Bangladesh Renal Journal

Volume 05 Number 01 January 2023

ISSN 1015-0889
Abstracted by
Excerpta Medica

CONTENTS

OFFICIAL JOURNAL OF
BANGLADESH RENAL ASSOCIATION

BANGLADESH RENAL JOURNAL

(A Journal of continuing education in kidney diseases)

Editorial Office : 89/2 Haque Chamber, Flat-HC8D, West Panthapath, Sher-e-Bangla Nagar, Dhaka-1215, Bangladesh.
E-mail: brabd.org@gmail.com Website: www.brabd.org

GENERAL INFORMATION

Bangladesh Renal Journal is the official organ of the Bangladesh Renal Association. Two issues of the Journal is being published each year. First one is in the month of June and another one in December. The Journal is devoted to continuing education in kidney diseases.

For Contributors

Papers for Publication should be sent to editorial office or submitted directly by e-mail to: bdrenaljournal@gmail.com. Only scientific papers written in English will be accepted. The message of a recently published paper may be communicated in the "recent advances in the renal disease section". Original articles, review articles, practical procedures, case reports, clinical communications are welcome. We would invite opinion and criticism regarding the journal through the letter to the editor column. Contributors are requested to follow the guidelines for submitting manuscripts.

For Readers and Subscribers

The annual subscription for this journal is as follows

Medical students :
Taka 250.00
Graduate and General practitioner :
Taka 500.00
Specialist :
Taka 1000.00
Overseas :
US dollar $ 50.00
(including postage by air)
Please write for regular supply of your copy to editor.

For Advertisers

Please send the advertisements to : Editorial Office : 89/2 Haque Chamber, Flat-HC8D, West Panthapath, Sher-e-Bangla Nagar, Dhaka-1215, Bangladesh.
E-mail: brabd.org@gmail.com Website: www.brabd.org

BANGLADESH RENAL JOURNAL

(A Journal of continuing education in kidney diseases)

INSTRUCTION FOR AUTHORS

Renal Association Journal appears twice in a year and it publishes original articles, review articles, clinical communications, recent advances in renal diseases and letters to the editors. The editors reserve the right to select from submitted manuscripts and the right of stylistic changes or abridgements. The manuscripts may not be offered elsewhere for printing and publication; following acceptance, the publisher acquires all copywright.

MANUSCRIPTS

Only scientific papers written in English will be accepted. Restriction to the essential is recommended. Original papers should normally not exceed 16 type- written pages including tables, illustration and references. The arrangement of the paper should include summary, introduction materials and methods, results and discussion. Each section being clearly marked. The manuscripts must be type-written on a white paper, on one side of the sheet only and double spaced on consecutively numbered pages. Figures and illustrations, tables. captions, references, summary (15-20) lines and acknowledgement are to be submitted on separate paper. The caption should be brief and should not represent a duplication of information provided in the text.

STYLE

Abbreviations and symbols of chemical terms must be in conformity with the regulation as published in J. Biol. Chem. 241-527, 1966. Spelling should conform to chambers twentieth century dictionary. Drugs should be spelt out when first used in the text. Scientific measurements should be given in SL. units, Followed, in the text by traditional units in parentheses.

Any statistical method used should be detailed in the method section of the paper.

CITATION

The authors name should be listed in the text with year, examples (Merrill, 1965, Gabrel and Margan, 1976) For 3 or more authors (Oreagan et al. 1979).

REFERENCES

References should be limited. Only paper quoted in the text are to be listed in the bibliography. The references should be numbered consecutively as it appear in text and listed at the end of the article as in index Medicus.

Examples :

I. **PAPERS PUBLISHED IN JOURNALS**

Patel R, Mickey MR and Tersaki PI : Leucocyte antigens and disease. Association of HLA A_2 and chronic glomerulonephritis. Br Med J 1969; 2 : 424-426.

II. **ARTICLE IN BOOKS**

Peters DK, and Lechmann PJ : The complement system in renal disease, In; Renal diseases (ED) DAK Black and NF Jones Oxford. Blackwell, 1976, P-169-384.

III. **BOOKS**

Grindley MF: Manual of histologic and special staining Nephrologic, Elammarion, Paris, 1965.

ABBREVIATIONS

Angstrom	A
body surface area	BSA
body weight	body wt.
centimeter	cm
celius	C
complement components	C1,C2,C3
Correlation coefficient	r
creatinine clearance	Ccr.
curie (s)	Ci
Equivalents	Eq
Fahrenheit	F
Glomerular fitration rate	GFR
gram (s)	g
Grams per cent	g/100mi
half-time	tf1/2
hour (s)	hr
inch	inch
International Unit (s)	IU
Intramuscular	im.

intraperioneal	i.p.
intravenous	i.v.
inulin clearance	Cln
Kilogram (s)	Kg
liter (s)	L
meter (s) or milli	m
microns (s) or micro	µ
milligram (s) per cent	mg/100ml
minute (s)	min
molar	M
mole (s)	mole (s)
Molecular weight	molwt
nanogram (s) (millimicrogram)	ng
nanoliter (s) (millimicroliter)	nl
normal (concentration)	N
not significant	NS
optical density	OD
osmole (s)	Osm
probability	P
second (s)	sec
standard deviation	SD
standard error	SE
standard error of the mean	SEM
ultraviolet	UV
unit (s)	U
volt	V

MANUSCRIPTS SHOULD BE SUBMITTED

Address : Editorial Office, 89/2 Haque Chamber, Flat-HC8D, West Panthapath, Sher-e-Bangla Nagar, Dhaka-1215, Bangladesh
E-mail: bdrenaljournal@gmail.com, brabd.org@gmail.com
Website: www.brabd.org

Editorial

Cadaveric Renal Transplant

Renal transplantation is the treatment of choice for selected patients with end stage kidney disease[1], since it improves the quality of life, reduce the mortality risk and is cost effective compared with dialysis[2,3] patient as well as graft survival also have been improved over the past decade. For cadaveric renal transplant recipients who were transplanted in 2006, 10- year all cause graft failure declined to 51.6% compared with 57.2% for transplants performed in 1998 and a 10-year death-censored graft failure declined from 33.7% to 26.2%.[4] Living donor recipient transplanted in 2006 had 34.2% 10-year all cause and 18% death censored graft failure rate.[4] The long term advantages of living donor versus cadaver donor kidney transplant could be observed in patient with long expected longevity and with no or fewer comorbidity as we can find in children.

Survival after renal transplantation depends on many factors like source of the kidney, age of the recipient and associated comorbid conditions and race, sex and degree of immunosuppression. one study[5] evaluated for patient survival after renal transplantation (among 86 living related and 916 cadaveric donor recipient) and found an increased death risk in patients of >40 years of age male gender, cadaveric donor recipients, having comorbid conditions like diabetes or hypertension and smokers.

The survival benefits of patients receiving a kidney from a living donor is superior to a kidney received from a cadaveric donor.[6,7]

For recipients of a living donor kidney a post transplantation five years survival is 91 percent.

For a patient who received a cadaveric kidney survival rate is 84% (non expanded criteria donor and 70% (expanded criteria donor) recipient. Cadaveric donor age is also important in terms of survival. The one and five year survival rates for children of age 6-10 years receiving a living donor kidneys were 96% and 85% respectively and for same age children who received cadaveric donor kidneys it was 95% and 77% respectively.[8]

Among recipients of any age survival is inversely correlated with the age of cadaveric donor.[9]

One study[10] published in 1999 showed substantial reduction in the long term risk of death after cadaveric transplantation compared with dialysis.

One Iranian study[11] showed that one year graft and patient survivals in cadaveric groups were 93% and 96% respectively and in living groups were 92% and 97% respectively i.e. there is no significant difference.

In South Asian countries renal transplant program relies mainly on live donor transplantation. In India, Cadaveric renal transplantation comprises around 2% of all transplants and over 90% of patients awaiting renal transplantation die without getting the organ.[12,13]

Situation seems to be similar in Bangladesh. Progress of cadaveric program has been halled by lack of awareness, religious stigmata and infrastructural deficiencies.

Hats off to Sarah Islam, her donation kicked off the cadaver donor transplantation in Bangladesh in 2023.

However, there is a need to sensitize and augment the rate of cadaveric transplantation to increase the donor pool.

A deeply committed cadaveric transplant program is needed to improve the cadaveric donation rate. Cadaveric organs are nations invaluable resources and an organ wasted is a life wasted.

(Bang. Renal J. 2023; 5(1): 1-2)

Prof. Dr. Muhammad Rafiqul Alam
Deputy Chair/Councillor ISN South Asia Regional Board
Former Chairman, Dept. of Nephrology, BSMMU
Former Pro-Vice Chancellor, BSMMU
Former President, Bangladesh Renal Association

References:

1. Suthanthiran M, Strom TB. Renal transplantation. N Engl J Med. 1994;331365.
2. Port FK, Wolfe RA, Mauger EA et al. Comparison of survival probabilities for dialysis patients vs cadaveric renal transplant recipients. JAMA. 1993;270:1339.

3. Ojo AO, Port FK, Wolfe RA et al. Comparative mortality risks of chronic dialysis and cadaveric transplantation in black end-stage renal disease patients. Am J Kidney Dis. 1994;24:59.

4. Hart A , Smith JM, Skeans MA et al. OPTN/SRTR 2016 Annual data report: Kidney Am J transplant 2018;18 suppl 1:18

5. Arend SM, Mallat MJ, Westendorp RJ et al. Patient survival after renal transplantation; more then 25 years follow up. Nephrol Dial Transplant 1997;12:1672.

6. Port FK, Dykstra DM, Merion RM, Wolfe RA. Trends and results for organ donation and transplantation in the United States 2004. Am J Transplant 2005;5:843.

7. McCullough KP, Keith DS, Meyer KH et al. Kidney and pancreas transplantation in the United States 1999-2007; access for patients with diabetes and end stage renal disease. Am J Transplant 2009;9:894.

8. The 2003 SRTR report on the state of transplantation. Am J Transplant 2004;4(suppl 9):54

9. Keith DS Demattos A, Golconda M et al.Effect of donor recipient age match on survival after first deceased donor renal transplantation. J Am Soc Nephrol 2004;15:1086.

10. Wolfe RA, Ashby VB, Milford EL,et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation and recipients of a first cadaveric transplant N Engl J Med 1999;341:1725-30.

11. Simforoosh N, Gooran S, Tabibi A, Bassiri A, Ghratti MR. Cadaver transplant in recent era: is cadaveric Graft survival similar to living kidney transplantation ? Int. J Org Transplantation 2011; 3(4): 167-70.

12. Shorff S. Indian transplant registry. Indian J Urol 2007; 23:272-77.

13. Modi GK, Jha V. The incidence of end stage renal disease in India: a population based study. Kidney Int 2006;70: 2131-33.

Assessment of Hypothalamic Pituitary Adrenal Axis Status in Patients of Membranous Nephropathy Receiving Ponticelli Regimen

Mony MB[1], Rahman HMM[2], Ansary EAF[3], Islam MN[4], Chowdhury NUA[5], Das D[6], Uddin SQ[7], Chowdhury MN[8]

Abstract:

Introduction: Hypothalamic pituitary adrenal axis suppression may occur in patients of membranous nephropathy receiving Ponticelli regimen as steroids are stopped abruptly without any tapering at the end of 1st, 3rd, and 5th month. This study was conducted to evaluate hypothalamic pituitary adrenal (HPA) axis suppression in patients of membranous nephropathy receiving Ponticelli regimen.

Objective: To evaluate hypothalamic pituitary adrenal axis status in patients of membranous nephropathy receiving Ponticelli regimen.

Methods: This cross-sectional study was conducted in Department of Nephrology, Dhaka Medical College and Hospital, Dhaka, Bangladesh. Total 31 patients of Membranous Nephropathy, confirmed by renal histopathology were included in this study. All patients received Ponticelli regimen and at the end of treatment HPA axis status was evaluated. Statistical analysis was done by Statistical Packages for Social Sciences (SPSS-20).

Results: The mean age was 41.0±15.0 years and male to female ratio was 2:1. Among total 31 patients, 8 (25.8%) patients had serum cortisol level < 80nmol/L. So, they were considered as confirmed cases of adrenal insufficiency and didn't require short synacthen test. Remaining 23 (74.2%) patients had serum cortisol level between 80-500 nmol/L and they underwent short synacthen test. After short synacthen test, 3 (13.0%) patients out of 23 patients were found to have cortisol level between 80-500 nmol/L and they are considered as confirmed cases of adrenal insufficiency. Remaining 20 (87.0%) patients out of 23 patients had raised cortisol level more than 500 nmol/L. So, they had no adrenal insufficiency. Therefore, among 31 patients, a total of 11 (35.5%) patients had adrenal insufficiency.

Conclusion: This study showed that 35.5% patients had asymptomatic HPA axis suppression after completion of the Ponticelli regimen.

(Bang. Renal J. 2023; 5(1): 3-7)

Introduction:

Membranous nephropathy (MN) is an immunologically mediated disease in which immune complex is deposited in the subepithelial space. These deposits activate complement, leading to podocyte injury (Mansur, 2014).

Over three decades ago, Ponticelli described an immunosuppressive regimen consisting of a combination of steroids and cytotoxic agents in the management of patients with idiopathic membranous nephropathy (Ponticelli et al. 1984). Ever since, this treatment has been in vogue and has been popularly known as the Ponticelli regimen. This therapy is of 6 months duration with corticosteroids being given on 1 st, 3 rd, and 5 th month and chlorambucil in the 2nd, 4th, and 6th month, respectively (Ponticelli et al. 1998).

1. Maksuda Begum Mony, Assistant Professor, Department of Nephrology, Medical College for Women and Hospital, Dhaka.
2. Hossain Muhammad Mustafijur Rahman, Assistant Professor, Department of Nephrology, Dhaka Medical College
3. Eusha Ahmad Fidalillah Ansary, Associate Professor, Department of Nephrology, Uttara Adhunik Medical College, Dhaka.
4. Md. Nazrul Islam, Professor, Department of Nephrology, Dhaka Medical College, Dhaka.
5. Nizam Uddin Ahmed Chowdhury, Consultant, Nephrology, Sheikh Fazilatunnessa Mujib Memorial KPJ Specialized Hospital, Gazipur.
6. Debabrata Das, Junior Consultant, Medicine, Upazila Health Complex, Gazaria, Munshiganj.
7. Sharif Qamar Uddin, Senior Medical Officer, Dhaka University Medical Centre and Hospital, Dhaka.
8. Md. Nizamuddin Chowdhury, Professor, Senior and Chief Consultant, Department of Nephrology, BRB Hospital, Dhaka.

Address of Correspondence: Maksuda Begum Mony, Assistant Professor, Department of Nephrology, Medical College for Women and Hospital, Dhaka. email: dr.mony.hf5@gmail.com

Each steroid course is initiated with pulse methylprednisolone 1 g/day for 3 days followed by oral prednisolone 0.5 mg/kg/day for the remaining 27 days. At the end of the 1st, 3rd, and 5th months in which the patient receives steroids, there is an abrupt change over to chlorambucil or cyclophosphamide in Ponticelli and modified Ponticelli regimen respectively without any steroid tapering (Jha et al 2007).

The short ACTH test using 250μg of ACTH has been validated by several studies as a good measure of HPA axis function (Dorin et al. 2003 & Kane et al. 1995). The same was used in this study.

Ramachandran et al. (2015) mentioned in their study, patients whose HPA axis is suppressed may require a prolonged period for recovery, which may extend even upto 1-year. HPA axis needs to be tested in the patients of idiopathic membranous nephropathy on Ponticelli regimen. Low basal levels of cortisol do not necessarily predict HPA axis suppression and a stimulation test need to be performed to detect the case.

Adrenal insufficiency often presents with only minimal and non-specific clinical prodromal symptoms but may suddenly become life-threatening if left untreated upon acute stress (e.g. infection, trauma or critical illness) (Cooper and Stewart 2003). Predicting adrenal insufficiency is challenging in clinical practice, the simpler low-dose corticotropin (ACTH) test is a useful and sensitive substitute as it reveals partial adrenal insufficiency by providing physiological adrenocortical stimulation (Abdu et al. 1999 and Thaler & Blevins 1998).

There have been few works in developed countries regarding the HPA axis suppresion. But few study has been done in our country. Thus, this study was carried out to evaluate the HPA axis status in membranous nephropathy patient receiving Ponticelli regimen.

1.2 Rationale of the Study:

In Ponticelli regimen, the steroids are stopped abruptly without any tapering at the end of 1st, 3rd, and 5th month which may result in inability of the adrenal gland to return to their normal physiological secretion., This study was conducted to evaluate hypothalamic pituitary adrenal (HPA) axis suppression in patients of IMGN receiving Ponticelli regimen. The result of this study may help to upgrade or modify the steroid protocol used in Ponticelli regimen in such a way that the HPA axis suppression could be avoided. Though this study alone may not be sufficient for such modification but it may contribute to the other study result on the same or similar topic.

Methodology:

This Cross-sectional study was conducted in the Department of Nephrology, Dhaka Medical College and Hospital, Dhaka, Bangladesh from March 2016 to February 2017. Total 31 patients with membranous nephropathy, diagnosed by renal biopsy and received ponticelli regimen were included. Those who had received corticosteroids prior to starting Ponticelli regimen and any clinical history suggestive of prior adrenal disease and HPA axis suppression were excluded from this study. All the subjects were purposively selected from the above-mentioned department. HPA axis was evaluated by doing basal serum cortisol level (3ml venous blood was collected at 8:00AM and measured by ELISA method) on 5th day of 6th month to see whether there is any suppression of the axis. Short Synacthen test was done for cortisol deficient patients within next 5 days (was done when serum cortisol is 80-500 nmol/L or 3-18mcg/dl. The test was done by using low dose ACTH stimulation test. The patients were given single bolus dose of synacthen 250μg I/V at 9:00AM after collecting the basal sample(0min). Further sample was collected at 30min and 60 min after ACTH dose for cortisol measurement).

Results:

Among the total study population of 31 patients, 23(74.2%) patients had serum cortisol level between 80-500 nmol/L (Table III) and they underwent short synacthen test. Rest of 8(25.8%) cases had serum cortisol level <80nmol/L.So they didn't require short synacthen test. After short synacthen test among 23 patients 3(13.0%) patients had cortisol level between 80-500 nmol/L and rest 20(87.0%) patients had raised cortisol level more than 500 nmol/L (Table IV). Therefore, among the 31 patients total of 11(35.5%) patients had adrenal insufficiency. Among twenty patients who had raised cortisol level at 60min during short synacthen test, the mean cortisol level of them during baseline was 286.8±113.6 nmol/L and at 60min during short synacthen test was 580.3±29.6 nmol/L, which was significantly ($P<0.05$) increased at 60min during short synacthen test. But 3 patients whose cortisol level had remained unchanged at 60min during short synacthen test, their mean cortisol level was almost similar between baseline and at 60min (Table V).

Table I

Distribution of the study patients by mean cortisol level at baseline (n=31)

Cortisol level (nmol/L)	n (%)	Mean±SD	Range (min, max)
<80	8(25.8%)	26.52±17.4	12.8, 50.1
80-500	23(74.2%)	299.8±145.1	97.2, 550

Table II

Distribution of the study patients by mean serum cortisol level at 60 min after giving inj Synacthen (n=23)

Serum Cortisol level (nmol/L)	n (%)	Mean±SD	Range (min, max)
80-500	3(13.0%)	129.4±17.3	82, 180
>500	20(87.0%)	580.3±29.6	552.1,650.0

Table III

Distribution of the study patients by mean serum cortisol level at baseline and at 60min during short synacthen test (n=23)

Serum Cortisol level (nmol/L)	n (%)	Baseline At 60 min Mean±SD	At 60 min Mean±SD	p value
80-500	3(13.0%)	127.5±28.5	129.4±17.3	0.526 ns
Range (min, max)		97.2, 153.8	82,180	
>500	20(87.0%)	286.8±113.6	580.3±29.6	0.001 s
Range (min, max)		175.6, 555.0	552.1, 650.0	

s = significant

p value calculated by paired t-test

Discussion:

Alternating cycles of steroids and cytotoxic agents are recommended as the first-line drugs for the management of idiopathic membranous glomerulonephritis. At present, this is the only therapy to have long-term preservation of renal function in patients with idiopathic membranous glomerulonephritis (Jha et al. 2007).

In the current study, baseline serum cortisol level (<80 nmol/L) was found in 8 (25.8%) cases, among them the mean level was 26.52±17.4 nmol/L. Serum cortisol level betweenn 80-500 nmol/L was found in 23 (74.2%) cases, among them the mean level was 299.8±145.1 nmol/L. Ramachandran et al. (2015) observed 46.2% had low basal serum cortisol levels (<550 nmol/L). However, only 23.0% had both basal and peak serum cortisol levels <550 nmol/L suggestive of HPA axis suppression. None of the patients had symptomatic adrenal insufficiency. No untoward incident was observed in patients undergoing the test.

In this study a total of 23 cases underwent short synacthen test. Among them 3(13.0%) cases had serum cortisol level between 80-500 nmol/L, where there mean level was 129.4±17.3 nmol/L and rest 20(87.0%) cases improved serum cortisol level >500 nmol/L where there mean level was 580.3±29.6 nmol/L.

In this study it was observed that 3(13.0%) cases had mean serum cortisol level 127.5±28.5 nmol/L at baseline (before giving short synacthen). Mean cortisol level was increased to 129.4±17.3 nmol/L at 60 minutes after giving short synacthen injection. The increment of the value is not significant and both the values are in between 80 - 500 nmol/L. On the other hand 20(87.0%) cases had mean serum cortisol level 286.8±113.6 nmol//L at baseline (before giving short synacthen. Mean cortisol level was increased to 580.3±29.6 nmol/L at 60 minutes after giving short synacthen injection. The increment of the value is significant and it is more than 500 nmol/L.

In this study it was observed that a total of 8(25.8%) patients had serum cortisol level <80 nmol/L and 3 patients

had cortisol level between 50-500, rest 20(87.0%) patients had serum cortisol level >500 nmol/L.

Ramachandran et al. (2015) observed nearly half of their patients had basal serum cortisol levels <550 nmol/L, of which only 23.0% had <550 nmol/L after ACTH administration suggesting an intact axis in the majority. Thus, low basal levels of serum cortisol do not necessarily predict HPA axis suppression and a stimulation test need to be performed to detect these cases. None of their patients had symptomatic HPA axis suppression. Although all of their patients received almost the same cumulative dose and duration of therapy, only 23.0% patients showed HPA axis suppression. Patients whose HPA axis is suppressed may require a prolonged period for recovery, which may extend even up to 1-year. Hence, they may need to take glucocorticoid supplements at times of illness or injury until the axis recovers. HPA axis needs to be tested in the patients of idiopathic membranous nephropathy on Ponticelli/modified Ponticelli regimen (Ramachandran et al. 2015). A well-documented adverse effect of steroid treatment is suppression of the hypothalamic pituitary adrenal (HPA) axis (Krasner 1999). Any patient who has received 20-30 mg/day of prednisone or more for more than 5 days is at risk for the above complication (Axelrod et al 1993). These patients are at risk of adrenal crisis when subjected to stress. A slow taper of corticosteroid therapy may facilitate recovery of HPA axis (Ramachandran et al. 2015).

Conclusion

This study showed a 35.5% prevalence of asymptomatic HPA axis suppression after completion of the Ponticelli regimen.

References

1. Abdu, T.A.M., Elhadd, T.A., Neary, R. and Clayton, R.N., 1999. Comparison of the low dose short synacthen test (1 jag), the conventional dose short synacthen test (250 ug), and the insulin tolerance test for assessment of the hypothalamo-pituitary-adrenal axis in patients with pituitary disease. *The Journal of Clinical Endocrinology & Metabolism, 84(3),* pp.838-843.
2. Arlt, W. and Society for Endocrinology Clinical Committee, 2016. Society For Endocrinology Endocrine Emergency Guidance: Emergency management of acute adrenal insufficiency (adrenal crisis) in adult patients. *Endocrine Connections,* 5(5), pp.Gl-G3.
3. Axelrod, L., 1993. Glucocorticoids. In: Kelly W.N., Harris, E.D., Jr, Ruddy, S., Sledge, C.B., editors. Text Book of Rheumatology. *Textbook of rheumatology,* pp.779-796.
4. Bansal, D., Gupta, P., Ghosh, A., Dawle, P. and Gupta, G.B., 2007. Study of Thyroid Profile in Patients Of Chronic Kidney Disease From Tribal Areas Of Chhattisgarh Presenting To A Tertiary Care Hospital. *Indian Journal of Nephrology, 17(3). pp. 110-111.*
5. Beck, Jr., L.H., Bonegio, R.G., Lambeau, G., Beck, D.M., Powell, D.W., Cummins, T.D., Klein, J.B. and Salant, D.J., 2009. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *New England Journal of Medicine, 361(1),* pp.11-21.
6. Cattran, D.C. and Brenchley, P.E., 2017. Membranous nephropathy: integrating basic science into improved clinical management. *Kidney International,* 91(3), pp.566-574.
7. Cooper, M.S. and Stewart, P.M., 2003. Corticosteroid insufficiency in acutely ill patients. *New England Journal of Medicine, 348(8),* pp.727-734.
8. Dorin, R.I., Quails, C.R., Crapo, L.M., 2003. Diagnosis of adrenal insufficiency. *An Intern Med,* vol. 139,pp. 194-204.
9. Fervenza, F.C., Sethi, S. and Specks, U., 2008. Idiopathic membranous nephropathy: diagnosis and treatment. *Clinical Journal of the American Society of Nephrology,* 3(3), pp.905-919.
10. Fish, H.R., Chernow, B. and O'Brian, J.T., 1986. Endocrine and neurophysiologic responses of the pituitary to insulin-induced hypoglycemia: a review. *Metabolism,* 35(8), pp.763-780.
11. Henzen, C, Suter, A., Lerch, E., Urbinelli, R., Schorno, X.H. and Briner, V.A., 2000. Suppression and recovery of adrenal response after short-term, high-dose glucocorticoid treatment. *The Lancet,* 355(9203), pp.542-545.
12. Hypothalamic-pituitary-adrenal axis Wikipedia Available from This Site https: //en. m. wikipedia. org/wiki/ Hypothalamic %E2 %80 %93 pituitary% E2%80%93adrenal_axis. [Accessed on: 07-09-2016].
13. Jha, V., Ganguli, A., Sana, T.K., Kohli, H.S., Sud, K., Gupta, K.L., Joshi, K. and Sakhuja, V., 2007. A randomized, controlled trial of steroids and cyclophosphamide in adults with nephrotic syndrome caused by idiopathic membranous nephropathy. *Journal of the American Society of Nephrology,18(d),* pp. 1899-1904.
14. Kane, K.F., Emery, P., Sheppard, M.C. and Stewart, P.M., 1995. Assessing the hypothalamo-pituitary-adrenal axis in patients on long-term glucocorticoid therapy: the short synacthen versus the insulin tolerance test. *Quarterly Journal of Medicine,* 88(4), pp.263-267.
15. Krasner, A.S., 1999. Glucocorticoid-induced adrenal insufficiency. *Jama, 282(1),* pp.671-676.
16. Kuperman, H., Damiani, D., Chrousos, G.P., Dichtchekenian, V., Manna, T.D., Filho, V.O. and Setian, N., 2001. Evaluation of the hypothalamic-pituitary-adrenal axis in children with leukemia before and after 6 weeks of high-dose glucocorticoid

therapy. *The Journal of Clinical Endocrinology & Metabolism, 86(1),* pp.2993-2996.

17. MacHale, S.M., Cavanagh, J.T.O., Bennie, J., Carroll, S., Goodwin, G.M. and Lawrie, S.M., 1998. Diurnal variation of adrenocortical activity in chronic fatigue syndrome. *Neuropsychobiology, 38(4),* pp. 213-217.

18. Malenka, R.C., Nestler, E.J. and Hyman, S.E., 2009. Chapter 10: Neural and Neuroendocrine Control of the Internal Milieu. *Sydor A, Brown RY. Molecular Neuropharmacology: A Foundation for Clinical Neuroscience,* p.266.

19. Mansur, A., 2007. Membranous glomerulonephritis. eMedicine. Link: http://www. emedicine. com/med/topic885. htm Consulted October 23th.

20. Mansur, A., 2014. Membranous Glomerulonephritis. Copyright © 1994-2016 by WebMD LLC. Sited by http:// emedicine.medscape.com/article/239799-overview. Assessed on 19th April 2017.

21. Margulies, P.L., Imperato-McGinley, J., Arthur, A. and Peterson, R.E., 1983. Remission of Cushing's syndrome during pregnancy. *International Journal of Gynecology & Obstetrics,* 21(1), pp.77-83.

22. Markowitz, G.S., 2001. Membranous glomerulopathy: emphasis on secondary forms and disease variants. *Advances in anatomic pathology,*8(3), pp.119-125.

23. Niewoehner, D.E., 2002. The role of systemic corticosteroids in acute exacerbation of chronic obstructive pulmonary disease. *American Journal of Respiratory Medicine, 1(4),* pp.243-248.

24. Niewoehner, D.E., Erbland, M.L., Deupree, R.H., Collins, D., Gross, N.J., Light, R.W., Anderson, P. and Morgan, N.A., 1999. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. *New England Journal of Medicine, 340(25),* pp.1941-1947.

25. Ramachandran R, Jairam A, Bhansali A, Jha V, Gupta KL, Sakhuja V, Kohli HS. Study of hypothalamic pituitary adrenal axis in patients of membranous nephropathy receiving modified Ponticelli regimen. Indian Journal of Nephrology. 2015 Jan;25(1):12.

26. Rasmuson, S., Olsson, T. and Hagg, E., 1996. A low dose ACTH test to assess the function of the hypothalamic-pituitary-adrenal axis. *Clinical endocrinology, 44(2),* pp.151-156.

27. Renal Pathology" 2008. Retrieved 2008-11-25. available from this site http://librarv.med.utah.edu/WebPath/ RENAHTML/RENAL088.html

28. Ronco, P. and Debiec, H., 2012. Pathogenesis of membranous nephropathy: recent advances and future challenges. *Nature Reviews Nephrology,* 8(4), pp.203-213.

29. Sampathkumar, K., Sooraj, YS, Mahaldar, A., Ramakrishnan, M., Ajeshkumar, R.P., 2007. Comparative Efficiency Of Low Dose Nicotinic Acid And Lanthanum In Lowering The Phosphorus Levels In Hemodialysis Patients. *Indian Journal of Nephrology, 17(3).*

30. Selye and Hans 1974. Stress without distress. *Philadelphia: Lippincott Williams and willkins,*\st Edition.

31. Soumita, B., Agarwal, S.K., Gupta, S. and Tiwari, S.C., 2007. Targeted Screening Of First Degree Relatives Of Patients With Non-Diabetic Chronic Kidney Disease. *Indian Journal of Nephrology, 17(3).*

32. Thaler, L.M. and Blevins Jr, L.S., 1998. The low dose (1-u.g) adrenocorticotropin stimulation test in the evaluation of patients with suspected central adrenal insufficiency. *The Journal of Clinical Endocrinology & Metabolism,* 53(8), pp.2726-2729.

33. Tritos, N.A., and klibanski, A., 2014. Hypopituitarism, Matfin, G., Endocrine and metabolic medical emergencies, Endocrine press, Washington, DC, Chapter 7, p.74-84.

34. Ziakas, P.D., Giannouli, S., Psimenou, E., Nakopoulou, L. and Voulgarelis, M., 2004. Membranous glomerulonephritis in chronic lymphocytic leukemia. *American journal of hematology,* 76(3), pp.271-274.

Original Articles

Outcome of Arterio–Venous Fistula in Shaheed Monsur Ali Medical College and Hospital Dialysis Centre

Chowdhury JK [1], Amin TMRBA [2], Chowdhury NUA[3], Ansary EAF[4], Samdani TS [5], Mony MB[6]

Abstract:

Background: The quality of vascular access for maintenance hemodialysis should be suitable for repeated puncture and allow high blood flow rate for adequate hemodialysis. A well-trained surgeon is necessary to construct a long-term functioning arterio-venous fistula (AVF). The aim of this study was to see the outcome of AVF and to analyze the factors that might influence the function of AVF.

Materials and methods: This retrospective observational study was conducted in hemodialysis unit of Shaheed Monsur Ali Medical College and Hospital (SMAMCH). We collected data from hospital records sheet from 2018 to 2022. Total 78 patients who were receiving hemodialysis for at least 3 months in the dialysis center of SMAMCH were selected. The outcome of fistula was recorded. All relevant clinical and laboratory parameters that could affect the function and survival of AVF were evaluated.

Results: Out of total 78 patients, most common cause of CKD was hypertension(55%). Distal radio-cephalic fistula 49 (62.82%) constructed in non-dominant hand of left upper limb in the most patients 74(94.87%). Out of 78 patients, 56(71.79%) patients had patent fistula at 3 months and 15(19.23%) patients had patent fistula at 6 months. Most common complications of AVF were primary failure and extravasation. The next commonest complications were aneurysm and stenosis. Three patients had infection and 3 had burst fistula. Two patients developed oedema of the hand.

Conclusion: The most common cause of CKD was hypertension in this study. The most common type of arterio-venous fistula was distal radio-cephalic type. The common complication was primary fistula failure followed by extravasation, aneurysm formation and stenosis.

Key words: Arterio-venous fistula, Haemodialysis.

(Bang. Renal J. 2023; 5(1): 8-12)

INTRODUCTION:

The prevalence of fistula among hemodialysis patients reflects both national, regional, and local practice differences as well as a set of evidence-based and opinion-based guidelines along with patient-specific demographic and clinical factors. The preferred form of vascular access for hemodialysis (HD) is a native arterio-venous fistula (AVF).[1] Properly functioning hemodialysis access is a critical need for these patients. Cimino-Brescia in 1966 described the distal radio-cephalic AVF which has since been considered as the gold standard. Among all hemodialysis access, arteriovenous fistula is considered as the most preferred form of vascular access due to low risk of infection or complications, high survival rate and more social acceptance than other hemodialysis access.[2,3] Complications of vascular access are the leading cause of

1. Jubaida Khanam Chowdhury, Associate Professor, Department of Nephrology, Shaheed Monsur Ali Medical College, Uttara, Dhaka, Bangladesh.
2. Tanveer Md. Rifat Bin Amin, Assistant Registrar, Shaheed Monsur Ali Medical College, Uttara, Dhaka, Bangladesh.
3. Nizam Uddin Ahmed Chowdhury, Consultant-Nephrology, Sheikh Fazilatunnessa Mujib Memorial KPJ Specialized Hospital.
4. Eusha Ahmed Fidalillah Ansary, Associate Professor, Department of Nephrology, Uttara Adhunik Medical College, Dhaka.
5. Tasrina Shamnaz Samdani, Associate Professor, Department of Internal Medicine, Enam Medical College and Hospital, Dhaka, Bangladesh.
6. Maksuda Begum Mony, Assistant Professsor of Nephrology, Medical College for Women and Hospital, Uttara, Dhaka.

Address of Correspondence: Jubaida Khanam Chowdhury, Associate Professor, Department of Nephrology, Shaheed Monsur Ali Medical College, Uttara, Dhaka, Bangladesh.

hospitalization of HD patients, which incurs significant engagement of resources. Moreover, prospective multicenter studies have established that, besides anatomical and biochemical parameters, the experience of the surgeon concerning the possibility and functionality of AVF can be affected by certain practices of different medical centers. Patency of arterio-venous fistula may be influenced by patient factors, technique and core of the fistula following operation. Ideally, in assessing the influence of patient related variables on fistula patency, other factors should be kept constant.

Materials and Methods:

This is a retrospective observational study. We collected data from hospital records from 2018 to 2022. Total 78 patients were selected for the study. We analyzed data of all patients who developed various complications and also who needed re-construction of their AVF due to thrombosis. Primary patency (intervention-free access survival) was defined as the interval from the time of access placement to any intervention designed to maintain or reestablish patency. All Chronic Kidney Disease G5 (CKD G5) patients of both genders attending to hemodialysis units of the Department of Nephrology of Shaheed Monsur Ali Medical College Hospital (SMAMCH) or got admitted to SMAMCH and received hemodialysis for at least 3 months were included in the study. Ethical approval was taken from ethical review board. The AVF was created in different centers of Dhaka city. Selection of patient was done as per inclusion and exclusion criteria. Informed written consent was taken. Detailed history was taken and physical examination was done. Data were recorded systematically in preformed data collection form.

Fistula was termed successful if there was distension of vein or presence of thrill at the end of the procedure. Immediate failure was defined as when there was absent of flow or thrill within 10 days of construction. Delayed failure was labelled when it cannot be used for dialysis or there was no thrill at 6 months follow up.

Results:

Total 78 patients underwent AVF formation in the study period. In this study, most common cause of CKD was hypertension (55%). Isolated diabetes was 48% and glomerulonephritis was 16%. Polycystic kidney disease and obstructive uropathy was 3.84% each.

Table –I

Causes of ESRD.

Causes of CRF	Frequency	Percentage
Diabetes Mellitus	38	48 %
Hypertension	43	55 %
Chronic glomerulonephritis	13	16%
Polycystic kidney disease	3	3.84%
Obstructive uropathy	3	3.84%

Table-II

Type of arterio-venous fistula created

Side of Fistula	Frequency (%)
Left upper limb	74(94.87%)
Right upper limb	12(15.38%)
Site / vessels used	
Distal radio-cephalic	49(62.82%)
Proximal radio-cephalic	15(19.23%)
Brachio-cephalic	23(29.48%)
Brachio-basilic	2(2.56%)
Anastomotic technique	
End to side	60 (76.92%)
Side to side	28(35.89%)
Fistula failure at 11 months	16(20.21%)
Patent fistula at 6 months	15(19.23%)
Patent fistula at 3 months	56(71.79%)

Table-II shows that distal radio-cephalic fistula was constructed in 62.82% of cases, and 94.87% of them was in non-dominant hand. End to side technique was most commonly used technique. Out of 78 patients, 56 (71.79%) patients had patent fistula at 3 months and 15(19.23%) patients had patent fistula at 6 months. Among all patients, 16(20.21%) patients had constructed their A-V fistula for the second time at 11th month.

Table-III

Patient characteristics

Patient characteristics	Number (%)
Age >65 years	36(46.1)
Coronary artery disease	28(35)
Cerebrovascular disease	9(11.5)
Congestive heart failure	3(3.84)
Antiplatelet therapy	59(75)

Table III shows that most of the patients had received antiplatelet therapy for successful fistula, some have other co-morbid condition–like coronary artery disease in 28(35%), cerebrovascular disease in 9(11.5%), congestive cardiac failure in 3 (3.84%) patients. Most of patients were of > 65 years of age.

Table-IV

Clinical features and incidence of most common Complications of arterio- venous fistula.

Complications of arterio- venous fistula associated with chronic use	Incidence
Thrombosis	1
Stenosis	4
Aneurysm	5
Infection	3
Burst fistula	3
Primary failure	6
Extravasation	6
Oedema of the hand	2

Table IV shows most common complications of A-V fistula was primary failure and extravasation. Next commonest were aneurysm and stenosis. Three patients had infection and 3 had burst fistula. Three patients had repeated history of construction of fistulas in the vascular unit of other hospitals. Two patients developed oedema of the hand.

Discussion:

Native AVF is universally recommended as a permanent access for patients receiving HD, but maintenance of AVF patency remains a challenge. Patency of arterio-venous fistula may be influenced by patient factors, technique and core of the fistula following operation. In our study, the leading cause of CKD was the presence of HTN (55%). Many centers have reported increased use of prosthetic material for grafts in diabetic patients in their dialysis populations, when compared with nondiabetic patients. Others found no significant difference between diabetic and nondiabetic patients in their population. Diabetic nephropathy was not an important parameter concerning the length of fistula duration. Agarwal et al in their study found diabetes and HTN were the leading causes of CKD, seen in 41% and 22.8% of the cases respectively.[4] In our study, chronic glomerolunephritis was found in 16% of the cases whereas Barsoum reported an incidence of 10%–20% in Africa.[5] In this study, we found subjects dominantly came with hypertension as underlying disease condition. Although the previous study has stated, there was a benefit value of hypertension in the maturation time and patency of AVFs, however, the mechanism remains unclear. It needs further research with a large population study. In this study 78 patients underwent arterio-venous fistula formation at wrist and elbow and were followed up for two years. Primary failure was commonly seen in diabetics and inadequately dialyzed patients. While primary patency rate was 71.79% at three months, 19.23% at six months. Fistula failure at 11 month was 20.21%.

Monroy-Cuadros M and colleague [7] found diabetes to be a significant risk factor for failure of fistulas within the 1st year. Diabetic patients also have a poor out comes with prosthetic fistula. The poorer results in diabetics might be explained by increased arterial disease or even impaired venous endothelial function.[8]

It could also be due to infectious complication because of immuno-suppression; in addition sclerosed arteries also make anastomotic techniques difficult. Preoperative evaluation is very important to avoid any operative or postoperative catastrophe.[9] The radiological mapping should be reserved for difficult cases.[10,11] Radiocephalic fistula is performed more successfully due to the adequate length of arteries and veins.[12] We think meticulous clinical evaluation is sufficient.

The left upper limb being the non-dominant limb in most of the patients was used for the creation of AVF in the majority (94.87%) of our patients. The preference for the nondominant limb is as a result of the need to carry out minimal work or activities with the limb to preserve the delicate AVF, especially in the first two weeks following surgery. Right upper limb was used in 15.38% cases. Similar preference for the non-dominant upper limb is also practiced in other tertiary hospitals like ours that offer AVF to patients [22,23]

End to side arteriovenous fistula proved to have better results than side to side arterio-venous fistula. It could be due to tension free anastomosis with longer patency rate. International literature series recommend the use of magnifying loupe over naked eye technique, which was used in all our cases with equally good outcomes.[13,14] The distal radio-cephalic and brachio-cephalic fistulas accounted for >90% of the fistulas created . This finding was also corroborated by other researchers who routinely carry out native AVF.[4,5] Shahbaaz and Prokash in India, showed the superiority of distal radio-cephalic AVF to

other forms owing to the very superficial location of the vein and preservation of the cubital fossa for future procedures.[15] The more proximal fistulas were reserved for patients with poor peripheral veins and repeat procedures. Primary failure (non-functional AVF after six weeks of maturation) rate seen in 6 patients which was lower than in most studies, though the follow-up of only one year restricted a longer-term assessment. [9,10,.16,17,]

Postdialysis hypotension with reduced flow through the AVF may be related to poor outcome, specifically in the first year after formation.[18] A subsequent prospective screening of 463 patients [19] also reported that low mean diastolic pressure correlated with poorer AVF. Systolic pressure has not been observed to relate to access survival. Mean arterial blood pressure in our patients was within normal findings and was not an influential factor for fistula duration.

Some medications possess potentially beneficial effects on AVF patency, like antiplatelet drug. This provides protective endothelial advantages, primarily in the arterial system. However, no medication has been consistently reported to have favorable effects on AVF patency.[20] There are diverse statements about the benefits of such therapy. Importantly, the current studies do not support the use of antiplatelet agents for maintenance of the HD vascular access. Individualized risk assessment should be considered before initiating antiplatelet agents in this population.[21] The use of antiplatelet medication in maintaining AVF patency was supported here as we have demonstrated a beneficial effect on the duration of AVF function. Using antiplatelet therapy (dipiridamol or acetylsalicylate as monotherapy), which was initially applied as a measure for prevention of cardiovascular events, independently predicted long term fistula duration, in our study most of our patients (75%) receiving antiplatelet therapy.

However, nowadays, in addition to the elderly and diabetics, patients suffering from congestive heart failure are considered to be risk groups for the creation of vascular access. Absolute contraindications to this are amputation of extremities and advanced peripheral artery disease with consecutive necrosis. However, the final decision on the quality of the vasculature is made after a noninvasive color Doppler ultrasound examination. In our study most of the patients aged>65(46.1%), Coronary artery disease were in 28(35%), cerebrovascular disease in 9 (11.5%), Congestive heart failure in 3(3.89%) patients and there was no patients having peripheral vascular disease.

Conclusion

Hypertension was the commonest cause of CKD. Distal radio-cephalic fistula was the commonest type of fistula in this series. Primary failure, Extravasation and Aneurysm formation were the most common complications among the study population. Stenosis, infection and burst fistula were also common. Other complications which have been reported in other studies such as steal phenomenon and pseudoaneurysm were not observed in this series. We found that artery size was the only predictor of both primary and secondary patency. Thus, if an adequately sized artery is found with preoperative Doppler mapping, then other patient characteristics or comorbidities should not preclude AVF placement, at least on the basis of patency outcomes.

References:

1. Brescia MJ, Cimino JE, Appel K, Hurwich BJ. Chronic hemodialysis using venipuncture and a surgically created arteriovenous fistula. N Engl J Med 1966; 275:1089-92.
2. Pokhrel A, Gyawali P, Pokhrel BR, Khanal MP, Manandhar DN, Bwititi P, et al. Prevalence of Cardiovascular Risk Factors among Chronic Kidney Disease Patients Undergoing Hemodialysis in a Tertiary Care Center, Kathmandu, Nepal. Nepal Med Coll J. 2019;21(4):313–8.
3. Santoro D, Benedetto F, Mondello P, Spinelli F, Ricciardi C, Cernaro V, et al. Vascular access for hemodialysis: current perspectives. Int J Nephrol Renovasc Dis. 2014;281.
4. Agarwal SK, Dash SC, Irshad M, et al. Prevalence of chronic renal failure in adults in Delhi, India. Nephrol Dial Transplant 2005;20: 1638-42.
5. Barsoum RS. Burden of chronic kidney disease: North Africa. Kidney Int Suppl (2011) 2013; 3:164-6. C. 12. Rezapour M, Khavaninzadeh M. Association between non-matured arterio-venus fistula and blood pressure in hemodialysis patients. Med J Islam Repub Iran. 2014;28(1):1–9.
6. Lopez-Vargas PA, Craig JC, Gallagher MP, Walker RG, Snelling PL, Pedagogos E, et al. Barriers to timely arteriovenous fistula creation: a study of providers and patients. Am J Kidney Dis. 2011;57(6):873-882.
7. Monroy-Cuadros M, Yilmaz S, Salazar-Bañuelos A, Doig C. Independent prediction factors for primary patency loss in arteriovenous grafts within six months. J Vasc Access. 2012;13(1):29-35.
8. Lumsden AB, MacDonald MJ, Kikeri DK, Harker LA, Allen RC. Hemodialysis access graft stenosis: percutaneous transluminal angioplasty. J Surg Res. 1997;68(2):181-185.
9. Weitzel WF. Preoperative hemodialysis fistula evaluation: angiography, ultrasonography and other studies, are they useful? Contrib Nephrol. 2008; 161:23-29.
10. Saad TF. Interventional Nephrology for Hemodialysis Vascular Access: Insight about an Evolving Branch. Saudi J

Kidney Dis Transpl. 2004; 15:239-250.

11. Turmel-Rodrigues L, Pengloan J, Bourquelot P. Interventional radiology in hemodialysis fistulae and grafts: A multi¬disciplinary approach. Cardiovasc Intervent Radiol. 2002; 25:3-16.

12. Ahmed GM, Mansour MO, Elfatih M, Khalid KE, Mohammed Ahmed ME. Outcomes of arteriovenous fistula for hemodialysis in Sudanese= patients: Single-center experience. Saudi J Kidney Dis Transpl. 2012;23(1):152-157.

13. Yiltok SJ, Orkar KS, Agaba EI, et al. Arteriovenous fistula for patients on long term haemodialysis in Jos, Nigeria. Niger Postgrad Med J 2005; 12:6-9.

14. Bakari A, Nwankwo E, Yahaya S, Mubi B, Tahir B. Initial five years of arterio-venous fistula creation for haemodialysis vascular access in Maiduguri, Nigeria. Internet J Cardiovasc Res 2006;4(2):1-6.

15. Shahbaaz K, Prokash S. A long term study for upper limb arterio-venous fistula creation for hemodialysis at a tertiary level hospital in Eastern India. Clin Pract 2016; 13:5-9.

16. Vahedian J, Jalayifar AM, Keramati MR, Nabavizadeh F, Vahedian M. Primary Success of bifurcated vein patch arteriovenous fistula and Brescia-Cimino methods. Iran J Kidney Dis. 2012;6(2):124-128.

17. Tannuri U, Aoun Tannuri AC. Experience with arteriovenous fistulas for chronic hemodialysis in children: technical details and refinements. Clinics. 2005;60(1):37-40.

18. Goodkin DA, Pisoni RL, Locatelli F, Port FK, Saran R. Hemodialysis vascular access training and practices are key to improved access outcomes. Am J Kidney Dis. 2010;56(6):1032-42.

19. Bakari A, Nwankwo E, Yahaya S, Mubi B, Tahir B. Initial five years of arterio-venous fistula creation for haemodialysis vascular access in Maiduguri, Nigeria. Internet J Cardiovasc Res 2006;4(2):1-6.

20. Sahasrabudhe P, Dighe T, Panse N, Deshpande S, Jadhav A, Londhe S. Prospective long-term study of patency and outcomes of 505 arteriovenous fistulas in patients with chronic renal failure: Authors experience and review of literature. Indian J Plast Surg 2014; 47:362-9.

21. Hiremath S, Holden RM, Fergusson D, Zimmerman DL. Antiplatelet medications in hemodialysis patients: A systematic review of bleeding rates. Clin J Am Soc Nephrol. 2009; 4:1347–1355.

22. Cawich SO, Brown H, Martin A, Newnham MS, Venugopal R, Williams E. Arteriovenous fistulas as vascular access for hemodialysis: The preliminary experience at the University Hospital of the West Indies, Jamaica. Int J Angiol 2009; 18:29-32.

23. Hiremath S, Holden RM, Fergusson D, Zimmerman DL. Antiplatelet medications in hemodialysis patients: A systematic review of bleeding rates. Clin J Am Soc Nephrol. 2009; 4:1347–1355.

High Serum Hyaluronic Acid is Associated with Chronic Kidney Disease than Acute Kidney Injury

Rahman MS[1], Anwar ASMT[2], Faisal ARM[3], Juthy SS[4], Khan MAR[5], Islam MN[6]

Abstract

Background: The incidence of acute kidney injury (AKI) and chronic kidney disease (CKD) is increasing worldwide and are associated with increased morbidity and mortality. The assessment of kidney function is commonly made using serum creatinine concentration (SCr), blood urea nitrogen (BUN) level.However accumulating evidence has shown that these parameters are suboptimal to detect kidney disease in early stages.During several kidney insults,such as ischemia-reperfusion injury, tubulointerstitial inflammation, renal transplant rejection, diabetic kidney disease and renal stone disease, Hyaluronic Acid(HA) is up-regulated and can be a useful tool for distinguishing between acute kidney injury and chronic kidney disease.

Aim: Therefore the aim of this study was to assess the role of serum Hyaluronic acid as a biochemical marker to differentiate between chronic kidney disease and acute kidney injury.

Materials and methods: This Cross-sectional study was conducted in Dhaka Medical College and Hospital, Dhaka from July 2019 to June 2020.Total 102 subjects were included into the study. Newly diagnosed uremic patients with diagnosis of AKI or CKD and healthy volunteers (control) were included. Subjects with age: ≥18 years of both sex, patient diagnosed as AKI according to RIFLE criteria and patient diagnosed as CKD according to NKF KDOQI and age and sex matched healthy volunteers with normal renal function and without any disease known to increase serum HA level were included in this study after purposive sampling.

Result: Most of the (49.03%) study participants were 40-59 years of age. Mean age of healthy control, AKI and CKD patients were 41.53±12.71, 42.50±14.12 and 52.94±12.30 years respectively. In this study, all CKD patients had increased level of serum hyaluronic acid (>100 ng/mL) which was significantly higher compared to AKI (5.88%) and healthy controls (0%).CKD patients had significantly higher serum hyaluronic acid (142.39 ± 28.61 ng/mL) compared to AKI (81.29±13.91 ng/mL) and healthy control (44.14 ± 11.28 ng/mL).

Conclusion: Serum Hyaluronic acid increases more in CKD than AKI.

(Bang. Renal J. 2023; 5(1): 13-17)

Introduction:

The incidence of acute kidney injury (AKI) and chronic kidney disease (CKD) is increasing worldwide and are associated with increased morbidity and mortality.[1] AKI could be resolved or could lead to CKD and ESKD .[1] On the other hand, CKD is an independent risk factor for the development of AKI.[1] Identification of patients early is of paramount importance in order to offer a prompt intervention and to improve the prognosis in both settings. The assessment of kidney function is commonly made using serum creatinine concentration (SCr), blood urea nitrogen (BUN) level; however accumulating evidence suggest that these biochemical markers are suboptimal to detect kidney disease in early stages.[2] Early detection of AKI and CKD could be beneficial for the better management and prognosis.

The glycosaminoglycan Hyaluronic acid/ hyaluronan (HA) is recognized as an important structural component of the extracellular matrix, but it also interacts with cells during embryonic development, wound healing, inflammation, and cancer.[3] During several kidney insults, such as ischemia-reperfusion injury, tubulointerstitial

1. Md. Saidur Rahman, Assistant Registrar, Department of Nephrology, Dhaka Medical College Hospital, Dhaka.

2. A. S. M Tanim Anwar, Assistant Professor, Department of Nephrology, Dhaka Medical College.

3. Amanur Rasul Md. Faisal, Transplant Coordinator, Department of Nephrology, Dhaka Medical College Hospital.

4. Shanjida Sultana Juthy, Specialist, United Hospital Limited, Dhaka.

5. Mohammad Ashiqur Rahman Khan, Dialysis Medical Officer, Department of Nephrology, Dhaka Medical College Hospital.

6. Md. Nazrul Islam, Professor & Head, Department of Nephrology, Dhaka Medical College, Dhaka.

Address of Correspondence: Md. Saidur Rahman, Assistant Registrar, Department of Nephrology, Dhaka Medical College Hospital, Dhaka.

inflammation, renal transplant rejection, diabetic kidney disease,and renal stone disease, HA is up-regulated.[3]

Renal HA expression is increased in some chronic disease states, such as diabetes mellitus and renal stone disease, which in turn have the potential to lead to chronic renal insufficiency.[4] High plasma hyaluronic acid levels have been described in ESRD and is reported that the duration on hemodialysis and certain markers of chronic inflammation, such as dialysis-related amyloid, is correlated with hyaluronic acid levels.[5]

However, the mechanism of increase of serum HA levels in patients with CKD is not fully known. One of the possible mechanisms that describe the HA increase in hepatic dysfunction is the disorder in HA intake of specific endothelial receptors and disorder of the liver endothelial cell function affecting pre-sinusoidal lipocyte's HA synthesis.[16] Besides, in uremic patients, in addition to high endothelial receptor dysfunction, another mechanism for the HA increase is the increase of HA synthesis-stimulating factors. Prostaglandins, cytokines (especially interleukin-1, interleukin-6, tumor necrosis factor-α, stimulate the synthesis of HA in the connective tissue), or both also contribute in the HA synthesis in patients with uremia.[17] Moreover, it is also assumed that uremic toxins also lead to generalized endothelin receptor dysfunction.[18]

HA is considered to be a marker for several fibrotic disease process such as liver and renal fibrosis.[5,6] Thus hyaluronic acid might be an important biomarker for differentiating CKD.Hyaluronic acid concentrations have been demonstrated to reflect the clinical condition of the CKD patients.[7,8,9] It is a strong independent predictor of long-term survival in CKD and may reflect abnormal connective tissue metabolism in this condition. [7,8,9] A more recent study have also suggested that serum HA level may be used as tool to differentiate AKI from CKD.[10]

The aim of this study was to assess the role of serum Hyaluronic acid as a biochemical marker to differentiate between chronic kidney disease and acute kidney injury.

Materials and Method

This cross-sectional analytical study was performed in the Department of Nephrology of DMCH, Dhaka over a period of one year.Total 102 participants were included in this study and categorized into three groups: group A – 34 newly diagnosed uremic patients classified as having AKI, group B - 34 patients with CKD, and group C- 34 healthy volunteers (control).

Results

Among CKD patients 55.88% were male, among AKI patients 50% were male and among healthy volunteers 50% were male.

Table I

Biochemical profile of study participants (n=102)

Variables	Healthy volunteers(control) (N=34) mean±SD	AKI(N=34) mean±SD	CKD(N=34) mean±SD	P value*
Hemoglobin (gm/dL)	14.60±0.84 $^{\alpha,\beta}$	10.00±1.08	9.89±1.16	<0.001
S. Creatinine (mg/dL)	0.92±0.09 $^{\gamma,\delta}$	7.91±4.04	9.40±4.61	<0.001
S. Urea (mg/dL)	31.42±6.61 $^{\gamma,\delta}$	197.47±97.97	158.79±72.76	<0.001
S. Albumin (gm/dL)	4.27±0.26 $^{\alpha,\beta}$	3.60±0.58	3.42±0.59	<0.001
S. Calcium (mg/dL)	9.90±0.43 $^{\alpha,\beta}$	8.96±0.88	8.42±1.0	<0.001
S. Phosphate (mg/dL)	3.41±0.45 $^{\gamma,\delta}$	4.66±1.12	6.23±1.70 $^{\mu}$	<0.001
S. Parathormone (pg/mL)	58.62±8.49 $^{\delta}$	100.44±41.46	200±137.88$^{\mu}$	<0.001
eGFR (1.73m^2/mL/min)	118.56±14.72 $^{\alpha,\beta}$	12.09±9.72	17.29±10.64	<0.001
24-hours Urine protein (gm)	0.20±0.12 $^{\gamma,\delta}$	0.98±0.90	1.58±0.95 $^{\mu}$	<0.001

Values are expressed as Mean±SD

* One way ANOVA test

Post-hoc analysis done by Bonferroni method:

$^{\alpha}$= significantly higher compared to AKI

$^{\beta}$= significantly higher compared to CKD

$^{\gamma}$= significantly lower compared to both healthy control and AKI

$^{\delta}$= significantly lower compared to CKD

$^{\lambda}$= significantly higher compared to CKD

$^{\mu}$= significantly higher compared to both healthy control and AKI

Table II

Distribution of serum hyaluronic acid status among groups (n=102)

Serum hyaluronic acid (ng/mL)	Healthy volunteers (control) (N=34) n (%)	AKI (N=34) n (%)	CKD (N=34) n(%)	P value
Increased(>100ng/ml)	0(0)	2(5.88)	34(100)	<0.001
Normal (≤100 ng/mL)	34(100)	32(94.12)	0(0)	

Values are expressed within parenthesis percentage over column in total.

* Chi-square Test (χ^2) was performed.

In this study, all CKD patients had increased level of serum hyaluronic acid (>100 ng/mL) which was significantly higher compared to AKI (5.88%) and healthy volunteers(0%).

Table III

Diagnostic performance of serum hyaluronic acid in detecting AKI and CKD (n=102)

Group	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
AKI	5.88	50	5.56	51.51	35.29
CKD	100	97.06	94.44	100	98.04

Serum hyaluronic acid >100 ng/mL had 100% sensitivity to correctly diagnose CKD but 97.06% specificity to differentiate CKD from non-CKD. Overall, the accuracy was 98.04%.

Figure 1: Box-plot distribution of serum hyaluronic acid (n=102)

CKD patients had significantly higher serum hyaluronic acid (142.39 ± 28.61 ng/mL) compared to AKI (81.29±13.91 ng/mL) and healthy volunteers (44.14 ± 11.28 ng/mL).

Figure 2: Correlation between serum hyaluronic acid and 24-hours urinary protein (n=102)

Pearson correlation model showed that serum hyaluronic acid had significant moderate positive relation with 24-hours urinary protein (r=+0.718, p value= <0.001).

Table IV

Independent variables for serum hyaluronic acid in multiple linear regression analysis. (n=102)

	Serum hyaluronic acid (ng/mL)		
	B	Beta	p value
Hemoglobin (gm/dL)	3.231	.174	.198
S. Creatinine (mg/dL)	-.463	-.053	.767
S. Urea (mg/dL)	-.036	-.079	.543
S. Albumin (gm/dL)	13.689	.188	.008
S. Calcium (mg/dL)	2.673	.060	.384
S. Phosphate (mg/dL)	6.017	.222	.05
S. Parathormone (pg/mL)	.088	.198	.05
eGFR (mL/min/1.73m^2)	-.510	-.596	.000
24 hours Urine protein (gm)	16.731	.350	.000

Multiple linear regression was performed to see the independent factors associated with serum hyaluronic acid and we observed that serum albumin, eGFR and 24-hours urinary protein were independently correlated with serum hyaluronic acid after adjusting hemoglobin, serum creatinine, urea, calcium, phosphate and parathyroid hormone.

Discussion

This study was conducted with an aim to determine the association of serum hyaluronic acid in differentiating between chronic kidney disease and acute kidney injury.Thirty four (34) newly diagnosed uremic patients classified as having AKI, 34 patients with CKD and 34 healthy volunteers(control) were included in this study after careful history taking, physical examination and appropriate investigations after fulfilling inclusion and exclusion criteria.

In this study, mean age of AKI and CKD patients were 42.50 ± 14.12 and 52.94±12.30 years, respectively, wherein maximum CKD patients (38.24%) were 50-59 years of age, and maximum AKI (29.41%) were 40-49 years of age. Previous studies also found high prevalence of CKD in the elderly.[11,12]

In this study, CKD patients had significantly higher serum hyaluronic acid (142.39±28.61 ng/mL) compared to AKI (81.29±13.91 ng/mL) and healthy volunteers (44.14±11.28 ng/mL). Besides, all CKD patients had increased level of serum hyaluronic acid (>100 ng/mL). In agreement with our research findings, Akin et al. also found that the mean serum HA was significantly higher in the CKD group (146.1 ± 119.3 ng/mL) than the AKI group (68.9 ± 69.1 ng/ mL; P < 0.001).[10] Turney et al. found that HA was elevated to greater than 80 micrograms/L in more than 90%, with median value 182 micrograms/L (range 39-898 micrograms/ L).[8] Several other studies also found elevated HA in CKD patients.[7,13,14,15]

In this study, serum hyaluronic acid >100 ng/mL found to be 100% sensitive and 97.06% specific to correctly diagnose and differentiate CKD from AKI. However, Akin et al. found a threshold for HA of 61 ng/mL for differential diagnosis of AKI and CKD with a sensitivity and specificity of 67% and 82%, respectively.[10]

In this study, 24-hours urinary protein were also significantly higher in CKD patients compared to both healthy control and AKI patients. Besides, Pearson correlation model showed that serum hyaluronic acid had significant moderate positive relation with 24-hours urinary protein (r=+0.718, p value= <0.001). Comparable to this study findings, Akin et al. also observed a significant correlation between serum HA levels and amount of 24-hours proteinuria (r = 0.716, P < .001)[10]. Moreover, Sano and coworkers' also showed that proteinuria increases the accumulation of HA. [10]

In this study, serum albumin was significantly lower in CKD patients compared to both healthy controls and AKI patients. Pearson correlation model showed that serum hyaluronic acid had significant weak negative relation with serum albumin (r=-0.317, p value= <0.001). Woodrow et al. also found significant weak negative correlation between hyaluronan concentrations and serum albumin concentrations (rs = -0.27, P = 0.02).[22]Akin et al. also noticed a significant negative correlation between serum HA and serum albumin (r = -0.599, P < .001) in the CKD group.[10]

Conclusion

In this study, serum hyaluronic acid is significantly higher in CKD than in AKI. So it may be used as a biochemical marker to differenciate chronic kidney disease from acute kidney injury. Besides proteinuria seems to have a correlation with raised hyaluronic acid.

References:

1. Chawla LS, Kimmel PL. Acute kidney injury and chronic kidney disease: An integrated clinical syndrome. *Kidney International*,2012; 82(5): 516–524.

2. Wasung ME, Chawla LS, Madero M. Biomarkers of renal function, which and when? *Clinica Chimica Acta*, 2015;438(1): 350–357.

3. Stridh S, Palm F,Hansell P. Renal interstitial hyaluronan: Functional aspects during normal and pathological conditions. *American Journal of Physiology - Regulatory Integrative and Comparative Physiology*, 2012;302(11).

4. Zarbock A, Meersch M, Van Aken H, Görlich D, Singbartl K. Urinary hyaluronic acid as an early predictor of acute kidney injury after cardiac surgery. *Journal of the American College of Cardiology*,2014; 64(7): 737–738

5. Orasan O, Ciulei, G, Cozma A, Sava M, DumitrascuDL. Hyaluronic acid as a biomarker of fibrosis in chronic liver diseases of different etiologies. *Clujul Medical*,2016; 89(1): 24–31.

6. Albeiroti S, Soroosh A, De La Motte. Hyaluronan's role in fibrosis: A pathogenic factor or a passive player? *BioMed Research International*, 2015; 9(4): 110-170.

7. Woodrow G, Turney JH, Davison AM, Cooper EH. Serum hyaluronan concentrations predict survival in patients with chronic renal failure on maintenance haemodialysis. *Nephrology Dialysis Transplantation*, 1996b;11(1): 98–100.

8. Turney JH, Davison AM, Forbes MA, Cooper EH. Hyaluronic Acid in End-Stage Renal Failure Treated by Haemodialysis: Clinical Correlates and Implications. *Nephrology Dialysis Transplantation*, 1991;6(8): 566–570.

9. Honkanen E, Fröseth B, Grönhagen-Riska C. Serum hyaluronic acid and procollagen III amino terminal propeptide in chronic renal failure. *American journal of nephrology*,1991; 11(3): 201–6.

10. Akin D, Ozmen S, Yilmaz ME. Hyaluronic acid as a new biomarker to differentiate acute kidney injury from chronic kidney disease. *Iranian Journal of Kidney Diseases*,2017; 11(6): 409–413

11. Masyeni S, Sri Wardani NW, Budiyasa DGA, SadgunaDM. Serum phosphate level among chronic kidney disease patients on chronic dialysis. *Biomedical and Pharmacology Journal*, 2020;13(1): 207–211.

12. Mallappallil M, Friedman EA, Delano BG, McFarlane SI, Salifu MO. Chronic kidney disease in the elderly: evaluation and management. *Clinical practice (London, England)*,2014; 11(5): 525–535.

13. Eddy AA. *Molecular insights into renal interstitial fibrosis.Journal of the American Society of Nephrology/* ,1996; 29(5):125-205.

14. Roberts AB, McCune BK, Sporn MB. TGF-beta: regulation of extracellular matrix. *Kidney international*,1992; 41(3): 557–559.

15. Border WA, Noble NA. Transforming growth factor beta in tissue fibrosis. *The New England journal of medicine*,1994; 331(19): 1286–1292.

16. Gressner AM, Haarmann R. Hyaluronic acid synthesis and secretion by rat liver fat storing cells (perisinusoidal lipocyte

17. Murota S, Abe M, Otsuka K. Stimulatory effect of prostaglandins on the production of hexosamine-containing substances by cultured fibroblasts (3) induction of hyaluronic acid synthetase by prostaglandin F2alpha. *Prostaglandins*,1977; 14(5): 983–9

18. Longaker MT, Adzick NS, Sadigh D, Hendin B, Stair SE, Duncan BW. Hyaluronic acid-stimulating activity in the pathophysiology of Wilms' tumors. *Journal of the National Cancer Institute*,1990; 82(2): 135–139.

19. Herrera MB, Bussolati B, Bruno S, Morando L, Mauriello-Romanazzi G, Sanavio F. Exogenous mesenchymal stem cells localize to the kidney by means of CD44 following acute tubular injury. *Kidney international*,2007; 72(4): 430–441.

20. Kuusniemi AM, Lapatto R, Holmberg C, Karikoski R, Rapola J, Jalanko H. Kidneys with heavy proteinuria show fibrosis, inflammation, and oxidative stress, but no tubular phenotypic change. *Kidney International*,2005; 68(1): 121–132.

21. Becker GJ, Hewitson TD. The role of tubulointerstitial injury in chronic renal failure. *Current Opinion in Nephrology and Hypertension*,2000; 9(2): 133–138.

22. Woodrow G, Turney JH, Davison AM, Cooper EH. Serum hyaluronan concentrations predict survival in patients with chronic renal failure on maintenance haemodialysis. *Nephrology, dialysis, transplantation/ : official publication of the European Dialysis and Transplant Association - European Renal Association*,1996a; 11(1): 98–100

Review Articles

Proton Pump Inhibitors and the Kidney; A Short Overview of Adverse Outcome

Ahammod T[1], Huda MN[2], Mahmud H[3], Paul R S[4], Mazumder MM[5]

Abstract:

Proton Pump Inhibitors are highest selling drug in Bangladesh and worldwide. These drugs were taken as safe and usually sold as over the counter product. But now a day's various informations about their renal and non-renal complications are being published. Number of studies have showed various kinds of renal complications including AIN, AKI, incident CKD, hypomagnesemia and CKD progression with injudicious use of PPI. So, we should be careful about prescribing PPI and should deprescribe them when necessary.

(Bang. Renal J. 2023; 5(1): 18-21)

Introduction:

Proton pump inhibitors are highest selling drug in Bangladesh as well as world market. In 2020 first five highest selling drug brand in Bangladesh was various kind of proton pump inhibitor and sixth one was an insulin brand.[1] Results of the National Health and Nutrition Examination Survey published in 2015 estimate that 7.8% of US adults had used prescription PPIs in the previous 30 days[2], whereas these drugs are mostly sold as over the counter product.[3] They are commonly prescribed for several acid-related disorders, including gastroesophageal reflux disease (GERD), peptic ulcer disease, esophagitis, gastritis, barrett esophagus, and (in addition to antibiotics) helicobacter pylori eradication. They are also often prescribed for prophylactic indications and as co-prescription with nonsteroidal anti-inflammatory drugs (NSAIDs). It was also evident that many patients attending both out-patient and in-patient departments of the hospital were receiving regular PPI treatment for poorly defined reasons or for conditions where PPIs have not been shown to be useful. Such unapproved or inappropriate indications include nonspecific abdominal symptoms without acid related features, co-prescription with aspirin, NSAIDs or corticosteroids in asymptomatic patients, but most often receiving a long-term repeat prescription for a previous problem which had since resolved. Current evidence suggests PPIs are often overused.[4]

The prevalence of PPI use in the chronic kidney disease (CKD) population is likely higher than for patients without CKD because some studies suggest that patients with CKD are prescribed more PPIs and for longer durations than patients without CKD.[5] They are frequently overprescribed, rarely deprescribed, and often initiated inappropriately during hospitalization, and their use is continued for the long term even in the absence of medical indication.[6,7]

Though PPIs were perceived to be safe now a days this perception was challenged with the emergence of evidence from multiple observational studies and some mechanistic studies suggesting increased risk for serious adverse health outcomes and death.[8-10] Evidence from these studies suggests that PPI use is associated with increased risk for cardiovascular disease, gastric cancer, dementia, pneumonia, osteoporotic fractures, Chloridoids difficile

1. Tofael Ahammod; Assistant Professor, Department of Nephrology, Shaheed Syed Nazrul Islam Medical College, Kishorganj.
2. Abu Ayub Md Nazmul Huda; Associate Professor, Department of Nephrology, Shaheed Syed Nazrul Islam Medical College; Kishorganj.
3. Hasan Mahmud; Assistant Professor, Department of Nephrology, Shaheed Syed Nazrul Islam Medical College, Kishorganj.
4. Rajat Shuvra Paul; Associate Professor, Department of Nephrology, International Medical College Gazipur.
5. Muhammed Mohiuddin Mazumder, Associate Professor, Department of Nephrology, East West Medical College, Dhaka.

Address of Correspondence: Tofael Ahammod; Assistant Professor, Department of Nephrology, Shaheed Syed Nazrul Islam Medical College; Kishorganj.

infections, and others.[9,11,12] It was also evidenced that PPI use is associated with an increased burden of all-cause mortality and increased burden of death due to cardiovascular disease, CKD, and upper gastrointestinal cancer.[13] A number of studies have provided evidence linking PPI use and increased risk for hypomagnesemia, acute kidney injury (AKI), acute interstitial nephritis, incident CKD, CKD progression, and kidney failure. [14,15]

In this review we have tried to summarize the evidences based on studies linking with adverse renal outcomes with PPI use and to discuss potential strategies of addressing safety concerns, including implementation of deprescription mechanisms.

AKI and PPI:

Proton pump inhibitor usage are associated with development of Acute kidney injury. Several studies demonstrated this association. A retrospective cohort study using data from a local HMO in Western New York was used to examine the relationships between acute kidney injury and prescription PPI use. This study shows the incidence rate of AKI was higher in the PPI group than nonusers (36.4 vs. 3.54 per 1000 person-years, $p<0.0001$, respectively). In adjusted models, PPI exposure was associated with an increased risk of AKI (Adjusted Odds Ratio (aOR) 4.35; 95% Confidence Interval (CI) 3.14–6.04; $p<0.0001$)[16]. Another study based on DATA mining of US FDA adverse event reporting system from 2004 to 2019 shows that more than three thousand AKI cases associated with PPI use in this period of time reported by health professional.[17]

On the other hand, a sentinel case report by Ruffenach et al in 1992 was followed by several anecdotal reports and multiple cross-sectional and cohort studies reporting a consistent association between PPI use and risk for AIN.[18] A study suggested that owing to the high prevalence of PPI use, this class of acid suppressants may be the leading cause of drug-induced AIN.[19]

So, it is easily attributable that using of PPI are associated with higher rate of acute Kidney injury including AIN.

PPI and CKD:

During the past years lots of evidences have accumulated from multiple large cohort studies suggesting PPI use is associated with increased risk for CKD outcome (incident CKD, CKD progression, and kidney failure)[15,20]. Xie et al. conducted a study to identify whether these increased risks of CKD are derived from the occurrence of AKI or AIN resulting from PPI use. But they found that about 50% of the association between PPI use and risk for CKD outcomes is not mediated by the occurrence of intervening AKI or AIN, suggesting a direct pathway of indolent chronic kidney injury.[15] Several meta-analyses have also supported the association between PPI use and increased risks for incident CKD, CKD progression, and kidney failure.[16,21,22]

A study conducted by Rodrigues-Poncelas A et al in Spain showed that the use of Proton Pump Inhibitors is associated with an increased risk of development of CKD, especially after a total exposure time of more than three months and if high doses are used.[23] So, it is clear that use of PPI is associated with CKD and it's risk is increased with higher dose and duration.

PPI and mortality in CKD:

There are controversies about whether PPI use in CKD patients increases risk of CKD progression and death. A study conducted in USA showed that chronic PPI use in patients with CKD Stages G3a to G4 was associated with a higher risk of CKD progression, dialysis, and all-cause death. Although not statistically significant, the study also suggested that PPI use favored the development of metabolic acidosis, conceivably contributing to more rapid progression of CKD.[24]

PPIs and Hypomagnesemia:

Several studies including cohort studies and cross-sectional studies and case series representing various populations including healthy, hospitalized and critically ill patients suggest that PPI use is associated with increased risk for hypomagnesemia, the risk is amplified in patients concomitantly using diuretics, and the risk is increased with prolonged duration of PPI exposure.[25-29] It is also seen that PPI use is associated with increased risk for hypomagnesemia in patients with CKD, especially those receiving maintenance hemodialysis but this association is not straight forward in renal transplant recipients.[30-32]

Non-renal adverse events with PPI uses:

Several studies suggest that PPI use is associated with increased risk for cardiovascular disease, gastric cancer, dementia, pneumonia, osteoporotic fractures, Clostridioides difficile infections and others.[9,11,12] Study carried out by Xie et al. comparative effect of PPIs and histamine H2-receptor antagonists (H2 blockers) on risk for all-cause and cause specific mortality suggests that

PPI use is associated with an increased burden of all-cause mortality and increased burden of death due to cardiovascular disease, CKD, and upper gastrointestinal cancer.[13]

Conclusion:

Though until the recent past PPIs are taken as safe drugs and are widely used for acid suppression therapy around the globe. They are usually prescribed for several acid related disorders, including gastroesophageal reflux disease (GERD), peptic ulcer disease, esophagitis, gastritis, barrett esophagus, (in addition to antibiotics) Helicobacter pylori eradication and as prophylactic with NSAIDs. Now it is seen that use of PPIs has lot of renal and non-renal adverse events. Reducing un-indicated exposure to PPIs may also be used in strategies aimed at prevention of these risks. Given their ubiquitous availability and abundant overuse, PPIs should be viewed as a public health risk. We urge all providers to consider reviewing the need for PPIs in every patient and to deprescribe when not necessary.

References

1. https://thefinancialexpress.com.bd/trade/anti-ulcerant-drugs-dominate-sales-chart-1610250086; published jan10;2021
2. Kantor ED, Rehm CD, Haas JS, et al. Trends in prescription drug use among adults in the United States from 1999-2012. JAMA. 2015;314: 1818–1831.
3. Xie Y, Bowe B, Li T, et al. Proton pump inhibitors and risk of incident CKD and progression to ESRD. J Am Soc Nephrol. 2016; 27:3153–3163.
4. Batuwitage BT, Kingham JG, Morgan NE, Bartlett RL. Inappropriate prescribing of proton pump inhibitors in primary care. Post Grad Med J 2007; 83: 66–68
5. Lee HJ, Lee H, Oh SH, et al. chronic kidney disease (CKD) patients are exposed to more proton pump inhibitor (PPI)s compared to non-CKD patients. PloS One. 2018;13(9): e0203878
6. Forgacs I, Loganayagam A. Overprescribing proton pump inhibitors. BMJ. 2008;336(7634):2-3.
7. Choudhry MN, Soran H, Ziglam HM. Overuse and inappropriate prescribing of proton pump inhibitors in patients with Clostridium difficile-associated disease. QJM. 2008;101(6): 445-448.
8. Linsky A, Simon SR. Reversing gears: discontinuing medication therapy to prevent adverse events. JAMA Intern Med. 2013;173(7):524-525.
9. Schoenfeld AJ, Grady D. Adverse effects associated with proton pump inhibitors. JAMA Intern Med. 2016;176(2):172- 174
10. Wilhelm SM, Rjater RG, Kale-Pradhan PB. Perils and pitfalls of long-term effects of proton pump inhibitors. Expert Rev Clin Pharmacol. 2013;6(4):443-451.
11. Li T, Xie Y, Al-Aly Z. The association of proton pump inhibitors and chronic kidney disease: cause or confounding? Curr Opin Nephrol Hypertens. 2018;27(3):182-187.
12. Gomm W, von Holt K, Thome F, et al. Association of proton pump inhibitors with risk of dementia: a pharmaco-epidemiological claims data analysis. JAMA Neurol. 2016;73(4): 410-416
13. Xie Y, Bowe B, Yan Y, Xian H, Li T, Al-Aly Z. Estimates of all-cause mortality and cause specific mortality associated with proton pump inhibitors among US veterans: cohort study. BMJ. 2019;365:l1580.
14. Antoniou T, Macdonald EM, Hollands S, et al. Proton pump inhibitors and the risk of acute kidney injury in older patients: a population-based cohort study. CMAJ Open. 2015;3(2):E166- E171.
15. Xie Y, Bowe B, Li T, Xian H, Yan Y, Al-Aly Z. Long-term kidney outcomes among users of proton pump inhibitors without intervening acute kidney injury. Kidney Int. 2017;91(6):1482-1494.
16. Hart E, Dunn T E, Feuerstein S, and Jacobs D M. Proton pump inhibitors and risk of acute and chronic kidney disease: a retrospective cohort study.Pharmacotherapy.2019 Apr:39(4):443-453.
17. Bin Wu, Dan Li1, Ting Xu, Min Luo , Zhiyao He & Yuwen Li. Proton pump inhibitors associated acute kidney injury and chronic kidney disease: DATA mining of US FDA adverse event reporting system. *Sci Rep* 11, 3690 (2021). https://doi.org/10.1038/s41598-021-83099-y
18. Ruffenach SJ, Siskind MS, Lien YH. Acute interstitial nephritis due to omeprazole. Am J Med. 1992;93(4):472-473.
19. Torpey N, Barker T, Ross C. Drug-induced tubulo-interstitial nephritis secondary to proton pump inhibitors: experience from a single UK renal unit. Nephrol Dial Transplant. 2004;19(6):1441-1446.
20. Xie Y, Bowe B, Li T, Xian H, Balasubramanian S, Al-Aly Z. Proton pump inhibitors and risk of incident CKD and progression to ESRD. J Am Soc Nephrol. 2016;27(10):
21. Qiu T, Zhou J, Zhang C. Acid-suppressive drugs and risk of kidney disease: a systematic review and meta-analysis. J Gastroenterol Hepatol. 2018.
22. Nochaiwong S, Ruengorn C, Awiphan R, et al. The association between proton pump inhibitor use and the risk of adverse kidney outcomes: a systematic review and meta-analysis. Nephrol Dial Transplant. 2018;33(2):331-342.
23. Hung SC, Liao KF, Hung HC, et al. Using proton pump inhibitors correlates with an increased risk of chronic kidney disease: a nationwide database-derived case-controlled study. Fam Pract. 2017.

24. Giusti S, Lin Y, Sogbetun F, Nakhoul N, Liu S, Shi L, Batuman V. The Effect of Proton Pump Inhibitor Use on the Course of Kidney Function in Patients with Chronic Kidney Disease Stages G3a to G4 -https://doi.org/10.1016/j.amjms.2021.05.017

25. Broeren MA, Geerdink EA, Vader HL, van den Wall Bake AW. Hypomagnesemia induced by several proton-pump inhibitors. Ann Intern Med. 2009;151(10):755-756.

26. Kieboom BC, Kiefte-de Jong JC, Eijgelsheim M, et al. Proton pump inhibitors and hypomagnesemia in the general population: a population-based cohort study. Am J Kidney Dis. 2015;66(5):775-782.

27. Zipursky J, Macdonald EM, Hollands S, et al. Proton pump inhibitors and hospitalization with hypomagnesemia: a population-based case-control study. PLoS Med. 2014;11(9): e1001736.

28. Koulouridis I, Alfayez M, Tighiouart H, et al. Out-of-hospital use of proton pump inhibitors and hypomagnesemia at hospital admission: a nested case-control study. Am J Kidney Dis. 2013;62(4):730-737.

29. Lindner G, Funk GC, Leichtle AB, et al. Impact of proton pump inhibitor use on magnesium homoeostasis: a cross-sectional study in a tertiary emergency department. Int J Clin Pract. 2014;68(11):1352-1357.

30. Nakashima A, Ohkido I, Yokoyama K, Mafune A, Urashima M, Yokoo T. Proton pump inhibitor use and magnesium concentrations in hemodialysis patients: a cross-sectional study. PloS One. 2015;10(11): e 0143656.

31. Van Ende C, Van Laecke S, Marechal C, et al. Proton-pump inhibitors do not influence serum magnesium levels in renal transplant recipients. J Nephrol. 2014;27(6):707-711.

32. Mikolasevic I, Milic S, Stimac D, et al. Is there a relationship between hypomagnesemia and proton-pump inhibitors in patients on chronic hemodialysis? Eur J Intern Med. 2016; 30:99-103.

Case Reports

A Case of Nephrocalcinosis due to Sarcoidosis

Ansary EAF[1], Ali ML[2], Islam MN[3], Khan MF[4]

Abstract:

About 10 to 50 percent of sarcoidosis patients get renal involvement, which is determined by either histologic changes in the kidney or a decline in kidney function, but it is frequently overlooked. Primary kidney manifestations are nephrolithiasis and nephrocalcinosis and acute interstitial nephritis with or without granuloma formation. The classic kidney lesion is noncaseating granulomatous interstitial nephritis, but this lesion rarely causes clinically significant kidney disease. Clinically significant kidney disease is most frequently caused by hypercalciuria and hypercalcemia. Glomerular disease, obstructive uropathy, and end-stage kidney disease (ESKD) may occur uncommonly.

(Bang. Renal J. 2023; 5(1): 22-25)

Introduction:

Sarcoidosis is an inflammatory disease characterized by the presence of noncaseating granulomas. While the disease can affect virtually every organ of the body, the lung is most commonly affected. Other organs commonly affected are the liver, skin and eye.[1] Clinically important kidney involvement occasionally occurs in sarcoidosis. Kidney manifestations include abnormal calcium metabolism, nephrolithiasis, nephrocalcinosis and acute interstitial nephritis with or without granuloma formation. The classic kidney lesion is noncaseating granulomatous interstitial nephritis. However, this lesion rarely causes clinically significant kidney disease. Hypercalciuria and hypercalcemia are most often responsible for clinically significant kidney disease. Glomerular disease, obstructive uropathy, and end-stage kidney disease (ESKD) may also occur but are uncommon.[2,3] The incidence and prevalence of kidney involvement in sarcoidosis remain uncertain.[4] The reported prevalence ranges widely due to the variation in study design and enrolled patient populations and due to the heterogenicity and often asymptomatic nature of kidney disease. Several small series have suggested that kidney involvement occurs in approximately 10 to 50 percent of patients with sarcoidosis,[5] although the disease may be silent and undetected for many years. A larger cohort found that kidney manifestations were present in 12 percent of cases.[6]

Nephrocalcinosis is a significant cause of chronic kidney disease (CKD).[2] Nephrolithiasis occurs in approximately 1 to 14 percent of patients with sarcoidosis.[2] Interstitial nephritis with granuloma formation occurs in approximately 20 percent of patients.[7] However, kidney function impairment is not always present.[3,7] Patients who have interstitial nephritis may also have nephrolithiasis or nephrocalcinosis.[8] In one study that included a cohort of 27 patients with renal sarcoidosis, the most commonly observed histologic lesion was nongranulomatous tubulointerstitial nephritis (44 percent), followed by granulomatous tubulointerstitial nephritis (30 percent), immunoglobulin A (IgA) glomerulonephritis (26 percent), and nephrocalcinosis (11 percent).[9] Another series of 34 patients with sarcoidosis and kidney function impairment reported tubulointerstitial disease in 71 percent.[5] Glomerular involvement is rare. A variety of different lesions have been described in isolated cases, including membranous nephropathy, IgA nephropathy, minimal change disease, a proliferative or crescentic glomerulonephritis, and focal segmental glomerulosclerosis.[3, 10-14]

1. Eusha Ahmad Fidalillah Ansary, Associate Professor, Department of Nephrology, Uttara Adhunik Medical College, Dhaka, Bangladesh
2. Md. Layakat Ali, Transplant coordinator, National Institute of Kidney Diseases and Urology, Dhaka, Bangladesh
3. Md. Nazrul Islam, Professor and Head, Department of Nephrology, Dhaka Medical College, Dhaka, Bangladesh
4. Md. Firoz Khan, Former Professor and Head, Department of Nephrology, Dhaka Medical College, Dhaka, Bangladesh

Address of Correspondence: Eusha Ahmad Fidalillah Ansary, Associate Professor and Head, Department of Nephrology, Uttara Adhunik Medical College, Dhaka, Bangladesh. E-mail: eushaansary@gmail.com

Case Report:

A- 55-year-old, male muslim, ex-smoker, normotensive, nondiabetic farmer hailing from Bakergonj, Barisal got admitted with the complaints of recurrent passage of stone during micturition for 3 years, associated with pain in lower back and reddish urine. The pain was colicky in nature radiates from loin to groin and subsided after passage of stone and the colour of urine become clear gradually. He gave history of increase thirst for 1 year. For which he had to drink about 6 to 8 liters of water in a day and associated with increased urination but not polyphagia. He also complaints of anorexia, nausea, significant weight loss for last 4 months. He gave history of fever for 4 months which was initially high grade intermittent in nature but for last 2 months it was low grade, maximum recorded temperature was 100^0F. Fever had no diurnal variation, subsided after taking antipyretic without profuse sweating. He gave no history of travelling to the endemic zone of malaria and kala-Azar and contact with known TB patients. His bladder and bowel habit were normal.

On examination, he was ill looking, anxious, moderately anaemic, not icteric and not cyanosed, pulse 88 beats/min, Blood Pressure 110/70 mm of Hg, respiratory rate 16 breaths/min at the time of examination. Generalized lympladenopathy involved in posterior cervicle, epitrochlear and inguinal region bilaterally; largest one is inguinal, measuring 3cm ×2 cm, firm to hard in consistency, discrete, non tender, mobile with no discharging sinus.

Apart from these, other systemic examination was unremarkable.

Investigation revealed; albumin: trace, RBC: 20-40/HPF, WBC: plenty, cast: nil on urine routine and microscopic examination. Urinary pH was 7 and culture revealed no growth. S. creatinine was 9.2mg/dl, Hemoglobin: 8.32 gm/dl, ESR 17, Total count 7500/ mm3, Neutrophil 78%, Lymphocyte 14%; peripheral blood film showed dimorphic RBC. Corrected serum calcium was 12.85 mg/dl (high) but serum phosphate, parathyroid hormone, albumin, alkaline phosphatase was within normal range. 24 hours urinary calcium was also high 454 mg/day (Normal 150-300 mg/day) whereas serum and urinary electrolytes were within normal range. X-ray chest P/A view revealed bilateral hilar lymphadenopathy and X-ray KUB revealed bilateral nephrocalcinosis (Figure 1), USG whole abdomen showed bilateral echogenic kidneys with nephrocalcinosis. The tuberculin skin test was negative. Lymph node biopsy showed non-caseating granulomatous lymphadenitis compatible with sarcoidosis (Figure 2). Serum ACE was 103 U/L (Normal up to 65). He was treated by some general treatment like avoidance of sun light, salt restricted diet and specific treatment by oral prednisolone.

Following discharge, the patient was feeling well and the serum creatinine declined. Follow up at three months revealed no new complaints and resolved previous complaints, no anaemia, lymph nodes were resolved with substantial improvement. Urine R/M/E showed trace albumin, RBC: 06-10/HPF, Pus cell: 7-8, Cast: Nil, S. Creatinine – 1.8 mg/dl, S. Calcium- 8.1 mg/dl, Hemoglobin: 11.1 gm/dl, X-ray chest P/A view - Bilateral prominent hilum and USG of KUB showed bilateral echogenic kidneys.

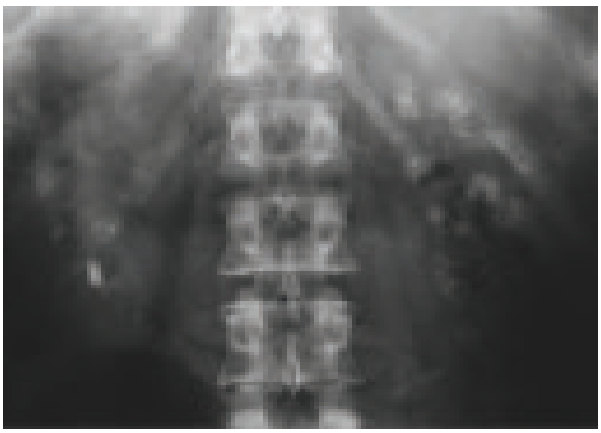

Figure 1 : *Plain X-ray KUB bilateral nephrocalcinosis*

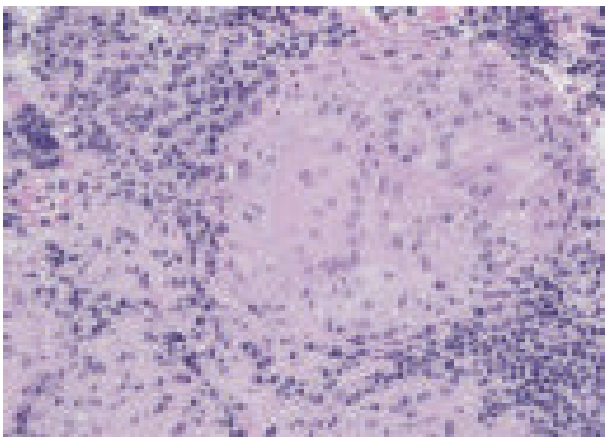

Figure 2 : *Histology of lymph node showing non-caseating granuloma*

Discussion:

Nephrocalcinosis is a pattern of renal injury characterized by abundant renal tubular and interstitial deposits of calcium phosphate. The calcium phosphate deposits are associated with varying degrees of acute tubular injury, as well as chronic, irreversible scarring in the form of tubular

atrophy and interstitial fibrosis. The finding of nephrocalcinosis on renal biopsy should prompt investigation into conditions associated with hypercalcemia, including hyperparathyroidism, malignancy, and excessive calcium or vitamin D intake.[15] Nephrocalcinosis and nephrolithiasis are caused by hypercalcemia and/or hypercalciuria. Hyperabsorption of dietary calcium occurs in up to 50 percent of cases of sarcoidosis.[2] The excess calcium is excreted in the urine, leading to hypercalciuria in approximately 40 percent and, in 2 to 20 percent of cases, to hypercalcemia.[2,3]

This abnormality in calcium metabolism is not limited to sarcoidosis, as it occurs in many other chronic granulomatous diseases. The defect in these disorders is increased production of calcitriol by activated mononuclear cells; particularly macrophages in granulomas, the lung, and lymph nodes. Increased calcitriol production appears to be due both to markedly enhanced activation and production of 1-alpha-hydroxylase, the enzyme that converts 25-hydroxyvitamin D to calcitriol, and the absence of feedback inhibition, which normally limits enzyme expression.[16] Nephrolithiasis may be the presenting feature of sarcoidosis.[2] In a retrospective study of 618 patients with sarcoidosis, kidney calculi were the first manifestations in 14 (2.2 percent).[17] In a prospective study, nephrolithiasis was the presenting feature of the disease in 4 percent of 204 consecutive patients with sarcoidosis.[18] Patients with nephrocalcinosis may present only with an elevated creatinine and benign urinalysis. Such patients will generally be found to have hypercalciuria with or without hypercalcemia. Patients with nephrocalcinosis may have polyuria, which is caused by hypercalcemia and possibly hypercalciuria, resulting in reduced responsiveness to antidiuretic hormone.[19] Polyuria in sarcoidosis may also reflect central diabetes insipidus; lack of antidiuretic hormone or primary polydipsia due to granulomatous infiltration of the hypothalamus.[20] Hypercalcemia may also cause a decreased glomerular filtration rate (GFR) through preglomerular arteriolar vasoconstriction.[21] There is no single diagnostic test for sarcoidosis. The diagnosis of sarcoidosis is based on the following criteria: a) a compatible clinical and/ or radiographic picture, b) histological evidence of non-caseating granulomas and c) exclusion of other conditions with similar histology[22]. The most common abnormalities on plain chest radiographs are bilateral, symmetric hilar adenopathy with or without lung infiltrates.[23] Most recent data indicate that serum angiotensin converting enzyme (ACE) levels are neither sufficiently sensitive nor specific to confirm a diagnosis of sarcoidosis although they may have some value as supportive evidence for or against the diagnosis.[24] However, most patients with sarcoidosis require histologic confirmation for diagnosis. Since sarcoidosis is a multisystem disorder, evidence of granulomatous inflammation in at least 2 organs is required to distinguish it from granulomatous disorders of individual organs.[24,25] However, biopsy confirmation from one organ is deemed sufficient if compatible clinical, laboratory, or radiologic findings are consistent with the diagnosis in at least one additional organ and alternative diagnoses have been excluded.[24,25] The choice of biopsy site should be guided by what is least invasive and most likely to yield diagnostic material. Enlarged peripheral lymph nodes, skin involvement, and conjunctival nodules permit minimally invasive procedures. Systemic corticosteroids are the drug of choice for the treatment of sarcoidosis, although no clear consensus exists regarding when to start treatment, the correct doses and or how long treatment should be maintained.[26] Other alternative treatments such as immunosuppressive agents (e.g. methotrexate, azathioprine, cyclophosphamide, leflunomide), cytokine inhibitors (e.g. thalidomide, pentoxifylline), antimalarial agents such as chloroquine are only indicated when the sarcoidosis does not respond to conventional treatment with oral corticosteroids, in patients with intolerance to corticosteroids, or in order to reduce the dosage of corticosteroids.[26]

Conclusion:

Sarcoidosis should be kept in mind when patient presented with history of passage of stone through urine, nephrocalcinosis on imaging along with hypercalcemia and hypercalcuria with or without deterioration of renal function. Early diagnosis and appropriate treatment favor prognosis with recovery of renal function.

References:

1. Samtsov A. Cutaneous sarcoidosis. Int J Dermatol 1989; 31: 385-91.
2. Muther RS, McCarron DA, Bennett WM. Renal manifestations of sarcoidosis. Arch Intern Med 1981; 141:643.
3. Casella FJ, Allon M. The kidney in sarcoidosis. J Am Soc Nephrol 1993; 3:1555.
4. Berger KW, Relman AS. Renal impairment due to sarcoid infiltration of the kidney; report of a case proved by renal biopsies before and after treatment with cortisone. N Engl J Med 1955; 252:44.

5. Gorsane I, Zammouri A, Hajji M, et al. [Renal involvement in sarcoidosis: Prognostic and predictive factors]. Nephrol Ther 2022; 18:52.

6. Lhote R, Annesi-Maesano I, Nunes H, et al. Clinical phenotypes of extrapulmonary sarcoidosis: an analysis of a French, multi-ethnic, multicentre cohort. Eur Respir J 2021; 57.

7. Longcope WT, Freiman DG. A study of sarcoidosis; based on a combined investigation of 160 cases including 30 autopsies from The Johns Hopkins Hospital and Massachusetts General Hospital. Medicine (Baltimore) 1952; 31:1.

8. Mahévas M, Lescure FX, Boffa JJ, et al. Renal sarcoidosis: clinical, laboratory, and histologic presentation and outcome in 47 patients. Medicine (Baltimore) 2009; 88:98.

9. Löffler C, Löffler U, Tuleweit A, et al. Renal sarcoidosis: epidemiological and follow-up data in a cohort of 27 patients. Sarcoidosis Vasc Diffuse Lung Dis 2015; 31:306.

10. Dahl K, Canetta PA, D'Agati VD, Radhakrishnan J. A 56-year-old woman with sarcoidosis and acute renal failure. Kidney Int 2008; 74:817.

11. Goldszer RC, Galvanek EG, Lazarus JM. Glomerulonephritis in a patient with sarcoidosis. Report of a case and review of the literature. Arch Pathol Lab Med 1981; 105:478.

12. Jones B, Fowler J. Membranous nephropathy associated with sarcoidosis. Response to prednisolone. Nephron 1989; 52:101.

13. van Uum SH, Cooreman MP, Assmann KJ, Wetzels JF. A 58-year-old man with sarcoidosis complicated by focal crescentic glomerulonephritis. Nephrol Dial Transplant 1997; 12:2703.

14. Bergner R, Löffler C. Renal sarcoidosis: approach to diagnosis and management. Curr Opin Pulm Med 2018; 24:513.

15. Leal C. Herlitz1, Robert Bruno2, Jai Radhakrishnan3 and Glen S. Markowitz1 A case of nephrocalcinosis; http://www.kidney-international.org; 2009

16. Inui N, Murayama A, Sasaki S, et al. Correlation between 25-hydroxyvitamin D3 1 alpha-hydroxylase gene expression in alveolar macrophages and the activity of sarcoidosis. Am J Med 2001; 110:687.

17. Rizzato G, Fraioli P, Montemurro L. Nephrolithiasis as a presenting feature of chronic sarcoidosis. Thorax 1995; 50:555.

18. Rizzato G, Palmieri G, Agrati AM, Zanussi C. The organ-specific extrapulmonary presentation of sarcoidosis: a frequent occurrence but a challenge to an early diagnosis. A 3-year-long prospective observational study. Sarcoidosis Vasc Diffuse Lung Dis 2004; 21:119.

19. Lower E. Renal sarcoidosis. In: Sarcoidosis, Baughman R (Ed), Taylor & Francis, New York 2006. p.651.

20. Stuart CA, Neelon FA, Lebovitz HE. Disordered control of thirst in hypothalamic-pituitary sarcoidosis. N Engl J Med 1980; 303:1078.

21. Levi M, Peterson L, Berl T. Mechanism of concentrating defect in hypercalcemia. Role of polydipsia and prostaglandins. Kidney Int 1983; 23:489.

22. Gerolemou L, Smith P. Basic diagnostic approaches in sarcoidosis. In: Motamedi M, ed. Sarcoidosis diagnosis and management. 1st ed. Rijeka: InTech; 2011. p.37.

23. Gerolemou L, Smith P. Basic diagnostic approaches in sarcoidosis. In Motamedi M, ed. Sarcoidosis diagnosis and management. 1st ed. Rijeka: InTech; 2011. p. 40-1.

24. Baughman R, Culver D, Judson M. A concise review of pulmonary sarcoidosis. Am Rev Respir Crit Care Med 2011; 183: 573-81.

25. Judson M. The diagnosis of sarcoidosis. Clin Chest Med 2008; 29: 415-27.

26. Jara-Palomares L, Cabellaro-Eraso CB, RodriguezPortal J. Updated guidelines for the treatment of pulmonary sarcoidosis. In: Motamedi M, ed. Sarcoidosis diagnosis and management. 1st ed. Rijeka: InTech; 2011. p. 125-6.

Primary Renal Amyloidosis: A Case Report from the Department of Nephrology of Dhaka Medical College Hospital

Rahman HMM[1], Islam MN[2], Ahmed AS[3], Rahman GMH[4], Hasan MR[5], Rahman MS[6], Siam MM[7]

Abstract

Amyloidosis is a disease characterized by deposition of abnormal misfolded fibril proteins leading to organ dysfunction and often multisystem involvement. It may be classified as primary or secondary. In rare case, the cause can be gene mutation leading to hereditary amyloidosis. The clinical manifestations of renal amyloidosis vary with the type of amyloid protein and the site and degree of amyloid deposition. Most common presentation is proteinuria (in 75% of cases) usually nephrotic syndrome and variable degrees of renal impairment (Acute Kidney Injury, Chronic Kidney Disease, End Stage Renal Disease). Microscopic hematuria is uncommon. Tubular dysfunction or defect including renal tubular acidosis can also occur. We hereby report a case of a 55 years old female presented with nephrotic syndrome who was further evaluated and confirmed as a case of primary renal amyloidosis (AL amyloidosis).

(Bang. Renal J. 2023; 5(1): 26-29)

Introduction

Amyloidosis is a group of diseases characterized by extracellular deposition of beta-sheet fibrils. It may be local form or systemic forms. Systemic forms of amyloidosis cause progressive organ dysfunction and may lead to death of the patients. Types of renal Amyloidosis includes AL amyloidosis (Previously referred to as primary amyloidosis), AA amyloidosis (Previously referred to as secondary amyloidosis, also called reactive amyloidosis or amyloidosis AA), ALECT2 amyloidosis, Apolipoprotein AIV amyloidosis, hereditary renal amyloidosis.[1] AL amyloidosis consist of monoclonal immunoglobulin light chains.[2,3] Immunofluorescence study can detect lambda/ kappa light chain. If it is inconclusive laser microdissection or tandem mass spectrometry should be used to establish the diagnosis.[4] Lambda light chain is more amyloidogenic than kappa light chain.[5] AA amyloidosis occurs in patients with chronic inflammatory disease such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis etc.[2,3] It may occur in patients with chronic infections such as tuberculosis, leprosy, chronic osteomyelitis etc.[1] It may also occur in patients with malignancies such as lymphoma, leukemia etc.[6] Apolipoprotein A4 is another renal amyloidosis which is not so common presentation like ESKD with minimal or no proteinuria.[7,8] The clinical manifestations of renal amyloidosis vary with the type of amyloid protein and the site and degree of amyloid deposition. Renal amyloidosis should be suspected in any patient presenting with proteinuria with or without the nephrotic syndrome.[9,10] Kidney biopsy is generally required to make a definitive diagnosis. Light microscopy typically reveals diffuse glomerular deposition of amorphous hyaline Congo red positive materials initially in the mesangium and then along the capillary loops. [11] In direct immunofluorescence test there was complement and immunoglobulin positive for lambda or kappa light chain in AL amyloidosis but negative for complement and immunoglobulin for non-AL amyloidosis. Electron microscopy shows straight, non-branching fibrils that are

1. Hossain Muhammad Mustafijur Rahman, Assistant Professor, Department of Nephrology, Dhaka Medical College
2. Md. Nazrul Islam, Professor & Head, Department of Nephrology, Dhaka Medical College
3. Abu Saleh Ahmed, Associate Professor, Department of N ephrology, Dhaka Medical College
4. G M Hafizur Rahman, Assistant Professor, Department of Nephrology, Dhaka Medical College
5. Mir Rashedul Hasan, Phase B Resident, MD (Nephrology), Dhaka Medical College
6. Md Saidur Rahman, Assistant Registrar, Department of Nephrology, Dhaka Medical College Hospital
7. Muhammad Masrur Siam, Assistant Registrar, Department of Nephrology, Dhaka Medical College Hospital

Address of Correspondence: Hossain Muhammad Mustafijur Rahman, Assistant Professor, Department of Nephrology, Dhaka Medical College

randomly arranged, typically in mesangium and along the glomerular capillary walls. [12,13]

Case Report

Mrs. Saitun, 55 years of age, normotensive, non-diabetic housewife hailing from Sherpur, Bagura, got herself admitted into Dhaka Medical College Hospital, in the Department of Nephrology with the complaints of recurrent swelling of whole body for one and a half years and occasional frothy urine for the same duration.

Swelling was first appeared at her face and then it became generalized. It was associated with frothy urine and occasional oliguria. But it was not associated with any loin pain, dysuria, jaundice, chest pain, palpitation, cold intolerance or constipation. Patient had no history of fever, joint pain, rash, alopecia. On query patient gave history of dyspnoea which was mild to moderate in severity (MRC scale 2). Her bowel habit was normal. The patient was normo-tensive, non-diabetic and had no significant past history. Patient was vaccinated according to Expanded Program on Immunization (EPI) schedule and was also vaccinated against covid-19 and Hepatitis-B.

She came from a middle-class family. On general examination the patient was found ill looking and her face was puffy. She was mildly anemic, moderately edematous and there was leukonychia. There was no lymphadenopathy or thyromegaly. Vitals were normal. Systemic examination revealed moderate ascites. There was no organomegaly.

Bed side heat coagulation test revealed 3 (+) proteinuria. Fundoscopic examination was normal. Apart from these, other systemic examination was unremarkable.

Urine routine examination revealed 3(+) proteinuria, there was no pus cells or RBCs. 24 Hours UTP was 4.47 gram. Serum albumin level was 1.35 gm/dl. Her Serum Creatinine was 1.0mg/dl. She was found moderately anemic with blood picture suggestive of anemia of chronic disease. Liver function tests were normal. X ray chest P/A view showed bilateral pleural effusion. Ultrasonogram of whole abdomen revealed moderate ascites and pleural effusion. Ascitic fluid was transudative, GeneXpert for MTB was negative and no malignant cell was found.

Urinary Bence Jones protein test was positive and plasma protein electrophoresis showed monoclonal gammopathy (Figure 1). Immunofixation electrophoresis revealed monoclonal protein IgG lambda (Figure 2). Echocardiogram revealed ground glass appearance suggestive cardiac amyloidoisis. Bone marrow study showed reactive marrow. Renal biopsy and histopathology showed features suggesting renal amyloidosis (Figure 3 & 4).

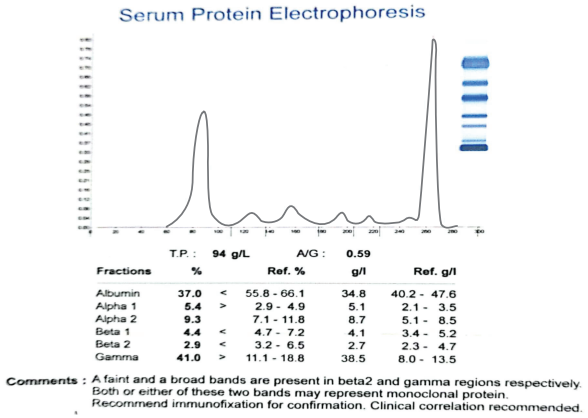

Figure - 1 : *Plasma protein electrophoresis*

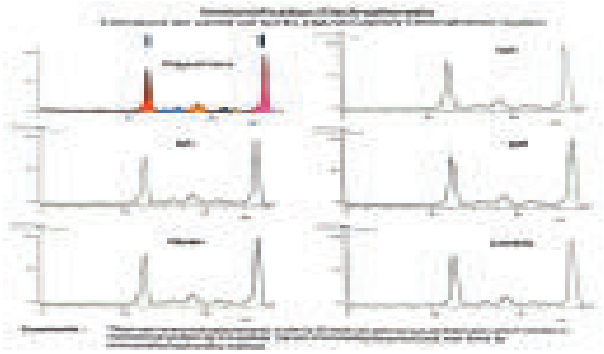

Figure - 2 : *Immune fixation study*

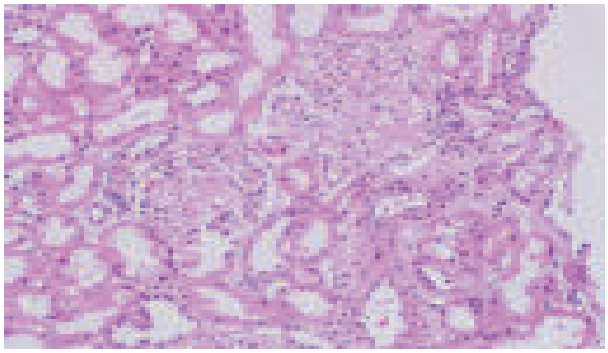

Figure - 3 : *Renal tissue histology (H &E staining)*

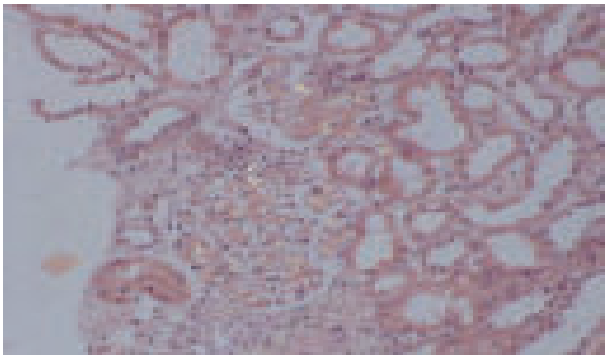

Figure - 4 : *Renal tissue staining suggesting renal amyloidosis*

Rheumatoid factor, Anti-neuclear antibody and Anti DS-DNA, ENA profile tests were done and found normal. So, it was diagnosed a case of Primary amyloidosis (AL amyloidosis) with renal and cardiac involvement.

As patient cannot afford Cyclophosphamide/Bortezomib/ Dexamethasone regimen, CTD- Regimen (Cyclophosphamide: 300/$m^{2,}$ Thalidomide: 200mg/d, Dexamethasone: 40mg/weekly) was started.

After 4 cycles of treatment, she was improved and her bed side heat coagulation test was negative. Urine routine examination revealed no albumin. She was doing well in terms of physical symptoms and was discharged with necessary advice regarding future treatment plan.

Discussion:

The amyloid fibrils in AL amyloidosis (previously referred to as primary amyloidosis) consist of monoclonal immunoglobulin light chains. The composition of deposits is confirmed by immunofluorescence microscopy with either anti-lambda or anti-kappa light chain antibodies in most cases. Staining for only a single type of light chain should suggest a monoclonal gammopathy such as AL amyloidosis or myeloma. In cases where the immunofluorescence is equivocal, laser microdissection and tandem mass spectrometry, when available, should be used to establish the diagnosis. Although AL amyloidosis is the result of clonal proliferation of plasma cells, most patients do not meet criteria for multiple myeloma. These patients are best categorized as having monoclonal gammopathy of renal significance. Furthermore, most patients with myeloma and overproduction of light chains (light chain myeloma) do not develop systemic amyloidosis. The clinical manifestations of renal amyloidosis vary with the type of amyloid protein and the site and degree of amyloid deposition. It includes:

- **Proteinuria and nephrotic syndrome** Proteinuria is the most common manifestation and is generally associated with glomerular deposition of amyloid. As an example, approximately 75 percent of patients with AL amyloidosis (most of whom have predominant glomerular deposition) present with proteinuria, often accompanied by edema. The degree of proteinuria can range from mild to massive (>20 g/day), depending upon the extent of glomerular involvement. Patients with AL amyloidosis frequently present with heavy proteinuria (mean of 6.2 g/day in one study).
- Slowly progressive CKD with little or no proteinuria
- Tubular dysfunction
- Crescentic glomerulonephritis
- Acute kidney injury
- Renal amyloidosis should be suspected in any patient presenting with proteinuria with or without the nephrotic syndrome. Suspicion is even higher if other systemic symptoms (such as heart failure, gastrointestinal symptoms, or neuropathy) are also present. A kidney biopsy is generally required to make a definitive diagnosis of renal amyloidosis.

The approach to the treatment of AL amyloidosis includes supportive measures in all patients like dietary sodium and protein restriction, antihypertensive therapy, renin-angiotensin system inhibition, lipid lowering, anticoagulation, treatment of edema. Specific management includes Bortezomib based therapy-Daratumumab, Cyclophosphamide, Bortezumab and Dexamethasone. Other regimen-Cyclophosphamide, Thalidomide, Dexamethasone.

Response criteria for renal amyloidosis is seen by reduction of proteinuria 50% from baseline or 24-hour urinary protein must be less than 0.5 gm/day.

Conclusion:

Primary amyloidosis (AL amyloidosis) should be kept in mind when patient presented with nephrotic syndrome. A kidney biopsy with Congo red stain is generally required to make a definitive diagnosis. Early diagnosis and appropriate treatment are necessary for better outcome.

References

1. Said SM, Sethi S, Valeri AM, Leung N, Cornell LD, Fidler ME, Herrera Hernandez L, Vrana JA, Theis JD, Quint PS, Dogan A, Nasr SH. Renal amyloidosis: origin and clinicopathologic correlations of 474 recent cases. Clin J Am Soc Nephrol. 2013 Sep;8(9):1515-23. doi: 10.2215/CJN.10491012. Epub 2013 May 23. PMID: 23704299; PMCID: PMC3805078.
2. Steddon, Simon and others, Oxford Handbook of Nephrology and Hypertension, 2 edn, Oxford Medical Handbooks (Oxford, 2014; online edn, Oxford Academic, 1 Mar. 2014), https://doi.org/10.1093/med/9780199651610.001.0001, accessed 2 Apr. 2023 Top of Form
3. Glenner GG. Amyloid deposits and amyloidosis. The beta-fibrilloses (first of two parts). N Engl J Med. 1980 Jun 5;302(23):1283-92. doi: 10.1056/NEJM198006053022305. PMID: 6154243.
4. Vrana JA, Gamez JD, Madden BJ, Theis JD, Bergen HR 3rd, Dogan A. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic

analysis in clinical biopsy specimens. Blood. 2009 Dec 3;114(24):4957-9. doi: 10.1182/blood-2009-07-230722. Epub 2009 Oct 1. PMID: 19797517.

5. Gertz MA, Leung N, Lacy MQ, Dispenzieri A, Zeldenrust SR, Hayman SR, Buadi FK, Dingli D, Greipp PR, Kumar SK, Lust JA, Rajkumar SV, Russell SJ, Witzig TE. Clinical outcome of immunoglobulin light chain amyloidosis affecting the kidney. Nephrol Dial Transplant. 2009 Oct;24(10):3132-7. doi: 10.1093/ndt/gfp201. Epub 2009 Apr 29. PMID: 19403931.

6. Lachmann HJ, Goodman HJ, Gilbertson JA, Gallimore JR, Sabin CA, Gillmore JD, Hawkins PN. Natural history and outcome in systemic AA amyloidosis. N Engl J Med. 2007 Jun 7;356(23):2361-71. doi: 10.1056/NEJMoa070265. PMID: 17554117.

7. Sethi S, Theis JD, Shiller SM, Nast CC, Harrison D, Rennke HG, Vrana JA, Dogan A. Medullary amyloidosis associated with apolipoprotein A-IV deposition. Kidney Int. 2012 Jan;81(2):201-6. doi: 10.1038/ki.2011.316. Epub 2011 Sep 7. PMID: 21900878.

8. Dasari S, Amin MS, Kurtin PJ, Vrana JA, Theis JD, Grogg KL, Alexander MP, Nasr SH, Fervenza FC, Leung N, Sethi S. Clinical, biopsy, and mass spectrometry characteristics of renal apolipoprotein A-IV amyloidosis. Kidney Int. 2016 Sep;90(3):658-64. doi: 10.1016/j.kint.2016.04.003. Epub 2016 Jun 2. PMID: 27262366.

9. Palladini G, Merlini G. Current treatment of AL amyloidosis. Haematologica. 2009 Aug;94(8):1044-8. doi: 10.3324/haematol.2009.008912. PMID: 19644136; PMCID: PMC2719026.

10. Wechalekar AD, Hawkins PN, Gillmore JD. Perspectives in treatment of AL amyloidosis. Br J Haematol. 2008 Feb;140(4):365-77. doi: 10.1111/j.1365-2141.2007.06936.x. Epub 2007 Dec 19. PMID: 18162121.

11. Dember LM. Amyloidosis-associated kidney disease. J Am Soc Nephrol. 2006 Dec;17(12):3458-71. doi: 10.1681/ASN.2006050460. Epub 2006 Nov 8. PMID: 17093068.

12. Vrana JA, Gamez JD, Madden BJ, Theis JD, Bergen HR 3rd, Dogan A. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. Blood. 2009 Dec 3;114(24):4957-9. doi: 10.1182/blood-2009-07-230722. Epub 2009 Oct 1. PMID: 19797517.

13. Sethi S, Theis JD, Leung N, Dispenzieri A, Nasr SH, Fidler ME, Cornell LD, Gamez JD, Vrana JA, Dogan A. Mass spectrometry-based proteomic diagnosis of renal immunoglobulin heavy chain amyloidosis. Clin J Am Soc Nephrol. 2010 Dec;5(12):2180-7. doi: 10.2215/CJN.02890310. Epub 2010 Sep 28. PMID: 20876678; PMCID: PMC2994078.

14. Glenner GG. Amyloid deposits and amyloidosis. The beta-fibrilloses (first of two parts). N Engl J Med. 1980 Jun 5;302(23):1283-92. doi: 10.1056/NEJM198006053022305. PMID: 6154243.

15. Vrana JA, Gamez JD, Madden BJ, Theis JD, Bergen HR 3rd, Dogan A. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. Blood. 2009 Dec 3;114(24):4957-9. doi: 10.1182/blood-2009-07-230722. Epub 2009 Oct 1. PMID: 19797517.

16. Gertz MA, Leung N, Lacy MQ, Dispenzieri A, Zeldenrust SR, Hayman SR, Buadi FK, Dingli D, Greipp PR, Kumar SK, Lust JA, Rajkumar SV, Russell SJ, Witzig TE. Clinical outcome of immunoglobulin light chain amyloidosis affecting the kidney. Nephrol Dial Transplant. 2009 Oct;24(10):3132-7. doi: 10.1093/ndt/gfp201. Epub 2009 Apr 29. PMID: 19403931.