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Research Article

## Dietary Restriction: A Major Factor in Prophylaxis against Calcium Oxalate Urolithiasis

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### ABSTRACT

Urolithiasis (Ur) Is A Worldwide Problem That Affects All Groups Of Ages. Nearly 80% Of Renal Stones Are Calcium Oxalate (Cao) And 50% Of The Affected Patients Have Recurrent Disease Within 10 Years. Our Prospective Study Was Conducted Over 4 And ½ Years And Evaluated The Role Of Dietary Manipulation In Prophylaxis Against Cao Ur. A Total Of 212 Patients With Recurrent Cao Ur, Who Lacked Anatomical Or Metabolic Derangement, Were Subjected To A Practical And Specific Diet. The Latter Had: (A) Low Salt, Red-Meat And Green Leafy Vegetable, (B) Moderate Amounts Of Milk, Dairy Products, Poultry And Certain Fish-Items, And (C) High Water Intake (2 Liters/Day). A Total Of 66/70 (96%), 87/108(88%) And 146/167(87.4%) Patients Were Stone-Free By The End Of 1, 2 And 3 Years Of Follow Up. The Median Time For Stone-Free Duration Was 33 (28.7-37.3) Months. Adding A Thiazide And Allopurinol To The 19 Patients Who Had Failed Dietary Prophylaxis Prevented Stone Formation In 16 More Patients Leaving Only 3 True Failures. Four Patients Could Not Tolerate The Latter 2 Drugs For Allergy. In Conclusion; Our Practical Dietary Modification Can Aid In Prophylaxis Against Cao Ur.

**Keywords:** Diet, Calcium Oxalate, Urolithiasis, Urinary Tract Stones, Prophylaxis

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### INTRODUCTION

Urolithiasis (Ur) Is A Worldwide Problem Which Can Affect All Groups Of Ages And Is A Major Source Of Morbidity Around The World. The Incidence Of Ur Is About 0.5% Per Year In North America And Europe [1]. Between 1-15% Of People Globally Are Affected By Kidney Stones At Some Point In Their Lives. In 2015, 22.1 Million Cases Occurred And Had Resulted In 16,000 Deaths Despite All The New Innovations In Its Urological Interventions [2, 3]. The Etiology Of Ur Includes; Genetic/Familial Predisposition, Metabolic Disorders And Anomalies In The Urinary Tract [4]. Nearly 80% Of Renal Stones Are Calcium Oxalate (Cao) And 50% Of Patients Have Recurrent Disease Within 10 Years Despite Lack Of Metabolic And Anatomical Diseases [5]. The Latter Phenomenon Manifests As An Effect Of The Socioeconomic Status And Geographic Residency (Stone Belts) [4]. Fortunately, A Wide-Range Of Surgical Options Are Currently Available For Treatment Of Cao Ur Yet The Role Of Its Prophylaxis Is Under-Estimated And Especially The Dietary One [6]. In The Present Study We Evaluated The Role Of Dietary Manipulation In Prevention Of New Stone-Formation In Patients With Recurrent Cao Ur.

### PATIENTS AND METHODS:

#### Study Design:

Patients With Uncomplicated Yet Recurrent Cao Ur Who Attended Dr. El-Reshaid Kidney Clinic From 1<sup>st</sup> January 2014 To 31<sup>st</sup> June 2019 Were Analyzed Prospectively For Stone Prophylaxis. The Clinic Was Established In 1997 In The Center Of Kuwait City. It Is A Referral Center And With Adequate Diagnostic As Well As Therapeutic Facilities To Care For Both In- And Out-Patients With All Medical And Renal Diseases.

#### Inclusion Criteria:

Patients Were Included, In The Study, If They Have Recurrent Cao Stones. The Latter Was Defined As (A) Having  $\geq$  Than 2 Radio-Opaque Renal Stones  $< 6$  Mm, (B) Has 1 Stone  $< 6$  Mm And Had Passed  $\geq 1$  Before, And (C) Had Passed  $\geq 2$  Stones Before.

#### Exclusion Criteria:

- 1- Patients Older Than 60 Years At Start Of Symptoms Or Less Than 14 Years.

- 2- Those With Morbid Obesity, Hyperparathyroidism, Nephrocalcinosis, Gastrointestinal Disorders (Short Bowels, Inflammatory Bowel Disease And Malabsorption), Chronic Inflammatory Conditions Associated With Hypercalcemia Viz. Sarcoidosis Or Malignancy, Cystinuria, Primary Hyperoxaluria, Distal Renal Tubular Acidosis. Moreover, Patients With Medullary Sponge Kidneys, Adult Polycystic Kidney Disease, Urinary Tract Obstruction Or Anomalies Were Also Excluded. The Exclusion Was Done With Laboratory And Radiological Testing (Vida Infra).
- 3- Patients with Hypercalcemia (Corrected Serum Calcium > 2.3 Mmol/L), Hyperuricemia (Serum Uric Acid > 450 Umol/L), Hypercalcuria (Urinary Calcium Excretion > 200 Mg/Day), Hyperuricosuria (Urinary Uric Acid > 800 Mg/Day), Hyperoxaluria (Urinary Oxalate > 50 Mg/Day), Hypocitraturia (Urinary Citrate < 320 Mg/Day) And Cystinuria (Urinary Cysteine > 350 Mg/Day) Or Positive Nitroprusside Cyanide Test.
- 4- Patients with Creatinine Clearance < 60 ml/Minute.
- 5- Patients with Osteoporosis Requiring Maintenance Calcium ± Vitamin D Supplementation.

#### Initial Assessment:

Included; Laboratory And Radiological Testing. The Laboratory Ones Were: (A) Serum Electrolytes Viz. Corrected Calcium, Magnesium And Bicarbonate Content, Uric Acid (B) Urine Routine And Microscopy (C) Urine Ph, Sodium, Calcium, Uric Acid, Oxalate, Citrate And Nitroprusside Cyanide Test. Radiological Tests Included; Ultrasound As Well As CT Of The Abdomen And Pelvis When Indicated Initially Or On Follow Up.

#### Follow Up Testing:

Included; Routine Clinical, Laboratory And Ultrasound Assessment Every 2 Months. Twenty Four Hour Urine Collections Were Done Every 6 Months To Ensure Compliance. Adherence To Low-Salt Diet Was Confirmed By Having Urinary Sodium < 225 Mmol/Day.

#### Stone Prophylaxis:

All Patients Had Instructions Regarding Dietary Measures That Included Increasing Water Intake To 2 Liters/Day Via 5 Bottles-Regimens. A 250 ml Of Water Upon Waking Up And 1 Hour Before Night Sleep As Well As 500 ml ½ Hour Before Respective Meals. In Addition; (A) Avoidance Of Calcium And Vitamin D Supplementation Yet Permission Of Moderate Low-Fat Milk And Dairy Products, (B) Avoidance Of Red Meat And Their Internal Organs Yet Permission Of < 30 G Of Lean Poultry Products As Well As Fish In Moderation Except For Sardines, Tuna And Shrimps, (C) Dark-Green Leafy Vegetables And (D) Stored Or Frozen Food-Products. The Latter Was Intended To Limit Salt Intake Which Was Complemented With Normal Intake Of Home Food Except For Extra Salt Addition After Cooking And Salty Appetizers Such As Pickles, Mustard, Salad Dressings, Yogurt And Frozen Foods. Patients Who Did Not Improve (Recurrent Renal Colics Or Had Increase Stone Load) Were Further Retested After Addition Of A Combination Of Thiazide (250 Mg Daily And Allopurinol 100 Mg Daily).

#### Statistical Analysis:

Since The Age, Duration Of Stone Formation Prior To Treatment And Duration Of Follow Up Were Not Normally Distributed; The Median And (Interquartile Range) Were Used To Express The Groups. Moreover, For Estimation Of Efficacy Of Prophylaxis/Treatment Years; The Kaplan-Meier Method Was Used To Calculate The Median Survival Time And Its 95% Confidence Interval.

#### RESULTS

Over The Past 4 And 1/2 Years, A Total Of 258 Patients With Ur Were Screened. Sixteen Patients Were Excluded For The Following Reasons; (A) 5 With Isolated Hyperuricosuria (B) 2 With Isolated Hypercalcemia (C) 2 Patients With Hyperuricemia (D) 2 Patients With Cysteine Stones (E) 2 With Distal Renal Tubular Acidosis (F) 2 With Primary Hyperoxaluria (G) 1 With Hyperparathyroidism. Moreover, 14 Had Congenital Or Acquired Urinary Tract Disease, 11 Had Creatinine Clearance < 60 ml/Minute And 5 Patients Lost To Follow Up. Demographical Data And Results Of Their Treatment Is Summarized In Table 1.

**Table 1. The Demographical Data on 212 Patients with Recurrent Idiopathic Cao Urolithiasis and Results of Their Treatment**

<u>Age (years):</u>	32 (11)	(min: 21, max: 56)
<u>Duration of follow up (months):</u>	30 (21)	(min: 3, max: 54)
<u>Efficacy of dietary prophylaxis:</u>		
At 1 year:	66/70	(96%)
At 2 years:	87/108	(88%)
At 3 years:	146/167	(87%)
<u>Median time for stone-free interval:</u>	33 (28.7-37.3)	
	(months)	
<u>Prophylaxis failure:</u>	21/212 (9.9%)	
A- <u>Improved with T/A:</u>	13/21 (61.9%)	
B- <u>Side effects of T/A:</u>	4/21 (19%)	
C- <u>True failure:</u>	4 (1.9%)	

Abbreviations: CaO: calcium oxalate stones, T/A: Thiazides and Allopurinol

**Demographical Data:**

A Total Of 212 Patients Were Included In The Study. All Patients Were Adults With A Median Age Of 32(11) And Youngest Was 21 And Eldest Was 56 Years. The Median Of Duration Of Follow Up Was 30(21) Months And Shortest Was 3 And Longest Was 54 Months.

**Efficacy of Prophylaxis:**

During The Study, Only 23 (11%) Patients Had Failed Dietary Prophylaxis And Formed New Stones. Using Survival Time Analysis; A Total of 66/70 (96%), 87/108(88%) And 146/167(87.4%) Patients Were Stone-Free By The End Of 1, 2 And 3 Years Of Follow Up. The Median Time for Stone-Free Duration Was 33 (28.7-37.3) Months.

**Management of the Initial Non-Responders:**

Adding A Thiazide And Allopurinol To Those Who Failed Dietary Prophylaxis Prevented New Stone Formation In 13 Of 19 Patients Who Could Tolerate The Drugs.

**Tolerance to Prophylaxis:**

In General There Was No Major Complaint With Our Dietary Management. However, 2 Patients Could Not Tolerate Thiazide For Pruritus. Two Patients Had Mild Hypokalemia That Was Corrected By Increase In Intake Of Lemon Juice. Two More Patients Could Not Tolerate Allopurinol For Urticaria Which Persisted Despite Shifting To Febuxostat.

**DISCUSSION**

Treatment of Patients with Recurrent Ur Is Cost Effective Even It Involves Drug Prophylaxis [7]. In The Latter Study, The Savings Achieved By Reducing Hospitalization And Urological Procedures In 1,092 Patients With Ur Prophylaxis By Using Diagnostic Testing, Metabolic Evaluation And Use Of Inexpensive Drugs Viz. Thiazides, Potassium Citrate And Allopurinol Was \$2,158 Per Patient Per Year. Given The Proven Benefit Of Prophylaxis, Medicare And Most Managed-Care Organizations Typically Cover The Costs Of Diagnosis And These Particular Medical Treatments. In Our Prospective Study; Few Patients with Recurrent Cao Ur Had Metabolic Disorders (Hypocitremia, Hyperoxaluria and Hyperuricemia) And Secondary (Anatomical, Infection And Metabolic) Causes. The Latter Indicates That The Most Cao Renal Stones Are Of Benign Nature And Amenable To Dietary Manipulations Aimed At Calcium And Urate Absorptive Mechanisms [8, 9]. Moreover, The Success Of Our Additional Drug-Therapy In Those Who Failed The Dietary Manipulation Confirms Our Findings. Thiazides Decrease Urinary Calcium Excretion and Zyloric Decrease Synthesis of Uric Acid and Hence It's Excretion Leading To Further Prevention Of Paroxysms Of Hypercalcuria And Hyperuricosuria In Partially Compliant Patients [10, 11]. Our Study Further Emphasizes The Role Of Metabolic Screening In Patients With Cao Ur To Decrease The Cost Of Their Management. Patients With Recurrent Stone-Formation And Normal Metabolic Screen; Can Benefit From Our Practical Dietary Manipulations And The Use Of Inexpensive Drugs Viz. Thiazides And Allopurinol If Compliance Is An Issue. In Our Study; And To Improve Our Patient's-Compliance, We Limited The Water Intake To 2 Liters Divided At Regular Intervals. The Timing Is Essential To Improve Patient's Compliance And The Night Dose Was 1 Hour Before Sleep With Instruction To Have A Minimum Of 2 Urinary Voids Prior To Sleep To Avoid Nocturia That May Decrease Compliance With The Last Dose. The Restriction Of Dietary Calcium, Sodium, Animal Proteins, And Leafy Vegetables Was Calculated To Improve Patient's-Compliance [12]. Dietary Calcium Was Moderate To Assist In Providing

Adequate Supply To The Growing Teeth And Bones As Well As To Bind With Meal-Oxalate And Prevent Their Absorption [13]. High Salt Intake Leads To Hypercalcuria Due To Inhibition Of Re-Absorbency Of Calcium In The Proximal Tubule [14]. Our Limitation Of Sodium-Intake Was Practical And Acceptable By Our Patients. It Kept The Members Of The Family Together By Just Limiting External Food Intake And In-House High Salt-Content Items. The Restrictions Of Animal Proteins Were Limited To Red Meat And Internal Organs Which Are Purine-Rich Items And Result In High Uric Acid Levels. Moderate Poultry Products and Most Fish-Items Were Acceptable Alternatives And Did Not Significantly Increase Uric Acid Excretion Or Result In Hyperuricosuria. The Latter May Have Been Due To Their Higher Content Of Guanine And Xanthine Compared To Adenine And Xanthine In Meat As Well As Their Alkalinization Effect (Similar To The Milk And Dairy Products) Which Facilitates Uric Acid Elimination In Urine [15]. Lastly, Leafy Vegetables Are A Major Source Of Oxalates. The Latter Is A Major Risk Factor For Cao Ur [16]. They Were Neglected By Most Of Our Patients And Even Large-Percentage Of Our Population Still Believes That The Drinks Containing "Bagdonis" Aids In Stone Expulsion. This Believe Stemmed From Misconception Of Higher Frequency Of Stone Passage Masquerading A Rather More New Ur. In Conclusion; Our Dietary Manipulations Offers Patients With Recurrent Idiopathic Cao Ur A Simple And Palatable Diet With Adequate Essential Elements To Improve Their Compliance And Prevent Disease Progression.

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