LIFE TIME RESEARCH ON URINARY STONES – A FORTY THREE YEAR EXPERIENCE

Author’s Name

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Abstract

During a period of 43 years, Sixty research projects on different aspect of urolithiasis were undertaken by the author. The different projects are mentioned. A gist of the findings of the research study is given based on the eight hundred papers presented from the work spanning over four decades.

Keywords: Urolithiasis, aetiology, pathology, investigations management.

INTRODUCTION

Urolithiasis is a common, recurring disorder, which has been researched in many parts of the world over the years. Former President of India, Mr. APJ Abdul Kalam had once told that any research has to find a solution to the problem within twenty years. However, research on urinary stone tends to slip out of this generalisation. In the span of 43 years of my research on urinary stone disease, new knowledge has been evolving and changes are continuing to conquer the continuing researcher. Over the years, the pattern of research topic has been changing all over the world as in seen from the types of reports emanating from the various research projects over the years from different parts fo the world. My work has been based on 42 funded research projects and many continuing self financing programmes, where research and treatment merge. Over 37,000 patients were registered in the stone clinic where the work was centred on. Over 800 papers have come out of the various projects undertaken. This paper gives a broad outline of the type of papers published on different aspect of urolithiasis and the basic knowledge that has emerged on each of these aspects of stone formation, presentation, investigation, treatment and prevention. The work was centred in South Kerala.

RESEARCH PROJECTS AND GRANTS

1976 Post Doctoral Research Fellowship (ICMR)
1981 - 1984 Study of the incidence and composition of urinary stones in Kerala (ICMR)
1985 – 1986 Study of the stone forming propensity of the Urolithiasis patient (KSST)
1985 Study of the ultra structure of urinary calculus (ASIKC).
1986 Clinical and Biochemical study of Urinary crystal growth (KSST)
1988 Assessment of inhibitory capacity of normal urine (ASIKC).
1988 - 1989 Inhibitors in urine (KSST).
1989 - 1990 Dietary calcium oxalate ratio and circadian rhythmicity in stone patients (KU).
1990 - 1993 Role of diet in urolithiasis (KSST).
1991 - 1992 Role of diet in altering the biochemistry of stone patients (SBMR).
1992 - 1993 Magnesium levels in urine related to the magnesium intake and magnesium content of water (ASIKC).
1993-1994 Prophylaxis and conservative Therapy clinical and basic aspects (ASIKC).
1994 - 1997 Role of citric acid containing diets and oral citrate in urinary crystalluria urinary citrate (ICMR).
1995 - 1996 Role of diet in altering the biochemistry of the urinary stone patients (KU).
1995 - 1996 Tissue changes in rate on administration of various anticalculogenic ayurvedic drugs (SBMR).
1996 - 1997 Relevance of Tamm-Horsfall mucoprotein in the genesis of urinary stone formation (SBMR).
1998 – 1999 Inhibition of Biomineralization (SBMR).
1999 – 2000 Infrared analysis of urinary stone (ASIKC)
2001- 2002 Instructional Module for patients with Urolithiasis.
2000 – 2003 Recent trends in the role of Diet and Drinking water in Urolithiasis (ICMR)
2002 – 2003 Scanning Electron Microscopic differences between crystals grown in vitro in silica gel with environmental changes. YM Fazil Marickar

IMPORTANT OBSERVATIONS

PREVALENCE

Kerala is a small state in India with 38863 sq.Km. Area. It represents only 1.18 percent of total area of India but 3.43% of the total population of the country. A sample survey was conducted in Kerala State to find out the prevalence of urinary stone disease. Among the 1483 persons interviewed from the three different districts, 45.2% were males and 54.8% were females. Of the 37 stone patients, 25 were males and 12 were females.

Out of 1483 persons interviewed, 64.7% belonged to the Hindu religion, 19.0% to Christian religion and 16.3% to Muslim religion. 70% of the total patients belonged to the Hindu religion followed by 16% in Muslim religion and only 14% were in Christian religion. From the total of 1483 interviewed persons, 78% males and 74% females were below the age of 50 years. 15% of males and 14% of females were in the age group 20 to 24 years.

The crude prevalence rate was 24.9 per 1000 population all over Kerala. In males it was 37.3 and in females the rate was 14.8 per 1000 population. The rate may vary according to region and different religion. Southern region showed a higher prevalence rate. Over all rate in the southern region was 32.8, for males 42.5 and for females the rate was 24.1 per 1000 population Religion wise prevalence showed that Hindus had a higher rate of 27.1 per 1000 population. The Muslims came second followed by the Christians. Among males, Hindus had a prevalence of 43.3 per 1000, against 29.2 for Christians and 27.8
for Muslims. Among females, the Muslims had a high incidence of 22.4 per 1000 compared to the other religions.

**INCIDENCE**

During all the years under consideration of the study, the rate of presentation of stone disease ranged between 3.7 to 4.5 per 1000 admissions, which depicted the Crude Incidence Rate. For males, the rate was steady during years 1991 to 1993.

**EPIDEMIOLOGY**

Data of 482 patients and 90 controls were included in the present study. Epidemiological factors studied included age, sex, religion, complexion, height, weight, income, place of domicile, occupation, family history of stone, diet, type of water and nature of water. Clinical factors studied were dysuria, haematuria, infection, obstruction, pain, sweating and vomiting. The data were statistically analysed.

44 paediatric patients were studied over a 20 year period (1968-87). The evaluation consisted of study of urinary deposits, blood and urine biochemistry, urine culture and stone analysis.

Majority of patients belonged to the age range of 20 to 50 years. The mean age at onset of disease was 38 years for male and 39 for female. The highest frequency was observed in 30 to 39 years. 94% were males. 61% were Hindus, 23% were Muslims and 16% were Christians. 78% were having medium complexion. 53% of the patients were in the group of 160 to 169 centimeters. 34% patients were in the group of 60 to 69 Kg. Majority of patients belonged to the middle income group (Rs. 1,000 to Rs. 3,000). 64% of patients were domiciled in the rural area. 74% were manual workers and the rest were sedentary workers. 13% of the patients had a family history of stone disease. 98% were non-vegetarians. 90% were well water drinkers. 90% patients were using soft water for drinking purposes. The clinical features encountered were as follows. 6% had dysuria. 22% of the patients were suffering from haematuria. 6% had urinary infection. Urinary obstruction was observed in 9% of the patient group. 39% had pain. Excessive sweating was observed among 23%. Vomiting tendency was observed in 17% of the group.

The incidence of paediatric stone patients was 2.5%. Maximum incidence was in the 8th year of life. Males predominated (7.8:1). Family history was positive in 5%. Bladder stones formed 53%, Renal 26%, Ureteric 16%, Urethral 12% and multiple sites 12%. 40% had crystalluria. 25% had urinary infection. The biochemical abnormalities observed were hyperuricemia (29%), hyperuricosuria (24%), hypercalcuria (24%), hypercalcemia (5%) and mixed abnormalities (24%). Congenital abnormalities of the lower urinary tract were observed in 21% of patients. 87% of the stones were mixed stones. Follow up indicated no recurrence of stone disease.
AETIOLOGY

It was observed that elevated urine oxalate (58%), high urine uric acid (47%), high serum uric acid (23%), elevated urine calcium (7%) and various indices were the most useful tools in the decision making of prophylaxis. Other indicators for decision making were relevant only in selective cases with specific metabolic problems like renal tubular acidosis, medullary sponge kidney, amino aciduria etc.

An abnormality in the 24 hr urinary Calcium, Oxalate or Uric acid was observed in 68% of stone patients. While serum abnormality was seen in 55%. 79% of the colic patients had urinary abnormality, while 71% had serum abnormality. Of the crystallurics, serum or urine abnormality was seen only in 50% of patients. 60% of stone patients and 50% of colic patients had crystalluria. Pyuria was seen in 50% of patients, while only 9% had positive urine culture, predominantly of E.Coli. 75% of the patients with UTI had a urinary pH of 5.0 to 5.5. A better correlation of positive bacteriological report was obtained when pyuria was seen in uncentrifuged sample of urine. A proper X ray KUB could demonstrate the site, size and shape of radio opaque stone and the renal outline to note for renomegaly. A confirmation of the backpressure effect of stone was done using Ultra sound scan abdomen. An emergency IVP had limited value since the same information was obtained from the safer USS. IVP was done only in those cases requiring surgery.

Even though it is mandatory to perform all possible biochemical investigations, the clinical relevance may be limited to a few investigations, which are pertinent to the metaphylactic advice advocated by the centre. This gains importance in the light of the fact that the vast majority of drugs administered to patients have many deleterious effects, doing more harm than good. Further, stone disease can be prevented by controlling some of the metabolic abnormalities so that the summation effect can be avoided.

A proper evaluation of the urinary symptoms is essential to diagnose the underlying disease. Pyuria may not always signify infection. An X ray KUB taken after proper preparation from an ideal centre backed up by USS abdomen for confirmation is the ideal procedure to note for back pressure due to a stone. IVP should be done only preoperatively in them.

A random group of 2300 patients was studied for the utility of the various parameters for deciding chemoprophylaxis. The utility of the values in deciding chemotherapy / chemoprophylaxis was assessed. It was observed that urine oxalate, urine uric acid, serum uric acid, urine calcium and various indices were the most useful tools in the decision making of prophylaxis. Other indicators for decision making were relevant only in selective cases with specific metabolic problems like renal tubular acidosis, medullary sponge kidney, amino aciduria etc. Other parameters which helped in the decision making included stone analysis, natural history of the disease and other epidemiological and environmental factors. It is concluded from the study
that even though it is mandatory to perform all possible biochemical investigations, the clinical relevance may be limited to a few investigations, which are pertinent to the metaphylactic advice advocated by the centre. This gains importance in the light of the fact that the vast majority of drugs administered to patients have many deleterious effects, doing more harm than good. Further, stone disease can be prevented by controlling some of the metabolic abnormalities so that the summation effect can be avoided.

The chief cations implicated in the genesis of urinary stone disease include calcium, sodium and magnesium. Of these, calcium and sodium are promotors of urolithiasis while magnesium is an inhibitor. This paper details the relative excretin of these cations in the urine of various classes of urinary stone patients.

400 urinary stone were included in the study. They were classified as (1) Single stone formers and multiple stone formers. (2) Male and female patients (3) Stone patients were analysed for calcium, sodium and magnesium. The relative excretion of these cations were then compared statistically using the student's 't' test.

The mean calcium and sodium levels in urinary stone patients were higher than that in normals, while magnesium was lesser. The mean calcium levels was higher in multiple stone formers (170.7 mg/day) compared to single stone formers (163.3. mg/day)while sodium was higher in single stone formers (275.1 and 253.9 mg/day respectively). Magnesium level was lesser in multiple stone formers (894.2 and 1865.6 mg/day) compared to females (246.3 mg/day) with a relatively low magnesium and calcium levels. Colic patients had elevated calcium and sodium levels compund to stone patient with relative low magnesium levels. The difference in these values are statistically significant.

High calcium level with a relatively low magnesium is common in multiple stone formers. While single stone formers had high sodium levels. Male patients have high sodium and low magnesium levels. The patients at the time of colic showed increased risk factors.

Low urine citrate level is identified to be a very important biochemical abnormality in the stone patients. But a statistical study to assess the relative importance compares to the other biochemical parameters has not been attempted so far. This paper presents the findings of such a statistical study.

Urine citrate levels were correlated with the other biochemical abnormalities of urine and blood. The probability testing was done centred on three main metabolic factors namely, urinary oxalates, citrates and uric acid. The urine citrate level was low in the patient group (181mg/day) as against the control group (227mg/day) with a p value of 0.034. It is seen that in the citrate oxalate combination, in males, the normal citrate high oxalate combination, which gave the maximum probability and high citrate normal oxalate which had the least probability value of stone formation. In females, the maximum probability was for normal citrate,
normal oxalate and minimum probability was for high citrate and high oxalate. From these and other values obtained it appears that citrate value is very important in protecting against stone disease, as evidence by the fact that when the citrate was not low, the probability was low. In the low citrate group, whether the oxalate level was normal of high, the probability was high (95.7, 93.7, 77.8). It is also noted that the patients with high citrate values were having a very low probability of stone formation.

The risk of urinary stone formation is related to the amount of crystalloides in urine. The main crystalloides aggravating the process of urolithiasis are calcium, uric acid and oxalate. Increased consumption of water was believed to wash off the excess crystalloids in urine, preventing their precipitation.

379 urinary stone patients attending the Stone Clinic of Medical College Hospital, Trivandrum were studied. They were classified as (1) Proved stone patients who had radiological or other evidence of stones of had a passed a stone. (2) Colic patients having no radiological or urinary microscopic abnormalities. (3) Crystallurics with stones. (4) Crystallurics without stones. These patients were asked to consume their regular normal diet and their 24 hr urine was collected. Their 24-hour urine was measured for its volume and analysed for Calcium, Phosphorus, Uric acid (UA), Magnesium, Creatinine and oxalate. The serum of such patients were analysed for Calcium, Phosphorus, Uric acid, Magnesium and Creatinine. The volume of urine was then correlated with the various biochemical parameters.

Of the 379 patients, 242 were proved stone patients, 67 were colics, 32 were crystallurics with stone and the rest 28 were crystallurics without stone. Of the stone patients, 42% had urine volume more than 2500 ml/day, while 35% of colic patients, 45% of the crystallurics with stone and 32% of the crystallurics without stone had urine volumes more than 25000 ml/day. The mean 24 hr urine volumes for various classes of patients were 2422 ml. For stone patients, 2246 for colics, 2489 for crystallurics with stone patients, 2246 for crystallurics without stones respectively. These patients almost always showed high urine volumes on follow up. 60% of patients had some sort of urinary biochemical abnormality, which included high UA (alone or with other abnormalities) in 15%, high oxalate (alone or with other abnormalities) in 46% and high calcium in 16%. Serum abnormality was seen only in 19% of patients, which included a pure or combined elevation of Uric acid in 74% cases and that of calcium in 21% cases.

Urine volume of less than 1000 ml/day was not seen in any of the patients. These patients on follow up, almost always showed high urine output, without reducing the propensity for formation of urinary stones or crystalluria until they were put on medical treatment. The biochemical values even when expressed as per unit volume of urine showed high values in such patients. These findings have been confirmed with animal experiments also.

**DIAGNOSING STONE**

Ancillary investigations of the patient with urinary stone These may be considered under two headings - Investigations relative to the specific clinical stone episode and Investigations relevant to determining the
aetiological cause of the patient’s stone in an attempt to provide therapy to avoid clinical recurrence of the stone disease. Investigations of the clinical episode include Urine examination: Urine is examined microscopically for excess red and white cells. A red cell excess is frequently found in the presence of a calculus and can provide supportive evidence when the diagnosis may be doubt as when non opaque stones are hidden in the bony shadows on X-ray. A white cell excess in usually found when infective stones are present. The most important element of the urinary examination is the identification of infection with any infecting organisms together with any antibiotic sensitivity. Blood Examination: A preliminary investigation of plasma urea or creatinine is made in most clinical cases of stone diseases prior to any operative intervention. Radiological investigation: These form the most important group of investigations undertaken in the preliminary management of the clinical stone episode. The investigations are as follows.

Plain abdominal X – ray. A plain abdominal X-ray will help to clarify diagnosis of stone in the urinary tract in about 70% of all cases seen. The majority of calculi are radio opaque and the film is examined for obvious radioopacities in the areas of kidneys ureters and bladder. Particularly in case of renal colic, it is possible to identify a calculus in the line of the ureter, which can clinch the diagnosis. Bladder stones in general show up well in the true pelvis lying with in the soft tissue bladder shadow. Radiolucent calculi on the other hand cannot be seen on the plain X-ray and require contrast radiography for identification. Contrast X-ray or Intra Venous Urogram (IVU). To confirm fully that a suspected calculus lies within the renal tract, contrast radiography is usually required. Here a tetra iodinated organic compound preferentially excreted by the renal glomeruli is injected intravenously. Timed sequential films are then taken as the compound passes through the kidneys, ureters and bladder. By examining these films it is possible to define accurately the size and position of the calculus and to determine whether or not secondary changes such as obstruction or distension are being caused within the urinary collecting system. Using the intra venous urogram in practically all cases of calculus disease a diagnosis can be accurately made. Retrograde pyelogram: Done occasionally owing to an obstruction to urinary outflow in the ureter. In this case, dye may be introduced into the ureter by way of a small catheter passed retrogradely through the ureteric orifice by means of a cystoscope thus defining the site of obstruction from below. Percutaneous nephrostogram: A fine needle is first passed into the pelvis of the ureter by percutaneous puncture under X-ray screen control. Dye is then injected down the ureter and defines the site of obstruction caused by the contained calculus. Radioisotope Renogram: This technique of introducing a radioisotope into the peripheral circulation and scanning it’s excretion over the renal areas with an automatic blood background subtraction system is useful in estimating the individual differential contribution of each kidney to overall renal function. Computer Assisted Tomogram: This has helped to demonstrate clearly the position of calculi with in the renal collecting system particularly in respect of their anterior, posterior location within the kidney prior to operation with a clear knowledge of stone orientation. Direct incision of the renal parenchyma over the stone or stones can be made by reference to the scan and the need for multiple exploratory incisions minimized.
The aetiopathogenesis of urinary stone disease and the decision for the treatment and prophylaxis is dependent entirely on the investigations. The biochemical and microscopical investigations form the basic investigations for studying the aetiopathogenesis of urinary stones, but the details of the stone and its amenability to surgical or sonar treatment is obtained from the radiological and ultrasonographic studies. Previously it was thought that an emergency I V U is an essential tool for this. But we have found that a proper plain X Ray abdomen could be a substitute for this and further confirmation was obtained from the ultrasonogram. A proper X Ray K U B could demonstrate the size, site and number of stone. It was also possible to assess renomegaly with the plain X Ray to note for back pressure due to a stone. Any confirmation of the back pressure was easily done with Ultrasonogram. The average renal size in U S S measured 8.5 tp 9.5 cms in patients without obstruction while it was upto II cms in patients with outflow obstruction. Pelvicalyceal differentiation was well made out due to marked difference in the acoustic density. Pelvic dilatation was seen in 25% of patients with persistent pain.

X Ray K U B taken from an ideal centre after proper preparation of the patient could easily substitute for I V U. Ultrasonography is a safe, painless, cheap and noninvasive technique useful for confirming the back pressure, management of complicated cases, recurrent stone patients and in the assessment of obstruction. It is safe in growing children and pregnant mothers since it is devoid of radiation hazards.

780 patients who presented with ureteric colic and had USS done before were assessed. 630 of these who did not have a plain x-ray KUB were submitted to a radiogram. The reliability of the USS in detecting stones was assessed during follow-up for six months to three years. Correlation between x-ray KUB and the USS was assessed.

78 patients had stones of over 10 mm in the kidney calyces or pelvis. All these were seen in the x-ray KUB also. 198 scans showed stones of size 3mm. to 10mm. in the kidneys, which were recognised in x-ray KUB also. 225 USS reports showed evidence of stones in the kidney region, but were not discernible in the x-rays. Of these 23 passed stone subsequently and the rest were reported to be clear in the subsequent USS performed which meant that these were originally falsely reported as stones or that the small stones were passed out without the knowledge of the patient. 78 patients had a repeat ultrasound performed within 48 hours of the first one in a different centre and the findings of the two scans tallied only in 31 patients, thus bringing out the nonreproducibility of the finding in USS in these cases. 63 USS reports identified stones in the ureter, 38 of them in the ureterovesical junction. Of these, 29 had radiological shadows. Of 127 patients who had stones identified in x-ray KUB, only 29 were reported in USS, identifying the deficiency of the USS in recognising ureteric stones. Of all the USS reports, 123 showed evidence of back pressure, 89 of them with stones and the rest without evidence of stones. From the observations, it is concluded that USS is not very suitable for detecting urinary stones. It is beneficial to recognise back pressure and in differentiating other pathological conditions.

MANAGEMENT
The aim of the study was to identify the role of chemotherapy in altering biochemistry in urinary stone patients. The primary objective of the project was to evaluate the biochemical changes produced in the urine and blood of proved urinary stone patients and colic patients on administration of anti stone medications. The secondary objective was to study the relationship of biochemical alterations to symptomatic relief in the patient under review.

A prospective study of 100 patients with proved calcium stones and patients with ureteric colic attending the urinary stone clinic of the Trivandrum Medical College with a follow up of 2 months to three years and on an average of six months chemotherapy with allopurinol and pyridoxine was done. 24 hour urinary calcium, phosphorus, magnesium, oxalate, citrate, uric acid and creatinine and serum calcium, phosphate, magnesium and uric acid values before and after the treatment were assessed to study the effects of chemotherapy in altering the biochemistry. The case records were analysed for simple demographic data, including Age, Sex, Educational status, Social and economic status, Clinical features, Radiological status, Urine microscopy, Microbiology and Biochemical parameters mentioned above. The chemotherapeutic / chemoprophylactic drugs administered to the patients with idiopathic calcium oxalate stone disease were classified as High Dose Chemotherapy (HDC), Moderate Dose Prophylaxis (MDP), Low dose prophylaxis (LDP) and Very low dose prophylaxis (VLDP) as detailed below

High Dose Chemotherapy Allopurinol (300 mg) + Pyridoxine (120 mg).
Moderate Dose Prophylaxis Allopurinol (200 mg) + Pyridoxine 80 mg)
Low Dose Prophylaxis Allopurinol (100 mg) + Pyridoxine 40 mg)
Very Low Dose Prophylaxis Allopurinol (50 mg) + Pyridoxine (20 mg)

A randomised selection of the patients were done, age and sex matched, in the 4 different groups. The differences were assessed for statistical significance using paired student t test. The intra group variation and the inter group variations were recognised using Anovar. The symptomatic relief in the extent of pain and passage of stone were assessed using clinical parameters. The extent of relief was correlated with the extent of biochemical alteration, using Pearson’s correlation coefficient. The r value and probability value were assessed. From the study, the role of different doses of standard medical management of stone disease as practiced in the urinary stone clinic of Trivandrum Medical College Hospital on the biochemical risk factors of stone formation and the clinical status of stone disease, as identified in the sample population role were recognised.

Author’s biography (200 words)

BIO DATA OF DR. Y.M. FAZIL MARICKAR
Dr. Fazil Marickar MS, MAMS, PhD (Urology), FAMS, FIMSA, FAS, FEMSI is Principal, Mount Zion Medical College. Has is surgical teacher for 43 years and has done extensive research on urolithiasis, completed 42 funded research projects of the ICMR, CSIR etc., presented 130 international and 850 national papers and published 389 papers and seven books. He has guided eleven Ph.Ds. He delivered the Pandalai Oration of ASI and was the first doctor to receive the Fellowship of the Electron Microscopic Society of India and Indian member of the International Consulting Committee on Urolithiasis. He is Inspector of MCI expert panelist of the Kerala State Council for Science, Technology and Environment. He was the best doctor of Kerala in 2000. He is President of Association of British scholars, Secretary of NAMS, Governing Council Member of ASI, Editorial Board Member of Urological Research and peer reviewer for many international journals. He was nodal officer medical curriculum for Kerala, Chairman of the ASI Kerala Chapter, President of ASI Trivandrum branch, Vice President of Urolithiasis Society of India, Secretary of Urological Association of Kerala, Editorial Secretary of Urolithiasis Society of India and editor of Kerala Surgical Journal.

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