determinations are particularly helpful if the degree of hydronephrosis is mild and the CT scan findings are not definitive.

Helical CT scanning without contrast material

a) Technological advances in CT scanning allow imaging of the entire abdomen in a single breath hold; (b) When performed with thin cuts and without intravenous contrast material, CT scanning is the most sensitive clinical imaging modality for calcifications. Even calculi that are radiolucent on a plain radiograph (except for indinavir-induced stones) are clear and distinct on a CT scan. (c) Contrast is not used because it makes the entire urinary collecting system appear white on the study, thus masking the stones. d) At most institutions that offer this examination, CT scanning has replaced or is replacing IVU for the assessment of urinary tract stone disease, especially for acute renal colic. e) Adding plain radiography to noncontrast CT scanning increases the value of the study by allowing visualization of the size, shape, and relative position of the stone. Visualization is especially useful if surgery is being considered. It is extremely helpful in observing the patient because only KUB radiography may be needed later to determine if the stone has moved or passed. A lucent stone on the KUB radiograph that is clearly visible on the CT scan may indicate a uric acid calculus. This suggests a different diagnosis and therapy (allopurinol and/or urinary alkalinization) than for a calcium stone. For these reasons, many institutions routinely perform KUB radiography whenever a renal colic noncontrast CT scan is performed.

• Advantages of a CT scanning include the following:

- It can reveal other pathology (eg, abdominal aneurysms, appendicitis, cholecystitis).
- It can be performed quickly.
- It avoids the use of intravenous contrast materials.

• Disadvantages of CT scanning include the following:

- It cannot be used to assess individual renal function.
- It can fail to reveal some unusual radiolucent stones, such

as those caused by indinavir, which are invisible on the CT scan. Because of this possibility, IVUs with contrast should be used for patients taking indinavir.

- At most institutions, CT scanning is still more expensive than IVU.

• Plain renal tomography

Although largely replaced by helical CT scanning without contrast (when available), plain renal tomography is often helpful in finding small stones in the kidneys, especially in patients who are large or obese whose bowel contents complicate observation of any renal calcifications. Tomography does not require extensive preparation and can be performed quickly. Plain renal tomography is most useful when monitoring a difficult-to-observe stone after therapy or for clarification of stones not clearly detected or identified with other studies. It is also useful in determining the number of stones present in the kidneys before a stone-prevention program is instituted. This information is used to better differentiate stones formed before therapy began from those formed later.

NUCLEAR SCINTIGRAPHY

Bisphosphonate markers can identify even small calculi that are difficult to appreciate in plain films.

RETROGRADE PYELOGRAM (RGP)

Delineates the upper urinary tract anatomy and localises small calculi.

MRI-MRU

- MRI not a very good investigation.
- MRU – may help in difficult cases/ collecting system abnormalities.

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RADIOLOGICAL INVESTIGATIONS IN UROLITHIASIS

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Abstract : Radiological investigations play a key role in diagnostic work up of urolithiasis . While conventional investigations like X ray KUB, USG and IVP are still considered essential for diagnosis ,newer modalities like CT Urography and MR Urography have increased the sensitivity and specificity of diagnostic work up. Decision on the appropriate radiological investigation is usually based on several factors which include the pretest probability of the disease, the prevalence of the disease, the accuracy of the test, the potential risks of the test and the discomfort it causes to the patients & the cost; the ideal test should improve the patient's treatment by providing answers to the clinical questions.

Acute flank pain or acute renal colic, secondary to urolithiasis, is a common problem in patients presenting to the emergency unit of a hospital and majority are between 30 and 60 years of age. Men are affected three times more often than women¹.

X-RAY KUB

A plain film of the abdomen/X-ray KUB is usually the first radiological investigation performed in these patients. The diagnostic accuracy of the plain film for the detection of urinary tract calculus depends on the chemical composition of the stone, its size, location, overlying bowel gas shadows and technical quality of the film. Approximately 90 percent of urinary stones contain calcium (calcium oxalate, magnesium ammonium phosphate) and 10 percent are calcium free (uric acid, cystine and xanthine)². Although 90% of urinary tract calculi are radio opaque, only 59% of urinary stones are visible on abdominal radiographs³.

Bowel gas or extrarenal calcification may lead to calculi being overlooked or obscured. In addition the ribs, transverse processes and the sacrum may obscure urinary tract calculi. The cortical margin of the lateral edge of the transverse process may mimic a ureteral calculus and can be particularly confusing. Common calcifications in the abdomen need to be distinguished from renal calculi. Gallstones need to be distinguished from renal calculi. Gallstones are large with a characteristic ovoid shape. However, renal calculi in a calyceal diverticulum or an obstructed portion of the collecting system may mimic gallstones⁴. In such cases a lateral or oblique radiograph of the abdomen helps. On the lateral view, the gallstones lie in an anterior location while renal calculi remain in a more posterior location (Fig. 1 A & B). Pancreatic calcification of chronic pancreatitis often involves the entire gland and this helps to distinguish these calcifications from renal stones. Calcification of the costal cartilage of the ribs and arterial calcification is usually linear which helps to separate them from renal stones. Mesenteric nodes have a characteristic mottled appearance. The calcifications most often confused with ureteric calculi are phleboliths. Typically phleboliths are rounded have a central lucency and are seen in the true pelvis often below the distal ureter.

RADIODENSITY OF THE VARIOUS TYPES OF CALCULI ON KUB

A careful examination of the shape and density of the calculi may provide a clue to the chemical composition of the calculus⁵.

Calcium Stones

Calcium oxalate and calcium phosphate stones crystallize when the

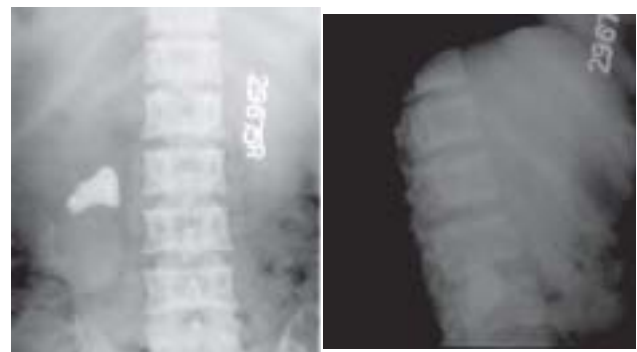


Fig. 1 A & B: Plain abdominal radiograph AP view(A) showing a densely calcified left renal stone and the lateral film(B) showing the calculus to lie posteriorly overlying the spine.

product of the two ions exceeds the solubility of the product. Hypercalcemia is a common cause of hypercalciuria and may result from a variety of metabolic processes. Hypercalciuria may be idiopathic and this is probably the most common cause of nephrolithiasis. Pure calcium phosphate and calcium monohydrate stones are the densest per volume of stone. (Fig. 2A & B) This fact is important since these stones are less amenable to ESWL. Calcium oxalate dihydrate stones are considered fragile and have a spiculated or mulberry / dotted configuration.



Fig. 2A & B: Plain abdominal radiographs showing densely calcified right renal stones (different patients) suggesting calcium containing stones.

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Infection stones

Magnesium ammonium phosphate (struvite) stones are usually infectious based stones and grow to become large branched calculi. (Fig. 3,4) These stones form in part due to urinary infection with bacteria that harbour a urea splitting enzyme that causes alkalization of the urine which favours stone formation. The calcium phosphate component often layers on the struvite and leads to a laminated appearance. Although these stones are easily fragmented with ESWL, their large size and infectious aetiology often precludes successful ESWL treatment⁵.



Fig. 3: Plain abdominal radiograph showing a branched calculus/staghorn calculus on the right side.



Fig. 4: Plain radiograph showing bilateral branched infection based struvite calculi

Cystine stones

Cystine stone contains no calcium and are rendered radio-opaque by their sulfur content. They are less opaque than calcium stones of a comparable size and have a homogeneous density. This appearance is described as opalescent or ground glass. (Fig. 5)



Fig. 5 : Plain X-ray showing a calculus in the left kidney. The stone has homogeneous density and has a ground glass or opalescent appearance suggesting cystine stone

Uric acid stones

Uric acid stones account for the majority of lucent stones. They are easily seen on CT.

Xanthine stones

These stones are relatively radiolucent because their density is similar to uric acid stones.

Matrix stones

Matrix stones are composed primarily of coagulated mucoids with little crystalline component. They are found in patients with proteus infection. Matrix stones are relatively radiolucent and may be confused with uric acid calculi⁶.

Composition of Renal Calculi and Radio Opacity (5)

Composition	Frequency (%)	Radio opacity
Pure Calcium Phosphate	10	4
Mixed Calcium Phosphate oxalate	40	3-4
Pure calcium oxalate	30	3
Struvite	10	2-3
Cystine	1	1
Uric acid	10	0



Fig. 6: Plain X-ray showing bilateral renal and left ureteric calculi. Calculi are seen in both the renal areas, opposite the transverse process of L₅ vertebra on the left side and overlying the left sacral ala suggestive of left ureteric calculi.

Calculi in the ureters can be difficult to visualize on plain X-rays in view of the fact that third of the ureter may overlies bone. (Fig. 6) Levine et al retrospectively reviewed abdominal radiographs and CT scans of 178 patients who had acute flank pain and found that abdominal radiographs had a sensitivity of 45% to 59% and specificity of 77% in the detection of urinary tract calculi³. Levine and colleagues found that the mean size of stones seen on abdominal radiographs was 4.2 mm and the mean size of stones not visualized was 3.1 mm³. Zagoria and colleagues found that 79% of calculi larger than 5mm and 95% of calculi with CT attenuation greater than 300 HU were detectable on conventional radiographs⁷. Stones composed purely of uric acid are not detectable on plain radiographs regardless of size. Phleboliths may be impossible to distinguish from ureteral stones by abdominal radiography alone, although radiographic findings such as central lucency or anatomic position may allow differentiation of these structures from true ureteric calculi.

Nevertheless, plain films are still good as baseline study and for follow-up of stone disease post – treatment. (Fig.7) The plain X-ray has the advantages of low cost, low radiation dose and wide availability.



Fig. 7: Plain radiograph showing a radio-opacity below the symphysis pubis suggestive of a urethral calculus.

INTRAVENOUS UROGRAPHY (IV) / EXCRETORY UROGRAPHY (EU).

Excretory urography is performed for the localization of the calculus and for the function of kidneys. The site, size, anatomy of the pelvicalyceal system can be clearly defined. The calculi are seen as filling defects within the opacified calyceal system. (Fig. 8 A & B) Urography is also useful for the radiolucent calculi which are missed on the plain abdominal radiographs. The presence/ absence of obstruction and the degree of obstruction if present can be clearly demonstrated on a urogram study⁶.



Fig. 8 A & B : Plain X-ray(A) showing a radio-opacity in the right renal area suggestive of right renal calculus. Excretory urogram(B) showing the calculus as a filling defect in the right renal pelvis. There is mild back pressure change seen as loss of normal cupping of the calyces.

The earliest urographic change in hydronephrosis is a flattening of the normal concavity of the calyx and blunting of the sharp peripheral angle produced by the papilla. The pelvis enlarges gradually with increasing or prolonged obstruction but pelvis and calyceal dilatation are not necessarily parallel. (Fig.9) The next calyceal change is that of “clubbing” in which the concavity produced by the papilla is reversed.(Fig. 10 A and B) Calyces then gradually enlarge with progressive destruction of the parenchyma and enlargement of the collecting system until the kidney becomes a nonfunctioning hydronephrotic sac in which the normal anatomy is obliterated⁶.



Fig. 9: Excretory urography film showing moderate hydronephrosis of the right kidney evidenced by loss of the normal concavity of the calyx and blunting of the angle produced by the papilla owing to the calculus in the right renal pelvis obscured by contrast. The left pelvicalyceal system is normal.

Renal function may be greatly diminished in severe hydronephrosis and there is accumulation of opaque material in the parenchyma adjacent to the grossly dilated calyces. This forms crescentic areas of faint opacification termed the crescent sign of hydronephrosis. In long standing chronic obstruction, there is gross pyelocalyceal dilatation with non-visualized kidney on urogram and obstructive

atrophy.

In patients with renal or ureteric colic, there is usually delayed excretion by the involved kidney. With the acute obstruction produced by the passage of a ureteric stone the intrapelvic pressure increases to the point at which there is decreased glomerular filtration of the contrast material. Increased density of the kidney (nephrogram) is due to the ongoing tubular water reabsorption in the nephrons resulting in an increased concentration of the opacified urine. Eventually there is some opacification of the calyces, pelvis and ureter. It is important to take delayed films when prolonged nephrogram is seen on the IVU images. The delayed films will show enough opacification to visualize the site of the obstructing ureteric calculus and confirm its presence within the ureter. (Fig. 11 A and B) IVU has a higher sensitivity and specificity than an abdominal radiograph in diagnosing urinary calculus disease as the cause of acute flank pain. (64% versus 97% and 92% versus 94% respectively)⁸. IVU has the advantages of providing exquisite information about the pelvicalyceal system anatomy and provides physiologic information about the kidneys. However it does not provide information about the extrarenal structures and extrarenal pathology. Also, there is need of intravenous contrast administration and hence the risk of contrast reactions. It is not the modality of choice in renal failure, contrast induced nephropathy and pregnant patients.



Fig. 10 A & B: Plain radiograph(A) showing a radio density in the left pelvis at the level of the ischial spine S/O lower left ureteric calculus. The left kidney shows marked hydronephrosis with clubbing of the calyces seen on the excretory urogram(B) in the patient.

In patients with renal or ureteric colic, there is usually delayed excretion by the involved kidney. With the acute obstruction produced by the passage of a ureteric stone the intrapelvic pressure increases to the point at which there is decreased glomerular filtration of the contrast material. Increased density of the kidney (nephrogram) is due to the ongoing tubular water reabsorption in the nephrons resulting in an increased concentration of the opacified urine. Eventually there is some opacification of the calyces, pelvis and ureter. It is important to take delayed films when prolonged nephrogram is seen on the IVU images. The delayed films will show enough opacification to visualize the site of the obstructing ureteric calculus and confirm its presence within the ureter. (Fig. 11 A and B) IVU has a higher sensitivity and specificity than an abdominal radiograph in diagnosing urinary calculus disease as the cause of acute flank pain. (64% versus 97% and 92% versus 94% respectively)⁸. IVU has the advantages of providing exquisite information about the pelvicalyceal system anatomy and provides physiologic information about the kidneys. However it does not provide information about the extrarenal structures and extrarenal pathology. Also, there is need of intravenous

contrast administration and hence the risk of contrast reactions. It is not the modality of choice in renal failure, contrast induced nephropathy and pregnant patients.



Fig. 11 A & B: Plain X-ray(A) showing a radio density below the sacral ala on the left side S/o left ureteric calculus. Excretory urogram image(B) showing a dilated collecting system and ureter with evidence of the radio opacity within the lumen of the left ureter.

Ultrasound / Sonography

A renal calculus may be seen as a highly reflective focus with a distal acoustic shadow. (Fig.12 A to C) The composition of the stone has no effect on whether it is seen, urate stones being as easy to identify as calcified stones. (Fig. 13 A to C) The larger the calculus the better is the visualization but calculi as small as 5mm can be identified sonographically⁹. Calculi are more easily detected in a dilated collecting system. Ultrasound is also helpful in demonstrating obstruction of the collecting system. Although the degree of ureteropelvicectasis from an acute ureteral obstruction may be mild, it can usually be distinguished from normal collecting system in patients with flank pain due to acute infections. Furthermore, the dilated ureter can be followed to the point of obstruction and the stone identified. (Fig. 14) Calculi in the upper and the lower ureter are more easily identified as compared to calculi in the mid ureter. (Fig. 15 A and B) .



Fig. 12 A, B & C : Plain X-ray(A) showing a calculus in the left kidney. Excretory urogram(B) demonstrates the calculus in the left renal pelvis as a filling defect. Sonogram image(C) showing the left renal calculus as a highly reflective focus with distal acoustic shadow in the renal pelvis.

Ultrasonographic evaluation of the ureteral jets correlates inversely with the degree of ureteral obstruction. With high degree of obstruction there may be no detectable jet¹⁰. In fact, the combination of plain abdominal radiography and sonography is reported to be virtually as effective as excretory urography in diagnosing stones.(Fig. 16 A to B).



Fig. 13 A, B & C: Plain film(A) showing a staghorn calculus in the right renal area. The staghorn calculus is obscured by contrast on the urogram image(B). No significant back pressure changes seen in the right kidney. Sonography(C) demonstrates dense acoustic shadowing from the renal sinus owing to the staghorn calculus filling the collecting system.



Fig. 14 Sonogram image showing a upper ureteric calculus with proximal hydronephrosis.



Fig. 15 A & B: Plain X-ray(A) reveals a faint radio opaque shadow opposite the transverse process of the L₄ lumbar vertebra on the left side S/o left ureteric calculus. Excretory urogram(B) showing the calculus as a filling defect in the mid- ureter. Sonography failed to demonstrate the calculus.



Fig. 16 A & B: Urogram image(A) showing left hydronephrosis and left hydroureter. Sonogram (B) showing a calculus at the left uretero vesical junction.

Ultrasonography, alone or combined with conventional radiography, has been compared with unenhanced CT. Sheafar in 2000 compared CT and ultrasound and found that CT depicted 22 or 23 ureteral calculi (sensitivity 96%). Ultrasound depicted 14 of 23 ureteral calculi (sensitivity 61%)¹¹. CT can give a rapid and definitive diagnosis of urinary calculus disease as well as other abdominal disorder with the same presentation. Sonography is often used as the first imaging procedure in patients where radiation is to avoided e.g. pregnant women and in the paediatric age group.

Computed Tomography (CT)

It has been established unequivocally that multidetector CT (MDCT)

is the most sensitive and specific test for the diagnosis of urinary tract calculi. Fielding et al have reported a 98% sensitivity and 100% specificity¹². Niall et al have reported a sensitivity of 100% and specificity of 92% in the detection of urolithiasis¹³. A non-contrast or unenhanced CT has been demonstrated to be the most accurate and efficient diagnostic imaging means to evaluate urinary lithiasis.

CT Stone Study

No preparation is necessary and because no contrast is used there are virtually no contraindications to performance of enhanced CT but the possibility of pregnancy must be addressed in women. No intravenous (i.v.) or oral contrast medium is indicated for the study as dense oral contrast in the bowel and contrast in the vessels can make detection of ureteral stones difficult. Using MDCT, thin collimation (3-5 mm) non-contrast scans are obtained through the abdomen from the superior aspect of the kidneys (or from the dome of the liver) through the inferior aspect of the bladder base or pubic symphysis within seconds. Regardless of the calcium content almost all urinary tract calculi are radio-opaque on the non-contrast scans. Reconstructed image such a MPR and CPR are useful in demonstrating the exact location of the stones and their relationship to the ureter. Non contrast CT is also helpful in detecting non obstructing calculi in patients who have hematuria. Stone size is the single most reliable indicator of stone passage and can be measured accurately on CT¹⁴. (Fig.17)

CT signs of a Ureteral Stone (5)

PRIMARY SIGN

Homogenous density in ureter lumen

SECONDARY SIGNS

- Unilateral hydronephrosis
- Unilateral hydroureter
- Enlarged kidney
- Perinephric stranding
- Periureter oedema
- Unilateral loss of white renal pyramids

The most specific diagnostic finding of urolithiasis is the identification of a stone within the ureter. The second important finding is the “rim sign,” seen as 1 to 2 mm of soft tissue thickening around the stone secondary to ureteral wall edema at the site of stone impaction¹⁵. (Fig.18) Other secondary CT findings of urolithiasis are dilatation of the ureter or collecting system, asymmetric enlargement or decreased density of the kidney, and perinephric stranding. Renal edema from obstruction results in loss of the hyperdense pyramid (white pyramid sign) and the attenuation of the parenchyma on the obstructed side is 5 to 14 HU less than on the normal side, an objective finding of obstruction¹⁶. (Fig. 19)



Fig. 17 : Non contrast CT shows a radiodense focus at the right ureterovesical junction suggestive of a calculus. The calculus is measuring 6 mm in size.



Fig. 18 : Non contrast CT scan showing a calculus in the left midureter with a soft tissue rim around it consistent with the “rim sign” seen in a calculus.



Fig. 19: Non contrast CT showing a hydronephrotic left kidney with attenuation of the renal parenchyma on the left side 10 HU less than that of the contralateral right side, an objective finding of obstruction on the left side.

Some degree of uretral edema and thickening can be seen if a stone already has passed into the bladder. To decide whether or not a distal ureteral stone is in the ureterovesical junction or in the bladder, prone position imaging can be useful.

Pelvic phleboliths, arterial vascular calcification, calcified vas deferens, and a calcified appendicolith can be considered a differential diagnosis of ureteric calculi. Phleboliths often show a central lucency, whereas true calculi are as dense or more dense at the center than at the periphery. Another useful sign for diagnosing phlebolith is the comet-tail sign, which is a linear or curvilinear soft tissue structure represented by the noncalcified vessel, extending from an abdominal or pelvic calcification; its positive predictive value for phlebolith is 100%.

Another advantage of CT is its ability to detect nongenitourinary and non stone disease which may be the cause of pain such as appendicitis, diverticulitis biliary colic etc¹⁷.

MULTIDETECTOR CT UROGRAPHY (MDCTU)

Multidetector CT urography may be defined as the examination of the urinary tract by MDCT in the excretory phase following intravenous contrast administration. (Fig. 20 to 22)



Fig. 20 : Volume rendering (VRT) technique displaying the entire urinary tract. This technique takes the entire volume of data and displays anatomic structures with different levels of opacity / attenuation.

MDCTU PROTOCOL

The most commonly used MDCTU protocol comprises a three phase protocol, which consists of an initial unenhanced phase, a second phase following the administration of non-ionic contrast material (100 – 150 ml of 300 mg/ml iodine concentration at a rate of 2-4 ml / second) acquired following 90 – 100 sec delay also known as the nephrographic phase. This phase is followed by pyelographic phase contrast taken 12 – 15 minutes following contrast to evaluate the urothelium from the pelvicalyceal system to the bladder¹⁸. A four phase protocol consists of two excretory phases (5 minutes and 7.5 minutes) to optimize ureteric distension and opacification. However, because of radiation dose a three phase protocol is considered sufficient.



Fig. 21: Normal CT urogram image using maximum intensity projection (MIP) with bone editing displaying the entire urinary tract.

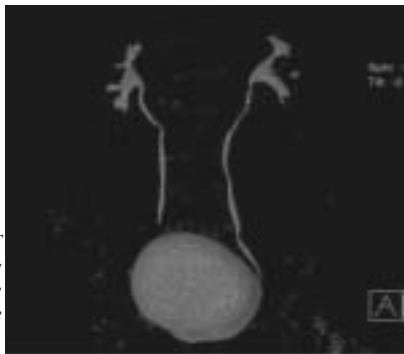


Fig. 22: Normal CT urogram image using volume rendering with bone editing displaying the entire urinary tract.

Split bolus MDCT urography with synchronus nephrographic and excretory phase enhancement:- Chai and colleagues have proposed the use of a split bolus technique in place of a single intravenous injection to facilitate a two phase protocol, namely an unenhanced series of images, and a second phase in which nephrographic and pyelographic phases are simultaneously acquired called the “nephropyelographic” phase¹⁹. With this protocol, after the initial non-contrast administration, 30 CC of non – ionic contrast material is infused intravenously and the patient is removed from the CT table. The patient is encouraged to walk for 10 minutes. 10 – 15 minutes later, the patient is placed in the CT table in the prone-position. A dynamic contrast enhanced CT is then performed following the administration of an additional 100 cc of non – ionic contrast material (300 mg / ml injected at 2 cc/second) following a delay of 100 seconds. Thus in a single “nephropyelographic phase” acquisition, the renal

parenchyma (nephrographic phase) and the collecting system, ureters and bladder (pyelographic phase) are assessed. The main objective with MDCT urography is to detect all possible causes of hematuria while using the lowest possible radiation dose to the patient. (Fig. 23 A and B) The split bolus technique has the potential to reduce both radiation dose and the number of images generated by MDCT urography²⁰.

Techniques to improve urinary tract distension and opacification have been done to achieve adequate opacification and distension of the pelvicalyceal system and ureters.



Fig 23 A & B : CT urogram using MIP technique (A) depicting a calculus at the pelviureteric junction on the right side and a calculus in the proximal left ureter. There are backpressure changes on both sides. VRT image (B) displaying the same.

CT urography is very useful in urinary calculi as it simultaneously evaluates the functional status of the kidney, detects dilatation of the pelvicalyceal system as well as the level and cause of obstruction.(Fig. 24 A to C) and (Fig. 25 A to C)

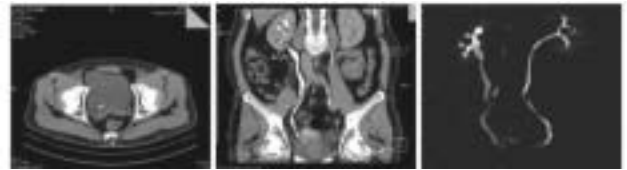


Fig. 24 A, B & C : Noncontrast axial CT (A) showing a radiodensity at the right ureterovesical junction (UV junction) s/o calculus. Curved MPR image after contrast opacification (B) depicting the calculus at the right UV junction with proximal hydronephrosis and hydroureter. CT urography using MIP (C) image showing the dilated hydroureter and hydronephrosis proximal to the calculus. The normal non dilated pelvicalyceal system and ureter is seen on the left side.

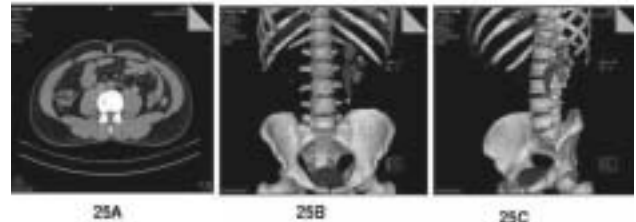


Fig. 25 A,B & C: Noncontrast CT (A) depicting a left ureteric calculus. CT urogram using volume rendering (B, C) shows the pelvicalyceal system to be bifid and the calculus in the upper left ureter.

CT AND CT UROGRAPHY

CT and CT urography have an increased radiation burden as compared with abdominal radiography. In a study by Pfister et al the mean applied radiation doses were 3.3 mSv for IVU and 6.5 mSv for unenhanced helical CT²¹. Lack of diagnostic accuracy however,

has led the radiologists to consider IVU a less optimal choice for the initial imaging in acute abdominal or flank pain.

The radiation dose can be substantially reduced by decreasing milliampere without decrease in diagnostic accuracy. Increase in pitch also lowers dose in CT examination²².

DUAL SOURCE CT IN THE CHEMICAL COMPOSITION OF URINARY TRACT CALCULI

With dual source CT the two X-ray tubes can be set at different energies Kvp i.e. at 80 Kvp and 140 Kvp and dual energy scans can be acquired concurrently. Uric acid and non uric acid stones behave differently with respect to their attenuation values when scanned with CT at different energies. A special software is available with dual source CT scanners that takes advantage of these differences and uses a decomposition algorithm to differentiate between the various calculi. Accurate determination of the chemical composition of calculi can lead to a quicker and more accurate treatment e.g. uric acid stones can be treated with oral dissolution medication and hydration while non-uric acid stones require surgical treatment.

MR UROGRAPHY

MR urography constitutes the evaluation of the collecting system and urinary tract. It is based on the principle that simple fluids, such as urine have very long T2-relaxation time and heavily T2-weighted pulse sequence generate images with high signal intensity from static fluid in the collecting system whereas lower signal intensity from parenchymal tissue is suppressed. It is performed using heavily T2-weighted images such as rapid acquisition with relaxation enhancement (RARE) and half fourier acquisition single-shot turbo spin-echo (HASTE) sequences. These sequences are extremely fast and are performed in one breathhold. The fat in the background is suppressed. This is useful in patients where use of ionizing radiation or iodinated contrast material is to be avoided. A T1 weighted gadolinium enhanced 3D FLASH sequence is used after a contrast injection of 0.1mmol/kg and multiple thin sections are obtained. These are processed with maximum-intensity-projection to produce images similar to conventional contrast urography and provide quantitative functional as well as high resolution anatomical information. Low doses of a diuretic agent can be administered before the examination for better filling of the pelvicalyceal system. Magnetic Resonance Urography (MRU) is an ideal technique in pregnancy, where there is contrast allergy, renal failure patients and if radiation dose is an issue (Fig 26 A & B). The level of obstruction is always identified, however, it is poor in the detection of urinary calculi specially those less than 4mm in size. Urothelial lesions, blood clots and debris can mimic calculi²³.

Decision on the appropriate radiological investigation is usually based on several factors which include the pretest probability of the disease, the prevalence of the disease the accuracy of the test, the potential risks of the test and the discomfort it causes to the patients & the cost the ideal test should improve the patients treatment by providing answers to the clinical questions.

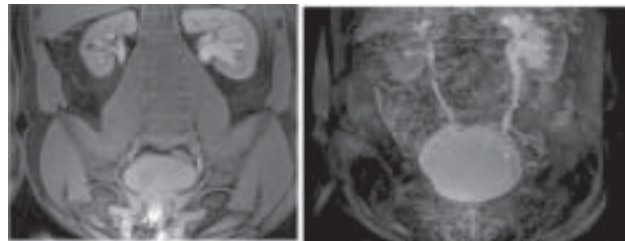


Fig. 26 A & B: T1 post gadolinium fat suppressed coronal (A) and MIP (B) MR urogram image showing a renal calculus on right side as a hypointense filling defect and left hydronephrosis due to a stricture in the left ureter.

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MEDICAL MANAGEMENT OF UROLITHIASIS - A SIMPLIFIED APPROACH

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Abstract : Although Extracorporeal Shock-Wave Lithotripsy (ESWL), Percutaneous Nephrolithotomy (PCNL) and Uretero-renaloscopy (URS) have considerably reduced the morbidity of stone disease, the incidence of stone recurrence is not altered by removal of stones. In contrast, a variety of medical treatments can prevent recurrence of stones. A detailed diagnostic work up is an essential prerequisite for medical management. Dietary modifications like high fluid intake and animal protein restriction are necessary for any type of stone disease. Specific modalities like potassium citrate, thiazide diuretics, allopurinol and treatment of infections might help in preventing recurrent stone disease in specific situations

INTRODUCTION

Urolithiasis denotes stones originating anywhere in the urinary tract, including the kidneys and bladder. Kidney stones form as a result of physicochemical or genetic derangements leading to supersaturation of the urine with stone-forming salts or, less commonly, from recurrent urinary tract infection with urease producing bacteria. In contrast, bladder stones form almost exclusively as a result of urinary stasis and/or recurrent infection due to bladder outlet obstruction or neurogenic bladder.

In the United States, the incidence of urinary stone disease is about 12% in men and 7% in women, and evidence suggests that these numbers are increasing. For patients who form stones, the likelihood of recurrence is nearly 50% within five years and up to 95% over a lifetime¹. After the first recurrence, the subsequent relapse risk is increased and the interval between recurrences gets shortened². While rarely fatal, urolithiasis causes substantial morbidity. In addition to the pain and suffering of an acute stone event, treatment incurs substantial costs, and additional costs result from the time lost from work, as many individuals are affected during their working years. Although Extracorporeal Shock-Wave Lithotripsy (ESWL), Percutaneous Nephrolithotomy (PCNL) and Uretero-renaloscopy (URS) have considerably reduced the morbidity of stone disease, the incidence of stone recurrence is not altered by removal of stones³. In contrast, a variety of medical treatments can prevent recurrence of stones⁴.

A meta-analysis of randomized medical therapy trials has shown that drug and dietary therapy can reduce the risk of urinary stone recurrence by 22.6%⁵. Hence, to reduce considerable morbidity and cost associated with treating recurrent urolithiasis, efforts should be directed at identifying the underlying pathophysiology and instituting appropriate general and specific preventive measures.

COMPOSITION OF STONES

Seventy percent of all renal stones primarily contain calcium, and approximately 26% of calcium stones are composed of pure calcium oxalate, 35% are composed of calcium oxalate and calcium phosphate, and approximately 5 to 10% are composed of calcium crystallized around a uric acid core⁶. Approximately 5 to 10% of renal stones are composed of pure uric acid. Magnesium ammonium phosphate or struvite stones account for approximately 10 to 15%

of stones and are more commonly found in women than in men. These stones are formed in urine infected with urease-producing organisms such as *Proteus* or *Morganella*. Cystine stones account for 1 to 2% of kidney stones and are found in patients who suffer from autosomal recessive cystinuria.

Prevalence of various types of urinary stones in India is as follows⁷:

- Calcium oxalate stones - 93.04%
- calcium oxalate monohydrate (COM)-80%
- calcium oxalate dihydrate (COD) - 20%
- Struvite -1.42% and
- Apatite -1.80%.
- Uric acid stones - 0.95%
- Mixed stones (COM + COD and calcium oxalate + uric acid, calcium oxalate + calcium phosphate, and calcium phosphate + magnesium ammonium phosphate) - 2.76%

A total of 89.98% of staghorn stones are made of oxalates (COM/+COD) and only 4.02% are struvite.

DIAGNOSTIC WORK UP OF UROLITHIASIS

There is paucity of reliable prospective data that can be used to formulate a definitive outcomes-based approach to managing the patient who has had one kidney stone. Several authors suggest that minimal investigations be performed in patients with their first stone provided no signs of infection or obstruction are present^{8,9}. A reasonable approach for a low risk patient would include a detailed history and physical examination (although specific clues are seldom noted on physical examination), selected laboratory tests, urinalysis and culture, review of any radiographs, and stone analysis (Table 1 and Fig. 1). For patients at high risk, an extensive evaluation should be done.

Table 1. Evaluation of a patient with a first kidney stone episode

Complete history, with emphasis on:

- Family history
- Occupation and hobbies that may predispose to dehydration
- Dietary history

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- Fluid intake (types and volumes of fluids ingested)
- Nonprescription medications (calcium supplements, vitamins, antacids)
- Infection/systemic disease/abdominal surgery

Physical examination

Laboratory evaluation

- Stone analysis (if retrieved)
- Urinalysis/culture
- Serum electrolytes, calcium, phosphate, uric acid, and creatinine levels

Abdominal radiograph (kidney, ureter, and bladder)

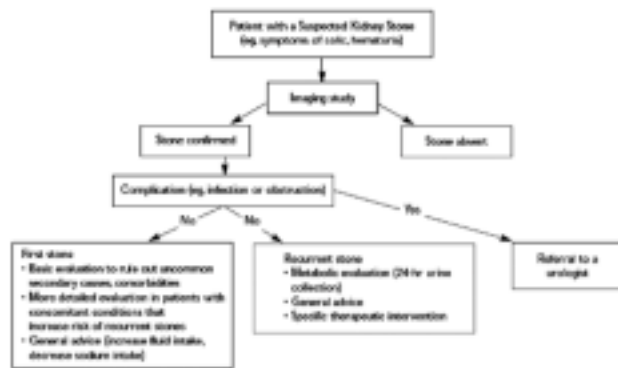


Fig. 1: Evaluation and management of a patient with kidney stones

After the diagnosis of urolithiasis and the implementation of appropriate initial management of the stones, the physician should evaluate the patient for the possibility of recurrence.

BIOCHEMICAL INVESTIGATIONS

Urine examination

Examination of urine is important in evaluation of patients with urolithiasis. A number of alternative options for collection of urine sample are available. The choice is influenced by the parameters being measured. A collection of urine without HCl is necessary for pH measurement. In this respect, a sample collected with sodium azide is useful. A night-time urine sample in which pH is measured soon after the urine has been collected is useful because the pH may be altered when urine is stored. A pH above 5.8 in fasting morning urine raises the suspicion of incomplete or complete renal tubular acidosis. In the same fasting morning or spot urine sample, bacteriuria and cystinuria can be checked by an appropriate test.

The recommendation to collect two urine samples is based on observations that such an approach will increase the likelihood of detecting urine abnormalities. It must be emphasized that the urine sample used for analysis of calcium, oxalate, citrate and phosphate has to be acidified, preferably with HCl. The reasons for acidification are:

- To maintain calcium, oxalate and phosphate in solution, during and after the collection period.
- To prevent bacterial growth and the associated alteration of urine composition.
- To prevent in-vitro oxidation of ascorbate to oxalate.

The variables that can be analyzed in the acidified sample include calcium, oxalate, citrate, magnesium, phosphate, urea, sodium, chloride and potassium. Although the creatinine concentration might

be slightly affected, it has to be assessed in the same sample when creatinine-related variables are used. In acidified samples, uric acid precipitates and has to be dissolved by alkalization, if urate excretion is of interest. Urate can be analyzed in samples collected with sodium azide.

Serum investigations

The purpose of analyzing serum or plasma calcium is to identify patients with hyperparathyroidism or other conditions associated with hypercalcaemia. In the case of a high calcium concentration (>2.60 mmol/L), the diagnosis of HPT should be established or excluded by repeated calcium analyses and assessment of the parathyroid hormone level. High serum urate level together with a radiolucent stone supports the suspicion of a uric acid stone. The aim of adding serum potassium, pH, bicarbonate and chloride to the biochemical analysis is to obtain further support for the diagnosis of suspected renal tubular acidosis.

Analysis of stone composition

Stones that pass spontaneously, are removed surgically, or excreted as fragments following disintegration, should be subjected to stone analysis to determine their composition¹⁰. The preferred analytical procedures are X-ray crystallography and infrared spectroscopy. All patients should have at least one stone analyzed. Repeated analysis is indicated if changes occur in urine composition, due to medical treatment, dietary habits, environment or diseases, can be expected to have influenced the stone composition. When stone or stone material has not been retrieved, conclusions on stone composition may be based on the following observations:

- Qualitative cystine test
- Bacteriuria/urine culture
- Demonstration of crystals of struvite or cystine upon microscopic examination of the urinary sediment
- Serum urate
- Urine pH (low in patients with uric acid stones, high in patients with infection stones)
- Radiographical characteristics of the stone

An appropriate quantitative or semi-quantitative analysis of the stone material should enable conclusions to be drawn regarding the main constituent or constituents.

TREATMENT OPTIONS TO PREVENT RECURRENT UROLITHIASIS

The **medical therapy** consist of two parts:

- Dietary modification
- Selective treatment of individual risk factors.

Dietary Modification

All patients of stone disease are advised to follow the dietary modification irrespective of normal investigation reports.

High fluid intake

Patient is advised to measure urine output once a week and then adjust the fluid intake to maintain urine output more than two litres per day. They are also advised to take maximum intake of fluid within three hours after taking the meals, during periods of physical exercise, bed-time and once at midnight. Plain water is good enough but potassium rich citrus fruit juices such as orange, grape fruit and cranberry are preferable to low potassium citrus fruits such as lime and lemon. Orange juice, for example, represents a natural form of potassium citrate and possesses alkalizing and citraturic action. Lime juice, on the other hand, is composed largely of citric acid, and does not affect acid base balance appreciably, so it does not alter

urinary pH and only modestly increases urinary citrate. Increasing fluid intake actually has been demonstrated to have positive effect on two urinary inhibitors, citrate and Tamm-Horsfall protein. Hydration augments urinary citrate excretion, which is thought to result from an increased fluid flux in the proximal tubule resulting in the delivery of more bicarbonate to the cells of this portion of the nephron. Urinary dilution has been found to increase the inhibitory activity of Tamm-Horsfall protein on the calcium oxalate monohydrate crystal aggregation in the urine of the stone formers¹¹⁻¹³.

Restriction of animal protein

Patient is advised to avoid or restrict nonvegetarian diet and the recommendation is of 8 oz or less of dry meat per day. Animal proteins are rich in sulphur-containing amino acids such as cystine and methionine, which on oxidation produce sulphate which forms a soluble complex with calcium in the nephron and limits the reabsorption of this cation. Bone serves as a buffer and the resultant osseous dissolution provides more calcium to be excreted. Chronic metabolic acidosis decreases calcium reabsorption within the nephron, which further augments excretion of this mineral. Increased protein consumption also augments glomerular filtration, thus delivering more calcium to the nephron, which promotes its excretion. Animal protein has a high purine content, which leads to increase in uric acid excretion. The associated acidosis results in a decrease in urinary pH that could potentiate uric acid urolithiasis. Acidosis also enhances citrate reabsorption in the proximal tubule, thus decreasing the excretion of citrate in the urine¹⁴⁻¹⁵.

Sodium restriction

Patient is asked to avoid high sodium-containing food with restriction of salt in the diet and salty shakes. Increased sodium intake may promote a variety of metabolic changes that may be detrimental to stone formers, including increase in the urinary pH, calcium and cystine excretion and a decrease in citrate excretion.

Oxalate restriction

Avoidance of nuts, spinach, dark roughage, chocolate, tea, and vitamin C coupled with the advice to maintain recommended daily intake of calcium and to ensure that calcium consumption accompanies the ingestion of oxalate rich foods to prevent the absorption of oxalate.

Restriction of calcium

Moderate restriction of calcium is recommended and about 250 ml of milk or milk products can be taken daily. In patients who are advised long-term restriction of calcium intake, measurement of bone density, particularly in the spine is recommended.

TREATMENT OF VARIOUS STONE RISK FACTORS

Hypercalciuria

The management of hypercalciuria depends on its type.

Absorptive hypercalciuria

Type I - Cellulose phosphate in the dose of 10-15 g orally in three divided doses is to be taken with meals. It is an effective nonabsorbable exchange resin, which binds the calcium in the gut and prevents bowel absorption. It has no impact on the calcium transport mechanism and the urinary calcium excretion returns to normal values with therapy. This therapy is contraindicated in postmenopausal women and in children during the period of active growth. Hydrochlorothiazide is an alternative treatment but the effect on calcium excretion is temporary. It causes a decrease in the renal excretion of calcium. The increased absorbed calcium is deposited in the bone. Gradually the bone reservoir reaches its capacity and the

drug becomes ineffective. Hydrochlorothiazide may be alternated with cellulose phosphate for an effective treatment regimen.

Type II - Since this is dietary dependent, reduction of the calcium intake to 400-600 mg/day reduces calcium excretion to normal.

Type III - Orthophosphate is administered in the dose of 250 - 2000 mg 3-4 times/day preferably after meals and before bedtime. It inhibits vitamin D synthesis, which finally decreases absorption of the calcium.

Renal hypercalciuria

Thiazide diuretic like hydrochlorothiazide is recommended; it has effect on the proximal and the distal tubules. Acting as a diuretic, it decreases the circulating blood volume and subsequently stimulates proximal tubular reabsorption of calcium.

Hyperoxaluria

Patients suffering from mild hyperoxaluria (<60 mg/day) are easily managed on the dietary restriction of oxalate rich foods such as spinach, dark roughage, tea, chocolate and nuts. Vitamin C supplementation should not increase more than 500 mg/day in such patients. Patients suffering from absorptive hypercalciuria maintained on calcium restriction could have mild hyperoxaluria due to insufficient amount of calcium left in the bowel to bind oxalate.

In patients with moderate to severe hyperoxaluria commonly seen in patients suffering from intestinal malabsorption of fat, inflammatory disease or resection of the small bowel, patients with absorptive hypercalciuria taking cellulose phosphate, a rigid restriction of dietary oxalate is critical. Solubilized calcium may further help to lower urinary oxalate by binding oxalate.

In the absence of bowel disease or absorptive hypercalciuria in the patients suffering from moderate to severe hyperoxaluria, mild metabolic hyperoxaluria or primary hyperoxaluria must be suspected and pyridoxine in the dosage of 100 to 200 mg/day is required for suppression of oxalate synthesis in vivo.

Hyperuricosuria

In patients with normouricemia, hyperuricosuria is caused by dietary excess of animal proteins. The general recommendation in these patients is a balanced diet with a reduced intake of animal proteins and increased intake of vegetables and fruits, although the long-term compliance in patients with dietary modification is very poor. Allopurinol (300 mg/day) is indicated in such patients if hyperuricosuria is more than 800 mg/day.

In patients with hyperuricemia e.g., gouty diathesis, allopurinol (300 mg/day) is indicated to reduce serum uric acid. Potassium citrate is also added to alkalinize the urine.

Cystinuria

The main goal of therapy is to lower cystine concentration in the urine below 200 mg/L. Dietary restriction is the primary therapy with the avoidance of diet containing essential amino acid methionine such as meat, poultry, fish, and dairy products. Increasing urine output on 3 L/day allows dissolution of existing stones and prevents new stone formation. The pH of the urine is kept high (>7.5) to allow dissolution of the stone. Sodium bicarbonate (15-25 g/day) and potassium citrate (15-20 mmol two to three times per day) are commonly used to alkalinize the urine. Acetazolamide 250 mg three times a day augments the alkalinization achieved by the citrate and bicarbonate. Glutamine 2 g/day can further reduce the excretion of the cystine especially if the intake of sodium is very high.

If hydration and alkalinization is ineffective in reducing the excretion of cystine or cystine formation then complexing agents such as penicillamine or alpha mercaptopurine can be used. These agents bind cystine, forming a complex solution that is soluble in the urine.

Captopril has also been used to lower cystine excretion by forming a captopril-cystine disulfide complex.

Hypocitraturia

Citrate is an important inhibitor of crystallization of stone-forming salts and hypocitraturia being common among patients with calcium nephrolithiasis. It is apparent that maneuvers that maintain urinary pH between 6 and 7 and that raise urinary citrate levels to the normal would be desirable in preventing the formation of calcium oxalate stones.

Potassium citrate taken orally is absorbed mostly under normal circumstances. The citrate after absorption is metabolized to bicarbonate. In the absence of a deficit of bicarbonate in plasma, the bicarbonate ions are excreted in urine that is rendered alkaline. The small amount of absorbed citrate that escapes oxidation in the urine contributes in a minor way to the citraturic action of potassium citrate. In the presence of hypokalemia, the potassium ion augments citrate excretion by correcting intracellular acidosis.

During long-term treatment, potassium citrate has been shown to cause a sustained rise in urinary citrate and pH. In patients with mild to moderate hypocitraturia (100-320 mg/day), potassium citrate (60 mEq/day) increases urinary citrate by about 400 mg/day. The urinary pH rises by about 0.5 units and can be maintained at about 6.5. The citraturic action is less prominent in those cases with severe hypocitraturia (e.g., complete renal tubular acidosis and severe chronic diarrhoeal syndrome). The total rise in urinary pH is less marked in renal tubular acidosis in which urinary pH is usually high. Potassium citrate has a hypocalciuric effect because of enhanced renal calcium absorption and is usually transient. In patients with renal tubular acidosis the hypocalciuric effect is sustained. This is in contrast to sodium citrate where calcium excretion is unaffected since alkali mediated hypocalciuric effect is offset by sodium linked calciuresis¹⁶.

Physiochemical effects of potassium citrate are due to its citraturic and alkalinizing action resulting in

- Inhibition of the crystallization of calcium salts in the urine¹⁷.
- Rise in pH contributes to the retardation of the crystallization of calcium salts and inhibits uric acid crystallization.
- At a high pH more phosphate and citrate ions become dissociated further augmenting the complexation of calcium.
- Dissociation of citrate, pyrophosphate and other macromolecules may accentuate their inhibitor activity against crystallization of calcium salts.
- The rise in urinary pH increases the dissociation of uric acid, reducing the concentration of undissociated uric acid and the propensity for the uric acid lithiasis¹⁸.

Distal Renal Tubular Acidosis Type 1

Potassium citrate therapy is capable of correcting both metabolic acidosis and hypokalemia. In severe acidosis, large doses (up to 120 mEq/day) may be required to restore normal urinary citrate level¹⁹. Urinary calcium declines with the correction of acidosis. The overall rise in urinary pH is generally below 7.5 during treatment unless there is a complication of urinary tract infection.

If there is a substantial renal sodium leak, alkali must be provided as a mixed sodium potassium salt, although renal sodium wasting is not prominent in most patients with renal tubular acidosis who present with stones.

Potassium citrate is contraindicated in patients with moderate to severe renal disease (endogenous creatinine clearance of <40 ml/mt). If it were to be used in those with moderate renal disease, it should be begun at a lower dosage and the serum potassium levels should be

carefully monitored.

Chronic diarrhoeal syndrome

In patients with mild to moderate severity of intestinal fluid loss and in whom hypocitraturia is not severe (100-320 mg/day), potassium citrate (40-60 mEq/day in 3-4 divided doses, is effective in restoring normal urinary citrate.

A liquid preparation is usually preferred in such cases rather than a slow release tablet because some of these patients have intestinal adhesion and may be prone to obstruction from a tablet preparation. Furthermore, a slow release medication may be poorly absorbed due to rapid intestinal transit. A frequent dose schedule (3-4 times/day) is advisable for the liquid preparation because of relatively short duration of biological action. Other drugs may be necessary for the treatment of additional disturbances. If hypomagnesuria is present, magnesium citrate (10 mEq two to four times/day) may raise urinary magnesium and increase urinary citrate and pH.

When hyperoxaluria coexists, dietary oxalate restriction is a must. In patients of hyperoxaluria with hypocalciuria, calcium citrate is useful which lowers renal excretion of oxalate by binding it in the intestinal tract, raises urinary citrate, corrects malabsorption of calcium and averts potential development of bone disease.

Thiazide induced hypocitraturia

Hypokalemia resulting from thiazide leads to hypo-citraturia, which may attenuate the beneficial hypocalciuric effects of therapy in urolithiasis²⁰. Use of potassium citrate with thiazide raises urinary pH and citrate. It is recommended that potassium citrate (15-20 mEq twice a day) be given to all patients being treated with thiazide for hypercalciuric nephrolithiasis²¹.

Idiopathic hypocitraturic calcium nephrolithiasis

This includes hypocitraturia occurring alone with calcium stones and hypocitraturia occurring in conjunction with absorptive and renal hypercalciuria and hyperuricosuric calcium oxalate nephrolithiasis. In these patients the stones are predominantly calcium oxalate.

Potassium citrate (15-30 mEq twice a day) produces a sustained increase in urinary citrate excretion, maintains pH between 6.5-7.0 and decreases the urinary saturation of calcium oxalate to normal limits.

Uric acid nephrolithiasis

Potassium citrate is recommended in patients with hyperuricosuric (gouty diathesis) for prevention of both calcium oxalate and uric acid stone formation.

Potassium citrate creates an environment less conducive to the crystallization of uric acid by increasing urinary pH and reducing the amount of undissociated uric acid. It inhibits urinary crystallization of calcium oxalate by reducing urinary saturation and augmenting the inhibitor activity owing to the rise in urinary citrate and pH.

Post-extracorporeal shock wave lithotripsy fragments

The natural history of residual stone fragments after ESWL shows growth and persistence of the calculus. In patients with residual fragments <5 mm or clinically insignificant residual fragments (CISF) with calcium oxalate and/or infection stones use of potassium citrate (6-8 gm in 2-3 divided doses) has significantly ameliorated the outcome of these residual fragments by decreasing growth or agglomeration, allowing spontaneous passage and finally improving the clearance rate²².

Advantages of potassium citrate compared with other alkali

Potassium citrate is a better substitute than potassium bicarbonate

because of more prolonged rise in urinary citrate and pH. The increment in urinary citrate is more pronounced with potassium citrate due to the renal excretion of small amount of absorbed citrate that has escaped oxidation¹⁹.

When compared with sodium citrate, potassium citrate reduces calcium excretion by augmenting the renal tubular absorption of calcium. Urinary sodium remains unaltered with potassium citrate but increases during sodium citrate therapy. In patients with hypokalemia, potassium citrate causes a more pronounced rise in citrate excretion than sodium citrate¹⁹.

INFECTION (STRUVITE STONES)

Struvite stones are usually the result of urinary tract infection by urease-producing organisms. Struvite stones are considered to be infected, and medical therapy alone has a limited ability to eradicate them and the infections associated with them. Early referral to a urologist for ESWL (for stones < 2 cm) or alternative intervention (for stones >2 cm) is recommended²³. Bacteria involved are usually proteus, klebsiella, pseudomonas and enterobacter species and never E. coli. Once in place, stones and their bacteria cannot be treated with antibiotics. The bacteria lodge in and stick to the stone and antibiotics cannot penetrate into the depth of crystal masses to kill all of the organisms. Resistance evolves easily under such circumstances. The only treatment option is surgical. When surgery is undertaken for infection stones, the goal must be removal of all fragments, for all parts of the stone are infected and can grow back.

SELECTIVE VERSUS NON-SELECTIVE THERAPY

The rationale for using selective therapy for nephrolithiasis based on urinary biochemistry is the assumption that normalization of urinary parameters prevents stone recurrences and that selective therapy is more effective and safer than random therapy in accomplishing this goal. Selective therapy induces a remission rate of between 70 and 91% and reduced stone formation in 88 to 100%. It is intellectually appealing to categorize stone disease on the basis of urinary metabolites and to use selective therapy (Table 2). There is no proof, however, that selective therapy is more efficacious than non-selective therapy. One advantage of using non-selective therapy is that it avoids the expense and the work involved in categorizing calcium oxalate stone disease. It is also sobering to note that in 3 of the 4 randomized trials in which thiazides were found to be effective, the agent was used on a non-selective basis, and only a minority had hypercalciuria.

SUMMARY

The preventive measures against the urolithiasis are fairly well defined and most of them have proved their efficacy in studies. However, in clinical practice it is very difficult as the patients may have all normal urinary parameters or multiple deranged parameters. The issue is the extent to which these patients should be investigated and rigour with which medical therapy is applied. As an oversimplified rule it can be said that instituting diet therapy, without any metabolic evaluation at all, is cost effective in first time stone formers. However, in recurrent stone formers detailed evaluation and directed therapy is better. Both surgical and medical treatment is necessary for the complete management of urolithiasis.

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Table 2. Selective treatment of recurrent stones

Disorder	Treatment	Mechanism of action
Low urine volume	High fluid intake	Increases urinary volume, decreases urinary saturation
Absorptive hypercalciuria, type I	Sodium cellulose phosphate, thiazides and other hypocalciuria diuretics	Decreases intestinal calcium absorption, decreases urinary calcium excretion
Absorptive hypercalciuria, type II	Low-calcium diet, sodium cellulose phosphate	Decreases intestinal calcium absorption
Absorptive hypercalciuria, type III	Orthophosphates	Decreases 1,25-dihydroxyvitamin D, and urinary calcium, increases urinary citrate and pyrophosphate
Hypocitraturia, including renal tubular acidosis	Potassium citrate	Increases urinary citrate, increases urinary pH
Hypomagnesiuria	Magnesium citrate	Increases urinary magnesium and citrate
Hyperuricosuria with calcium oxalate stones	Allopurinol Potassium alkali salts Reduced urine intake	Decreases urinary uric acid, increases urinary citrate and pH, decreases urinary uric acid
Uric acid stones	Potassium alkali salts Allopurinol	Increases urinary citrate, increases urinary pH, decreases urinary uric acid
Enteric hyperoxaluria	Pyridoxine Oral calcium supplementation	Decreases urinary oxalate, increases oxalate binding in the intestine
Chronic diarrheal syndromes	Cholestyramine Potassium alkali salts	Decreases oxalate absorption, increases urinary citrate
Infection stones	Acetohydroxamic acid	Decreases urease, ammonium, and pH
Cystinuria	D-penicillamine or (MPG)	Increases solubility of cystine

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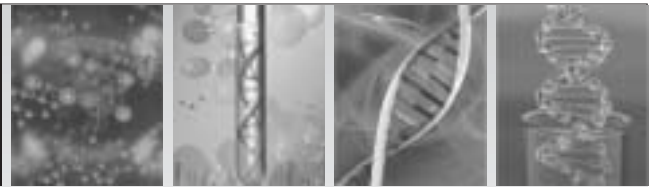
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MANAGEMENT OF URINARY STONES- CURRENT PERSPECTIVES

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Abstract : Percutaneous Nephrolithotomy (PCNL) was established as a minimal invasive treatment option for removal of kidney stones in the seventies and was further developed in the following years. However, PCNL-frequency diminished with the introduction of extracorporeal shock wave lithotripsy (ESWL) in the early eighties. In recent years, as clinical experience with ESWL revealed its limitations, the role of PCNL for treating urolithiasis was redefined. Today, PCNL should be the first line treatment of large or multiple kidney stones, and stones in the inferior calyx. Furthermore, improvements in instruments (i.e. ureteroscopes) as well as lithotripsy technology (i.e. ultrasound / pneumatic devices, Holmium-YAG-Laser) increased the efficacy of percutaneous stone disintegration yielding stone free rates of >90%.

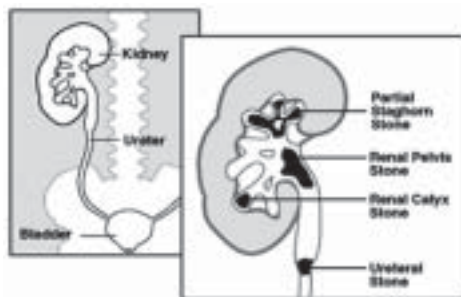
PERCUTANEOUS NEPHROLITHOTOMY (PCNL)

Since Fernstrom and Johansson first removed a renal calculus through a nephrostomy tract in 1976¹, percutaneous nephrolithotomy (PNL) has significantly changed and is continuing to evolve. Certain indications for percutaneous management of renal calculi have been established; then depend on the size and the composition of the stone, the site of the stone

PNL INDICATIONS AND LIMITATIONS

Size of the stone:

PNL as monotherapy has advantages in the removal of large stones, achieving excellent results with minimal morbidity. The point of transition for the term "large stone" is believed to be 2cm. Partial or complete staghorn calculi may require multiple punctures or the combination of PNL and SWL followed by repeat PNL (sandwich therapy). PNL should be the preferred technique for patients with struvite stones. When these infected stones are removed completely by PNL, the patient has a 90% chance of remaining stone free for at least 3 years. Compared to SWL or open surgery, PNL, alone or in combination with SWL, results in higher stone free rates, less number of procedures needed per patient, lower morbidity, shorter operative time, shorter hospital stay and earlier return to work. Treatment of lower pole calyceal stones should be guided by the diameter of the stone. In a metaanalysis, limitations of SWL included lower stone free and higher retreatment rates, compared to PNL². Large stones of the lower pole are best managed by PNL as a first treatment option, irrespective of the anatomy of the lower pole.



However, PNL has a higher success rate at the cost of higher complication rates. As an alternative, flexible ureteroscopy and laser disintegration have been proposed for lower pole stones upto 2 cm. Despite recent technological advances, such as the use of ureteral access sheaths, which in theory increases irrigant flow and improves visualization, the success rate does not exceed 88%. These rates necessitated two sessions on several occasions.

Calyceal diverticula :

Although no prospective randomized trials comparing PNL, laparoscopy and ureteroscopy exists, percutaneous nephrolithotomy is considered the gold standard for managing calyceal diverticula³. High rates of stone clearance and diverticular obliteration have been published in contemporary series, while complications ranged from 0 to 30 %. When compared to SWL, PNL achieved a higher stone free rate with similar recurrence rates and complication rates. Ureteroscopic management yielded poor results with regard to stone free (19 to 58 %), symptom free and diverticular obliteration status (20 %). Ureteroscopy should be reserved for patients with anterior, mid or upper pole diverticula or for patients who are unable to undergo PNL. The laparoscopic approach, although applied in few patients, seems appropriate for those with thin overlying renal parenchyma or with anterior lesions that are too large or not accessible to ureteroscopy.



Renal anomalies

PNL in the horseshoe kidney⁴, malrotated and pelvic kidneys⁵ has been safe and effective, especially when large stones or ureteropelvic junction obstruction existed. Renal access is obtained mostly through an upper pole calyx and vascular injury is less likely in these conditions. However, a second look procedure is occasionally necessary to render the kidney free of stones. Currently, there is a growing evidence suggesting that for patients suffering by large or complex stone burden in an ectopic kidney, a laparoscopic-assisted PNL is the optimal treatment, resulting in higher stone free rates and shorter hospital stay compared to standard PNL technique.

Patient Factors

Pediatric: There are no randomized controlled studies comparing different treatment modalities for pediatric nephrolithiasis standard PNL with the use of adult instruments or mini-PNL with specifically designed pediatric instruments is safe and highly effective treatment alternative for stone disease in infants, preschool or older children. Although there is a no evidence supporting a better functional outcome or a lower complication rate. When specific criteria are followed PNL, SWL and ureteroscopy are all valuable treatment options for pediatric calculi. PNL in children is recommended when SWL or ureteroscopy have failed, when a large stone burden is treated, and when anatomical abnormalities, that may impair urinary drainage and stone clearance, exist. Stone free rates with a single session of PNL range from 67 % to 100 %. Retained calculi are more common with staghorn and multiple stones compared to solitary stones. The need for more than one session or for the combination of PNL with SWL or URS has been realized in these situations⁶.

Obesity: Several retrospective studies indicate that PNL in obese patients can be performed with stone-free rates (as high as 100 %), complication rates and hospital stays comparable to those achieved in an unselected population. In a recent retrospective study, no statistically significant differences were found in decrease in haemoglobin concentration, hospital stay, and complication rate when patients were stratified in four groups according to their body mass index. The need for auxiliary procedures and stone free rates were comparable⁷.

H/o Surgery: Success and complication rates of PNL between the patients who had and those who did not have previous renal surgery is not significantly different.

Rigid Intracorporeal Lithotrites : The great advantage of rigid intracorporeal lithotrites is the efficiency with which they fragment and remove a stone burden. The rigid devices are a mainstay of PNL, and should be used in the treatment of renal calculi whenever a rigid nephroscope will permit their passage. An obvious shortcoming of rigid lithotrites is that they cannot be used with flexible endoscopes.

The Holmium: YAG laser is the intracorporeal lithotripter of choice when a flexible device is required. Its superior safety profile and ability to fragment stones of all compositions has helped advance the technique of flexible ureteroscopic treatment of stone disease.

The site of kidney puncture: An optimal and atraumatic access to the desired calyx is a crucial step in a successful PNL. In the majority of cases this is possible by a subcostal puncture. However, a supracostal approach is preferable in patient with staghorn, complex renal and proximal ureteral calculi, as it offers direct access to most parts of collecting system and upper ureter. In retrospective studies stone free rates upto 87 % have been reported

with a single session of supracostal PNL. The disadvantage is the high incidence of intrathoracic complications as well as a higher rate of spleen and hepatic injury. The overall pleural complication rates in the retrospective studies published in the literature range from 0 %, 37 %. The overall complication rate for supracostal access tract was 16.3 % compared with 4.5 % for infracostal access. Punctures above the 11th rib resulted in a tremendously higher intrathoracic complication rate (34.6%) compared to the supra 12th rib access (1.4 %); This corroborates the strategy of avoiding this high approach if possible⁸.

MINI-PNL

Attempts have been made to popularize techniques of mini-percutaneous nephrolithotomy in the hope to decrease the morbidity associated with larger nephroscopes and tubes, especially regarding patient discomfort and potential renal damage. PNL with a 13 F nephroscope followed by placing in 8 F nephrostomy tube with a 7 F double pigtail ureteric stent. There were no conversions to conventional PNL and no transfusions were necessary. Although a high stone free rate was achieved, visibility with the smaller nephroscope was hindered with larger stones, than for standard PNL⁹.

EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY (ESWL)

The introduction of shock wave lithotripsy (SWL) and endourologic techniques such as ureteroscopy (URS) and percutaneous nephrolithotomy (PNL) radically changed the treatment paradigm for upper urinary tract calculi. That is, stones that once required an open surgical procedure to effect cure could be treated with a minimally invasive approach (URS, PNL) or in a completely non-invasive manner (SWL). Within 5 years of its introduction, SWL became the most common intervention for patients suffering from renal or ureteral calculi. SWL remains very popular, however, where shock waves (SW's) were once considered the treatment of choice for virtually all stones, it is now recognized that SWL has practical limitations. Some urologists are now less likely to turn to SWL, and some no longer see SW's as a first line option.

Since the introduction of Dornier HM3, lithotripters have become compact and transportable. This evolution has made lithotripsy more accessible but has introduced new problems such as the challenge of achieving good coupling with a dry treatment head. Lithotripsy employs three modes of SW generation: electrohydraulic, electromagnetic, and piezoelectric. Electromagnetic lithotripters deliver more consistent pulses than do electrohydraulic machines, and the shock sources have a much longer lifetime (millions of SW's). Electrohydraulic lithotripters tend to have a wider focal zone than do electromagnetic lithotripters, and generate lower acoustic pressures and lower energy densities. Most new lithotripters either have a measurably wide focal zone on the order of 17-18 mm, or they have settings that procedure a relatively wide focal zone. Imaging for stone localization is very effective, but imaging quality is rarely sufficient to determine when stone breakage is complete. Diagnostic US is available with many lithotripters but most urologists choose to use fluoroscopy for stone localization and monitoring during treatment.

Extracorporeal shock wave lithotripsy (ESWL) is still the first line treatment for renal calculi with success rate of 70 % for all renal calculi. The success rates of ESWL for lower pole calyceal stones vary from 63 to 74 % and 23 to 56 % less than 1 cm and 1

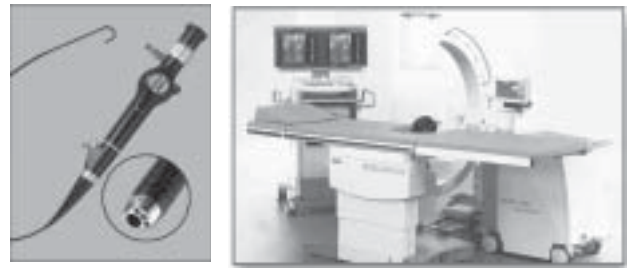
to 2 cm, stone respectively. Higher failure rates for lower pole calyceal stones have been attributed to diminished infundibular width, longer infundibular length and narrow infundibulopelvic angle. Percutaneous removal of renal stones (PNL) is widely used with a success rate of more than 90 % with greater morbidity comparing to ESWL and ureteroscopy (URS). Advances in design of flexible ureteroscopes, use of nitinol baskets and graspers, developments of smaller caliber flexible holmium laser (200 micron) and electrohydraulic (EHL) probes (1.6- 1.9 F) allowed to treat intrarenal stones retrogradely with higher success rate and minimal morbidity.

Retrograde intrarenal surgery (RIRS) has been mostly used for stones failed with ESWL. In a retrospective study¹⁰, the records of 81 patients who had RIRS after multiple ESWL sessions were reviewed¹⁰. Rigid ureteroscope in 8, flexible in 67 and both in 6 patients were used. The fragmentation was achieved by holmium : YAG laser mostly and EHL occasionally. They reported 67 % success rate and 46 % stone free rate (SFR) with minor complications, based on KUB or US findings within 3 weeks postoperatively; the procedure was unsuccessful in 13 patients with larger stones or obstructed system in which subsequent ancillary procedures were used. They concluded that RIRS could be used as a salvage therapy in patients with renal stones smaller than 2 cm that failed with ESWL. Similarly in another study¹¹ 38 patient underwent RIRS for ESWL resistant renal stones. Stones were disintegrated by 150-200 micron holmium : YAG laser probes in 32 patients through both semirigid and flexible ureteroscopes. Stone free rate was 58 % after a single procedure and overall success rate was 76 % after second session. In conclusion they recommended RIRS as a safe procedure with high success rate for ESWL resistant renal stones less than 1 cm and stones in anomalous kidney.

Extracorporeal shock wave lithotripsy was recommended for 1 cm or less lower pole calyceal stones (LPS) and PNL for larger stones by lower pole study group¹². However, recently effectivity of RIRS for LPS has been investigated by many authors. Lower pole calyx is one of the most difficult location to have an access with flexible ureteroscope. The secondary deflection maneuver and the use of nitinol tipless baskets and graspers, facilitated the access into the lower calyx and subsequently improved the success of stone treatment.

The treatment of renal stones in morbidly obese patients is often associated with problems and complications. Extracorporeal shock wave lithotripsy can not be performed in some morbidly obese patients because of poor imaging, weight limitation of the equipment and the skin to stone distance exceeding the F1 to F2 focal point distance. *Percutaneous nephrolithotripsy* has higher risk of bleeding, anesthetic problems and postoperative thromboembolic complications especially in patients with a BMI greater than 40.

In the study¹³, by Grasse, success rate for PNL was ranging from 74 % to 83 % however this was associated with higher transfusion rate (14 % to 24 %) and significant complication such as acute renal loss, acute renal failure, colonic injury, vascular injury, pneumothorax, prolonged urine leakage, pyelonephritis, sepsis, deep venous thrombosis and pulmonary embolus. Poor visualization or inability to access stone bearing calyx. The conclusion of the study was that RIRS for larger renal stones was a safe and effective alternative to PNL and open surgery. They also mentioned that smaller stone burden had greater success rate with less operating time for the procedure.



RETROGRADE INTRARENAL SURGERY

The increased success rate is not only due to advances in flexible ureteroscopy and intracorporeal lithotripsy technology, but also the use of ureteral access sheath and tipless nitinol baskets, graspers. The use of nitinol tipless basket or grasper is another development enables to reach the stone in any calyx or calyceal diverticulum. Ureteroscopes deflecting capability is not affected by 2.6 or 3.2 F nitinol basket or graspers. The stones located in the lower pole calyx can be easily entrapped with a nitinol basket or grasper. If the stone is larger than 4 mm it is relocated into the mid or upper calyx for further disintegration.

Holmium YAG laser has been widely used for any ureteroscopic lithotripsy. For intracorporeal lithotripsy, 550 and 365 micron holmium: YAG laser fibers can only be used through semirigid ureteroscopes while 200 micron fibers should be used with flexible ureteroscopes. It has been demonstrated that 200 micron laser fiber compromise the flexible ureteroscopes tip deflection by 7%-16%. This decreases the success rate if the lower calyceal stone is fragmented in situ. Painting vaporization technique with holmium: YAG laser is described by Preminger which allows to disintegrate the stone into the smaller particles not required active removal¹⁴. Electrohydraulic lithotripsy is another option that can be used in conjunction with flexible ureteroscopy. Especially, 1.6 or 1.9 F EHL probes are used with no limitation of tip deflection. Electrohydraulic lithotripsy even with smaller probes may cause mucosal injury and destroy the tip of the instrument. RIRS for stones greater than 20 mm is associated with lower success rate and longer operating time while multiple procedures are needed. Retrograde intrarenal surgery for renal stones is reported to be safe in patients with bleeding diathesis. There is not enough experience with RIRS for stone in anomalous kidneys. However, Weizer et al reported 88 % complete clearance of the stone in 8 patients who had pelvic or horseshoe kidney. There are few reports combining the RIRS with ESWL and PNL in the same session¹⁵. In the series that RIRS was combined with ESWL, all 14 patients were not suitable candidates for PNL because of having risk of bleeding, not to tolerate prone position, anatomic location of the kidney and previous unsuccessful experience with the technique. The stones were fragmented either intracorporeally with 200 micron holmium laser probe or ESWL monitored by flexible ureteroscope with a success rate of 76.9%. One patient underwent percutaneous nephrostomy and subsequent PNL because of urosepsis. The authors reported that there was no damage to the ureteroscope because of the narrow focal zone of the ESWL system. In patients who had multiple or branched renal calculi, PNL was combined with retrograde ureteroscopy to decreased the number of percutaneous access without any complication and blood transfusion. Simultaneous bilateral flexible ureteroscopic treatment of renal stones has been reported but required more

facilities and experience.

In the review of current literature, holmium : YAG laser seems to be the choice of method for intracorporeal lithotripsy during RIRS for intrarenal stones in most of the series. Flexible ureteroscopes are used mostly and semirigid instruments occasionally. The use of ureteral access sheath is still controversial but there are some data showing that it facilitates the procedure while improving the stone free rates. Prospective randomized studies are needed to prove the benefit of ureteral access sheath use. Moreover, presence of 4 mm and smaller fragments after the procedure is accepted as success by some authors while 2 mm by others.

LAPAROSCOPIC RENAL STONE EXTRACTION

The management of calculus disease has changed with the advent of extracorporeal shock wave lithotripsy (ESWL), percutaneous nephrolithotomy (PNL) and rigid or flexible ureteroscopy (URS). However, despite the technical development and the expanding indications, the new technologies have not been able to completely replace open surgery. There are still some situations where open surgery could be the most suitable option for treating calculus disease. These are the cases that should be considered for potential management with laparoscopic surgery.

Gaur and colleagues¹⁶ introduced the retroperitoneoscopic Pyelolithotomy in five patients in 1994 and recommended the procedure for stones not amenable to SWL or PNL or when both the facilities were unavailable. Review of the literature by Hoening et al¹⁷ revealed 11 pyelolithotomies with a conversion rate of 27 % and an operative time of 2 to 5 hours ; this review confirmed the feasibility of laparoscopic pyelolithotomy.

Since then many authors have reported their experience with laparoscopic pyelolithotomy. Indications for the laparoscopic approach included: study of the feasibility of the procedure, previous failed endourologic approach, treatment of complex staghorn calculi, stone-removal from an anomalous or ectopic kidney, assistance of getting access during percutaneous nephrolithotomy, concomitant correction of a pelvi-ureteric junction obstruction, and finally absence of endourologic facilities in developing countries.

The results of these studies indicated that the laparoscopic pyelolithotomy, performed either transperitoneally or retroperitoneally, is a feasible as well as an effective and a safe procedure for selected cases. Depending on indication, overall success rates and stone free rates ranged from 71 % to 100 %. Open conversion rates ranged from 0 % to 27 %. Mean operative time, hospital stay and complication rate were all within acceptable rates. However, all these studies were either case reports or retrospective studies enrolling a small number of patients and presented no comparison with other treatment modalities.

Laparoscopic pyelolithotomy was associated with longer operating time, longer recuperation, was more invasive, less cosmetic, and required more skill as compared to percutaneous nephrolithotomy. Advanced endourologic facilities, such as laparoscopic ultrasound were required for removal of calyceal stones in the event of migration or for localization of stone. PNL is the best treatment modality for renal stones and laparoscopy should be offered to those who need adjunctive procedure such as pyeloplasty or punctures under vision during PNL.

Current relative indications for laparoscopic nephrolithotomy include the ablation of diverticular mucosa for symptomatic

calyceal diverticula with stones and the removal of Staghorn calculi via an anatomic nephrolithotomy performed laparoscopically.

Several authors have explored the role of laparoscopy for calyceal diverticula containing calculi, and 18 cases have been published in literature. Of these, 6 were performed by a tranperitoneal and 12 by a retroperitoneal approach included a stone located in anterior diverticula, with or without a thin overlying renal parenchyma, need for ablation of the diverticula and previously failed endourologic procedures such as PNL or flexible ureteroscopy. All stones were located in the upper pole with one exception¹⁸. Stone localization was achieved by palpation and visual contact, especially when the overlying renal cortex was either bulging or depressed because of scarring, and by retrograde injection of indigo carmine, fluoroscopy or ultrasonography. Stones and diverticula were successfully treated without open conversion in all cases. The diverticula were generally managed by fulguration, although in some cases, the cavity was closed with perirenal fat, gelatine resorcinol formaldehyde glue, or suture closure of the diverticular neck. Operative times ranged from 60 to 200 minutes. These studies indicate that laparoscopic diverticulectomy and stone removal is an efficient and a safe alternative or adjunct to endourologic procedure.

Relative contraindications to the laparoscopic approach include failed PNL with perirenal adhesions overlying the side of surgical interest and a thick rim of renal parenchyma obscuring the diverticula and make the localization of its cavity and the stone difficult. These cases could be challenging and impose an indication for a limited anatomic nephrolithotomy.

Shock wave lithotripsy and endourologic approaches are highly successful and constitute the treatment of choice for urinary calculi. Laparoscopic pyelolithotomy is feasible but rarely indicated in the present era. Laparoscopic nephrolithotomy may be indicated to remove a stone from an anterior diverticulum or when PNL or flexible ureteroscopy have failed.

MANAGEMENT OF URETERIC STONES

The ureter may be divided anatomically into two segments, proximal ureter (ureter above iliac vessels) and distal ureter (ureter below iliac vessels).

Spontaneous passage of Ureteral Stones

Ideally, patients with ureteral stones will pass them spontaneously while enduring minimal pain and complications. The majority of stones which pass spontaneously do so within 4-6 weeks. Miller and Kane reported that of stones < 2 mm, 2-4 mm and 4-6 mm, 95% of those which passed did so by 31, 40 and 39 days, respectively¹⁹.

Medical Expulsive Therapy

It should be considered for ureteric stones size less than 1 cm²⁰. Calcium Channel blockers and alpha receptor antagonists have reported that patients given such treatment have a significant reduced time to stone passage, fewer, pain episodes, and lower analogue pain scores and they needed significantly smaller doses of analgesics.

Proximal Ureteral Calculi

URS with Holmium Laser Lithotripsy has higher stone free rate than SWL for stones larger than 10 mm.

Distal Ureteral Calculi

Overall, SWL and URS seem to have comparable stone free rates for distal ureter stones. While the advantage of SWL is its non-

invasiveness. The advantage of URS is immediate stone removal.

Endoscopes

Semirigid URS: The semirigid ureterorenoscope consists of a stainless steel shaft and fibre optic bundles as well as working channel for irrigation and insertion of working instruments²¹.

Flexible URS: Flexible ureterorenoscopes with shaft diameters of 6.5-9 Fr also allow easy access to the upper urinary tract in most cases without previous dilation. Flexible ureterorenoscopes should not be used in the distal ureter, where semirigid instruments are a lot easier to handle²².

SWL: should be the first line therapy for patients with stones < 1 cm in proximal ureter. Stone push-back for upper ureteric calculi is not mandatory in the absence of infection, and noted benefits may be outweighed by the morbidity and cost associated with stent insertion. Lower ureteric calculi may be treated equally successfully by either SWL or ureteroscopic stone extraction based on the experience of the operator and facilities available. Results of SWL are institution dependant and as such clinicians should be guided by their institution's experience and choice of equipment as to whether mid and lower ureteric calculi are subjected to SWL as a first line treatment.

Open Surgery (Ureterolithotomy)

The clinical use of incisional surgery for ureteral stones has, however, been reduced dramatically due to its high degree of invasiveness in comparison with newly developed methods. The complication, the process of wound healing and the scarring are obvious drawbacks of open surgery. Today this method is an uncommon tool for removal of ureteral stones because of the successful results obtained with SWL and URS. The major indication for incisional surgery is when the stone removal has to be combined with reconstructive surgery for correction of anatomical abnormalities or when all other therapeutic possibilities have failed.

Laparoscopic Surgery

When compared with open surgery treatment results are similar, but laparoscopic approach resulted in a shorter hospital stay less need of analgesics and superior cosmesis. Major disadvantage of laparoscopy is long duration of procedure. Major indication are impacted stone in proximal ureter.

Percutaneous approach with or without antegrade URS

Impacted or hard stones in proximal ureter; ureteral stones in patients with urinary diversion should be considered for percutaneous

approach before open or laparoscopic approach.

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NOBLE PRIZE IN MEDICINE

Australian- American Researchers Elizabeth Blackburn, Carol Greider and Jack Szostak jointly won the 2009 Nobel Prize in Medicine for their discovery of a key molecular switch in cellular aging. The trio was honoured for their discoveries about how chromosomes are protected by telomeres and the role of an enzyme called 'telomerase' in maintaining or strapping away this vital shield. This award recognises the discovery of a fundamental mechanism of the cell, which has led to the development of new therapeutic strategies. Telomeres are like minute, protective caps, fitting at the end of the DNA strands which are packed into chromosomes. These scientists identified the 'Telomerase' enzyme that made telomerase in DNA. This concept has broad medical implications for patients of cancer, certain inherited diseases like aplastic anemia, genetic, skin and lung ailments and also aging process. The enzyme allows cells to divide continuously without dying and could play a role in uncontrolled spread of cancer.

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CURRENT MANAGEMENT OF UROLITHIASIS IN CHILDREN

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INTRODUCTION

Two to 3% of all patients of urolithiasis are children. Pediatric urolithiasis is endemic in developing countries including India. An underlying metabolic disorder is the cause in about half of children, infection being the cause in the other half. In Uttar Pradesh, parts of Gujrat and Maharashtra, vesical calculi are very frequent. This is attributed to dietary cereals being the predominant source of proteins. Structural urinary tract malformations predispose to stones because of "obstruction-stasis-infection" relationship. Urinary reconstructions using intestines or hair bearing skin predisposes to stone disease.

EPIDEMIOLOGY

The mean age of presentation is 6.9 years for girls and 5.2 years for boys. Infected stones generally present early before 4 years of age. Recurrence rates range from 3.6% to 68% and is the highest for children with metabolic risk factors. Endemic vesical calculi mostly affect boys between 1-5 years. In this group metabolic abnormalities are seldom detected and the recurrence rate is low.

CLASSIFICATION

The following is the classification proposed by Smith and Segura:

Renal Calculus Formation

Enzyme disorders

- Primary hyperoxaluria (deficiency of hepatic enzyme)
- 1,8-Dihydroxyadeninuria
- Lesch—Nyhan syndrome

Renal tubular syndromes

- Cystinuria
- Renal tubular acidosis (types 1-4) (calcium phosphate stones)

Hypercalcemic states

- Hyperparathyroidism
- Immobilization

Uric acid lithiasis

Enteric urolithiasis

Idiopathic calcium oxalate urolithiasis

Solute excess:

- Hypercalciuria
- Hyperoxaluria
- Hyperuricosuria
- Hypocitraturia
- Medications excreted into the urine

Endemic bladder stone formation

Secondary urolithiasis

- Infection (struvite stones, secondary to UTI with bacteria that produce urease)
- Obstruction (PUJ, VUJ, Neurogenic bladder, diverticulum)
- Bladder augmentation with intestines (mucus provides nidus, chronic bacteriuria contributes)
- Foreign body (ureteral stents, remnants of catheters, suture, etc.)

PATHOPHYSIOLOGY

Urinary calculi consist of crystalline and matrix components. Matrix, a gelatinous glycoprotein, forms the predominant feature of infective stones. Matrix also accounts for the softness of such stones. On the other hand metabolic stones such as xanthine and cystine are predominantly crystalline and accordingly hard. Lithogenesis is a complex physical process involving supersaturation of lithogenic ions and crystallization of compound in the urine. The process is influenced by *urinary dilution, pH*, and the presence of urinary ions or compounds that function as promoters or inhibitors of crystallization. Spontaneous nucleation takes place because of supersaturation of compounds. Secondary nucleation occurs on cellular debris and other particles in the urine. A damaged uro-epithelium, following urinary tract infection, may provide a nidus on which crystal growth occurs (heterogenous nucleation). An acidic ($\text{pH} < 6$) urine increases the solubility of calcium phosphate and a pH between 6 and 7, that of uric acid. An alkaline pH helps to keep cystine in solution. The formation of calcium oxalate is independent of changes in pH. Urinary tract infection with urea splitting organisms such as *Proteus* is also an important factor for precipitation of ammonium salts. *Anatomical abnormalities* such as reflux, diverticulae etc produce stasis thereby encouraging precipitation of lithogenic compounds. Infective stones have a soft glycoprotein matrix on which inorganic constituents such as magnesium ammonium phosphate, ammonium phosphate and calcium phosphate deposit. Only calcified stones are radio-opaque. Stag horn calculus is an infective calculus that grows into the configuration of the renal pelvis and calyces. Occasionally it progresses to the entire kidney parenchyma to produce an inflammatory mass – xanthogranulomatous pyelonephritis.

CLINICAL FEATURES

Flank pain, urinary infection and hematuria are predominant features of renal stones. Radiating pain from loin to groin is a typical feature of ureteric stone. Vesical stones present as lower urinary tract symptoms, stranguary and retention. Small vesical stones may get

impacted in the urethra and cause sudden interruption in the stream. In the endemic stone belt a diagnosis of stones should always be kept in mind if the child presents with lower urinary tract symptoms. Passage of gravel or a small stone in urine may be forthcoming.

INVESTIGATIONS

Laboratory Studies

- CBC count
- Electrolytes, BUN, creatinine, calcium, phosphorus, alkaline phosphatase, uric acid, total protein, albumin, parathyroid hormone (PTH), and vitamin D metabolite levels
- Spot urinalysis and culture, including ratio of calcium, uric acid, oxalate, cystine, citrate, and magnesium to creatinine
- Urine tests, including a 24-hour urine collection for calcium, phosphorus, magnesium, oxalate, uric acid citrate, cystine, protein, and creatinine clearance

Imaging Studies

- A plain abdominal film KUB is the first line imaging in any child presenting with a urinary infection or hematuria.
- Ultrasound is a sensitive modality for detection of stones and is often used as a screening modality. solid stones produce acoustic shadow that differentiates them from other echogenic shadows. Radio-opaque as well as radio-lucent stones can be picked up. However, small ureteric and bladder stones are often missed.
- The most sensitive test for identifying stones in the urinary system is noncontrast helical CT scanning; it is safe, rapid, and has been shown to have 97% sensitivity and 96% specificity.
- Intravenous pyelography is useful for planning treatment such as PCNL, ESWL, localizing ureteric stones and detecting underlying anatomical abnormality.

Stone analysis

- Attempting to obtain a stone for crystallographic evaluation is essential. It is usually obtained by straining urine in older children or examining diapers in young children.
- Content (i.e., cystine versus calcium versus uric acid) of the stone may be the most important element in developing a treatment program to prevent further stone formation.

MANAGEMENT

The components of treatment are:

- (1.) Stone clearance and prevention of recurrence
- (2.) Prevention of renal damage, treatment of infection
- (3.) Treatment of associated anatomical abnormality

There are **three different modalities** of treatment:

- (1.) *Traditional open surgery*: Pyelolithotomy, ureterolithotomy, cystolithotomy
- (2.) *Minimally invasive (laparoscopic surgery)*: Lap pyelolithotomy, ureterolithotomy
- (3.) *Endo-urological treatment*: PCNL, URS, Cystoscopic stone removal, Dormia basketing etc. In conjunction with

ESWL.

General *guidelines* regarding treatment are as follows:

- An obstructed infected portion of the urinary tract is a surgical emergency requiring drainage, antibiotic treatment, and supportive care. This is best exemplified by pyonephrosis secondary to an impacted upper ureteric stone.
- A child presenting with acute renal colic and / or hematuria can be managed with analgesics. If the stone is small, it may pass spontaneously.
- When a stone is small and at the ureteropelvic or ureterovesical junction, it may pass spontaneously; a few days of observation for spontaneous passage are justified.
- A vesical stone that completely obstructs the bladder outlet should be treated with catheterization using a Foley catheter. Once urine outflow has been established, removal of stone could be done endoscopically or open method.
- If there is an associated anomaly of the urinary tract such as PUJ obstruction, diverticulum etc, open surgery to correct the anomaly and removal of stone is the preferred approach.
- For other stones endoscopic removal is the currently favoured approach if the case is suited to this and the logistics is available. However, open surgery has a definite role.
- Endoscopic treatment of stones comprises of breaking the stone into small pieces and removing them. Small stones can be removed without breaking. Several energy sources are available to break the stones. These are: shock waves, ultrasound, Laser and mechanical breaking. The choice depends upon the stone size and location and surgeons preferences.
- Laparoscopic pyelolithotomy and ureterolithotomy are gradually replacing open surgery for stones.
- With advancement in miniature endourological equipment and finer optics, **endoscopic management** of stones has become popular in children. However, there is still a definite role for **open surgery** in the following situations:
 1. When facilities and/or experience for endourological treatment are not available and referral to the regional center is not feasible.
 2. Associated anatomical abnormality such as PUJ / VUJ obstruction and calyceal, bladder or urethral diverticulum. Both the stone and associated abnormality can be treated simultaneously through an open or laparoscopic approach,
 3. Failed endourological treatment.
 4. Complex cases with large stone burden involving the upper and lower urinary tracts
 5. Large stones in augmented bladders.

EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY (ESWL)

ESWL provides an excellent mode of fragmenting stones of upper tracts that can allow spontaneous passage of the

stone fragments. It is a safe technique and can produce a stone clearance rate of up to 75%. Shock waves are delivered at the centre of the stone from an external source. This leads to the stone getting fragmented into small pieces that pass spontaneously. A JJ stent in the ureter helps drainage in the post operative period for about 6-8 weeks. Multiple sittings are sometimes required if the stone burden is large. The procedure requires General anesthesia in children.

Indications

- Single or multiple pelvi- calyceal stones.
- Stag horn calculus (as a part of staged surgery with percutaneous surgery)
- Upper ureteric stones.
- Bladder stones (controversial).

Contraindications

- Anticoagulation.
- Sepsis.
- The stone is associated with distal urinary tract obstruction secondary to a stone or a structural malformation

Preoperative preparation

The child is consented for general anesthesia and the procedure. A current plain KUB film and an ultrasound are obtained. Urine must be sterile before treatment. Antibiotic prophylaxis with broad spectrum antibiotic is administered at the induction of anesthesia.

Technique

A JJ ureteric stent is inserted cystoscopically prior to the procedure. The stone is localized with USG and fluoroscopy. The patient is strapped to maintain a position so that the stone is always focused and the shock wave delivery machine is coupled to the skin through a water bath. A variable number of shocks (2000-3000) are administered to cause fragmentation. This may take up to 60 minutes. Fragmentation is confirmed on fluoroscopy.

Postoperative care

Child can be discharged on oral analgesics. Plain abdominal film and USS is obtained after 2-3 weeks. Repeat procedure is carried out if the stone burden dictates so. Several sittings may be required.

Complications

- Transient hematuria: no active treatment is required.
- Urinary infection is rare.
- Hemoptysis may rarely occur as a result of acoustic impedance between the lung tissue and chest wall. Covering the lower chest wall with a bubble-wrap dressing during the procedure can prevent this.
- Ureteric obstruction caused by fragments or sand. Usually responds to hydration and JJ stenting. Occasionally requires URS.

Ureteroscopic removal of ureteric stones / Ureterorenoscopy (URS)

Ureteric stones may be accessed using appropriate- sized instruments in a retrograde manner and then manipulated, fragmented and retrieved. Almost all ureteric stones and some pelvic stones in small children can be dealt with by this technique. Paediatric rigid compact ureterorenoscopes are now available in small sizes (6-8 Fr) with built in telescope that can be passed per urethra and advanced into the ureter and the pelvis. There is a working channel for instruments / laser fibres and irrigation channel. Children as small as two to three

years can also be treated.

Choice of energy source

Various options available are:

1. *Laser lithotripter*: Holmium laser (2150 nm wavelength) delivered in pulses is highly effective. It gently breaks the stone with low risk of mural damage. However, it requires patience and at times the vaporization bubbles can obscure the view.
2. *Pneumatic and electro magnetic ballistic devices*: good for impacted stones as they achieve rapid fragmentation at a low cost.
3. *Electro hydraulic lithotripters (EHL)*: achieves rapid and good fragmentation but carries higher risk of damage to the urethral wall.
4. *Ultrasound*: provides a safe and reasonable fragmentation alternative, although it tends to be slower.

Fragment retrieval

It depends on the size of the fragments. Small stones and relatively large fragments are retrieved by Dormia basket or forceps. Small fragments may pass spontaneously.

Technique

Patient is placed in a Lloyd- Davis position under GA. Preliminary cystoscopy is done. Position of the stone can be assessed by using contrast material and fluoroscopy. Guide wire is advanced into the ureteric orifice and then into the renal pelvis. The ureteroscope is then advanced under vision along side the guide wire. This may require positioning the contralateral leg straight up to provide angulations to the scope. Having visualized the stone it is either retrieved directly if small or fragments if large. If using Laser, precautions should be taken to safeguard the personnel against Laser hazards. The Laser fiber is positioned to touch the stone and energy is fired in bursts. Care should be taken not to touch the ureteric wall. Very small fragments of stone will pass spontaneously, larger fragments are may have to be retrieved by forceps or baskets.

Same techniques are applied to vesical stones using the standard cystoscope sheaths. Even larger stones (up to 1cm) may be removed without fragmenting by introducing a forceps suprapubically through the bladder wall and visualizing the stone through a cystoscope.

PERCUTANEOUS NEPHROLITHOTOMY (PCNL)

PCNL is evolving as an alternative to open surgery in children. It is suited for renal stones with hydronephrosis or stones where ESWL has failed. Uncorrected coagulopathy is an absolute contraindication. It can not be applied to very small children and where the kidney is shriveled up and the pelvis is not dilated.

Technique

GA and full muscle relaxation is required. Cystoscopy is done first and an appropriate sized guide wire is placed retrogradely into the renal pelvis. A catheter is then fed over it and a pyelogram is obtained to confirm the anatomy and to decide the course of percutaneous access. The catheter is secured; patient is repositioned for percutaneous access. Usually the lower posterior calyx is punctured and position is confirmed by aspirating urine from it. Under image intensifier a j tip guide-wire is inserted and the tract is dilated. An

Amplatz sheath (usually 16- 18fr for infants, 18-24 for older children) is then passed over the dilator to maintain the track. The Amplatz sheath is to be kept in position by the assistant. A nephroscope is then passed through the sheath and stone visualized. Fragmentation and retrieval techniques are similar to those for ureteric stones.

Complications

- Significant hemorrhage
- Inadvertent puncture of pleura.
- Inadvertent puncture of abdominal viscera.
- Significant macroscopic hematuria.

SPECIAL SITUATIONS

Stones after surgery for ano rectal malformations

Boys who have undergone surgery for ano-rectal malformations and present with lower urinary tract stones should be carefully evaluated to exclude stone in a urethral diverticulum. The diverticulum results from elongation of a remnant of the recto-urinary fistula which is a component of ano-rectal malformation. The senior author has treated such a case in a nine year old boy who presented with multiple "vesical" stones. He had undergone a pull through for high imperforate anus at one year of age. Plain film showed multiple faceted stones immediately behind and below the pubic symphysis (bladder stones show above the pubic symphysis). Retrograde urethrogram revealed a large urethral diverticulum from the posterior urethra and filled with multiple stones. The diverticulum was excised through a posterior sagittal approach. The catch point in this case was that the stones were multiple (bladder stones are single) and on X-ray they appeared below the bladder.

Urethral stones after reconstruction for hypospadias and epispadias

A combination of stricture and stasis can predispose to stone formation in the urethra. A major contributor in the past was hair bearing skin used in the reconstruction. The stones may be multiple and often quite large at presentation. They almost invariably require open surgery unless picked up early when endoscopic removal is feasible.

Often the hair bearing skin has to be replaced with buccal mucosa or non hair bearing skin. Skin from inner thigh is often used for staged reconstruction in failed cases of hypospadias. The senior author uses split thickness graft from the thigh so that the hair follicles are left behind in the lower layers of dermis and the grafted skin becomes hair free.

Vesical stone after bladder augmentation

Bladder augmentation is often required for exstrophy or neurogenic bladder. Most cases will also have a Mitrofanoff stoma and a closed bladder neck. The incorporated intestinal segments produce mucus which is a good nidus for stone formation. This, coupled with chronic infection (secondary to repeated catheterization) and metabolic alterations leads to large stone formation. They require open surgery. Recurrence is common unless an effective preventive strategy is adopted. Regular washouts with citrate solution, timely drainage by catheterizing the Mitrofanoff stoma and regular follow up is the key to prevention.

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DRUG PROFILE

Moxonidine

Moxonidine (4 chloro – N (4,5-dihydro-1, H-imidazol-2-yl)-6 – methoxy-2 methylpyrimidin-5 amine) is a selective antihypertensive and acts on imidazoline-1-1 and alpha-2 receptor against that reduces arterial pressure by inhibiting sympathetic activity, this reducing peripheral vascular resistance. **Pharmacokinetics:** About 90% of the oral dose is absorbed from the gastrointestinal tract bioavailability is about 89%, food does not affect absorption, peak plasma concentration (C_{max}) 1.526 ng /mL is reached 0.66 hours (T_{max}) after oral intake. It crosses the blood brain barrier, only 7% of the drug is bound to plasma proteins. The elimination half life (T_{1/2}) is approximately 1.85 hours and Kel is 0.386 l / hr., half life is increased in renal insufficiency. Only 10 to 20% of the administered dose is metabolised. 90% of the dose gets excreted in the urine within 24 hours, mainly in the unchanged form, only 1% of the dose was excreted in the feces. Maximum antihypertensive effect is observed 2 to 4 hours after the peak plasma concentration is reached and the effect persists for several hours after the drug disappears from the blood. Compared to the older central acting antihypertensives, moxonidine binds with much greater affinity to the imidazoline 1 receptor than to the α₂ – receptor. In contrast, clonidine binds to both receptors with equal affinity. In addition, moxonidine may also promote sodium excretion, improve insulin resistance and glucose tolerance and protect against hypertensive target organ damage, such as kidney disease and cardiac hypertrophy. **Indication:** The drug is indicated in the treatment of mild to moderate essential hypertension. **Contraindications:** Moxonidine is contraindicated in heart failure, in patients with bradycardia, heart block, severe liver disease or renal impairment (glomerular filtration rate < 30 ml / minute) and in people over 75 years of age. Caution must be exercised in patients with a history of unstable angina, severe coronary artery disease, angioneurotic oedema, intermittent claudication, raynaud's syndrome, Parkinson's syndrome, epilepsy, glaucoma. **Dosage and Administration:** The usual starting dose is 0.2 mg tablet given once daily, which may be titrated up to 0.6 mg in two divided doses, Blood pressure should be observed for three weeks before increasing the dose. A single dose should not exceed 0.4 mg and no more than 0.6 mg per day should be given. In case of mild to moderate renal dysfunction, a single dose should not exceed 0.2 mg and no more than 0.4 mg per day should be given. **Drug Interactions:** Administration with beta blockers causes greater reduction of blood pressure, followed by strong rebound phenomenon when these drugs are stopped. Alcohol, sedatives and anesthesia in combination, can increase its antihypertensive effect. **Precautions:** Since this drug may induce drowsiness, reduction of attention, concentration and ability of reflexive motion etc. patients should be cautioned against engaging in machinery activities, requiring alertness such as while driving. **Use in elderly:** Elderly patients may be very sensitive to the initial dose. Similarly caution should be observed during pregnancy, lactation etc. it is not recommended in children below 16 years. **Adverse Reactions:** At the beginning of the treatment, there may be weakness, fatigue, nausea and headache. Occasionally, dizziness asthenia and insomnia may occur. Gastrointestinal discomfort and individual skin allergies are rare. Rebound hypertension is not a major problem if used alone.

ALTERNATE SYSTEMS OF MEDICINE FOR RENAL STONE DISEASE

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Abstract : Although medical and surgical management constitutes the cornerstone of management of nephrolithiasis, in India alternative and complimentary systems provide many opportunities and claims for cure for this recurring disease. This review highlights some of the important remedies in alternative system which many patients resort to in order to escape surgery.

INTRODUCTION

Nephrolithiasis is one of the most painful and common disorders of the urinary tract. As such, there is much interest among physicians and patients to identify effective measures to promote stone passage, stone dissolution and stone prevention. Besides surgery most patients find relief and solace in alternate systems of medicines like Ayurveda, Homoeopathy Acupuncture and many others.

AYURVEDIC MEDICINE FOR RENAL CALCULI

Most Ayurvedic medicines are believed to have a complex antimicrobial, diuretic, antispasmodic properties and litholytic and anticalcifying activities. Some of the scientifically proven medicines in use are

Gokshura (*Tribulus terrestris*)

Tribulus terrestris is one of the most commonly utilized herbs in Ayurvedic medicine for renal dysfunction. It is proposed to be effective through diuretic, analgesic and litholytic properties and is also reported to have haemostatic properties. It has been traditionally used to have haemostatic properties. It has been traditionally used as treatment for cystitis and renal calculi and as a diuretic. The mechanism of preventing nephrolithiasis is thought to occur by decreasing urinary oxalate excretion through alteration in hepatic oxalate synthesizing enzymes, glycolate oxidase (GAO) and glycolate dehydrogenase (GAD).

In a study, *T. terrestris* administration to sodium glycolate-fed male rats produced a significant decrease in urinary oxalate excretion and a significant increase in urinary glycolate excretion as compared with controls.

Uva-ursi

This compound acts as a urinary antiseptic through its active ingredient arbutoside, the glycoside arbutin, which is chemically transformed in the gastrointestinal, hepatic and urinary tracts to the antimicrobial hydroquinone. In a study two formulations were utilized a film coated tablets and aqueous solutions, high performance liquid chromatography (HPLC) cool array and capillary electrophoresis were utilized to evaluate the urine samples. The maximum urinary concentrations of hydroquinone equivalents was higher and peaked earlier in the quinone equivalents was higher and peaked earlier in the aqueous solution group versus the film-coated tablet group.

Though *Uva-ursi* is commonly prescribed for the therapy of calculus disease, only few studies supporting the use of *Uva-ursi* in the prevention or management of urolithiasis, are reported

Bahupatra (*Phyllanthus niruri*)

Phyllanthus niruri grows in India, China and tropical locations ranging from the Philippines to Cuba. It has been used for over 2000 years in treating kidney stones. Barros and colleagues evaluated the in vitro effect of *P. Niruri* extract on calcium oxalate (CaOx) crystallization through the addition of the extract to unfiltered rat and human urine samples. The presence of CaOx crystals was evaluated immediately and 24 h later. *P. niruri* extract failed to inhibit CaOx nucleation but was effective at reducing crystal growth and aggregation. Barros and colleagues subsequently demonstrated that *P. niruri* impacts crystal aggregation and stone growth in a rat model, seeded with a CaOx calculus.

Human studies have also shown the efficacy of *P. niruri* in treatment of stone disease. Nishiura and colleagues showed *P. niruri* to significantly reduce urinary calcium excretion in patients with prior hypercalciuria.

Java Tea (*Orthosiphon stamineus and grandiflorus*)

This herb has been used for treatment of kidney and bladder stones and urinary tract infections. The proposed active ingredients are flavonoids in the *Orthosiphon* that are believed to have diuretic, antiseptic, and litholytic properties.

A prospective randomized trial of 48 patients compared the efficacy of *O. grandiflorus* to sodium potassium citrate in the treatment of patients with renal calculi at least 10 mm in size. Patients were either given a 2.5g tea bag of *O. grandiflorus* to be boiled in 250mL of water twice daily or titrated sodium potassium citrate to keep their urinary pH between 6.2 and 6.8. Efficacy was determined by the rate of stone size reduction per year, which was 28.6% ± 16% for the group receiving *O. grandiflorus* and 33.8% ± 23.6% for the group receiving sodium potassium citrate. The difference between these results was not statistically significant; however, the side effect profile was more pronounced for those patients taking sodium potassium citrate.

Horse Gram (*Dolichos biflorus*)

Dolichos biflorus has traditionally been used to dissolve existing renal calculi, provide symptom relief and prevent recurrence. Investigations have studied the litholytic properties of *D. biflorus* and demonstrated the in vitro mechanism of action to be inhibition

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of calcium phosphate crystallization. This properly decreases in seeds that had been stored for greater than 6 months postharvest.

Rotula aquatica lour

Traditional Indian medicine has used *Rotula aquatica lour* as a remedy for urolithiasis. In a rat model of calcium oxalate urolithiasis, *R. aquatica lour* was demonstrated to reduce urinary calcium and oxalate levels and prevent the histopathologic abnormalities noted in the untreated animals dilated renal tubules, microcrystals, and epithelial cell damage. No significant change was noted in serum calcium, phosphate, or magnesium.

Fish Stone (Sangesarmahi)

Fish stones are calcified material present in the skull of *Channa fish* and are part of an Ayurvedic approach to treatment of urolithiasis. In the clinical study, patients with existing ureteric and renal pelvic stones ranging in size from 4-9 mm were given 75 mg of fish stone powder three times a day for 5 days. No change was seen in the urinary profile; however, 36% of the patients passed a stone within 5 days of starting therapy. The authors attribute this to ureteric smooth muscle for relaxation properties of fish stones; however, this was an uncontrolled study.

HOMOEOPATHY FOR RENAL CALCULI

Apis Mellifica

It is indicated when there is scanty, high colored or red urine renal pain due to stones along with soreness on pressure or when stooping or frequent sudden attacks of pain along with strangury and retained urine.

Berberis Vulgaris

Mostly used when there is drawing pain often arising in lumbar region on one or both sides extending into different parts, as in renal colic and from passage of calculi. When the renal colic runs down the spermatic cord into the testes, and the patient is greatly disturbed, *Berberis* will very quickly relieve this particular kind of renal colic. *Berberis* makes the function of the kidneys normal and it has been shown to throw out the stones.

Benzoic Acid

The grand central characteristic of this remedy is found when the smell of the urine is very very offensive like the urine of a horse along with kidney stones and gout of the joints. This bad smell of the urine is found in connection with kidney colic along with cystitis.

Pareira Brava

Indicated when there is great straining, pain going down thighs during efforts to urinate. It is more indicated in bladder stones. Symptoms include violent pain in glans penis, itching along urethra and urethritis.

Lycopodium

Used in patients with severe backache, relieved by passing urine and graveluria. This drug has been used in many urethral conditions too.

Sarsaparilla

This drug is useful in condition associated with lower urinary tract symptom along with stones.

The list of homoeopathic medicines is long and only an expert can help identify one drug for a particular situation. However, there is ample scientific literature to show that the drugs are more effective than placebos.

Acupuncture has been effectively used to treat renal colic and result in stone passage. In one study acupuncture was shown to be more effective than morphine in treatment of renal colic due to calcium disease.

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LITERATURE REVIEW

Patterns of Alcohol Consumption in Medical Students Garg Ashish; Chavan B. S. ; Pal Singh Gurvinder; Bansal Ekta ; *Kidney Int.* 2009; 75:1088-1098

A prospective study was carried out among undergraduate medical students of three different medical colleges in North India. The aim of this study was to assess the consumption pattern of alcohol among medical students and correlate psychiatric disturbance and parental alcohol consumption with the patterns of alcohol use in them. Using an anonymous, self-administered questionnaire, we surveyed 168 subjects who were at various stages of their undergraduate medical career. Alcohol was the frequently used substance by all groups; 56.57% ever used alcohol and 41.46% showed patterns of problem drinking. Alcohol dependence was found in 6.09% of the students; 71.95% students started consuming alcohol after admission in the medical college. Almost one-third of respondents (37.50%) were found to be clinically depressed, anxious, or experiencing psychiatric disturbances. Such students had a greater frequency of alcohol consumption ($p = 0.05$). Also, a strong association between positive family history of alcohol use/abuse and use of alcohol among medical students was found ($p=0.001$). Alcohol abuse amongst medical students should be taken more seriously because their own attitudes towards substances may influence their professional behaviour.

Next Issue Highlights

- **Editorial** : Oral hypoglycemic agents: A critical Appraisal
- **Update** : Managements of Anosmia : An update
- **Update in Therapy** : New Anti-micro bials: Challenges and issues
- **Symposium** : Menorrhagia : Management Strategies



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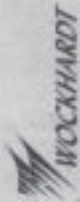
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