Bangladesh Renal Journal

Volume 05 Number 02 July 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

Editorial

Chronic Kidney Disease of Unknown Etiology

Chronic kidney disease of unknown etiology (CKDu) is a form of tubulointerstitial disease of kidney with world wide distribution along with regional hot spots involving agricultural communities in rural areas. Researches are ongoing to determine the epidemiology, potential cause , clinical manifestation and prognosis.[1-2]

CKDu refers to chronic kidney disease in the absence of diabetes, long standing hypertension, glomerulonephritis, obstructive uropathy or other apparent causes. In fact it is a diagnosis by exclusion and a high index of suspension is needed for diagnosis especially in certain geographical regions and also in some regional hot spots. These regional nephropathies share some common attributes : (a)Affect low and middle income tropical countries (b) Predilection for rural agricultural communities.(c) Male preponderance (d)Insignificant proteinuria (e) Absence of hypertension, (f) Tubulointerstitial nephritis on renal biopsy.

It is prevalent in several central American countries, Srilanka, Egypt and India.

Inspite of a drastic worldwide increase in the incidence and prevalence of CKDu, there is a paucity of data. Indian CKD registry revealed that CKDu is the second most common underlying cause of CKD (16%) after diabetic nephropathy.[3] In Srilanka the reported prevalence is 8-21%,which is felt to be under reported.[4]

The current body of literature suggests that CKDu has a multifactorial etiology of different environmental and occupational exposures, such as heat stress, dehydration, agrochemicals (pesticides, herbicides, fertilizers) heavy metals (cadmium, lead, arsenic etc.) water sources and infections. It is life threatening due to late recognition and progressive deterioration of renal function. Early screening of etiological risk factors for CKDu is essential to reduce mortality and morbidity.

Heat stress and dehydration are presently the largest research focus in Latin America whereas contamination of drinking water is primary focus in Asia.

Research studies to date that aim to pin point risk factors associated with CKDu are varied. Without conducting studies that look at all possible etiologies across the countries using a standardized approach, it is difficult to draw a standard management guideline.

Research should focus on developing novel biomarkers to detect CKDu in its early stage.

Surveillance and standardized disease registries and monitoring system is essential .

Since CKDu mostly prevalent in resource limited areas, WHO should declare it as global epidemic and allocate funding.

(Bang. Renal J. 2023; 5(2): 30

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

Dr. Hossain Muhammad Mustafijur Rahman
Assistant Professor, Dept. of Nephrology, Dhaka Medical College, Dhaka

Reference:

1. Jhon O, Gummudi B, Jha A et al. Chronic kidney disease of unknown etiology in India: what do we know and where we need to go . Kidney Int Rep. Nov 2021;6 (11) 2743-275
2. Gifford FJ, Gifford RM, Eddleston M, Dhaun N. Endemic Nephropathy around the world. Kidney Int Rep. Mar 2017; 2(2): 282-292
3. What do we know about chronic kidney disease in India : First report of the Indian CKD registry. Rajapurkar MM, Jhon GT, Kirpalani AL et al. BMC Nephrol. 2012;13:10
4. Chronic kidney disease of unknown etiology in agricultural communities. Almaguer-Lopez MA, Herrera-Valdes R, Orantes -Navarro CM. MEDIC Rev. 2014;16:9-15

Original Articles

Immune Response to Hepatitis B Vaccination in CKD Patients and Factors Associated with Non- response

Moitry MI[1], Rahman GMH[2], Faisal ARM[3], Jannat G[4], Islam Z[5], Hasan F[6], Khatun S[7], Islam MN[8]

Abstract:

Background: Chronic kidney disease (CKD) patients gradually become immunocompromised with declining renal function. They become highly susceptible to various infections specially blood-borne infections like Hepatitis B Virus (HBV). Active immunization against HBV is recommended routinely for them. But immune response following vaccination is usually suboptimal in these patients, specially those who are on hemodialysis than healthy individuals. Immune response to Hepatitis B vaccination may vary due to different reasons.

Aims: This study was aimed to determine the immune response to hepatitis B vaccination in CKD patients and possible factors associated with non-response.

Methods: This prospective study was carried out in the Department of Nephrology, Dhaka Medical College Hospital. A total of 100 patients were distributed in two groups- 50 patients of CKD stage 3-5 on conservative management and 50 patients on maintenance hemodialysis (MHD) who were receiving routine Hepatitis B vaccination were enrolled in the study. Demographic, clinical, and laboratory data were collected initially. Patients from both groups received 40 µg recombinant DNA Hepatitis B vaccine intramuscularly in the deltoid region at 0, 1, 2, and 6th month schedule. Then after 8 weeks of the last dose of vaccine anti-Hepatitis B surface antibody (Anti- HBs Antibody) titer was measured. Seroconversion was defined as an antibody titer ≥10mIU/ml and according to the titer study population was divided into 3 sub-groups: adequate (>100mIU/ml), inadequate (10 - 100mIU/ml) and non-responders (<10mIU/ml) and then different variables were compared among them to find out possible factors that may be associated with non-response following Hepatitis B vaccination in CKD patients.

Result: The seroconversion rate was 79.5% in patients with CKD stage 3-5 (ND) whereas among MHD patients it was 55.1% following Hepatitis B vaccination. 52.2% of CKD (ND) and 20.4% of MHD patients achieved adequate immune response. Despite complete vaccination, 20.4% patients of CKD stage 3-5 and 44.9 % patients of MHD were non-responders. Non-responders were comparatively older in age with higher BMI, lower serum albumin and eGFR levels than the responders.

Conclusion: An adequate immune response following Hepatitis B vaccination may be achieved if it is administered during early stages of CKD, preferably before initiating dialysis. Modification of certain factors before immunization may bring better results.

Keywords: hepatitis B vaccination; immune response; HBV vaccination in CKD.

(Bang. Renal J. 2023; 5(2): 32-40

Introduction:

Chronic kidney disease (CKD) has been increasingly recognized as a global public health problem. Worldwide 1 in 10 adults is affected by CKD.[1] Cardiovascular disease, various infections, neoplastic disorders etc. are the leading causes of morbidity and mortality in CKD patients.[2] As patients with CKD are immuno-compromised, they always remain in a risk of various infections, especially blood-borne infections due to frequent exposure to blood and blood products.[3] Hepatitis B virus is one of them and is a major public health problem worldwide.

1. Mahnaz Islam Moitry, Resident Physician, M Abdur Rahim Medical college and Hospital, Dinajpur
2. G M Hafizur Rahman, Assistant Professor, Department of Nephrology, Dhaka Medical College
3. Amanur Rasul Md. Faisal, Transplant Coordinator, Dhaka Medical College Hospital
4. Gul Jannat, Medical Officer, Mugda Medical College Hospital
5. Zakia Islam, Resident Medical Officer, Shaheed Ahsanullah Master General Hospital, Tongi
6. Farucul Hasan, Medical Officer, Department of Nephrology, Rangpur Medical College Hospital
7. Samira Khatun, Medical Officer, Upazilla Health Complex, Godagari, Rajshahi.
8. Md. Nazrul Islam, Professor and Head of the Department, Dhaka Medical College

Address of Correspondence: Mahnaz Islam Moitry, Resident Physician, M Abdur Rahim Medical College and Hospital, Dinajpur
E-mail: moitry.islam@gmail.com, Mobile: +88 01717523630

According to the World Health Organization (WHO), 296 million people (about one-third of the global population) are living with chronic Hepatitis B Virus (HBV) infection. More than 75% of this population resides in the Asia Pacific region. Bangladesh is recognized as a country of moderate prevalence together with the Indian subcontinent.[4-6] Prevalence is very high worldwide among some high-risk groups; like drug abusers (30%), HIV patients (15%) and CKD patients.[7] Among CKD patients specially hemodialysis patients, prevalence varies between countries and between different centers within the same country. [8] Patients receiving dialysis in developed countries have 6.2% prevalence whereas, it is around 12% in our country.[9]

In comparison to the Hepatitis C virus (HCV) and Human Immunodeficiency Virus (HIV), Hepatitis B Virus particles are more infectious, they remain viable and infectious for more than 7 days in the environment (medical supplies and utensils at room temperature) which is a real risk for transmission from a small amount of blood or even from infected surfaces that may appear clean.[10] CKD patients are at high risk because of frequent exposure to blood products, use of injectable medications, frequent hospitalization, vascular access for dialysis, from contaminated equipments or through a simple breach on the skin or mucus membranes and above all, due to their compromised immune system.[11]

Once infected they may develop asymptomatic to fatal infections.[12] As these patients are immunocompromised chronicity rate is also high among them. About 5% of CKD and more than 60% patients on hemodialysis become chronic carriers,[10] which in turn increases the risk of contamination to other family members, patients and medical staffs. As a result, there are increasing difficulties for separate medical devices and staff. Antiviral treatment does not result in cure and most patients require prolonged treatment possibly lifelong which increases cost and suffering.[10] So, prevention is the most efficient and cost-effective way to tackle this problem. Routine vaccination is recommended for CKD patients since 1982.[13] But seroconversion rate and antibody titer are much lower and less sustained in this group compared to healthy population.[14] Chronic kidney disease (CKD) patients specially, when they progress to end-stage kidney disease (ESKD) usually have suboptimal responses following hepatitis B vaccination. Compared to response rate over 90- 95% in immunocompetent individuals, only 40- 70% of ESKD patients achieve immune response/ seroconversion following primary vaccination.[15] Few studies reported that CKD patients had higher response rates before they become dialysis dependent.[16] But despite adequate response only approximately 40% can maintain protective titers (>100mIU/ml) 3 years after initial vaccination.[17]

As renal function declines both innate and adaptive immune system becomes dysfunctional. Impairment of immune system in these patients are multifactorial. There are potential links between endothelial dysfunction, uremic toxin, inflammation, malnutrition, anemia, aging, gender, co-morbidities (e.g., diabetes mellitus), obesity, smoking as well as racial, genetic and environmental factors with this immune dysfunction.[6,10,18] Various strategies to improve immune response have been attempted including adding one extra dose of vaccine, doubling the dose from 20 to 40 µg etc. but still the response rate is low. As a result, this group of people are having less protection and remaining in a risk of transmission, despite having vaccination.[19]

One of the targets of Sustainable Development Goal (SDG) is to combat hepatitis and other communicable diseases by 2030.[20] As a fast-growing economy Bangladesh has drawn attention worldwide and achieved success in many indicators of development.[21] As Bangladesh has a moderate prevalence of hepatitis B infection and chronic kidney disease (CKD) patients are regarded as one of the high-risk groups, special attention should be given to this group. Moreover, immune response may vary with geographical location and genetic factors.[22] In our country, there are limited studies in this issue. With this background in mind, this study intends to determine the immune response to Hepatitis B vaccination in CKD patients of our country and to find out possible modifiable factors that might be responsible for non- response. This study may aid in future research and in taking necessary steps while formulating new health policies.

Materials & Methods:

The prospective study was conducted in the Department of Nephrology, Dhaka Medical College Hospital. Total 100 patients distributed in two groups: 50 patients of chronic kidney disease (CKD) stage 3-5 on conservative management and 50 patients on maintenance hemodialysis (MHD) who were advised to start routine Hepatitis B vaccination were included in the study.

Patients with active Hepatitis B virus infection or history of liver disease (Acute or chronic hepatitis and cirrhosis due to Hepatitis B Virus), malignancy, history of organ transplantation, taking immunosuppressive medications (including cytotoxic agents and systemic corticosteroids), HIV/AIDS infection, pregnancy and age <18 years were not considered for enrollment in the study.

Following informed about the study aim, objectives and procedures, informed written consent was taken from each participant. Baseline demographic information of the patients was recorded initially. Detailed history and clinical examination were done focusing on age, gender, underlying cause of CKD, smoking habit, comorbid conditions, medications, weight, height and body mass index (BMI). KDIGO 2012 clinical practice guideline for chronic kidney disease (CKD) was utilized for diagnosis and staging of CKD. CKD patients were withdrawn from the study if their renal function had deteriorated to the point that dialysis was needed.

Each patient who was negative for HBsAg, Anti- HBc (total) and anti- HBs antibody received 40µg (double the usual dose) recombinant DNA Hepatitis B vaccine through intramuscular route in deltoid region at 0, 1, 2 and 6th month schedule. Data regarding Hepatitis B vaccination was documented (e.g., date of the doses, name of vaccine, any reaction etc.)

Following investigations were done in the Department of Laboratory Medicine, Dhaka Medical College Hospital: serum creatinine, complete blood count, serum albumin and HbA1c. Eight weeks after last dose of vaccination anti- HBs antibody titer was measured at Department of Virology, BSMMU by Abott Architect plus ci 4100 machine through chemiluminescence method.

The antibody titer of each patient was recorded in the data collection sheet. "Seroconversion / immune response" was regarded as an antibody titer ≥10mIU/ml. Then study population was subdivided into three groups according to anti- HBs antibody titer as follows: Among responders: `!. Adequate responders (> 100 mIU/ ml) & Inadequate responders (10- 100 mIU/ ml) and non-responder (<10 mIU/ ml). Then different clinical and laboratory variables were compared among them to find out any possible modifiable factors associated with non- response.

Statistical Analysis of the study:

All data was recorded systematically in preformed data collection form. Results were presented as mean ± standard deviation and numbers and percentage for qualitative variables. Data analysis was carried out by using SPSS version 26 (IBM Corp., Armonk, NY). The difference in means or percentages of different variables was calculated using either Unpaired Student's t-tests or ANOVA test for continuous (numerical) variables and Chi-square test for categorical (nominal) variables. ANOVA test was followed by post-Hoc test (Bonferroni) to measure the level of significance between three groups. A logistic regression model was used to identify important predictors of seroconversion. Variables included in multivariate analysis were patient age, BMI, albumin level, hemoglobin level, HbA1c level and eGFR (CKD- EPI formula). All The level of significance was selected as $P < 0.05$.

Results:

This study was conducted in the Department of Nephrology, DMCH. 50 patients of chronic kidney disease (CKD) stage 3-5 on conservative management and 50 patients on maintenance hemodialysis (MHD) who were advised to start routine Hepatitis B vaccination were included in the study. After completion of Hepatitis B vaccination, immune response was observed by measuring Anti-HBs antibody titer after 8 weeks of the last dose. Then according to antibody titer, participants were subdivided into adequate (>100 mIU/ml), inadequate (10-100 mIU/ml) and non-response (<10mIU/ml) groups respectively. Different demographic, clinical and biochemical variables were compared among these groups. Seven patients could not complete vaccination/ lost from the study due to: the COVID-19 pandemic and acute illness, lost to follow-up and death.[1,2,4]

Among the patients of CKD (stage 3-5) on conservative management and 55.1% among the CKD patients on MHD had seroconversion (> 10 mIU/ml titer) following Hepatitis B (HB) vaccination. The study population was divided into three groups according to anti- HBs antibody titer. It was observed that more than half (52.27%) of CKD (Non-Dialytic) patients had shown adequate immune response (> 100mIU/ml), 27.3% had an inadequate immune response (10- 100mIU/ml) and 20.45% had no response (< 10mIU/ml). On the other hand, only one-fourth (20.40%) of MHD patients had an adequate response, 34.7% had inadequate response and 44.9% MHD patients had no immune response after completing full vaccination schedule.

On comparison of different demographic characteristics with immune response, it was observed that adequate responders were comparatively younger than non-responders (44.5± 8.9 vs 56.2± 7.4). There was no significant difference in immune response between males and females. The differences in mean BMI were statistically significant between different immune response groups (22.1±2.1 vs 23.0±3.2 vs 24.3±3.7 kg/m^2 in adequate, inadequate and non-responders respectively). No statistically significant difference was found between smokers and non-smokers. In this current study, it was

observed that individuals with comparatively good renal function (higher eGFR value) had better immune responses. It was observed that patients who achieved adequate immune response, had higher mean eGFR value (30.01 ± 18.5 ml/ min/ 1.73 m² BSA) than non-responders (13.15 ±10.1 ml/ min). It was also observed that patients with better immune status had higher serum hemoglobin and albumin levels than those who had no response. Patients with good glycemic control had better immune response. The differences in eGFR, serum hemoglobin, serum albumin, HbA1c and anti-HBs antibody titer were statistically significant (P<0.05) between the three groups. In multivariate logistic regression analysis among the significant variables that may influence vaccine responsiveness, it was observed that age (OR 2.15), BMI (OR 1.28), serum albumin (OR 1.95) and eGFR (OR 1.10) were independent predictors of immune response; non-responders were older in age with low hemoglobin and albumin, with advanced CKD and higher BMI.

Table I shows the baseline characteristics of the study population. The mean age of CKD stage 3-5 (ND) and MHD patients were 51.02 and 50.2 years respectively. There were no statistically significant differences regarding different clinical and laboratory characteristics between two groups.

Figure 1 showing pattern of immune responses following Hepatitis B vaccination in CKD stage 3-5 (ND) and MHD patients. The study population was divided into three groups according to anti- HBs antibody titer. It was observed that more than half (52.27%) of CKD (ND) patients developed adequate immune response (> 100mIU/ ml), 27.3% inadequate immune response (10- 100mIU/ml) and 20.45% no immune response (< 10mIU/ml) following vaccination. On the other hand, only one-fourth (20.40%) of MHD patients developed adequate immune response, 34.7% had an inadequate immune response and 44.9% of MHD patients developed no immune response despite completion of the full vaccination schedule.

Table II shows the immune response to Hepatitis B

Table-I

Baseline characteristics of the study population (N= 93)

Characteristics	CKD stage 3-5 (ND) (n=44)	MHD (n=49)	*p* value
Age (years)			
Mean ± SD	51.02 ± 10.5	50.2 ± 9.4	0.452^{ns}
Gender			
Male (50)	24 (54.5%)	26 (53.1%)	0.841^{ns}
Female (43)	20 (45.5%)	23 (46.9%)	
BMI (kg/m^2)			
Mean± SD	23.9± 2.9	22.3± 3.2	0.070^{ns}
Smoking status			
Smoker (21)	14 (31.8%)	7 (14.3%)	0.106^{ns}
eGFR (ml/ min/ 1.73 m² BSA)	32.5 ±16.1	—	
Hemoglobin (g/dl)	10.01±1.2	9.08±1.47	0.051^{ns}
Serum Albumin (g/dl)	3.2±0.4	3.02±0.6	0.178^{ns}
HbA1c (%)	6.33±1.63	6.17±1.25	0.583^{ns}

CKD= Chronic kidney disease ND= Non-dialytic MHD = Maintenance hemodialysis BMI= Body mass index ns= not significant

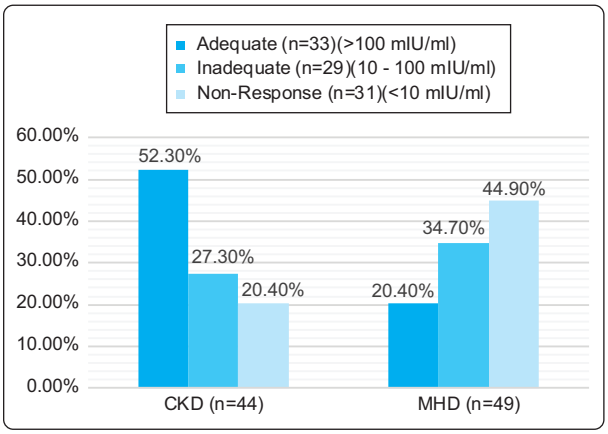

Fig.-1: *Distribution of study population according to the level of anti- HBs antibody titer following Hepatitis B vaccination.*

vaccination in relation to different clinical and laboratory characteristics. It was observed that adequate responders were comparatively younger than non-responders. More than half (51.5%) of the patients who had an adequate response were female but it was not statistically significant. Patients who achieved an adequate immune response, had higher mean eGFR values, serum hemoglobin, and albumin levels than non-responders. Patients with good glycemic control had better immune responses. The differences in age, BMI, eGFR, serum hemoglobin, serum albumin, HbA1c, and anti-HBs antibody titer were statistically significant ($P<0.05$) between three groups.

Table III shows the multivariate logistic regression analysis among the significant variables that may influence vaccine responsiveness. It was observed that age (OR 2.15), BMI

Table-II

Comparison of immune response in relation to different clinical and laboratory variables among CKD patients (N=93)

Variables	Adequate Responder (n=33)	Inadequate Responder (n=29)	Non Responder (n=31)	*p* value
Age (years)				
Mean ± SD	44.5 ±8.9	52.2±9.9	56.2 ± 7.4	0.001^{s}
Gende				
Male (50)	16(48.4%)	17(58.6%)	17(54.8%)	0.719^{ns}
Female (43)	17(51.5%)	12(41.3%)	14(45.1%)	
BMI (Kg/m^2)				
Mean ± SD	22.1±2.1	23.0±3.2	24.3±3.7	0.018^{s}
Smoking status				
Smoker (21)	4(12.12%)	8(27.58%)	9(29.03%)	0.200^{ns}
Non-smoker (72)	29(87.87%)	21(72.41%)	22(70.96%)	
e GFR(ml/ min/ 1.73 m² BSA)	30.01 ± 18.5	19.91 ±11.9	13.15 ±10.1	0.001^{s}
Hemoglobin	10.6±0.79	9.75±0.99	8.14±1.15	0.001^{s}
Serum Albumin	3.47±0.31	3.18±0.39	2.7±0.49	0.001^{s}
HbA1c	5.53±0.19	6.17±1.24	7.07±1.89	0.001^{s}
Anti- HBs Antibody	237.78±132.47	72.97±22.54	6.16±2.67	0.001^{s}

BMI= Body mass index s= significant ns= not significant

Table-III

Multivariate logistic regression analysis among the significant variables that may influence vaccine responsiveness

Variables	B	S.E.	*p* value	OR	95% C.I.	
					Lower	Upper
Age	-0.096	0.062	0.002[s]	2.15	1.21	23.83
BMI	-0.516	0.195	0.026[s]	1.28	1.14	9.45
Albumin	5.117	1.673	0.008[s]	1.95	1.84	17.07
Hemoglobin	1.031	0.537	0.055[ns]	0.36	0.12	1.02
eGFR	0.102	0.046	0.033[s]	1.10	1.97	5.24
HbA1c	0.528	0.351	0.053[ns]	0.59	0.30	1.17

s=significant ns= not significant

(OR 1.28), serum albumin (OR 1.95) and eGFR level (OR 1.10) were independent predictors of immune response following Hepatitis B vaccination in CKD patients.

Discussion:

The discovery of "Australian Antigen" (HBsAg) in 1964 by Dr. Baruch S. Blumberg was one of the most fascinating scientific advances in the world's history. Eventually, this discovery brought the first-ever vaccine against Hepatitis B virus by genetic engineering. It was also the first anti-cancer vaccine; preventing Hepatocellular carcinoma.[23] Vaccination against hepatitis B virus (HBV) brought revolutionary changes, but still, its prevalence is not negligible worldwide. Recently, in developed countries, the prevalence of HBV infection among CKD patients has been reducing due to limited use of blood products, increased use of erythropoiesis-stimulating agents (ESA), provision of high-quality logistic supports, maintaining universal precautions strictly and overall low prevalence among general population.[9,11,19] But in our country the scenario is different: due to financial reasons most of our patients are still dependent on blood transfusion for correction of anemia, healthcare providers are not always strict about maintaining hygiene rules during handling patients, poor resource setting of health care facilities, lack of awareness among the general population, etc. are some reasons behind the high prevalence of HBV in our country.[9]

On observation of immune response, 79.54% among the CKD (stage 3-5) patients and 55.1% of MHD patients achieved seroconversion (> 10 mIU/ml titer) following Hepatitis B vaccination. In healthy adults, the seroconversion rate is usually more than 90%. Patients on conservative management developed more adequate response (52.27%) than patients on MHD (20.40%). In the MHD group, 44.9% patients were non- responders (<10mIU/ml titer) at all. As a result, a significant portion of MHD patients may remain unprotected, despite complete vaccination. There may be a significant degree of inflammation, malnutrition and uremia in patients receiving hemodialysis, which impair antigen presentation and T cell activation and finally cause reduced antibody production.[19] These findings are supported by other studies in different countries.[12,24,25] There is variation in immune response rate in different studies following the same dose and schedule of vaccination. Such differences may be due to various factors such as sample size, age, BMI and gender distribution; presence of comorbidities and possibly, genetic differences between study populations.[11,22]

Immune response pattern was divided into three groups because in different studies it was observed that antibody titers decline with time. Within one-year period, it was found that adequate responders did not become unprotected. But among the inadequate responders, many of them became susceptible to Hepatitis B virus (titer falls < 10mIU/ml) infection before the next routine serological test (which is usually performed 1 year after vaccination as advised by CDC).[24]

When stratified by clinical and laboratory variables, this current study showed a lower response in older adults, males, obese, smokers, advanced CKD patients specially those on dialysis, anemic and in diabetic patients. As degeneration of bone marrow occurs with aging, impairment of humoral and cellular immune response occurs. As a result, there is less seroconversion following vaccination in old age.[26] In this present study, there was no significant difference in immune response between

males and females. This result is supported by a study done by Asan et al.[26]

Regarding observation of BMI in relation to immune response, it was found that patients having extreme BMI (either underweight or obese) had lower immune response than normal. Another study done by Al Saran et al stated that there was no significant difference in BMI among response groups, which did not support our study.[27] But Asan et al stated that BMI ≥30 kg/m² has a significant association with non-response to Hepatitis B vaccine.[26] There may be multiple reasons behind this reduced immune response in obese patients such as - the amount of HBsAg in the vaccine may be too low in relation to body mass, substantial immune dysfunction in obese population due to hyperinsulinemia and hyperlipidemia and may be needles were too short to reach the muscle.[28]

This present study showed malnutrition was also associated with poor immune response and among MHD patients there were more underweight patients (14%) than CKD. Four out of 7 underweight patients were in the non-response group. Patients from both groups with higher serum albumin and hemoglobin levels had shown better immune responses. These findings were supported by other studies, where they stated that malnutrition is a recognized reason for poor response to the Hepatitis B vaccine as it impairs the ability to form antibodies.[12,29] Smoking has a bad impact on immune response and in our study, there were less response in smokers to HB vaccination. However it was not statistically significant. This was supported by the study by Meier and Berger.[2]

In this current study, it was observed that individuals with comparatively good renal function (higher eGFR value) had better immune responses. These findings were supported by Ghadiani et al and DaRoza et al.[25,30] As in earlier stages of CKD, patients are supposed to have better general conditions (less chance of malnutrition, uremia, anemia etc.) they can achieve better immune response following Hepatitis B vaccination.

In this current study, no significant association between the underlying causes of CKD and immune response was found. However patients with diabetes mellitus had comparatively less immune response than others. There are controversial findings about the effect of diabetes mellitus on the seroconversion rates. Al Saran et al stated that diabetes mellitus has no significant effect on seroconversion.[27] On the other hand, El-Charabaty et al stated that diagnosis of diabetes mellitus is an independent risk factor of being a non-responder to the vaccine.[12] Such conflicting influence of the diabetic state on the response to Hepatitis B vaccine between populations may be related to genetic differences between populations.[11] Diabetes mellitus is associated with HLA DQ- 2,3 and DR- 3,4 which may impair antigen presentation and suppress T-cell responses.[31] However, in our study it was found that good control of glycemic status was associated with good immune response though it was not found to be an independent predictor of seroconversion in multivariate analysis. These findings were consistent with Schillie et al.[32]

A multivariate regression analysis was performed using significant variables. The results showed that age (OR 2.15), serum albumin (OR 1.95), BMI (OR 1.28) and e GFR (OR 1.10) were independent predictors of seroconversion following Hepatitis B vaccine. These findings were supported by other studies conducted in different countries worldwide.[25,27,29]

Conclusion:

This study showed that the immune response after Hepatitis B vaccination was better in CKD patients (stage 3-5) who were not on dialysis. A significant number of patients who are on maintenance dialysis remain unprotected despite completing scheduled vaccination. Moreover, better immune response was observed in patients who were younger with normal BMI and higher serum albumin levels. So, Hepatitis B Vaccination may be recommended at earlier stages if possible, preferably before starting dialysis.

Limitations

- It was a cross-sectional study; hence sustainability of immune response could not be observed.
- Genetic analysis could not be done

Recommendation

- Vaccination during early stages of CKD; possibly when they are younger and in better general condition and without significant comorbidities.
- Modification of certain factors that may interfere with the immune response: i.e., Lifestyle modification: physical activity, balanced diet to maintain proper nutrition and avoid malnutrition and obesity, control of hyperglycemia, correction of anemia, cessation of smoking.

- Further large cohort study for any change in vaccination protocol as there are racial, regional and genetic variations in immune response.
- The patients in whom we can predict to have non-response, alternative dosage, formulations and route of Hepatitis B vaccine can be used. Newer formulation: Heplisav, Fendrix; increasing the usual dose (60µg), using intradermal route etc. may be a promising choice.
- Further Genetic analysis in Bangladeshi population.
- Development of a specialized and individualized immunization protocol and monitoring program for advanced kidney disease patients.

References:

1. Kaze FF, Meto DT, Halle MP, Ngogang J, Kengne AP. Prevalence and determinants of chronic kidney disease in rural and urban Cameroonians: a cross-sectional study. BMC nephrology. 2015 Dec;16(1):1-0.
2. Fabrizi F, Cerutti R, Dixit V, Ridruejo E. Hepatitis B virus vaccine and chronic kidney disease. The advances. Nefrología (English Edition). 2021 Mar 1;41(2):115-22.
3. Jha V, Prasad N. CKD and infectious diseases in Asia Pacific: challenges and opportunities. American Journal of Kidney Diseases. 2016 Jul 1;68(1):148-60.
4. Who.int. 2021. *Hepatitis B*. [online] Available at: <https://www.who.int/news-room/fact- sheets/detail/hepatitis-b> [Accessed 16 April 2021].
5. Mahtab MA, Rahman S, Karim MF, Khan M, Foster G, Solaiman S, Afroz S. Epidemiology of hepatitis B virus in Bangladeshi general population. Hepatobiliary & pancreatic diseases international: HBPD INT. 2008 Dec 1;7(6):595-600.
6. Somi MH, Hajipour B. Improving hepatitis B vaccine efficacy in end-stage renal diseases patients and role of adjuvants. International Scholarly Research Notices. 2012;2012.
7. Amjad A, Kumar J, Chaudary N, Kumar K, Nazar CM, Khan K. Hepatitis B Vaccination status in chronic kidney disease: Experience at Pakistan institute of medical sciences. Cureus. 2019 Jul 30;11(7).
8. Shamim M, Khan MA, Biswas PS, Islam M, Mukta P. Prevalence of Hepatitis B Infection Among Kidney Patient Attending for Haemodialysis in Gazi Medical College Centre, Khulna, Bangladesh.
9. Hossain RM, Iqbal MM, Rahman ZF, Sultana R, Rahman MH, Islam MN, Khan NN, Mansur MA, Rahman MA, Iqbal S, Hassan MS. Hepatitis B and Hepatitis C Virus Infection among End Stage Renal Disease Patients on Maintenance Hemodialysis, Their Family Members and Dialysis Staffs-A Prevalence Study. BIRDEM Medical Journal. 2018;8(1): 42-6.
10. Urbánek P. Viral hepatitis infections in chronic kidney disease patients and renal transplant recipients. Kidney and Blood Pressure Research. 2013 Jun 6;35(6):454-67.
11. Almueilo SH. Evaluation of response to hepatitis B vaccination in chronic hemodialysis patients. Saudi Journal of Medicine & Medical Sciences. 2017 Sep;5(3):218.
12. El-Charabaty E, Saifan C, Samarneh MM, El-Sayegh S. Variability in response to hepatitis B vaccine in hemodialysis patients. Journal of Clinical Medicine Research. 2015 May;7(5):315.
13. Centers for Disease Control and Prevention. Recommendations for preventing transmission of infections among chronic hemodialysis patients. MMWR. 2001; 50:1-43.
14. Hashemi B, Mahdavi-Mazdeh M, Abbasi M, Hosseini-Moghaddam SM, Zinat NH, Ahmadi F. Efficacy of HBV vaccination in various stages of chronic kidney disease: is earlier better? Hepatitis Monthly. 2011 Oct 10;11(10):816.
15. Elhanan E, Boaz M, Schwartz I, Schwartz D, Chernin G, Soetendorp H, Gal Oz A, Agbaria A, Weinstein T. A randomized, controlled clinical trial to evaluate the immunogenicity of a PreS/S hepatitis B vaccine Sci-B-Vac™, as compared to Engerix B®, among vaccine naïve and vaccine non-responder dialysis patients. Clinical and experimental nephrology. 2018 Feb;22(1):151-8.
16. Janssen RS, Mangoo-Karim R, Pergola PE, Girndt M, Namini H, Rahman S, Bennett SR, Heyward WL, Martin JT. Immunogenicity and safety of an investigational hepatitis B vaccine with a toll-like receptor 9 agonist adjuvant (HBsAg-1018) compared with a licensed hepatitis B vaccine in patients with chronic kidney disease. Vaccine. 2013 Nov 4;31(46):5306-13.
17. Eleftheriadis T, Antoniadi G, Liakopoulos V, Kartsios C, Stefanidis I. Basic science and dialysis: disturbances of acquired immunity in hemodialysis patients. InSeminars in dialysis 2007 Sep (Vol. 20, No. 5, pp. 440-451). Oxford, UK: Blackwell Publishing Ltd.
18. Haddiya I. Current knowledge of vaccinations in chronic kidney disease patients. International Journal of Nephrology and Renovascular Disease. 2020; 13:179.
19. Nahar K, Jahan M, Nessa A, Tabassum S. Antibody responses after hepatitis B vaccination among maintenance haemodialysis patients. Bangladesh Medical Research Council bulletin. 2011;37(3):88-91.
20. Mustafa MG, Alam MS, Azam MG, Alam MM, Islam MS, Khan M. Eliminating Hepatitis B from Bangladesh by the Year 2030. Journal of Bangladesh College of Physicians and Surgeons. 2020 May 12;38(3):145-9.
21. Munir MH. Bangladesh Needs to Fight Against Illicit Finance Flow and to Achieve SDGs. report. www. socialwatch. org/node/18286. 2019.
22. Shaha M, Hoque SA, Ahmed MF, Rahman SR. Effects of risk factors on anti-HBs development in hepatitis B vaccinated

and nonvaccinated populations. Viral immunology. 2015 May 1;28(4):217-21.

23. Zhao H, Zhou X, Zhou YH. Hepatitis B vaccine development and implementation. Human vaccines & immunotherapeutics. 2020 Jul 2;16(7):1533-44.

24. Ayub MA, Bacci MR, Fonseca FL, Chehter EZ. Hemodialysis and hepatitis B vaccination: a challenge to physicians. International journal of general medicine. 2014;7:109.

25. Ghadiani MH, Besharati S, Mousavinasab N, Jalalzadeh M. Response rates to HB vaccine in CKD stages 3-4 and hemodialysis patients. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences. 2012 Jun;17(6):527.

26. Asan A, Demirhan H, Sorkun HÇ, Özkan S, Aydýn M, Akýn D, Tatar B, Çatak B, Þener A, Köse Þ. Factors affecting responsiveness to hepatitis B immunization in dialysis patients. International urology and nephrology. 2017 Oct;49(10):1845-50.

27. Al Saran K, Sabry A, Al Halawany Z, Ismail M. Factors affecting response to hepatitis B vaccine among hemodialysis patients in a large Saudi Hemodialysis Center. Saudi Journal of Kidney Diseases and Transplantation. 2014 Jan 1;25(1):185.

28. Meier MA, Berger CT. A simple clinical score to identify likely hepatitis B vaccination non-responders–data from a retrospective single center study. BMC Infectious Diseases. 2020 Dec;20(1):1-6.

29. Cordova E, Miglia I, Festuccia F, Sarlo MG, Scornavacca G, Punzo G, Menè P, Fofi C. Hepatitis B vaccination in haemodialysis patients: an underestimated problem. Factors influencing immune responses in ten years of observation in an Italian haemodialysis centre and literature review. Ann Ig. 2017 Jan 1;29(1):27-37.

30. DaRoza G, Loewen A, Djurdjev O, Love J, Kempston C, Burnett S, Kiaii M, Taylor PA, Levin A. Stage of chronic kidney disease predicts seroconversion after hepatitis B immunization: earlier is better. American journal of kidney diseases. 2003 Dec 1;42(6):1184-92.

31. Mormile R, Pannullo G. Hepatitis B Vaccine Nonresponse: An Alarm Signal for Latent Type 1 Diabetes. J Diabetes Metab. 2013;4(6).

32. Schillie SF, Spradling PR, Murphy TV. Immune response of hepatitis B vaccine among persons with diabetes: a systematic review of the literature. Diabetes care. 2012 Dec 1;35(12):2690-7.

Histopathological Pattern of Patients with Chronic Kidney Disease of Unknown Aetiology

Hossain MR[1], Khan ASMF[2], Chowdhury MN[3], Islam MN[4]

Abstract

***Background:** Chronic kidney disease (CKD) is a global public health issue. Epidemics of CKD of unknown etiology (CKDu) are emerging around the world.*

***Objective:** This study aimed to find out the histopathological features of CKDu patients.*

***Methods:** This cross-sectional study was conducted in the Department of Nephrology, Dhaka Medical College Hospital, Dhaka from January 2017 to December 2017. Thirty-four patients with CKDu were evaluated. Patients with diabetes mellitus, hypertension, glomerulonephritis, and bilateral contracted kidneys were excluded from the study. All patients underwent a thorough clinical examination, which included vital signs and anthropometric measurements, as well as examination of respiratory system, cardiovascular system, alimentary system and nervous system. All eligible patients who have given informed written consent were subjected to an ultrasound-guided renal biopsy. For statistical analysis, SPSS 12.0 was used.*

***Results:** Mean age of the patients was 36.2 ± 11.4 years. Males (70.6%) were predominant than female (29.4%). Most of the patients were from rural area. Maximum patients were farmers (35.3%). Fifty percent patients had smoking habit and 3 (8.8%) patients consumed alcohol. In this study, 4 (11.8%) patients had family history of CKD. Six (17.6%) patients had agrochemical and 1 (2.9%) patient had history of industrial chemical exposure. Most of the patients had chronic tubulointerstitial nephritis (44.1%) followed by focal segmental glomerulosclerosis (14.7%), membranoproliferative glomerulonephritis (14.7%), chronic sclerosing glomerulonephritis (11.8%), IgA nephropathy (5.9%), cresentic glomerulonephritis, amyloidosis of kidney and C3 glomerulonephritis each 2.9%. In this study, maximum (44.1%) patients were in CKD stage 4 followed by stage 3b (35.3%), stage 5 (11.8%) and stage 3a (8.8%). Mean serum creatinine was 3.19 ± 2.34 mg/dl and mean eGFR was 26.91 ± 12.24 ml/min/1.73 m^2 in this study. Mean proteinuria was 1.40 ± 0.68 gm/day. Urine albumin was (+1) in 12 (35.3%) patients and (+2) in 7 (20.6%) patients.*

***Conclusion:** Predominant histopathological patterns of CKDu are chronic tubulointerstitial nephritis with various pattern of glomerulonephritis.*

***Keywords:** chronic kidney disease; chronic kidney disease with unknown etiology; estimated glomerular filtration rate; renal biopsy, tubulo-interstitial disease.*

(Bang. Renal J. 2023; 5(2): 41-45

Introduction:

A condition known as chronic kidney disease (CKD) is characterised by a progressive decline in kidney function over time. It includes a variety of clinical and laboratory abnormalities that show up as a chronic and progressive decline in renal functions.

The composite median prevalence of CKD is 7.2% in people aged 30 or older, according to a systematic review of population-based studies conducted across the globe.[1] In many countries, CKD without a clear aetiology has been reported. Balkan endemic nephropathy, which was first identified in Bulgaria, Bosnia, Croatia, Romania, and Serbia in the 1950s, is a well-known example.[2] Epidemics of chronic kidney disease with unknown aetiology have started to appear in Sri Lanka, Central America, and southern Mexico since the beginning of the twenty-first century.[3-7] Rural areas of Egypt's El-Minya and Canal Governorates as well as the coastal regions of India's Andhra Pradesh are also affected.[8,9] Most of the areas mentioned above are agricultural lands where agrochemicals are used intensively.

Major aetiological factors for CKD include hypertension and diabetes mellitus. Patients without the traditional risk factors have different etiological profiles of CKD.[10]

1. Mohammad Rezaul Hossain, Assistant Registrar, Department of Nephrology, Colonel Maleque Medical College Hospital, Manikganj
2. A.S.M Farhad Khan, Junior Consultant (Nephrology), Kuwait- Bangladesh Friendship Govt. Hospital, Uttara, Dhaka.
3. Md. Nizamuddin Chowdhury, Head of the Department of Nephrology, BRB Hospital, Panthopath,Dhaka
4. Md Nazrul Islam, Head of the Department of Nephrology, Dhaka Medical College, Dhaka

Address of Correspondence: Mohammad Rezaul Hossain, Assistant Registrar, Department of Nephrology, Colonel Maleque Medical College Hospital, Manikganj. Email: dr.rezaul38@gmail.com, Mobile: +88 01717497061

According to several studies, chronic kidney disease has become increasingly prevalent without being caused by usual risk factors like diabetes, high blood pressure, glomerulonephritis, or obstructive nephropathy. Populations in central America, southern Asia, and Egypt are among those who are affected.[3-9] Although the exact causes are unknown, there is growing evidence that chemicals used in agriculture are to blame. According to research, pesticides, herbicides, fungicides, insecticides, and fertilisers have negative effects on human health, including kidney damage.[11] Ochratoxin A, fluoride (in combination with sodium and calcium), and heavy metals like cadmium are examples of potential etiological agents.[12-14]

CKDu was most frequently associated with a family history of CKDu, agricultural occupation, men, middle age, contaminated water supplies, smoking, alcohol intake, heat stress.[15]

Interstitial fibrosis and tubular atrophy, with or without nonspecific interstitial mononuclear cell infiltration, were found to be the most common histopathological features in CKDu patients. Glomerular sclerosis, glomerular collapse, and features of vascular pathology such as fibrous intimal thickening and arteriolar hyalinosis are also prevalent.[16] Tubular damage has also been identified as an early pathophysiological mechanism, as evidenced by increased excretion of the tubular marker alpha 1 microglobulin and N-acetyl-beta-D: Glucosaminidase in the urine of CKDu patients.[16] The purpose of this research was to identify clinical, laboratory and histological features of CKDu.

Methods:

It was a cross-sectional study, conducted in the Department of Nephrology, Dhaka Medical College Hospital, Dhaka from January 2017 to December 2017. A total of 34 adult clinically diagnosed CKDu patients with normal sized kidney were included in this study as per selection criteria. Patients with diabetes mellitus, hypertension, glomerulonephritis, bilateral contracted kidney, urological diseases, systemic diseases like systemic lupus erythematosus, vasculitis, multiple myeloma were excluded from this study.

After selection of the patient; aims, objectives and procedures of the study was explained with understandable language to the patient. Risks and benefits were also made clear to the patient. The patients were encouraged for voluntary participation and they were allowed being free to withdraw themselves from the study. Then, informed written consent was taken from each patient. All patients underwent a thorough clinical examination, which included vital signs, respiratory, cardiovascular, gastrointestinal and nervous system examinations. Sociodemographic and epidemiological data were also recorded. Ultrasound-guided renal biopsy was performed on all eligible, consenting patients. Histological examination was done by consultant pathologists. Immunofluorescence studies were performed. All biopsy specimens were assessed for adequacy.

Statistical analysis of the study was done by computer software device as the Statistical Package for Social Science (SPSS-12.0). The results were presented as tables, figures and diagrams. Categorical data were presented as frequency and percentage and numerical data as mean and standard deviation. P value of <0.05 was considered statistically significant.

Results:

Total patients were 34, including 24 males. Mean age of the study participants was 36.2 years. Males (70.6%) were predominant. Most of the patients were from rural area (94.1%). Base-line characteristics are shown in Table I.

Table-I

Base-line characteristics of the study participants (N = 34)

	Frequency	Percentage
Age (years)		
20 – 29	9	26.5
30 – 39	11	32.4
≥40	14	41.2
Total	34	100.0
Mean ± SD	36.2 ± 11.4	
Min-max	20 – 70	
Gender		
Male	24	70.6
Female	10	29.4
Residence		
Rural	32	94.1
Urban	2	5.9
Habit		
Smoking	17	50
Alcohol	3	8.8
Drug history		
Chronic analgesic	12	35.5
Herbal	7	20.6
Family history of CKD	4	11.8
Chemical exposure		
Agrochemical	6	17.6
Industrial chemical	1	2.9

Table-II

Distribution of patients according to occupation

Occupation	Frequency	Percentage
Farmer	12	35.3
Employed	5	14.7
Housewife	9	26.5
Student	6	17.6
Industrial worker	2	5.9
Total	34	100.0

Table II shows maximum patients were farmer followed by housewife (26.5%), student (17.6%), employed (14.7%) and industrial worker (5.9%) (Table II).

Table-III

Laboratory findings of the study subjects.

	(Mean ± SD)/ n	(Min – Max)/ %
Serum creatinine (mg/dl)	3.19 ± 2.34	1.60 – 13.48
eGFR	26.91 ± 12.24	5.00 – 57.00
Proteinuria(gm/day)	1.40 ± 0.68	0.30 – 2.90
RBC/HPF (Urine)	4.06 ± 7.65	0 – 40
Albumin (Urine)		
Nil	9	26.5
Trace	6	17.6
+	12	35.3
++	7	20.6

Table III shows mean serum creatinine was 3.19 ± 2.34 mg/dl, mean eGFR was 26.91 ± 12.24 ml/min. mean proteinuria was 1.40 ± 0.68 gm/day.Seven (20.6%) patients had albumin (++) and 12 (35.3%) had albumin (+).

Table-IV

Distribution of patients according to renal histology

Renal histology	Frequency	Percentage
Chronic tubulointerstitial nephritis (TIN)	15	44.1
Crescentic GN(Fibrous)	1	2.9
Amyloidosis kidney	1	2.9
Chronic sclerosing GN	4	11.8
IgA Nephropathy	2	5.9
Focal segmental Glomerulosclerosis	5	14.7
Membranoproliferative GN	5	14.7
C3 GN	1	2.9

Most of the patients had chronic tubulointerstitial nephritis (44.1%) followed by focal segmental glomerulosclerosis (14.7%), membranoproliferative glumerulonephritis (14.7%), chronic sclerosing glumerulonephritis (11.8%), IgA nephropathy 5.9% and crescentic glumerulonephritis (Fibrous), amyloidosis kidney and C3 glumerulonephritis each 2.9% (Table IV).

Table V shows laboratory findings of the patients in chronic TIN and various pattern of glomerulonephritis. No significant difference was observed in serum creatinine, eGFR and proteinuria between two groups.

History of chronic analgesic user is significantly high among the chronic TIN patients (Table VI).

Table V

Laboratory findings of the study subjects (n=34)

	Chronic TIN	Various pattern of Glomerulonephritis	p-value
Serum creatinine (mg/dl)	2.78 ± 0.81	3.52 ± 3.05	0.607
eGFR	26.33 ± 9.32	27.37 ± 14.38	0.656
Proteinuria	1.41 ± 1.39	1.86 ± 1.29	0.063

Mann Whitney U test was done to find the level of significance

Table-VI

Risk factors of CKDu in different type of histopathologic findings

	Chronic tubulointerstitial nephritis	Various pattern of Glomerulonephritis	p-value
History of smoking	7 (46.7)	10 (52.6)	0.730
History of chronic analgesic taking	10 (66.7)	2 (10.5)	0.001
Farmer	7 (46.7)	5 (26.3)	0.218

Chi-square test was done to find the level of significance

Discussion:

In this study mean age of the patients were 36.2 years. In the study of Selvarajah et al. (2016) mean age of the CKDu patient was 46 years.[17]

In terms of gender, males (70.6%) outnumbered females (29.4%). The male-female ratio was 2.4:1. Selvarajah et al. (2016) and Senevirathna et al. (2016) found a similar male predominance (2012).[17,18]

The majority of the patients in this study came from rural areas. Farmers were the most common patients. According to the findings of Selvarajah et al. in 2016, the majority of the patients were from rural Sri Lanka.[17] According to Wesseling et al. (2013), CKDu primarily affects rural agricultural workers in Central America.[19]

Half of the patients had smoking habit, one third took chronic analgesic drugs and 17.6% of patients had agrochemical exposure. Associations were reported with agricultural work, agrochemical exposure, dehydration, homemade alcohol use and family history of chronic kidney disease.[20]

Four (11.8%) of the patients in this study had a family history of CKD. Selvarajah et al. (2016) discovered that 35.8% of patients had a family history of CKD.[17] Similar associations were investigated in native tribes of New Mexico with CKDu patients. The clustering of patients suggests a polygenic inheritance pattern and exposure to the same risk factors.[21]

In this study, the most diagnosis was chronic tubulointerstitial nephritis. Selvarajah et al.[17] discovered that the most common histopathological forms of CKDu were consistent with chronic tubulointerstitial nephritis. Badurdeen et al. revealed that histology was consistent with interstitial nephritis, with acute and chronic tubulointerstitial lesions and glomerular scarring.[25] Almaguer, Herrera, and Orantes discovered that chronic tubulointerstitial nephritis was the most common histopathological diagnosis.[20]

The majority of the patients (44.1%) in this study were in stage 4 followed by stage 3b (35.3%), stage 5(11.8%) and stage 3a(8.8%). Selvarajah et al. found that the CKD stages of CKDu patients were stage 2 (15.2%), stage 3 (61.4%), and stage 4 (20.8%).[17] Wijetunge et al. discovered 79.2%, 55.0%, 49.1%, and 50.0% at the time of biopsy in stages 1, 2, 3, and 4, respectively.[26]

In this study, the mean serum creatinine was 3.19 ± 2.34 mg/dl and the mean eGFR was 26.91 ± 12.24. According to Selvarajah et al. (2016),[17] the CKDu patients had a mean serum creatinine of 1.9 ± 0.79 mg/dl and an eGFR of 43.3 ± 17.60. The average RBC was 4.06 ± 7.65 HPF. Selvarajah et al. (2016) noticed that RBC was nil in 57.6% of cases, <5 in 32.8% of cases and >5 in 9.6% of cases.[17] The average proteinuria (UTP) was 1.40 ± 0.68.

A urinary dipstick revealed that 26.5% of patients had nil proteinuria, 17.6% of patients had trace proteinuria, 35.3% had (+1) proteinuria, 20.6% had (+2) proteinuria. Selvarajah et al. (2016) found that 25.6% of patients had undetectable proteinuria, 28.8% had trace proteinuria, 24% had (+1) proteinuria, 22% had (+2) proteinuria, and 4% had (+3) proteinuria as measured by a urinary dipstick.[17]

Limitations

There are some limitations in this study. Some are mentioned below

1. The study population was selected from one selected hospital in Dhaka city so that the results of the study may not reflect the exact picture of the country.
2. Small sample size was also a limitation of the present study.
3. Electron microscopic examination was not done because of lack of facilities.

Recommendations

1. Further studies can be undertaken by including large number of patients.

Conclusion

In this study, among CKDu patients, males were predominant, and most of the patients were from rural areas, aged between 20 and 70 with a positive history of agricultural workers, a smoking habit, and chronic analgesic use. Furthermore, the predominant histopathological pattern of are chronic tubulointerstitial nephritis followed by various forms of glomerulonephritis.

References:

1. Zhang QL, Rothenbacher D. Prevalence of chronic kidney disease in population-based studies: systematic review. BMC public health. 2008 Dec;8(1):1-3.doi: 10.1186/1471-2458-8-117;2008
2. Grollman AP, Jelakoviæ B. Role of environmental toxins in endemic (Balkan) nephropathy. Journal of the American Society of Nephrology. 2007 Nov 1;18(11):2817-23. DOI: 10.1681/ASN.2007050537;2007
03. Gorry C. Sounding the alarm on chronic kidney disease in farming communities: María Isabel Rodríguez, MD. MEDICC Review. 2013 Sep 29;15(3):8-10. DOI: 10.37757/MR2013V15.N3.3;2013

04. Athuraliya NT, Abeysekera TD, Amerasinghe PH, Kumarasiri R, Bandara P, Karunaratne U, Milton AH, Jones AL. Uncertain etiologies of proteinuric-chronic kidney disease in rural Sri Lanka. Kidney international. 2011 Dec 1;80(11):1212-21.DOI: 10.1038/ki.2011.258;2011

05. Torres C, Aragón A, González M, López I, Jakobsson K, Elinder CG, Lundberg I, Wesseling C. Decreased kidney function of unknown cause in Nicaragua: a community-based survey. American Journal of Kidney Diseases. 2010 Mar 1;55(3):485-96.DOI: 10.1053/j.ajkd.2009.12.012;2010

06. Cerdas M. Chronic kidney disease in Costa Rica. Kidney International. 2005 Aug 1;68:S31-3.Doi.org/10.1111/j.1523-1755.2005.09705.x;2005

07. Brooks DR, Ramirez-Rubio O, Amador JJ. CKD in Central America: a hot issue. American Journal of Kidney Diseases. 2012 Apr 1;59(4):481-4. Doi.org/10.1053/j.ajkd.2012.01.005;2012

08. El Minshawy O. End-stage renal disease in the El-Minia Governorate, upper Egypt: an epidemiological study. Saudi Journal of Kidney Diseases and Transplantation. 2011 Sep 1;22(5):1048-54.

09. Reddy DV, Gunasekar A. Chronic kidney disease in two coastal districts of Andhra Pradesh, India: role of drinking water. Environmental geochemistry and health. 2013 Aug; 35:439-54.

10. Chandrajith R, Nanayakkara S, Itai K, Aturaliya TN, Dissanayake CB, Abeysekera T, Harada K, Watanabe T, Koizumi A. Chronic kidney diseases of uncertain etiology (CKDue) in Sri Lanka: geographic distribution and environmental implications. Environmental geochemistry and health. 2011 Jun; 33:267-78. DOI: 10.1007/s10653-010-9339-1;2011

11. Mostafalou S, Abdollahi M. Pesticides and human chronic diseases: evidences, mechanisms, and perspectives. Toxicology and applied pharmacology. 2013 Apr 15;268(2):157-77.

12. Peiris-John RJ, Wanigasuriya JK, Wickremasinghe AR, Dissanayake WP, Hittarage A. Exposure to acetylcholinesterase-inhibiting pesticides and chronic renal failure. Ceylon Med J. 2006.DOI: 10.4038/cmj. v51i1.1382 ;2006

13. Wanigasuriya KP, Peiris H, Ileperuma N, Peiris-John RJ, Wickremasinghe R. Could ochratoxin A in food commodities be the cause of chronic kidney disease in Sri Lanka? Transactions of the Royal Society of Tropical Medicine and Hygiene. 2008 Jul 1;102(7):726-8. DOI: 10.1016/j.trstmh.2008.04.007 ;2008

14. Chandrajith R, Dissanayake CB, Ariyarathna T, Herath HM, Padmasiri JP. Dose-dependent Na and Ca in fluoride-rich drinking water—another major cause of chronic renal failure in tropical arid regions. Science of the total environment. 2011 Jan 15;409(4):671-5. Doi.org/10.1016/j.scitotenv.2010.10.046;2011

15. Lunyera J, Mohottige D, Von Isenburg M, Jeuland M, Patel UD, Stanifer JW. CKD of uncertain etiology: a systematic review. Clinical journal of the American Society of Nephrology: CJASN. 2016 Mar 3;11(3):379. DOI: 10.2215/CJN.07500715;2016

16. Nanayakkara S, Senevirathna ST, Karunaratne U, Chandrajith R, Harada KH, Hitomi T, Watanabe T, Abeysekera T, Aturaliya TN, Koizumi A. Evidence of tubular damage in the very early stage of chronic kidney disease of uncertain etiology in the North Central Province of Sri Lanka: a cross-sectional study. Environmental health and preventive medicine. 2012 Mar;17(2):109-17. DOI: 10.1007/s12199-011-0224-z ;2012

17. Selvarajah M, Weeratunga P, Sivayoganthan S, Rathnatunga N, Rajapakse S. Clinicopathological correlates of chronic kidney disease of unknown etiology in Sri Lanka. Indian journal of nephrology. 2016 Sep;26(5):357. DOI: 10.4103/0971-4065.167280 ;2016

18. Senevirathna L, Abeysekera T, Nanayakkara S, Chandrajith R, Ratnatunga N, Harada KH, Hitomi T, Komiya T, Muso E, Koizumi A. Risk factors associated with disease progression and mortality in chronic kidney disease of uncertain etiology: a cohort study in Medawachchiya, Sri Lanka. Environmental health and preventive medicine. 2012 May;17(3):191-8. doi: 10.1007/s12199-011-0237-7;2012

19. Wesseling C, Crowe J, Hogstedt C, Jakobsson K, Lucas R, Wegman DH. The epidemic of chronic kidney disease of unknown etiology in Mesoamerica: a call for interdisciplinary research and action. American journal of public health. 2013 Nov;103(11):1927-30.

20. Almaguer M, Herrera R, Orantes CM. Chronic kidney disease of unknown etiology in agricultural communities. MEDICC review. 2014 Apr;16(2):09-15.

21. Wanigasuriya K. Update on uncertain etiology of chronic kidney disease in Sri Lanka's north-central dry zone. Medicc Review. 2014;16:61-5.

22. Allen WR, Travis LB, Cavallo T, Brouhard BH, Cunningham III RJ. Immune deposits and mesangial hypercellularity in minimal change nephrotic syndrome: clinical relevance. The Journal of Pediatrics. 1982 Feb 1;100(2):188-91. Doi.org/10.1016/S0022-3476(82)80632-X;1982

23. Schoeneman MJ, Bennett B, Greifer I. The natural history of focal segmental glomerulosclerosis with and without mesangial hypercellularity in children. Clinical Nephrology. 1978 Feb 1;9(2):45-54.

24. Sterzel RB, Schulze-Lohoff E, Marx M. Cytokines and mesangial cells. Kidney International Supplement. 1993 Jan 2(39).

25. Badurdeen Z, Nanayakkara N, Ratnatunga NV, Wazil AW, Abeysekera TD, Rajakrishna PN, Thinnarachchi JP, Kumarasiri R, Welagedera DD, Rajapaksha N, Alwis AP. Chronic kidney disease of uncertain etiology in Sri Lanka is a possible sequel of interstitial nephritis!. Clinical nephrology. 2016;86(7):106. DOI: 10.5414/CNP86S115, 2016

26. Wijetunge S, Ratnatunga NV, Abeysekera TD, Wazil AW, Selvarajah M. Endemic chronic kidney disease of unknown etiology in Sri Lanka: Correlation of pathology with clinical stages. Indian journal of nephrology. 2015 Sep;25(5):274. doi: 10.4103/0971-4065.145095;2015.

Detection of Lupus Nephritis and Assessment of Disease Activity with Serum Soluble Interleukin-2 Receptor Alpha

Ahmed SI[1], Faisal ARM[2], Singha AK[3], Khan SB[4], Rahman HMM[5], Alam MR[6], Mizan MSB[7], Hossain MS[8]

Abstract

Background: *Systemic Lupus Erythematosus (SLE) is a multi-system auto-immune disease resulting from auto-antibody mediated inflammation of different organs. Lupus nephritis (LN) is one of the most serious manifestations of systemic lupus erythematosus (SLE) which can involve all four renal compartments: glomeruli, tubules, interstitium and blood vessels. Higher levels of serum soluble interleukin-2 receptor alpha (sIL-2R alpha) were found to be related to severe lupus nephritis. The specificity of sIL-2R alpha was shown to be higher and more significant than that of other markers (anti-dsDNA, C3, C4) in the diagnosis of renal flares.*

Objective: *The main objective of this study was to compare Serum sIL-2R alpha with other commonly used markers as diagnostic and disease activity assessment tool in lupus nephritis.*

Methods: *This cross-sectional study was conducted in the Department of Nephrology and Department of Rheumatology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from February 2018 to July 2018. Normal healthy populations and newly diagnosed patients with active SLE with or without renal involvement were enrolled as the study population. ACR 1997 criteria is used for the diagnosis of SLE. Patients with SLE, suspected to have lupus nephritis on the basis of urine RME, 24 hour UTP, anti-dsDNA, C3, C4, underwent renal biopsy and confirmed as lupus nephritis were enrolled in group A. According to the histological findings Group A patients were divided into different classes. Group B consisted of patients with active SLE without renal involvement and group C consisted with healthy population with no family history of connective tissue disease. Serum soluble interleukin-2 receptor alpha level was measured in all the three groups. Renal histology obtained was classified according to ISN/RPS 2004 criteria. SLE disease activity and LN activity was measured as per SELENA-SLEDAI and Renal-SLEDAI score.*

Results: *Most (72.4%) patients had severe disease activity in group A with mean renal activity score 10 ± 3.8. Serum IL-2R alpha levels were significantly higher in patients of group A than group B (1525.28 ± 716.32 vs 144.20 ± 147.85 ng/L). Serum IL-2R alpha level positively correlated with renal activity score and negatively with C3 in LN patients. Class III and IV LN patients had higher Serum IL-2R alpha levels than Class II and V.*

Conclusions: *Serum sIL-2R alpha might be a valuable serological biomarker to diagnose and to monitor disease activity of lupus nephritis.*

Keywords: *SLE; serum sIL-2Rα; disease activity; lupus nephritis.*

(Bang. Renal J. 2023; 5(2): 46-53

Introduction:

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease which affects almost every systems in the body with different degrees of severity.[1] In this disease, organs and cells are damaged by auto-antibodies binding tissues and immune complexes.[2] Clinical features may vary from person to person, ranging from mild joint and skin involvement to severe, life-threatening internal organ disease.[3] One of the major complications in SLE is lupus nephritis (LN).[4] All four renal compartments- tubules, interstitium, glomeruli, and blood vessels may be affected. End-stage renal disease (ESRD) develop up to 25% of these patients, 10 years after onset of renal involvement.[4] If LN develops early in the course of SLE, it becomes a major predictor of poor prognosis.[5]

1. Syed Imtiaz Ahmed, Assistant Registrar, Department of Nephrology, National Institute of Kidney Diseases and Urology
2. Amanur Rasul Md. Faisal, Transplant Coordinator, Department of Nephrology, Dhaka Medical College Hospital
3. Anirban Kishor Singha, Registrar (Nephrology), Kurmitola General Hospital
4. Saiful Bahar Khan, Assistant Professor, Department of Nephrology, Ad-Din medical College and Hospital, Dhaka
5. Hossain Muhammad Mustafijur Rahman, Assistant professor, Department of Nephrology, Dhaka Medical College
6. Muhammad Rafiqul Alam, Department of Nephrology, Bangabandhu Sheikh Mujib Medical University
7. Md. Saif Bin Mizan, Associate Professor, Department of Nephrology, Dr. Sirajul Islam Medical College & Hospital, Dhaka.
8. Md. Shahadat Hossain, Assistant Registrar (Nephrology), National Institute of Kidney Diseases and Urology, Dhaka

Address of Correspondence: Syed Imtiaz Ahmed, Assistant Registrar, Department of Nephrology, National Institute of Kidney Diseases and Urology, Dhaka. E-mail: drimtiaz31@gmail.com, Mobile: +88 01712577088,

Active lupus nephritis can be defined clinically with some laboratory findings, including histopathological features. Lupus nephritis is classified histopathologically, according to classification revised by the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) in 2003.

Hypocomplementemia and raised titres of anti-dsDNA are reported to be associated with the activity of the disease.[6,7,8] Several autoantibodies, especially those against double stranded DNA (anti-dsDNA) are believed to play a major role in the induction of glomerular inflammation.[9,10,11] Laboratory markers currently used for diagnosis of lupus nephritis and assessment of its activity are creatinine clearance, proteinuria, urine protein creatinine ratio, complement levels, and anti-dsDNA.[12] However, these markers are often not as specific as desired.[12] Hence future research should be undertaken to evaluate novel biomarkers to detect renal flare and also for assessment of disease activity with high specificity and sensitivity. Although a large number of novel biomarkers have been studied, none of them have been rigorously validated in large-scale longitudinal cohorts of patients with different ethnic backgrounds.[4]

Interleukin 2 (IL-2) is produced by activated T cells and plays a pivotal role in the proliferation of T lymphocytes. Previous studies have reported that sIL-2R levels were higher in patients with SLE than that in controls.[13,14] Furthermore it is also found that in SLE with LN, the level of serum sIL-2R alpha is significantly higher than the other forms of active SLE.[15] Serum IL-2R levels have been correlated with histological activity index in SLE with LN and with various serological parameters.[16,17]

To date, sIL-2R alpha levels have not been evaluated more specifically in relation to clinical and histological changes in lupus nephritis. Higher level of s1L-2 in the serum was found to be related to severe lupus nephritis & serum s1L-2R alpha levels was found to be correlated positively with anti-dsDNA titres and negatively with serum C3 and C4 levels in such patients.[16,18] Serum sIL-2R alpha correlated to the activity of the disease as well.[17] Follow up of the lupus nephritis patients after treatment showed decreased serum 1L-2R levels with reduction of disease activity. Another study showed serum 1L-2R have a modest sensitivity and high specificity for detection of lupus nephritis. Thus, this marker may have the potential to serve as novel marker for detection of lupus nephritis and assessment of its activity.[17]

Results and Observation

A total number of 58 patients and 29 healthy individuals were recruited for this study of which Group A (lupus nephritis) consisted of 29 patients, Group B (SLE without renal involvement) consisted of 29 patients and the rest 29 patients were in GSroup C (healthy individuals).

Figure 1 shows age distribution of the patients. Maximum patients were in the age group of 21 – 30 years in all three groups.

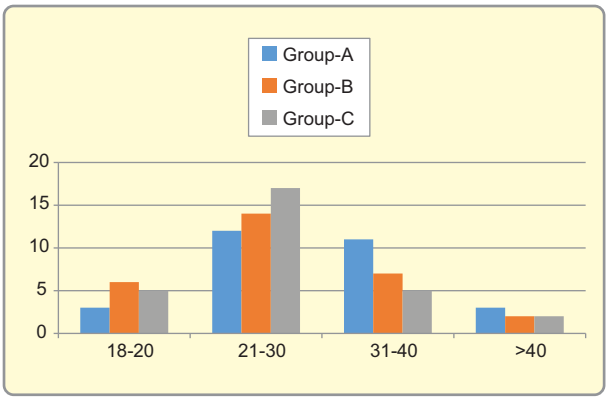

Fig.-1: *Distribution of patients according to age (N=87)*

Table I shows clinical and biochemical findings of group A and group B Patients. All the patients of group A and B were anaemic. All the patients of group A but none of the patients of group B had edema. In group A 13 patients has Serositis and in group B patients 10 of them has serositis.

Table II shows comparison of immunological findings (eg. Anti-ds DNA, serum C3 and C4) level between group A (lupus nephritis) and group B (SLE patients without renal disorder) at the time of renal biopsy. Anti-ds DNA was positive in 58.6 % and 51.7% of group A and group B patients respectively which was not statistically significant (p= 0.596). C3 was low in 65.5% group A patients and 37.9% group B patients. C4 was low in 58.6 % group A patients and 31.0% group B patients. The differences of both C3 and C4 level in between two groups were statistically significant (p= 0.036 and p= 0.035).

Table III shows number of different classes of LN and mean renal activity(SELENA SLEDAI) score, Class III and IV has higher mean renal activity score than class II and V.

Table-I

Clinical biochemical findings of group A and group B Patients

Clinical/Biochemical Parameters	Group		P value
	A n (%)	B n (%)	
Anemia			
• Mild	18 (62.0)	19 (65.0)	0.001#
• Moderate	4 (13.7)	05 (17.0)	
• Severe	5(17.3)	0 (0)	
• Absent	2 (7.0)	5 (18.0)	
Edema			
• Mild	14 (48.0)		
• Moderate	12 (42.5)		
• Severe	3 (10.0)		
ACR criteria for SLE			
• Malar rash	08(27.5)	26(92.5)	0.001#
• Discoid rash	0 (0)	09 (30.0)	0.001#
• Photosensitivity	7 (22.5)	20 (70.0)	0.001#
• Oral ulcers	16(57.5)	22(77.5)	0.094#
• Arthritis	18(62.9)	15 (52.5)	0.498#
• Serositis	13 (45.0)	10 (35.0)	0.494#
• Renal disorder	29 (100)	0 (0)	
• Neurological disorder	0 (0)	0 (0)	
• Hematologic disorder	17 (42.5)	14(35.0)	0.491#
• Immunologic disorder	23 (82.5)	22(77.5)	0.781#

Chi-square test was done to measure the level of significance. ##Unpaired t test was done to measure the level of significance.SD: Standard deviation, BP: Blood Pressure.Group A: Lupus nephritis patients, Group B: SLE without renal involvement.

Table-II

Immunological findings among the groups (n=58)

Parameters	Group		p-value
	Group A	Group B	
Anti-ds DNA			
• Positive	17 (58.6)	15 (51.7)	0.596
• Negative	12 (41.4)	14 (48.3)	
Serum C3			
• Low	19 (65.5)	11 (37.9)	0.036
• Normal	10 (34.5)	18 (62.1)	
Serum C4			
• Low	17 (58.6)	9 (31.0)	0.035
• Normal	12 (41.4)	20 (69.0)	

Chi-square test was done to measure the level of significance

Table-III

Number of different classes of LN and mean renal activity(SELENA SLEDAI) score

Histological Class	Number (%)	Mean±SD
Class II	6 (20.7%)	7.33±5.31
Class III	5 (17.2%)	12.00±2.82
Class IV	13 (44.8%)	13.69±2.56
Class V	5 (17.2%)	7.20±3.34

SD: Standard deviation

Table IV shows number of different classes of LN and mean histological activity index. Class III and IV has higher mean activity index than Class II and V.

Table V shows disease activity of SLE measure and renal activity score of the study subjects. Most (72.41%) patients had severe disease activity of SLE and mean renal activity score was 10 ± 3.8 among group A (lupus nephritis) patients. Most patients (89.7%) had mild to moderate disease activity in the group B (SLE without any renal disease). The difference between two groups were statistically significant (p= 0.001) regarding SLE disease activity index.

Table VI shows that Serum IL-2 receptor alpha level was significantly higher in group A (lupus nephritis) than that of group B (SLE patients without renal disorder). The mean Serum IL-2 receptor alpha level in group A and group B were 1525.28 ± 716.32 ng/L and 144.20 ± 147.85 ng/L with the range of 442 – 2804 ng/L and 42 – 699 ng/ L with the p value of less than 0.001.

Table VII and Table VIII show that the serum sIL-2 receptor alpha level in different classes of lupus nephritis with comparison of serum sIL-2 receptor alpha level between classes. Class II has lowest level among the classes with a mean value of 520.67 ± 92.50, with the range of 442-663 ng/L, followed by class V with a mean value of 1041.00 ± 76.21 with a range of 928 – 1123 ng/L. Class III and IV have the highest level with a mean of 1783.60 ± 480.11 and 2075.85 ± 395.46 respectively. There is significant difference between class

II and III, class II and IV, Class III and V & class IV and V.

Table X shows serum IL-2R alpha is 93.1% sensitive and 93.1% specific in diagnosis of LN on the basis of best cut off value 456.5 ng/L.

Table X shows correlation between serum IL-2R alpha with Anti-ds DNA, C3 and C4 in each group. Serum IL-2R alpha significantly correlate with Anti-ds DNA and C3 in group A patients, in group B patients there is no significant correlation between serum IL-2 R alpha with Anti-ds DNA, C3 and C4.

Table IV

Number of different classes of LN and mean histological activity index

Histological Class	Number (%)	Activity index (Mean±SD)
Class II	6 (20.7%)	3.50 ±0.54
Class III	5 (17.2%)	10.40 ±0.89
Class IV	13 (44.8%)	12.07 ±1.18
Class V	5 (17.2%)	5.80 ±0.44

SD: Standard deviation

Table-V

Distribution of patients according to disease activity of SLE and renal activity score (SELENA SLEDAI) among the groups (n=58)

Parameters	Group		p-value
	Group A	Group B	
Disease activity score			
• Mild to moderate	8 (27.59)	26 (89.7)	<0.001
• Severe	21 (72.41)	3 (10.3)	
Renal activity score (SLEDAI)	10±3.8		

Chi square test was done to measure the level of significance Group A: Lupus nephritis patients, Group B: SLE without renal involvement, Group C: Healthy population.

Table-VI

Serum IL-2 receptor alpha level in different groups (n=87)

Serum IL-2 receptor alpha (ng/L)	Mean ± SD	Min – Max	p-value
Group A	1525.28 ± 716.32	442 - 2804	<0.001
Group B	144.20 ± 147.85	42 – 699	
Group C	59.34 ± 21.71	20 – 113	

Kruskal Wallis test was done to measure the level of significanceSD: Standard deviation.
Group A: Lupus nephritis patients, Group B: SLE without renal involvement, Group C: Healthy individuals

Table-VII

Serum IL-2 receptor alpha level in different classes of lupus nephritis patient (n=29)

Serum IL-2 receptor alpha(ng/L) (n; %)	Mean ± SD	Min – Max	p-value
Class II (6; 20.7%)	520.67 ± 92.50	442 - 663	<0.001
Class III (5; 17.2%)	1783.60 ± 480.11	1474 – 2633	
Class IV (13; 44.8%)	2075.85 ± 395.46	1525 – 2804	
Class V (5; 17.2%)	1041.00 ± 76.21	928 – 1123	

Table-VIII

Comparison of serum sIL-2 receptor alpha level between classes

Class	p-value
II vs III	<0.001
II vs IV	<0.001
II vs V	0.106
III vs IV	0.680
III vs V	0.011
IV vs V	<0.001

Kruskal Wallis test was done to measure the level of significance among the groups and Bonferroni test was done to measure the level of significance between groups.SD: Standard deviation

Table-IX

Sensitivity and specificity at different cut off value of serum IL-2 receptor alpha in diagnosis of Lupus Nephritis

Serum IL-2 receptor alpha(ng/L)	Sensitivity	Specificity
444.5	96.6	89.7
451.5	93.1	89.7
456.5	93.1	93.1
462.0	89.7	93.1
489.5	89.7	96.6

Serum IL-2 receptor alpha level 456.5 is the best cut off value in this study to diagnosis Lupus Nephritis.

Table-X

Correlation of serum IL-2R alpha with anti-ds DNA, C3 and C4 between two groups (n=58)

Parameters	Group A		Group B	
	r value	p value	r value	p value
Anti-ds DNA	0.388	0.038	0.019	0.923
Serum C3	-0.398	0.033	0.107	0.580
Serum C4	-0.311	0.101	-0.118	0.556

Pearson's correlation test was done to measure the level of significance

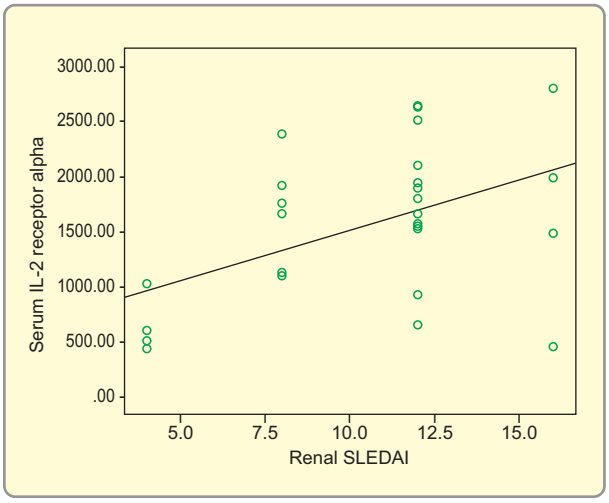

Fig.-2: *Correlation of Renal SLEDAI with S. sIL-2R alpha in lupus nephritis patients (r=+0.505; p=<0.005)*

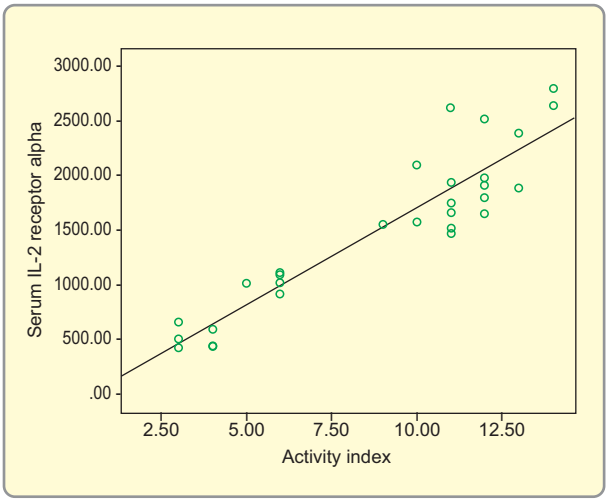

Fig.-3: *Correlation of histological Activity index with S. s IL-2R alpha in lupus nephritis patients (r=+0.925; p=<0.001)*

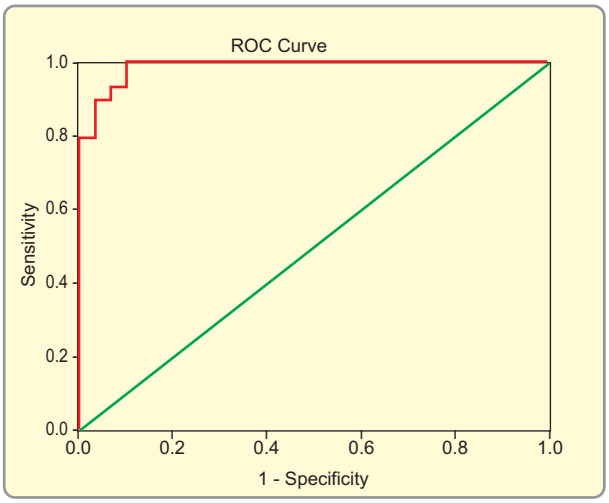

Fig.-4: *ROC curve of serum Serum IL-2 receptor alpha.*

Area under curve (AUC) of Serum IL-2 receptor alpha level was 0.987 (95% CI 0.967 – 1.000).

Discussion

In this cross-sectional study, a total number of 58 patients and 29 healthy individuals were recruited. Most (72.4%) patients had severe disease activity of SLE and mean renal activity score was 10 ± 3.8 among Group A (lupus nephritis) patients. Most patients (89 %) had mild to moderate disease activity in the Group B (SLE without any renal disease). Serum IL-2R alpha level was significantly higher in Group A (lupus nephritis) than that of Group B (SLE patients without renal disorder) and Group C. The mean serum IL-2R alpha level in Group A, Group B and group C were 1525.28 ± 716.32 ng/L, 144.20 ± 147.85ng/ml and 59.34 ± 21.71 ng/L, with the p value of less than 0.001. Similar findings were observed in a study done by EL SHAFEY et al. (2008) where 55 SLE patients were recruited, of them 20 patients were SLE without lupus nephritis (group 2) and 35 patients had LN (group 3), 20 healthy individuals were also recruited as control (group 1).[16] Serum IL-2R alpha level was significantly higher in group 2 and 3 compared to group 1. Furthermore, serum IL-2R alpha levels were significantly higher in lupus nephritis (group 3) than SLE without nephritis (group 2) with a p value of <0. 001. In a prospective study done by J Laut et al. 62 lupus patients were taken, of them 39 patients had clinical nephritis and 23 patients did not have nephritis.[17] 15 normal controls were also taken. Soluble IL-2R level were measured and correlated prospectively with clinical, histological and serological findings over a period of 9 months.[18] Result showed that the 62 lupus patients has significantly higher sIL-2R than 15 normal controls, most of this difference attributable to patients with nephritis. During lupus nephritis flare 9 of 10 patients showed significant elevations of sIL-2R, while only 6 of the 10 patients showed elevation of anti dsDNA antibody. During disease remission or stable clinical activity changes in IL-2R levels paralleled changes in anti-DNA antibody. IL-2R correlated strongly with histologic activity and C3 deposition whereas anti-DNA antibody did not. IL-2R levels did not correlate with serum creatinine suggesting that elevations of IL-2R were not simply due to decreased clearance. These observations suggest that serum IL-2R level is a useful marker of disease activity in lupus nephritis and may serve

as a helpful adjunct in management of this disorder. This result also supports the current study.

In this study Anti-ds DNA was positive in 58 % of lupus nephritis patients (group A) and 48 % patients of active SLE without renal involvement (group B) which was not statistically significant (p= 0.596) which is compatible to our finding.[18]

C3 was low in 65.5 % of lupus nephritis patients (group A) and 38% SLE patients without lupus nephritis (groupB). C4 was low in 58.6% group A patients and 31% group B patients in this study. The differences of both C3 and C4 level in between two groups were statistically significant (p=0.036 and p=0.035). Birmingham DJ et al. (2010) in their study, also found low C3 and C4 in substantial number (70 %) of lupus nephritis patients also. High level of serum IL-2R alpha was correlated negatively with C3, (P< 0.001) but not with C4 (P =0.58) in lupus nephritis patients in a study[17]. This finding was similar to current study.

In this study mean serum IL-2R alpha levels were found to be greater in patients with higher renal activity scores. Serum IL-2R alpha level was correlated positively with renal activity score in patients with lupus nephritis which can be helpful for assessing disease activity. This finding is similar to another study.[17]

Among 29 lupus nephritis patients (group A), 44.8 % were class IV lupus nephritis, 20.7% were class II, 17.2 % were class III and 17.2 % were biopsy proven class V patients. Mean serum IL-2R alpha was highest in class IV (2075.85 ± 395.46) followed by class III (1783.60 ± 480.11), Class V (1041.00 ± 76.21) and Class II (520.67 ± 92.50). The differences of serum IL-2R alpha level among different classes of lupus nephritis patients were statistically significant (p=0.001). These higher levels of serum IL-2R alpha in class III and IV lupus nephritis can be explained by their high renal activity score (renal- SLEDAI) in these patients.

In this study serum sIL-2R alpha showed significant positive correlation with histological activity index with a p value <0.001. Shafy et al. (2008) also found strong positive correlations between soluble IL-2R alpha levels and histological activity index.[17] This study showed that that serum IL-2R alpha level can detect lupus nephritis with high sensitivity and specificity (93.1%, 93.1%) which is comparable to the results (93%, 77.7%) in the study conducted by another study.[17]

Conclusions:

This study permits to conclude that serum soluble IL-2R alpha in patients with active SLE with nephritis, is significantly higher than those without nephritis and correlates significantly with disease activity. Other markers of lupus activity cannot differentiate renal from systemic involvement. Hence, serum soluble IL-2R alpha might be a valuable serological biomarker to reflect kidney involvement and to specifically monitor disease activity of lupus nephritis.

Limitations: There are some limitations of this study. The sample size was small. The study was done in limited time span; subjects were collected from only one center; hence it may not represent the whole population of the country.

References:

1. Gurevitz S, Snyder J, Wessel E, Frey J, Williamson B. Systemic lupus erythematosus: a review of the disease and treatment options. The Consultant Pharmacist®. 2013 Feb 1;28(2):110-21.
2. Longo D, Fauci A, Kasper D, Hauser S, Jameson J, Loscalzo JH. s Principles of Internal Medicine.3.Yazdany, J., Dall'Era, M. (2013). Definition and classification of Lupus and Lupus related disorder. In: Wallace and Hahn (2012) DUBOIS', Lupus Erythematosus and Related Syndromes, 8th edn. China, Elsevier Saunders.
4. Mok CC. Biomarkers for lupus nephritis: a critical appraisal. BioMed Research International. 2010 Jan 1;2010.5. Anaya, J.M., Cañas, C., Mantilla, R.D. (2011) . Lupus nephritis in colombians: contrasts and comparisons with other populations. Clinical Reviews in Allergy and Immunology, 40 (3),199–207.
6. Isenberg DA, Ravirajan CT, Rahman A, Kalsi J. The role of antibodies to DNA in systemic lupus erythematosus—a review and introduction to an international workshop on DNA antibodies held in London, May 1996. Lupus. 1997 Mar;6(3):290-304.
7. LLOYD W, SCHUR PH. Immune complexes, complement, and anti-DNA in exacerbations of systemic lupus erythematosus (SLE). Medicine. 1981 May 1;60(3):208-17.
8. Swaak AJ, Aarden LA, Statius Eps LV, Feltkamp TE. Anti dsDNA and complement profiles as prognostic guides in systemic lupus erythematosus. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 1979 Mar;22(3):226-35.
9. Lefkowith JB, Gilkeson GS. Nephritogenic autoantibodies in lupus: current concepts and continuing controversies. Arthritis and rheumatism. 1996 Jun 1;39(6):894-903.
10. Klumb EM, Silva CA, Lanna CC, Sato EI, Borba EF, Brenol JC, Albuquerque EM, Monticielo OA, Costallat LT, Latorre LC, Sauma MD. Consensus of the Brazilian Society of

Rheumatology for the diagnosis, management and treatment of lupus nephritis. Revista brasileira de reumatologia. 2015 Jan;55:1-21.

11. Hahn BH, Mcmahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, Karpouzas GA, Merrill JT, Wallace DJ, Yazdany J, Ramsey Goldman R. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis care & research. 2012 Jun;64(6):797-808.

12. Bertsias, G.K., Tektonidou, M., Amoura, Z., Aringer, M., Bajema, I., Berden, J.H., Boletis, J., Cervera, R., Dörner, T., Doria, A. and Ferrario, F., 2012. Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. *Annals of the rheumatic diseases*, *71*(11), pp.1771-1782.

13. EL SHAFEY EM, EL NAGAR GF, EL BENDARY AS, Sabry AA, Selim AG. Serum soluble interleukin-2 receptor alpha in systemic lupus erythematosus

.14. Davas EM, Tsirogianni A, Kappou I, Karamitsos D, Economidou I, Dantis PC. Serum IL-6, TNFá, p55 srTNFá, p75 srTNFá, srIL-2á levels and disease acitivity in systemic lupus erythematosus. Clinical rheumatology. 1999 Jan;18: 17-22.

15. Tokano YO, Murashima AT, Takasaki Y, Hashimoto H, Okumura K, Hirose S. Relation between soluble interleukin 2 receptor and clinical findings in patients with systemic lupus erythematosus. Annals of the rheumatic diseases. 1989 Oct 1;48(10):803-9.

16. EL SHAFEY EM, EL NAGAR GF, EL BENDARY AS, Sabry AA, Selim AG. Serum soluble interleukin-2 receptor alpha in systemic lupus erythematosus.

17. Laut J, Senitzer D, Petrucci R, Sablay LB, Barland P, Glicklich D. Soluble interleukin-2 receptor levels in lupus nephritis. Clinical nephrology. 1992 Oct 1;38(4):179-84.

18 Brugos B, Vincze Z, Sipka S, Szegedi G, Zeher M. Serum and urinary cytokine levels of SLE patients. Die Pharmazie-An International Journal of Pharmaceutical Sciences. 2012 May 1;67(5):411-3.

Vitamin D Level and It's Relation with Anemia in Patients with CKD Stage 5 in a Tertiary Care Hospital

Khan ASMF[1], Hossain MR[2], Rahman HMM[3], Chowdhury MN[4], Islam MN[5],

Abstract

Background: Anemia is a common complication in patients with CKD stage 5. Vitamin D may play a protective role in CKD-associated anemia and can reduce the dose of erythropoietin requirement for correction of anemia.

Objective: To observe the vitamin D level and its relation with anemia in CKD stage 5 patients.

Method: This cross-sectional study was conducted in the Department of Nephrology, Dhaka Medical College Hospital, Dhaka from July 2017 to June 2018. Total 88 CKD stage 5 patients were included in this study; among them 44 patients were on maintenanace hemodialysis and 44 patients were not on dialysis and age was between 18 to 75 years. Patients with history of blood transfusion in last three months, history of recent infection, history of malabsorption syndrome like inflammatory bowel disease, history of bleeding peptic ulcer i.e hematemesis, melena were excluded from this study. Demographic and clinical data were recorded. Hemoglobin, 25(OH) Vitamin D_3, Serum Iron, Total Iron Binding Capacity (TIBC), Transferrin Saturation (TSAT), Ferritin, iPTH, Serum Phosphate, S. Calcium, S. Albu-min, eGFR and hs-CRP levels were done. Patients were further divided into two groups. Group I had 25(OH) Vitamin D_3 < 10 ng/ml and Group II had 25(OH) Vitamin D_3 ≥10ng/ml. Statistical analysis was done using SPSS 22.0. A p value <0.05 was considered as statistically significant.

Results: In multivariate regression analysis, 25(OH) Vitamin D_3 and erythrocyte-stimulating agent (ESA) dose were found to be significantly associated with hemoglobin level [25(OH)D_3: â=0.822, p<0.001; ESA dose: â=-0.212, p=0.048]. In addition, Pearson's correlation analysis showed that a significant positive correlation between 25(OH) Vitamin D_3 and hemoglobin levels (r=+0.831; p***<0.001) both in dialytic (r=+0.829; p=<0.001) and non-dialytic patients (r=+0.810; p=<0.001).***

Conclusion: Vitamin D deficiency is common in patients with CKD stage 5 and may be independently associated with anemia in these patients.

Keywords: anemia; CKD and vitamin D; vitamin D and anemia.

(Bang. Renal J. 2023; 5(2): 54-59

Introduction

Chronic Kidney Disease (CKD) is on the rise worldwide. In Bangladesh, Hasan et al. (2012) revealed a prevalence of CKD of 19.0% and 19.5% using the Cockcroft-Gault and MDRD equations, respectively.[1] Chronic kidney disease (CKD) is becoming more common as the prevalence of diabetes mellitus rises and the population ages, and CKD patients suffer from a variety of complications such as anemia, abnormal mineral and bone metabolism, volume overload, and electrolyte imbalances.[2,3]

As renal function declines, particularly in advanced stages of chronic kidney disease, the prevalence and severity of anemia are rising.[3] Additionally, anemia causes a variety of clinical symptoms and signs which raises their risk of morbidity and mortality, which is more prevalent during end stage renal disease.[4,5]

Although usual causes of anemia in CKD patients are erythropoietin deficiency, iron deficiency, other nutritional deficiency and inflammation, recent studies show a

1. A.S.M Farhad Khan, Junior Consultant (Nephrology), Kuwait-Bangladesh Friendship Government Hospital, Uttara, Dhaka. Email: farhadrazib42@yahoo.com; Mobile: +88 01717507120
2. Mohammad Rezaul Hossain, Assistant Registrar, Department of Nephrology, Colonel Maleque Medical College Hospital, Manikganj
3. Hossain Muhammad Mustafijur Rahman, Assistant Professor, Department of Nephrology, Dhaka Medical College
4. Md. Nizamuddin Chowdhury, Professor, Senior and Chief Consultant, Department of Nephrology, BRB Hospital, Dhaka
5. Md. Nazrul Islam, Professor, Department of Nephrology, Dhaka Medical College, Dhaka

Address of Correspondence: Dr. A.S.M Farhad Khan, Junior Consultant (Nephrology), Kuwait-Bangladesh Friendship Government Hospital, Uttara, Dhaka. Email: farhadrazib42@yahoo.com; Mobile: +88 01717507120

potential effect of vitamin D deficiency as an additional pathophysiological factor of CKD-associated anaemia.[6,7]

One billion people worldwide have inadequate levels of 25-hydroxy vitamin D. About 40% of Americans suffer from low vitamin D levels, which are becoming more common. Compared to Caucasians, the prevalence is higher among African-Americans and Hispanics. According to recent studies, at least 75% of people with end-stage renal disease are vitamin D deficient. This is most likely caused by inadequate sun exposure due to other co-morbidities, poor dietary intake, and insufficient 25(OH)D production by the skin.[8,9]

According to recent research, vitamin D may have pleiotropic effects in a variety of organs depending on the body's distribution of vitamin D receptors.[10] Vitamin D also plays a protective role in a number of chronic diseases like cardiovascular disease, diabetes mellitus, myopathy, cancer, infection, and autoimmune disease, including CKD-associated anemia, in addition to its well-known effects on bone and mineral metabolism.[11] In fact, prior research using data from the Third National Health and Nutrition Examination Survey and the Study to Evaluate Early Kidney Disease showed that vitamin D deficiency was significantly and independently associated with anemia in patients with CKD who did not require dialysis.[7,12]

The purpose of this study was to elucidate the correlation of 25(OH)D_3 with anemia in CKD stage 5 patients undergoing maintenance hemodialysis also in non-dialytic patients and to find out that vitamin D treatment can be an adjunct to traditional anemia management in these patients.

Methods

This cross-sectional study was conducted in the Department of Nephrology, Dhaka Medical College Hospital, Dhaka from July 2017 to June 2018. A total of 88 diagnosed CKD stage 5 patients, among them 44 dialytic and 44 non-dialytic patients of between 18 to 75 years of age were included in this study by purposive sampling technique. Patients with history of blood transfusion in last three months, history of recent infection, history of malabsorption syndrome like inflammatory bowel disease, history of bleeding peptic ulcer i.e., hematemesis, melena were excluded from this study. Patients were further divided into two groups, group I: 25(OH)D_3<10 ng/ml and group II: 25(OH)D_3 ≥10ng/ml. Group I consists of 55 patients and Group II consists of 33 patients.

Demographic and clinical data were recorded including age, sex, dialysis modality, dura-tion of dialysis, co-morbidities and drug history. The results of the following biochemical laboratory tests were also collected: hemoglobin, serum iron, total iron-bind-ing capacity (TIBC), transferrin saturation (TSAT), ferritin, serum calcium, phosphate, intact parathyroid hormone (iPTH), albumin, estimated glomerular filtration rate (eGFR), and high sensitivity C-reactive protein (hs-CRP) levels. Blood sample for 25-OH vitamin D_3 were collected. Vitamin D assay were done by ELISA in DMCH laboratory. Statistical analysis was done by using SPSS version 12. When the distribution was asymmetric, numerical data were presented as medians with ranges, and mean with standard deviation when the distribution was normal. The Chi-square test was used to compare categorical variables expressed as proportions. Pearson correlation was used to assess correlations between variables. Linear regression analysis was also done. P value <0.05 was considered statistically significant for all tests.

Results and observations:

Table I shows mean age of group I and group II which were 45.73 ± 13.60 and 44.82 ± 12.66 respectively (p>0.05). Total 59 males (67.0%) and 29 females (33.0%) were enrolled in this study. Out of 55 patients in group I, 38 were male (69.1%) and 17 patients were female (30.9%) and out of 33 patients in group II, 21 patients were male (63.6%) and 12 patients were female (36.4%)

Table II showing total 68 patients were anemic (77.3%), among them 48 patients in group I (87.3%) and 20 patients in group II (60.6%) which was statistically significant but there were no significant differences between group I and group II regarding DM, HTN, BMI and smoking.

Table III shows Hb level were significantly lower in group I (7.76 ± 1.02) than group II (10.50 ± 1.80) (p<0.001). Mean 25(OH) Vitamin D_3 level in group I was 7.20 ± 1.16 and in group II was 19.81 ± 5.44 and the difference was statistically significant (p<0.001). Level of S. albumin (36.76 ± 4.70 vs 38.98 ± 4.97; p=0.012), s. calcium (8.10 ± 1.27 vs 8.72 ± 1.12; p=0.023) and s. phosphate (5.34 ± 1.72 vs 6.24 ± 1.57; p=0.017) were significantly lower in group I than group II. iPTH level was higher in group I than group II (329.6 ± 294.3 vs 267.9 ± 243.6) but not statistically significant.

Table IV shows hemoglobin level was significantly higher in CKD 5D patients (9.34 ± 2.00) than CKD 5ND patients (8.24 ± 1.63). 25(OH)D_3 level was also higher in CKD 5D patients (13.69 ± 7.72) than CKD 5ND patients (10.17 ± 5.82).

Pearson's correlation analysis revealed a significant positive correlation between 25(OH) D3 and hemoglobin

levels (r=+0.831; p<0.001) in both dialytic (r=+0.829; p<0.001) and non-dialytic (r=+0.810; p<0.001) patients.

On univariate linear regression analysis, Hb concentration was found to be significantly correlated with $25(OH)D_3$ level (â=0.822; p<0,001), ESA dose (â=-0.212; p=0.048) and s. albumin (â=0.263; p=0.013). But on multivariate analysis, Hb concentration was significantly correlated with both $25(OH)D_3$ (β=0.860; p<0.001) & ESA dose (â=0.138; p=0.038).

Table VII shows Logistic regression analysis and revealed that patients in group I had a significantly higher risk for developing anemia than group II patients, even after adjusting for age, ESA dose, iPTH, Phosphate, hs-CRP, serum ferritin, serum iron, TIBC, TSAT, sex, diabetes and smoking.

Table-I

Demographic profile of the patients (N=88)

	Total (N=88)	Group I (n=55)	Group II (n=33)	p value
Age (years)				
Mean ± SD	45.40 ± 13.19	45.73 ± 13.60	44.82 ± 12.66	0.752
Min - max	18-71	18-71	22-71	
Gender				
Male	55 (62.5)	38 (69.1)	17 (30.9)	
Female	33 (37.5)	22 (63.6)	12 (36.4)	

Unpaired t test was done to measure the level of significance

Table-II

Comparison of clinical parameters of patients between group I and group II (N=88)

Variables	Total (N=88)	Group		p value
		Group I(n=55)	Group II(n=33)	
DM	28 (31.8%)	17 (30.9%)	11 (33.3%)	0.813
HTN	87 (98.9%)	54 (98.2%)	33 (100.0%)	1.000
Anemia	68 (77.3%)	48 (87.3%)	20 (60.6%)	0.004
Smoking	35 (39.8%)	24 (43.6%)	11 (33.3%)	0.339
BMI	22.16 ± 2.88	21.99 ± 2.91	22.44 ± 2.85	0.398

Chi-square test and Unpaired t test was done to measure the level of significance

Table-III

Biochemical findings of the patients according to $25(OH)D_3$ (N=88)

Variables	Group		p value
	Group I (n=55) (Mean±SD)	Group II (n=33) (Mean±SD)	
Hb(g/dl)	7.76 ± 1.02	10.50 ± 1.80	[a]<0.001
S.Creatinine (mg/dl)	8.72 ± 3.27	8.58 ± 2.68	[a]0.901
eGFR(ml/min/1.73m^2)	6.91 ± 2.63	6.64 ± 1.93	[a]0.901
S. calcium(mg/dl)	8.10 ± 1.27	8.72 ± 1.12	[b]0.023
S. phosphate(mg/dl)	5.34 ± 1.72	6.24 ± 1.57	[b]0.017
iPTH(pg/ml)	329.6 ± 294.3	267.9 ± 243.6	[a]0.328
Serum iron(ug/dl)	86.78 ± 64.94	81.14 ± 42.06	[a]0.724
TIBC (ug/dl)	209.75 ± 47.64	224.64 ± 53.88	[a]0.253
S. ferritin(ug/L)	889 ± 921	834 ± 779	[a]0.853
TSAT(%)	40.14 ± 26.29	39.23 ± 16.57	[a]0.955
$25(OH)D_3$(ng/ml)	7.20 ± 1.16	19.81 ± 5.44	[a]<0.001
S. albumin(gm/L)	36.76 ± 4.70	38.98 ± 4.97	[a]0.012
hs CRP(mg/L)	13.71 ± 28.05	10.03 ± 5.41	[a]0.423

[a]Unpaired t test and [b]Mann-Whitney U test was done to measure the level of significance

Table-IV

Hemoglobin and 25(OH)D_3 level in dialytic and non-dialytic patients (N=88)

Variables	Group		p value
	Dialytic (CKD 5D) patients(n=44)	Non-dialytic (CKD 5ND) patients (n=44)	
Hb	9.34 ± 2.00	8.24 ± 1.63	[a]0.001
25(OH)D_3	13.69 ± 7.72	10.17 ± 5.82	[b]0.064

[a]Unpaired t test and [b]Mann-Whitney U test was done to measure the level of significance

Table-V

Correlation of 25(OH)D_3 level with hemoglobin in dialytic and non-dialytic patients (N=88)

	R	p-value
All Patients(CKD 5D+CKD 5ND)	+0.831	<0.001
Dialytic (CKD 5D) patients	+0.829	<0.001
Non-dialytic (CKD 5ND) patients	+0.810	<0.001

Pearson's correlation was done

Table VI

Association between Hb and clinical/biochemical parameters

	Univariate analysis		Multivariate analysis	
	β	p value	B	p value
25(OH)D_3	0.822	<0.001	0.860	<0.001
Age	-0.040	0.712		
ESA dose	-0.212	0.048	0.138	0.038
iPTH	-0.101	0.348		
S. Phosphate	0.189	0.079		
S. Albumin	0.263	0.013	0.067	0.282
hs-CRP	-0.137	0.204		
Ferritin	0.098	0.366		
Serum iron	0.038	0.726		
TIBC	0.011	0.922		
TSAT	0.038	0.727		
Sex (male)	0.047	0.662		
Diabetes (yes)	0.111	0.302		
Smoking (yes)	0.160	0.136		

Table-VII

Risk factors for developing Anemia (Hb<10g/dL)

	OR	(95% CI)	p value
$25(OH)D_3$ <10 vs ≥10	1.941	(1.394-2.703)	<0.001
Age (per 1-year increase)	1.003	(0.962-1.045)	0.889
ESAdose(per 1 unit increase)	1.000	(1.000-1.000)	0.403
iPTH	1.000	(0.998-1.002)	0.714
Phosphate	1.545	(1.090-2.191)	0.014
hs-CRP	0.991	(0.955-1.028)	0.620
Ferritin	1.000	(1.000-1.000)	0.229
Serum iron	1.000	(0.991-1.010)	0.946
TIBC	1.003	(0.993-1.014)	0.571
TSAT	0.998	(0.976-1.021)	0.893
Sex (male)	1.768	(0.584-5.352)	0.310
Diabetes (yes)	2.305	(0.600-8.855)	0.215
Smoking (yes)	2.268	(0.667-7.714)	0.182

Discussion:

Total 88 patients of CKD stage 5 (44 patients on maintenance hemodialysis and 44 patients not on dialysis) were enrolled in this study. They were also further divided into two groups based on 25(OH) VitaminD_3 level: group I, $25(OH)D_3$ <10ng/ml and group II, $25(OH)D_3$ ≥10ng/ml. In multivariate regression analysis, 25(OH) Vitamin D_3 and erythrocyte-stimulating agent (ESA) dose were found to be significantly associated with hemoglobin level [$25(OH)D_3$: â=0.822, p<0.001; ESA dose: â=-0.212, p=0.048]. In addition, Pearson's correlation analysis showed that a significant positive correlation between 25(OH) Vitamin D_3 and hemoglobin levels (r=+0.831; *p*<0.001) both in dialytic (r=+0.829; p=<0.001) and non-dialytic patients (r=+0.810; p=<0.001).

In this study the proportion of patients presents with anemia was significantly higher in group I than group II (87.3% vs 60.6%; p=0.004) which is similar to Kim et al. (2016) where the proportion of patients who met the criteria for anemia was also significantly higher in vitamin D deficient patients (60.2%: p<0.001).[13] Nand et al. (2017) also found that significantly higher risk of developing anemia in vitamin D deficient patients.[8] In this study, the mean 25(OH) Vitamin D_3 level was 11.93±7.03 ng/ml, while the mean 25(OH) Vitamin D_3 level was 7.20±1.16 ng/ml in group I and 19.81±5.44 ng/ml in group II. In comparison to Kim et al. (2016) the mean serum 25(OH) Vitamin D_3 concentration was 11.1±6.4 ng/ml, while the mean 25(OH) D_3 concentration level was 6.5±1.8 ng/ml in group I and 17.2±5.6 ng/ml in group II which is similar to this study.[13] Moreover, the monthly ESA dose was significantly higher in group I (18563±2885; p=0.031) in this study which is similar to Kim et al. (20656.2±17627.7; p=0.003).[13] In this study hemoglobin was significantly low in vitamin D deficient group (Group I) (7.76 ± 1.02) than that of vitamin D insufficient group (Group I) (10.50 ± 1.80) which was statistically significant (p<0.001). Kim et al. (2016) and Nand et al. also observed less hemoglobin level among low vitamin D group (9.7±2.0 vs 10.5±1.6 and 6.94±0.42 vs 7.15±0.42 respectively; p<0.001).[8,13] In biochemical parameter, serum phosphate, calcium and albumin concentration were significantly lower in group I than in group II. There were no significant differences in serum level of iPTH, serum iron profile, eGFR, ESR and hs-CRP which is similar to Kim et al. (2016).[13] Nand et al. showed that all these biochemical parameters except serum albumin is significantly lower in vitamin D insufficient group ($25(OH)D_3$ <30 ng/ml) than sufficient group.[8] On univariate linear regression analysis, Hb cocentration was found to be significantly correlated with 25(OH) Vitamin D_3 level (â=0.822; p<0,001), ESA dose (â=-0.212; p=0.048) and S. albumin (â=0.263; p=0,013). But on multivariate analysis, Hb concentration was only significantly correlated with 25(OH) Vitamin D_3 (â=0.860; p<0.001). Pearson's correlation analysis revealed a significant positive correlation between 25(OH) Vitamin D_3 and hemoglobin levels (r=+0.831; *p*<0.001). 25(OH) D_3 had significant positive correlation with hemoglobin in dialytic (r=+0.829; p=<0.001) and non-dialytic patients (r=+0.810; p=<0.001). There was a stepwise decrease in hemoglobin concentrations with decreasing of vitamin D

concentrations.[12] Kim et al. demonstrated that patients with 25(OH)D_3 levels <10 ng/dl had a higher risk of developing anemia than ESRD patients with 25(OH)D_3 levels ≥10 ng/dl.[13]

Conclusion:

Hemoglobin level was significantly lower in low vitamin D group (7.76 ± 1.02) than high vitamin D group (10.50 ± 1.80) ($p<0.001$). Logistic regression analysis also revealed that patients in low vitamin D group had a 1.941 times higher risk for developing anemia than high vitamin D group.

References:

1. Hasan MJ, Kashem MA, Rahman MH, Qudduhush R, Rahman M, Sharmeen A, & Islam N. Prevalence of chronic kidney disease (CKD) and identification of associated risk factors among rural population by mass screening. Community Based Medical Journal. 2012; 1(1): 20-26. Doi.org/10.3329/cbmj.v1i1.13825
2. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P & Levey AS. Prevalence of chronic kidney disease in the United States. Jama. 2007; *298*(17): 2038-2047. DOI: 10.1001/jama.298.17.2038
3. Moranne O, Froissart M, Rossert J, Gauci C, Boffa JJ, Haymann JP & NephroTest Study Group. Timing of onset of CKD-related metabolic complications. Journal of the American Society of Nephrology. 2009; *20*(1):164. Doi: 10.1681/ASN.2008020159
4. Wittwer I. Iron deficiency anaemia in chronic kidney disease. Journal of Renal Care. 2013; *39*(3):182-188. Doi.org/10.1111/j.1755-6686.2013.12026.x
5. Shimizu Y, Nakazato M, Sekita T, Kadota K, Sato S, Arima K & Maeda T. Association between alkaline phosphatase and anemia in rural Japanese men. The Nagasaki Islands study. Acta Medica Nagasakiensia. 2014;58(4):125-130. Doi.org/10.11343/amn.58.125
6. Kalantar-Zadeh K, Lee GH, Miller JE, Streja E, Jing J, Robertson JA, Kovesdy CP. Predictors of hyporesponsiveness to erythropoiesis-stimulating agents in hemodialysis patients. American journal of kidney diseases. 2009 May 1;53(5):823-34. Doi.org/10.1053/j.ajkd.2008.12.040
7. Kendrick J, Targher G, Smits G, Chonchol M. 25-Hydroxyvitamin D deficiency and inflammation and their association with hemoglobin levels in chronic kidney disease. American journal of nephrology. 2009 Feb 13;30(1):64-72. Doi.org/10.1159/000202632
8. Nand N, Mittal R. Evaluation of Effect of Vitamin D Deficiency on Anemia and Erythropoietin Hyporesponsiveness in Patients of Chronic Kidney Disease. The Journal of the Association of Physicians of India. 2017 Feb 1;65(2):38-42.
9. Porter A, Gilmartin C, Srisakul U, Arruda J, Akkina S. Prevalence of 25-OH vitamin D deficiency in a population of hemodialysis patients and efficacy of an oral ergocalciferol supplementation regimen. American journal of nephrology. 2013 May 30;37(6):568-74.Doi.org/10.1159/000351185
10. Icardi A, Paoletti E, De Nicola L, Mazzaferro S, Russo R, Cozzolino M. Renal anaemia and EPO hypo-responsiveness associated with vitamin D deficiency: the potential role of inflammation. Nephrology Dialysis Transplantation. 2013 Jul 1;28(7):1672-9.*28*(7):1672-1679. Doi.org/10.1093/ndt/gft021
11. Besarab A, Coyne DW. Iron supplementation to treat anemia in patients with chronic kidney disease. Nature Reviews Nephrology. 2010 Dec;6(12):699-710.10.1038/nrneph.2010.139
12. Patel NM, Gutiérrez OM, Andress DL, Coyne DW, Levin A, Wolf M. Vitamin D deficiency and anemia in early chronic kidney disease. Kidney international. 2010 Apr 2;77(8):715-20.Doi.org/10.1038/ki.2009.551
13. Kim YL, Kim H, Kwon YE, Ryu DR, Lee MJ, Park KS, Ryu HJ, Park JT, Oh HJ, Han SH, Yoo TH. Association between vitamin D deficiency and anemia in patients with end-stage renal disease: A cross-sectional study. Yonsei medical journal. 2016 Sep 1;57(5):1159-64.Doi.org/10.3349/ymj.2016.57.5.1159

Review Articles

Fasting Ramadan in Chronic Kidney Disease, Kidney Transplant and Dialysis Patients

Nomany MS[1], Rashid HU[2], Alam MR[3]

Abstract:

Ramadan fasting is considered an honored act in the Muslim community. They start fasting before sunrise with Suhoor, and complete after sunset with Iftar. Muslims who have moderate to severe chronic kidney diseases and use regular medications may harm their health by fasting. Risk stratification of kidney patients based on IDF-DAR risk categories revealed that patients in CKD stage 3 with stable serum creatinine are in mild to moderate risk and can fast with regular follow-up. But patients in CKD stage 3 with rising serum creatinine are in high risk and should not fast. Patients in CKD stage 4, 5, hemodialysis (HD), peritoneal dialysis (PD), Kidney transplantation (KT), CKD stage 3 to 5 with cardiovascular disease (CVD), CKD with pregnancy are in very high risk of disease progression, and therefore, must not fast. Moreover, drugs with thrice daily dose should be changed to once- or twice daily dose before Ramadan. Although multi-morbid patients may be exempt from fasting for religious or medical reasons, some insist in fasting and placing themselves in danger. According to the IDF-DAR guideline, high-risk patients are encouraged to discontinue their fasting and to consider fidyah.

Keywords: ramadan; ramadan in CKD; ramadan and kidney transplant; ramadan & dialysis

(Bang. Renal J. 2023; 5(2): 60-64

Introduction:

There are more than 2 billion Muslim people worldwide now. Most of them live in Middle East, South East Asia, Northern and Central Africa. Moreover Muslims are the largest minority populations in many western countries, e.g. UK, USA. About 1.6 billion Muslims are fasting in Ramadan.[1,2] Ramadan fasting is considered an honored act. They start fasting before sunrise with a meal known as Suhoor, and complete after sunset with Iftar. Obviously fasting duration is not always same. Muslims who live in the southern countries of the world such as New Zealand or Chile fast for 11 to 12 hours, but those living in northern countries such as Iceland or Norway may fast up to for 18 to 20 hours.

Medical illness and Ramadan fasting:

Muslims who have moderate to severe chronic diseases and use regular medications may harm their health by fasting. Therefore, from medical ground these patients may need abstain from fasting.[3,4] Despite that, some multi-morbid patients insist on fasting in Ramadan, even during the long days of Ramadan. These patients challenge their treating physicians. Longtime fasting leads to changes in lifestyle, sleep pattern, meal time, meal item, dose and timing modification of medicine, resulting in some changes in metabolic and endocrine process. There is also increased risk of dehydration in fasting.[5]

DM, CKD and fasting:

DM is a common cause of CKD. Most published guidelines concern DM and immediate complications such as hypoglycemia, diabetic ketoacidosis (DKA), and hyperglycemia rather than changes in eGFR in CKD patients. It is well known that the fasting and progressive loss of eGFR cause less requirement of insulin and oral hypoglycemic agent (OHA).[6] Progressive loss of eGFR results in less insulin requirement by 25% when the eGFR is10 to 50 mL/min/1.73m2 and less insulin requirement by 50% when eGFR is < 10.[7,8] Therefore, it is advised that diabetic kidney disease (DKD) patients, especially those with advanced diseases, should check their blood sugar regularly and break their fasting if any harm is expected or

1. Dr. Md. Shoeb Nomany, Associate Professor of Nephrology, Kidney Foundation Hospital & Research Institute (KFH&RI), Bangladesh.

2. Prof. Harun-Ur-Rashid, Professor of Nephrology, KFH&RI, Bangladesh.

3. Prof. Muhammad Rafiqul Alam, Professor and ex-chairman of Nephrology, BSMMU, Bangladesh.

Address of Correspondence: Dr. Shoeb Nomany, Associate Professor of Nephrology, Kidney Foundation Hospital & Research Institute (KFH&RI), Bangladesh. E-mail: shoebnomany@googlemail.com, Mobile: +88 01718385487

observed. They may stop fasting for good after consulting their treating physicians.

Published articles' summary of CKD and Ramadan fasting:

In an observational study in UK by Chowdhury et al. (2019) on 68 CKD stage 3 diabetic patients fasted for about 19 hours observed no significant differences in outcome measures and adverse events.[9]

In one study by NasrAllah & Osman (2014) observed 106 CKD stage 4 fasting patients and found serum creatinine increased by 60% after 1 week of fasting. They inferred that fasting increased the risk of CKD deterioration with significant increase of cardiovascular events. But deterioration was possibly due to CKD progression, rather than fasting.[10]

Eldeeb et al. (2020) monitored CKD stage 3 and 4 and hypertension in Egyption patients and found improved BP control, eGFR and serum crteatinine. Ultimately, they concluded that Ramadan fasting improves renal function, most probably due to improved BP control in hypertensive CKD patients.[11]

In a retrospective cohort study, Al Abdan et al. (2022) observed 1199 patients without significant change in renal function parameters during fasting. They concluded that Ramadan fasting has no negative effects on patients with comorbid conditions. Larger prospective studies were advised to confirm the conclusion.[12]

It is difficult to speculate the explanations for the differences in different studies. One explanation may be heterogeneity of study populations, CKD severity, number of fasting days, duration of fasting hours, changing in food habit in Ramadan and observation period. Majority of the studies included stable CKD stage 3 patients and only a small number of CKD stage 4 and 5 patients. In the reported literature, it appears that stable CKD stage 3 patients would be able to fast without significant adverse consequences. But these patients need close monitoring to ensure the compliance to medical advice. On the other hand, fasting may not be safe in CKD stage 4 and 5 patients who are at higher risk of renal function deterioration due to dehydration and life-threatening electrolyte abnormalities. The studies on CKD stage 4-5 patients did not have a comparator group, so it is difficult to make an authentic conclusion in this group. Additionally, patients with CKD and known cardiovascular disease should be discouraged from fasting due to higher risk of adverse cardiovascular outcomes, that was observed by NasrAllah & Osman.[10]

Published articles' summary of kidney transplantation and Ramadan fasting:

In one study in Saudi Arabia by Qurashi et al.(2012) on 43 renal allograft patients showed that fasting in the month of Ramadan during the most hot months in two consecutive years had no significant difference between the fasted and the non-faster participants. Therefore, KT patients are able to fast.[13]

A meta-analysis and systematic review by Bragazzi (2014, 2017) showed that fasting did not affect kidneys functional parameters and fasting was well tolerated in kidney transplant recipients.[14,15]

In another single-centered retrospective study by Ibrahim et al. (2018) on 280 kidney transplant patients revealed no difference in eGFR between fasting and non-fasting groups.[16]

Published articles' summary of dialysis and Ramadan fasting:

A 24 years retrospective: study by Imtiaz et al. (2015) on 1840 HD patients showed higher mortality during Ramadan. They concluded that possibly death was due to co morbidity. Therefore, do not urge patient to fast.[17]

On 2016, Imtiaz et al. observed clinical and biochemical parameters of HD patients before and during Ramadan. They inferred that fasting HD patients need close observation for increased Phosphorus and potassium level in blood.[18]

In a retrospective cohort study by Adnan et al. (2020) on 68 HD patients showed that 20 days of fasting improved BMI, serum urea, creatinine, phosphorus and intradialytic weight but serum albumin level dropped without long-term adverse effects.[19]

Although there are some reports that fasting might be harmful to some HD-dependent patients, but overall conclusions suggest that fasting is relatively well- tolerated and does not affect the morbidity and mortality rates. However, careful monitoring of serum electrolytes is advisable, especially for sodium, potassium and phosphate.

Table-I

Risk stratification of kidney patients based on International Diabetes Federation and the Diabetes and Ramadan International Alliance (IDF-DAR) risk categories:[20]

Low to moderate risk	High risk	Very high risk
1.CKD stage3 with stable kidney function (stable serum creatinine, no edema or dehydration) 2.CKD patients with recurrent UTI and repeated stone formation.	1.CKD stage 3 with unstable kidney function (rapid rising serum creatinine.) 2.CKD patients with recurrent electrolytes imbalance. Patients on high dose of ACEi/ARB/ SGLT2i /diuretics / mineralocorticoid receptor antagonist (MRA).	1.CKD 4,5,HD,PD. (A selective group of stable HD & P D patients can fast.) 2.CKD 3,4,5 with cardiovascular dis ease. 3.CKD with pregnancy. 4.Patients on tolvaptan (Aquaretic).
Advice: Patient may fast. Ability to tolerate fasting also should be considered	Advice: Patient should not fast	Advice: Patient must not fast

Some proposed guidelines for Ramadan fasting in chronic kidney disease (CKD), dialysis and kidney transplant (KT) patients:[21]

1. During Ramadan, patients who have chronic kidney disease (CKD) stages 3-5, HD, PD and have received a kidney transplant (KT) are at a higher risk of worsening of renal function. Therefore, these patients need evaluation, risk stratification, monitoring and individualized advice before Ramadan.
2. Stable CKD stage 3 patients can fast. They should, however, be cautious, and be aware that if their health deteriorates, they may need to discontinue fasting.
3. Ramadan fasting puts CKD stage 4, 5 patients at a higher risk of complications and they may need to discontinue fasting for medical or religious exemptions. The alternate options should be explored to them, like fasting on short days or winter season, giving fidyah.
4. CKD patients with symptomatic cardiovascular disease should not fast because their kidney function may deteriorate quickly.
5. If patients still insist on fasting, they should be educated on risk of deterioration, fluid overload, dehydration, electrolytes imbalance. Self-monitoring of BP, daily body weight and edema is important.
6. These patients should avoid food containing high level of phosphorous (cola, fast food, seeds, canned fish, cheese, etc) and potassium (coconut water, banana, watermelon, cucumbers, lentils, potatoes, etc). Plain water hydration is essential.
7. In cases who have an increase of serum creatinine by 30% from the baseline or a significant change in serum electrolytes levels (low or high Na+, K+, high phosphorous) must be advised to discontinue their fasting.
8. The frequency of urea, creatinine and electrolytes assessment may vary. In CKD patient with significant change in body weight (2 kg), edema, breathlessness, dehydration, anorexia, fatigueness, once to twice weekly monitoring is necessary.
9. ESRD on MHD patients are very high risk group for fasting. It is highly recommended for those patients to discourage fasting. If they insist on fasting, they may be able to fast on non-dialysis days. Hemodialysis is a catabolic state and these patients should follow potassium and phosphate restricted diet. But many food item and drinks in Iftar may be rich in potassium and phosphate. Therefore, they require regular monitoring.
10. Patient on PD wishing to fast:

· For CAPD, complete 3 nighttime exchanges between iftar and suhoor with daytime dry or with last icodextrin filling before suhoor.

- For CCPD, complete nighttime exchanges by cycler with daytime dry or with last icodextrin filling before suhoor.
- Maximum fasting duration for PD patients should be 16 hours and non-fasting duration 8 hours for minimum 3 exchanges.
- Icodextrin fill to be completed before the sunrise (suhoor) and should be drained out before sunset (iftar).

11. In kidney transplant (KT) patients who have a stable renal function and taking their immunosuppressive regularly, can fast Ramadan safely if their physicians follow-up them before and after Ramadan. However, these patients need to drink enough fluids and take immunosuppressive drugs during the non-fasting period.
12. Few patients are more prone to develop recurrent urinary stone. They need to drink 2.5 to 3 liter of fluid daily, 0.5 liter during Iftar and rest of the fluid thereafter.
13. Dose adjustment of some drugs in Ramadan fasting:
    - Before Ramadan fasting, drugs with thrice daily dose should be changed to once- or twice daily dose.
    - Metformin / DPP-4 inhibitors /Acarbose / voglibose /Pioglitazone: No dose modification is required.
    - Second generation sulfonylureas (e.g. gliclazide): Morning dose at Iftar and 50% of night dose reducton at suhoor.
    - SGLT2 inhibitor: Take at Iftar. Increase fluid intake at night.
    - Insulin: Morning dose at Iftar and 50% of night dose reduction at suhoor.
    - If fasting blood glucose is <4 or > 16 mmol/L during fasting, adjust next dose of insulin by at least 4 units.
    - Self-monitoring of blood glucose: At mid-day, mid-afternoon, at anytime of unwell being.
    - According to sick day rules, the following medications should be stopped during an acute illness: Diuretics, ACEi, ARB, SGLT2 inhibitor (e.g. Empagliflogen), MRA (e.g. spironolactone), tolvaptan (water diuretic).
14. Trial fasting: Following change in necessary medication and dialysis schedule, patients may consider a trial of fasting for few days 1 month before Ramadan with close monitoring to evaluate safety and tolerability.
15. Over all, risk stratification, patient-centred discussion, assisting patients in decision- making, and sharing of a safe and tolerable winter Ramadan experience (which is 8 to 10 hours fasting only) are important for CKD patients.

Religious considerations on fasting for Kidney Disease patients:

According to Islamic rule, any form of food, fluid, nutrition and medication, taken via oral, nasal or rectal route is not permitted for a fasting person. Use of topical, intramuscular, subcutaneous medications such as insulin is permitted and do not invalidate the fast. For HD and PD, there are religious edicts (fotuwa) that fasting would be invalidated by dialysis. Therefore, these patients are advised to fast on non-dialysis days or to dialyze on non-fasting hours (at night).

It is also well known that fasting is associated with many beneficial changes to general wellbeing. Therefore, the decision to fast or not to fast depends on the physical, mental and spiritual strength of the patients. Islam permits the patients with appropriate ailments to discontinue fasting or to be exempted from fasting. Regarding fasting with ailment, there are two main options:

1. Making up the missed fasts—(a) in case of acute illness, after recovery; (b) in case of chronic illness, when health is not deteriorated by fasting at small days, e.g. in the winter.
2. An exemption from fasting for those serious patients whose illness will not recover, rather progress. These patients have option to feed the poor, known as fidyah.

Ailments that enable the above exemptions can also include very old age, frailty, or a stable condition that will be adversely affected by fasting. This also includes abstaining from the use of medication which increases the risk of decompensation of chronic illness. This can be determined by prior experience of fasting with the ailment, or common knowledge. Muslims are also encouraged to seek counsel from a trusted religious authority, if they feel any uncertainty.[21]

Conclusions:

Fasting for longer period (particularly during summer) increases the risk of AKI and worsening of CKD, due to dehydration. Although individuals may be exempted from fasting for religious or medical reasons, some insist on fasting and placing themselves in danger. According to the IDF-DAR guideline, high-risk patients are encouraged to discontinue their fasting and to consider fidyah.

References:

1. Pew Research Center.The future of the global Muslim population. (2022). Accessed: April 16, 2022: http://www.pewforum.org/2011/01/27/the-future-of-the-global-muslim-population.
2. Puri-Mirza A. Ramadan - statistics & facts. Statistica. (2022). Accessed: May 14, 2022: https://www.statista.com/topics/6363/ramadan/#topicHeader__wrapper.
3. Emami-Naini A, Roomizadeh P, Baradaran A: Ramadan fasting and patients with renal diseases: a minireview of the literature. J Res Med Sci. 2013, 18:711-6.
4. Hassanein M, Al-Arouj M, Hamdy O, et al.: Diabetes and Ramadan: practical guidelines.Diabetes Res Clin Pract. 2017, 126:303-16. 10.1016/j.diabres.2017.03.003.
5. Meo SA, Usmani AM, Qalbani E: Prevalence of type 2 diabetes in the Arab world: impact of GDP and energy consumption. Eur Rev Med Pharmacol Sci. 2017, 21:1303-12.
6. Ioannidis I: Diabetes treatment in patients with renal disease: Is the landscape clear enough? World J Diabetes. 2014, 5:651-8. 10.4239/wjd.v5.i5.651.
7. Rabkin R, Ryan MP, Duckworth WC: The renal metabolism of insulin . Diabetologia. 1984, 27:351-7. 10.1007/BF00304849
8. Reilly JB, Berns JS: Selection and dosing of medications for management of diabetes in patients with advanced kidney disease. Semin Dial. 2010, 23:163-8.
9. Chowdhury A, Khan H, Lasker SS, Chowdhury TA: Fasting outcomes in people with diabetes and chronic kidney disease in East London during Ramadan 2018: The East London diabetes in Ramadan survey. Diabetes Res Clin Pract. 2019, 152:166-70. 10.1016/j.diabres.2019.05.022
10. NasrAllah MM, Osman NA: Fasting during the month of Ramadan among patients with chronic kidney disease: renal and cardiovascular outcomes. Clin Kidney J. 2014, 7:348-53. 10.1093/ckj/sfu046
11. Eldeeb AA, Mahmoud MA, Ibrahim AB, Yousef EA, Sabry AA: Effect of Ramadan fasting on arterial stiffness parameters among Egyptian hypertensive patients with and without chronic kidney disease. Saudi J Kidney Dis Transpl. 2020, 31:582-8. 10.4103/1319-2442.289444
12. AlAbdan NA, Almohammed OA, Altukhaim MS, et al.: Fasting during Ramadan and acute kidney injury (AKI): a retrospective, propensity matched cohort study. BMC Nephrol. 2022, 23:54. 10.1186/s12882-022- 02674-1
13. Qurashi S, Tamimi A, Jaradat M, Al Sayyari A: Effect of fasting for Ramadan on kidney graft function during the hottest month of the year (August) in Riyadh, Saudi Arabia. Exp Clin Transplant. 2012, 10:551-3. 10.6002/ect.2012.0139
14. Bragazzi NL: Ramadan fasting and chronic kidney disease: does estimated glomerular filtration rate change after and before Ramadan? Insights from a mini meta-analysis. Int J Nephrol Renovasc Dis. 2015, 8:53-7. 10.2147/IJNRD.S61718
15. Bragazzi NL: Ramadan fasting and chronic kidney disease: a systematic review . J Res Med Sci. 2014, 19:665- 76.
16. Ibrahim IA, Hassan EA, Alkhan AM, et al.: Ramadan fasting in kidney transplant recipients: a single-centre retrospective study. J Transplant. 2018, 2018:4890978. 10.1155/2018/4890978
17. Imtiaz S, Nasir K, Dhrolia MF, et al.: Mortality trend among hemodialysis patients during the islamic month of Ramadan: a 24 years retrospective study. J Coll Physicians Surg Pak. 2015, 25:189-92.
18. Imtiaz S, Salman B, Dhrolia MF, et al.: Clinical and biochemical parameters of hemodialysis patients before and during Islamic month of Ramadan. Iran J Kidney Dis. 2016, 10:75-8.
19. Adanan NI, Md Ali MS, Lim JH, et al.: Investigating physical and nutritional changes during prolonged intermittent fasting in hemodialysis patients: a prospective cohort study. J Ren Nutr. 2020, 30:e15-26. 10.1053/j.jrn.2019.06.003
20. International Diabetes Federation and the Diabetes and Ramadan International Alliance (IDF-DAR) Practical guidelines 2021.
21. Malik S, Bhanji A, Abuleiss H, et al. Effects of fasting on patients with chronic kidney disease during Ramadan and practical guidance for healthcare professionals. *Clinical Kidney Journal,* Volume 14, Issue 6, June 2021, Pages 1524-1534.

Post-transplant Malignancy: A Review

Ansary EAF[1], Mony MB[2], Chowdhury JK[3], Azim MAU[4]

Abstract:

Compared to the general population, kidney recipients are more likely to develop a malignancy, and this risk increases with age. The standard incidence ratio (SIR), which measures this elevated risk, varies widely, but it is highest in cancers brought on by oncogenic viruses. This elevated risk for other malignancies is a direct result of acceleration of tumor growth and decrease of immune system tumor surveillance by the effect of immunosuppressant. Major cancers with higher risks following kidney transplantation are briefly covered in this overview, along with the benefits of surveillance and current preventative and treatment guidelines.

Keywords: cancer screening; immunosuppression; kidney transplant; malignancy.

(Bang. Renal J. 2023; 5(2): 65-71

Introduction:

In comparison to the general population, recipients of solid organ transplant have a higher long-term risk of developing cancer due to the chronic use of immunosuppressive medications to avoid allograft rejection. A number of different malignancies are more likely to develop after solid organ transplantation.[1,3] The most comprehensive data originate from a major cohort research that examined the prevalence of cancer in over 175,000 recipients of solid organ transplants from 1987 to 2008.[1] The kidney, liver, heart, and lung were the most frequently transplanted organs (58, 22, 10, and 4% of patients, respectively). Malignancy was found in 10,656 cases overall, resulting in a greater than average absolute risk of 719 cases per 100,000 person years and a standardized incidence ratio (SIR) of 2.1 (95% CI 2.06-2.14) versus the general population. And viral infections are linked to the following cancers.

- Kaposi sarcoma (KS; SIR 61.5)
- Skin (nonmelanoma, nonepithelial; SIR 13.9)
- Non-Hodgkin lymphoma (SIR 7.5)
- Liver (SIR 11.6)
- Anus (SIR 5.8)
- Vulva (SIR 7.6)
- Lip (SIR 16.8)

Additionally, but to a lesser extent, the prevalence of primary malignancies in the upper GIT, genitalia, thyroid, urinary bladder, soft tissue sarcomas, small intestine, biliary tract, leukemia increased.

Alternatively, the risk of prostate cancer (SIR 0.92) and the incidence of breast cancer (SIR 0.85) both declined.

The results of this investigation also revealed that the incidence of particular cancers varied according to the donated organ.[1] For instance, compared to individuals who got kidney, liver, or heart transplants; lung transplant patients had a roughly two-fold higher incidence of non-Hodgkin lymphoma. On the other hand, lung cancer rates among recipients of lung transplants increased by around three times, and rates of liver and kidney cancer increased in recipients of liver and kidney transplants, respectively.[2,3]

Sun exposure, the type, degree, and duration of immunosuppression, as well as concurrent viral infection, have all been connected to an increased prevalence of secondary cancers among transplant recipients. Rarely, a donor's cancer has been transplanted.

The different viral infections that may promote post-transplant malignancy:

The Epstein-Barr virus (EBV), human papillomavirus (HPV), human herpesvirus 8 (HHV-8), and Merkel cell

1. Eusha Ahmad Fidalillah Ansary, Associate Professor, Department of Nephrology, Uttara Adhunik Medical College, Dhaka, Bangladesh
2. Maksuda Begum Mony, Associate Professor, Department of Nephrology, Medical College for Women and Hospital, Dhaka
3. Jubaida Khanam Chowdhury, Associate Professor, Department of Nephrology, Shaheed Monsur Ali Medical College, Uttara, Dhaka, Bangladesh
4. Muhammad Arshad Ul Azim, Assistant Professor, Department of Nephrology, Shaheed Sheikh Abu Naser Specialized Hospital, Khulna, Bangladesh

Address of Correspondence: Dr. Eusha Ahmad Fidalillah Ansary, Associate Professor and Head, Department of Nephrology, Uttara Adhunik Medical College, Dhaka, Bangladesh. E-mail: eushaansary@gmail.com, Mobile: +88 01712215146

polyomavirus (MCV) are at least four viruses that may co-cause cancer in transplant recipients.

The Epstein-Barr virus causes lymphomas, which are among the most common transplant-related issues and are typically connected to EBV infection.

Kaposi sarcoma (KS) is associated with Human herpesvirus 8. All types of KS, including classic KS, endemic KS, post-transplant KS, and KS associated with the acquired immune deficiency syndrome (AIDS), have been shown to contain HHV-8 in tumor tissue; serologic evidence of infection is also frequently present.[4,5]

Human papillomavirus (HPV) infection may contribute to the etiology of squamous cell skin cancers. It is also thought that Merkel cell polyomavirus is linked to Merkel cell cancer.

The pathogenesis of post-transplant malignancies:

Maintenance immunosuppression reduces acute and chronic rejection as well as allograft loss. Although the precise mechanisms are unknown, immunosuppression's effect on dampening the immune system may open up a multitude of pathways for the development of cancer. The failure of immunosuppressed patients to properly control known cancer-causing viruses is one potential explanation.

For instance, patients with reduced immunity frequently experience increases in viral-associated Post-transplant Lymproliferative Disease (PTLD) (Epstein-Barr virus [EBV]), Kaposi sarcoma (human herpesvirus 8), and lip and anal tumors (HPV) are examples of malignancies.[6] Another way that tumors associated with immunosuppression develop is by the accumulation of mutations that the immune system would typically identify or correct. Because immunosuppression decreases the cells' ability to repair DNA damage brought on by ultraviolet (UV) radiation, this pathway may be more common in skin cancers. More specifically, immunosuppression can be used to lessen complementation groups A and G from xeroderma pigmentosum, which are involved in nucleotide excision repair.[7]

There isn't enough proof yet to say that one kind of immunosuppression causes more cancer than another.[8] However, research has revealed that, adenocarcinoma of lung, renal cell carcinoma, and hepatocellular carcinoma cells, tacrolimus increases TGF-b levels, which in turn promote tumor growth and spread.Additionally, calcineurin inhibitors prevent activated T cells from signaling via calcineurin and NF, which can activate p53, a feature of some Non-melanoma Skin Cancer (NMSCs).[9]

Through routes involving the overexpression of TGF-b or IL-6, cyclosporine also directly affects the growth and progression of tumors.[10] According to recent research, Cyclosporine can drive activated T cells into apoptosis, inhibit cell death by opening mitochondrial permeability transition pores, delay DNA repair, which results in mutation accumulation, and accumulate mutations.[11]

The possibility that azathioprine may have an oncogenic effect is generally recognised and confirmed and it raised the risk of NMSCs by sensitizing the skin to UVA radiation and accumulating 6-thioguanine in the DNA.[12]

On the other hand, mTOR inhibitors may have potential anticancer effects by slowing the development of cancer cells by arresting cell cycle as well as starting apoptosis.

The surveillance of post-transplant viral infections associated with the potential to develop malignancy:

After a kidney transplant, viral infections continue to be a major source of morbidity and mortality. The most significant viruses with the ability to cause cancer are those listed below.

The Epstein Barr Virus (EBV), persists latently in lymphocytes after primary infection, much like other herpesviruses. B cells act as its main reservoir for replication and clonal proliferation, along with other cell lines, are all susceptible to EBV. Though, a strong immune system, particularly a T cell response, stops the spread of these cells. PTLD may emerge in patients with decreased T cell activity and compromised immune surveillance system, as is the situation in kidney transplant recipients.[13] Since 90% of individuals have EBV antibodies by the time they are 40 years old, symptomatic infection is most frequently observed in pediatric groups. Compared to other organ transplant, renal transplants carried the lowest chance of developing PTLD (about 1 to 3%). The first year after a transplant is when PTLD most frequently occurs.[14] Prior to donation, serological tests for EBV should be carried out for both donor and recipient. The most vulnerable individuals for PTLD are allograft recipients who are EBV negative prior to transplant and get an organ from a seropositive donor. There is currently no one proven method to stop PTLD. Some hospitals routinely screen high-risk patients for EBV viremia, and immunosuppression is lowered when viremia is discovered. By minimizing the effects of CMV on immunological modulation, effective CMV prophylaxis may help prevent EBV infections.[15]

Human Herpes Virus 8 (HHV8) has been linked to lymphoproliferative disorders such as Multicentric Castleman's Disease and Kaposi's Sarcoma as well as primary exuberant lymphoma. Although it is possible for primary infections to develop after transplant and to be contracted by the allograft itself,[16] it is believed that infection in the renal transplant population more frequently happens through reactivation of latent virus. Either immunohistochemistry on biopsy tissue samples or nucleic acid testing on peripheral blood lymphocytes must be used to diagnose the virus.[17]

Human papillomavirus, which is also connected to cervical intraepithelial neoplasia, squamous cell carcinoma, and anogenital cancer, causes skin and anogenital warts. Among organ transplant recipients, premalignant cervical and skin lesions are more prevalent and advance to malignancy more quickly. Anogenital warts, cutaneous warts, and keratoses should all be kept an eye on and referred for fast evaluation, biopsies, and treatment for colorectal or dermatologic conditions. The placement of Squamous Cell Carcinomas (SCCs) on the lips, oral cavity, and genitalia is a reflection of the causative role of the human papillomavirus, and oncogenic viruses play an essential etiologic role in addition to the influence of certain immunosuppressive drugs. Human papillomavirus has been related to the etiology of squamous cell carcinoma of the skin, vulva, vagina, and likely the uterine cervix. Before or after transplantation, the inactivated human papillomavirus vaccine is advised for both the adult and pediatric groups.[18]

The diagnosis of various post-transplant viral-associated malignancies:

The following viruses may cause malignancies in transplanted patients: Epstein-Barr virus (EBV), human papillomavirus (HPV), human herpesvirus 8 (HHV-8), and the Merkel cell polyomavirus (MCV).

Post-transplant lymphoproliferative diseases (PTLDs) occur in the presence of immunosuppression and reduced T cell immune surveillance and Epstein-Barr virus (EBV) positive B cell proliferation.[19]

Since PTLD can manifest softly and/or extranodally, a high index of suspicion is necessary for an appropriate diagnosis.[20] Lymphadenopathy, B symptoms (fever, weight loss, night sweats), unexplained hematologic or biochemical abnormalities, and/or signs or symptoms linked to the infiltration of extralymphatic tissues should all be taken into consideration in patients who have undergone allogeneic transplantation. PTLD may also result in symptoms resembling organ rejection or adverse reactions to immunosuppressive drugs. Similar to how lymphoma suspicion is assessed in the non-transplant population, the initial assessment is based on the patient's current symptoms.

The presence of elevated blood indicators, such as elevated lactate dehydrogenase levels, radiologic indications of a mass, and positive positron emission tomography (PET) scanning are suggestive of PTLD.[21] The diagnosis is further supported by a growing viral load of the Epstein-Barr virus (EBV). A tissue biopsy is necessary for diagnosis and categorization, particularly an excisional biopsy is adequate enough to provide complete characterisation of the lesion.[22] An experienced hematopathologist should study the biopsy tissue and evaluate it based on morphology, immunophenotype, the presence or absence of EBV, cytogenetics, and studies of antigen receptor gene rearrangement.[23]

After a kidney transplant, the development of Kaposi sarcoma has been linked to human herpesvirus-8. Fever, enlarged spleen, hyperplasia of lymphoid tissue, pancytopenia, and often rapid-onset KS may be associated with apparent primary HHV-8 infection in immunocompromised individuals, such as solid organ transplant recipients.

The emergence of the unique lesions, such as the distribution of purplish, reddish blue, or dark brown or black patches, plaques, or nodules on the skin, most usually on the lower extremities are typically used to make the diagnosis of classic KS.

A biopsy is necessary for a conclusive diagnosis. The diagnosis can be confirmed using immunohistochemical staining in the biopsy specimens and using polymerase chain reaction to detect human herpes virus 8 (HHV-8). Due to their persistent, mostly indolent history, asymptomatic patients with classic KS rarely need to have the affected extremity radiographically evaluated. Due to the rarity of radiographically visible metastatic disease, screening for involvement of distant organs is unnecessary.[24]

The pathogenesis of squamous cell cancer of the skin, female genitalia and probably the uterine cervix has been linked to the human papillomavirus. Uncertainty surrounds the contribution of the human papillomavirus (HPV) to the emergence of cutaneous Squamous Cell Carcinoma(cSCC). Organ transplant recipients with SCC

have higher HPV detection rates in lesional skin compared to nonlesional skin.[25]

Any surface of the body that is exposed to sunlight might develop cSCC. Lesions of the genitalia and periungual region that are associated with high-risk human papillomavirus (HPV) infection are less frequent. Histopathologic analysis is required to confirm the diagnosis of cSCC, even though clinical and dermoscopic evidence may strongly support it. Assessment of perineural invasion, tumor differentiation, and tumor depth using histopathology is helpful for determining tumor stage and prognosis.[26]

Markel Cell Carcinoma (MCC) has been causally associated with Merkel cell polyomavirus.[27] frequently manifests in older individuals with light skin tones as a rapidly developing, firm, non-tender, glossy, flesh-colored or bluish-red intracutaneous nodule. A benign tumor, such as a cyst, lipoma, or pyogenic granuloma, is frequently clinically misinterpreted as Merkel cell carcinoma (MCC).[28] In order to quickly make the diagnosis, a strong index of suspicion is necessary. To distinguish MCC from other weakly differentiated cancers, routine hematoxylin and eosin examinations and immunohistochemical stains are frequently needed. MCC commonly spreads into the subcutis and typically manifests as a cutaneous lump. The Merkel cells have characteristics of both epithelial and neuroendocrine cells on immunohistochemistry.[29]

Treatment, prevention, and post-transplant surveillance of post-transplant malignancies:

Malignancies, which are common after solid organ transplants are skin cancers, Kaposi sarcoma, cervical cancer and lymphoproliferative disorder.

Skin cancer: Long-term immunosuppression has been found to increase the risk of cutaneous malignancies in solid organ transplant recipients, most often squamous cell carcinoma. Given that some skin malignancies have aggressive biologic behavior when there is immunosuppression, caution must be exercised while identifying and treating early lesions. Modulation of immunosuppression and preventive measures are crucial in the care of these patients, in addition to therapies that specifically target cutaneous malignancies. Skin cancer survivors undergoing organ transplants need to be regularly monitored for the emergence of new lesions.

Treatment:

Squamous cell carcinoma: Invasive SCCs are typically regarded as high-risk lesions in this patient population.[30] In order to stop local recurrence and disease spread in these patients with invasive SCCs, techniques that offer pathologic confirmation of complete surgical removal.

Basal cell carcinoma (BCC): A topical immunostimulatory drug called imiquimod is occasionally used to treat superficial BCC. Imbiquimod appears to be safe when used on small areas (60 to 100 cm2) for certain period in patients who have had organ transplantation.[31]

Melanoma: The treatment of melanoma in people who have had organ transplants typically resembles that of given to people without organ transplant.[32] Surgery is routinely used to treat patients with early-stage melanoma; sentinel lymph node biopsy is advised for tumors that are deeper than 1 mm.

Immunosuppression reduction: Immunosuppression should typically be scaled back to the strictest regimen necessary to maintain organ tolerance. The right treatment for immunosuppression in people with melanoma has not yet been established. Immunosuppression with sirolimus has been associated with a decrease in cancer incidence in organ transplant recipients.[33]

Prevention: In patients who have undergone organ transplantation, squamous cell carcinoma (SCC), which can be aggressive and have a significantly higher mortality rate than in the general population, is 65 to 250 times more likely to develop.[34] The dermatologist and transplant team must work closely together to provide these patients with preventive care, which may include educating patients about sun protection and self-examination of skin, choosing and adjusting immunosuppressive therapies, chemoprevention, and post-transplantation surveillance.

Skin self-examination: Organ transplant recipients should be advised to conduct a monthly skin self-examination since it is crucial.

Kaposi sarcoma (KS):

In patients with mucocutaneous disease and visceral involvement, respectively, eradication of KS was associated with decreasing immunosuppressive treatment in 17 and 16 percent of cases reported in the Cincinnati registry.[35] Reducing or stopping the immunosuppressive treatment should be the first therapeutic step because KS might respond to it.[36] Furthermore, in a total of 17 kidney transplant recipients, complete regression of KS has been connected to the substitution of sirolimus for cyclosporine.[37]

Cervical cancer: It makes up 3% of post-transplant cancers. It frequently affects female transplant recipients. Cervical

cancer is mostly brought on by the oncogenic human papillomavirus (HPV), HPV 16, and HPV 18. Cervical intra-epithelial neoplasia (CIN) is caused by high-risk HPV infections in 60% of cases after kidney donation. Treatment depends on the stage of the disease. It is advised to get vaccinated against HPV to prevent it. For people who are immunocompromised, a cervical cancer screening program is also advised as a kind of surveillance.[18]

Lymphoproliferative disorders: B cell-derived disorders make up the majority of malignant lymphoproliferative diseases that arise following solid organ donation, with non-Hodgkin lymphoma being the most prevalent.

Choice of treatment: Reducing immunosuppression, immunotherapy with the CD20 monoclonal antibody rituximab, chemotherapy, radiation therapy, or a combination of these are the primary options for initial treatment. Other therapies, like adoptive immunotherapy using EBV-specific cytotoxic T cells, are typically saved for patients who continue to experience symptoms after receiving initial therapy, are being treated at specific facilities equipped to provide these therapies, or are willing and able to travel to such facilities.

Reduction in immunosuppression: After the immunosuppression is reduced, the majority of early lesions either totally disappear or markedly improve within three to five weeks.[38]

Rituximab: It has been demonstrated that rituximab used with combination chemotherapy lowers the incidence of renal graft impairment.[39] Some medical professionals advocate using rituximab as a single agent with the intention of switching to alternate therapy if the drug's effects are insufficient.[39,40]

Chemoimmunotherapy: Rituximab is typically given along with chemotherapy to individuals with CD20+ PTLD. For the majority of patients with PTLD, recommendation includes R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone); or CHOP (without rituximab) to individuals whose PTLD does not express CD20. In some circumstances, additional non-Hodgkin lymphoma treatment regimens may be suitable.[38]

Radiation therapy: Patients with localized disease and those whose central nervous system has been affected may benefit from radiation therapy, whether it is used alone or in combination.[41]

Adoptive immunotherapy: In adoptive immunotherapy, EBV-associated PTLD is treated with donor lymphocyte infusion (DLI) or EBV-specific cytotoxic T lymphocytes (EBV-CTLs) in an effort to eradicate dividing B cells.[42]

Prevention: Antiviral prophylaxis, quick drug withdrawal and/or tapering, and limiting patient exposure to strong immunosuppressive regimens are the key preventative strategies. Paying attention to such precautions may reduce the prevalence of PTLD. In addition, several transplant facilities monitor EBV in patients with a high risk of developing PTLD as part of routine evaluations, and they treat PTLD in advance of viral reactivation with anti-B cell monoclonal antibodies.

Conclusion:

Solid organ transplantation is linked to an elevated risk of a wide variety of malignancies. Depending on the donated organ, it appears that different cancers have a different incidence. Sun exposure, the kind, degree, and duration of immunosuppression, as well as concurrent viral infection, have all been connected to an increased prevalence of secondary cancers among transplant recipients. Rarely, a donor's cancer has been transplanted.

Solid organ cancers in transplant patients must be prevented and detected with the use of regular screening exams and strict adherence to prevention measures, especially early-stage tumors. Direct data to back up specific screening procedures in this population are, however, insufficient. In general, solid organ transplant patients receive age-appropriate cancer screening from us.

Malignancies that develop after organ transplants are treated using a general preventive strategy first. Avoid using antilymphocyte drugs frequently, severe immunosuppression in particular. Prior to transplantation, the patient and donor should undergo careful screening to help identify any underlying, pre-existing malignancies.

References:

1. Engels EA, Pfeiffer RM, Fraumeni JF Jr, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA 2011; 306:1891.
2. Asch WS, Bia MJ. Oncologic issues and kidney transplantation: a review of frequency, mortality, and screening. Adv Chronic Kidney Dis 2014; 21:106.
3. Laprise C, Cahoon EK, Lynch CF, et al. Risk of lip cancer after solid organ transplantation in the United States. Am J Transplant 2019; 19:227.
4. Miller G, Rigsby MO, Heston L, et al. Antibodies to butyrate-inducible antigens of Kaposi's sarcoma-associated herpesvirus in patients with HIV-1 infection. N Engl J Med 1996; 334:1292.

5. Munoz P, Alvarez P, de Ory F, et al. Incidence and clinical characteristics of Kaposi sarcoma after solid organ transplantation in Spain: importance of seroconversion against HHV-8. Medicine (Baltimore) 2002; 81:293.

6. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM: Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: A meta-analysis. Lancet 370: 59–67, 2007

7. Kuschal C, Thoms KM, Boeckmann L, Laspe P, Apel A, Schon MP, Emmert S: Cyclosporin A inhibits nucleotide excision repair via downregulation of the xeroderma pigmentosum group A and G proteins, which is mediated by calcineurin inhibition. Exp Dermatol 20: 795–799, 2011

8. Gallagher MP, Kelly PJ, Jardine M, Perkovic V, Cass A, Craig JC, Eris J, Webster AC: Long-term cancer risk of immunosuppressive regimens after kidney transplantation. J Am Soc Nephrol 21: 852–858, 2010

9. Wu X, Nguyen BC, Dziunycz P, Chang S, Brooks Y, Lefort K, Hofbauer GF, Dotto GP: Opposing roles for calcineurin and ATF3 in squamous skin cancer. Nature 465: 368–372, 2010

10. Hojo M, Morimoto T, Maluccio M, Asano T, Morimoto K, Lagman M, Simbo T, Suthanthiran M: Cyclosporine induces cancer progression by a cell-autonomous mechanism. Nature 397: 530–534, 1999

11. Durnian JM, Stewart RM, Tatham R, Batterbury M, Kaye SB: Cyclosporin-A associated malignancy. Clin Ophthalmol 1: 421–430, 2007

12. McGurgan IJ, McGuigan C: Nonmelanoma skin cancer risk awareness in azathioprine-treated myasthenia gravis patients. Brain Behav 5: e00396, 2015

13. Hanto DW: Classification of Epstein-Barr virus-associated posttransplant lymphoproliferative diseases: Implications for understanding their pathogenesis and developing rational treatment strategies. *Annu Rev Med* 46 :381 –394,1995

14. Cockfield SM, Preiksaitis JK, Jewell LD, Parfrey NA: Post-transplant lymphoproliferative disorder in renal allograft recipients: Clinical experience and risk factor analysis in a single center. *Transplantation* 56 :88 –96,1993

15. Funch DP, Walker AM, Schneider G, Ziyadeh NJ, Pescovitz MD: Ganciclovir and acyclovir reduce the risk of post-transplant lymphoproliferative disorder in renal transplant recipients. *Am J Transplant* 5 :2894 –2900,2005

16. Diociaiuti A, Nanni G, Cattani P, Lesnoni La Parola I, Masini, Capuano M, Pozzetto U, Fadda G, Castagneto M, Cerimele D: HHV 8 in renal transplant recipients. *Transpl Int* 13[Suppl 1] :S410 –S412,2000

17. Kotton CN, Fishman JA: Viral infection in the renal transplant recipient. *J Am Soc Nephrol* 16 :1758 –1774,2005

18. Gabriel M. Danovitch. Handbook of Kidney Transplantation.

19. Sixth Edition. Wolters Kluwer; 2017. 151-153p.

20. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, revised 4th edition, Swerdlow SH, Campo E, Harris NL, et al. (Eds), International Agency for Research on Cancer (IARC), Lyon 2017.

21. Kasiske BL, Vazquez MA, Harmon WE, et al. Recommendations for the outpatient surveillance of renal transplant recipients. American Society of Transplantation. J Am Soc Nephrol 2000; 11 Suppl 15:S1.

22. Bakker NA, Pruim J, de Graaf W, et al. PTLD visualization by FDG-PET: improved detection of extranodal localizations. Am J Transplant 2006; 6:1984.

23. Paya CV, Fung JJ, Nalesnik MA, et al. Epstein-Barr virus-induced posttransplant lymphoproliferative disorders. ASTS/ ASTP EBV-PTLD Task Force and The Mayo Clinic Organized International Consensus Development Meeting. Transplantation 1999; 68:1517.

24. Parker A, Bowles K, Bradley JA, et al. Diagnosis of post-transplant lymphoproliferative disorder in solid organ transplant recipients - BCSH and BTS Guidelines. Br J Haematol 2010; 149:675.

25. Schwartz RA. Kaposi's sarcoma: an update. J Surg Oncol. 2004;87(3):146.

26. Nindl I, Gottschling M, Stockfleth E. Human papillomaviruses and non-melanoma skin cancer: basic virology and clinical manifestations. Dis Markers 2007; 23:247.

27. Eliezri YD, Silverstein SJ, Nuovo GJ. Occurrence of human papillomavirus type 16 DNA in cutaneous squamous and basal cell neoplasms. J Am Acad Dermatol 1990; 23:836.

28. Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science 2008; 319:1096.

29. Heath M, Jaimes N, Lemos B, et al. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. J Am Acad Dermatol 2008; 58:375.

30. Warner TF, Uno H, Hafez GR, et al. Merkel cells and Merkel cell tumors. Ultrastructure, immunocytochemistry and review of the literature. Cancer 1983; 52:238.

31. Moloney FJ, Comber H, O'Lorcain P, et al. A population-based study of skin cancer incidence and prevalence in renal transplant recipients. Br J Dermatol 2006; 154:498.

32. Ulrich C, Bichel J, Euvrard S, et al. Topical immuno-modulation under systemic immunosuppression: results of a multicentre, randomized, placebo-controlled safety and efficacy study of imiquimod 5% cream for the treatment of actinic keratoses in kidney, heart, and liver transplant patients. Br J Dermatol 2007; 157 Suppl 2:25.

33. Zwald FO, Christenson LJ, Billingsley EM, et al. Melanoma in solid organ transplant recipients. Am J Transplant 2010; 10:1297.

34. Kauffman HM, Cherikh WS, Cheng Y, et al. Maintenance immunosuppression with target-of-rapamycin inhibitors is

associated with a reduced incidence of de novo malignancies. Transplantation 2005; 80:883.

35. Moloney FJ, Comber H, O'Lorcain P, et al. A population-based study of skin cancer incidence and prevalence in renal transplant recipients. Br J Dermatol 2006; 154:498.

36. Chan AW, Fung K, Austin PC, et al. Improved keratinocyte carcinoma outcomes with annual dermatology assessment after solid organ transplantation: Population-based cohort study. Am J Transplant 2019; 19:522.

37. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. N Engl J Med 2003; 348:1681.

38. Campistol JM, Gutierrez-Dalmau A, Torregrosa JV. Conversion to sirolimus: a successful treatment for posttransplantation Kaposi's sarcoma. Transplantation 2004; 77:760.

39. Swinnen LJ, Mullen GM, Carr TJ, et al. Aggressive treatment for postcardiac transplant lymphoproliferation. Blood 1995; 86:3333.

40. Trappe R, Hinrichs C, Appel U, et al. Treatment of PTLD with rituximab and CHOP reduces the risk of renal graft impairment after reduction of immunosuppression. Am J Transplant 2009; 9:2331.

41. Dierickx D, Habermann TM. Post-Transplantation Lymphoproliferative Disorders in Adults. N Engl J Med 2018; 378:549.

42. Parker A, Bowles K, Bradley JA, et al. Management of post-transplant lymphoproliferative disorder in adult solid organ transplant recipients - BCSH and BTS Guidelines. Br J Haematol 2010; 149:693.

Case Report

An Atypical Case of Anti GBM Disease

Sabrina S[1], Mahmud A[2], Alam MB[3]

Abstract:

Anti GBM (Glomerular Basement Membrane) disease is a very rare type of small vessel vasculitis. The incidence is around less than 1 per million per year. This disease is also known as "Good Pasture Disease". Usually, it presents with rapidly progressive glomerulonephritis with or without lung haemorrhage. The pathognomonic hallmark of the disease is strong linear IgG deposition along the GBM and positive anti GBM antibody. But when the circulating antibody is absent in the blood, with mild to severe renal impairment and linear IgG deposition along the GBM, it is called atypical anti GBM disease. Recently we have found a 26-year-old gentleman who presented with leg swelling for 1.5 months along with decreased urine output. He was non diabetic, normotensive, there was no history of joint pain, rash, sore throat, no history of taking any offending medication or coughing out of blood. His urine R/E report showed Alb+++, RBC-plenty. After admission his serum creatinine was increasing rapidly. We have done renal biopsy and started treatment with I/V methylprednisolone followed by oral steroid. He had nephrotic range proteinuria. His auto antibody profile and HBsAg, Anti HCV was negative. We have done renal biopsy and it showed crescentic GN with strong linear deposition of IgG. His anti GBM Ab was negative. Thus, we labelled the case as atypical anti GBM disease.

(Bang. Renal J. 2023; 5(2): 72-75

Case Report:

Here, we report a case of 26 years old male who presented to us with gradual swelling of the whole body with decreased urine output. With these complaints he consulted with a local physician and was diagnosed as a case of renal impairment. He was diagnosed as a case of UTI with Glomerulonephritis. After giving anti-proteinuric therapy for 1 month his proteinuria did not decrease, rather his proteinuria and serum creatinine was increased. At this point the patient was admitted with the plan of renal biopsy.

He gave no significant past medical history; he was immunized with covid vaccines and was non-smoker. All other histories like family, drug and socio-economic history were not significant. On examination we found him hugely edematous with bilateral pleural effusion and ascites.

After admission his renal function further deteriorated and he became oligo anuric. His urine R/E report showed proteinuria +++, with plenty of RBCs with significant dysmorphic RBCs. His blood urea and serum creatinine were also rising, and it became 8.2 mg/dl. We considered as a case of Rapidly Progressive Glomerulonephritis (RPGN). Further investigation revealed nephrotic range proteinuria (3.5 gm/d) and normal serum albumin and other auto antibody panel such ANCA, ANA etc & C 3 and C 4 levels. His viral markers were negative as well. We treated him accordingly with 3 doses of IV methylprednisolone followed by oral steroid and haemodialysis. We have done renal biopsy.

Renal biopsy report revealed crescentic glomerulonephritis featuring crescents over 8/10 glomeruli (80%) (6 glomeruli contains fibro cellular and 2 cellular crescents). Direct Immunofluorescence (DIF) study revealed strong intensity (3+) linear staining for IgG along glomerular capillaries.

IgA, IgM, C3, C1q were absent but there was kappa, lambda light chain along the glomerular capillaries. Anti-GBM

1. Sabrina Shahrin, Registrar (Nephrology), National Institue of Kidney Diseases and Urology, Dhaka.
2. Al Mahmud, Assistant Professor (Nephrology), National Institue of Kidney Diseases and Urology, Dhaka.
3. Md. Babrul Alam, Professor of Nephrology and Director, National Institue of Kidney Diseases and Urology, Dhaka.

Address of Correspondence: Sabrina Shahrin, Registrar (Nephrology), National Institue of Kidney Diseases and Urology, Dhaka.
E-mail: sssharna99@gmail.com, Mobile: +88 01711890998

antibody was found negative and it was done in immunofluorescence method. We started pulse I/V cyclophosphamide therapy associated with therapeutic plasma exchange (PE). After five sessions of PE along with other immunosuppressives his urine output was increased and became dialysis free.

Introduction:

Anti GBM disease is a very rare small vessel vasculitis that affects the basement membrane of the lung and kidney. In this condition antibodies are formed against the alpha3 subunit of collagen 4 of the basement membrane of different organs specially lung and the kidney.[1]

The incidence is only <1 per million case per year.[2]

This disease is also known as the "Good Pasture Disease". It comprises around 10%- 15% of the crescentic GN.[2]

Abrupt presentation is noted in most of the patients and 90% patients present with RPGN with or without lung haemorrhage [3] and represents most important pathology of the pulmonary renal syndrome.

The anti GBM antibodies are usually of IgG type of antibody. But it can be of other sub classes like IgA, IgM.[3] In anti-GBM disease usually the anti-GBM Ab is positive (in around 90% cases). When the histology strongly suggests anti-GBM disease but the circulating Ab is absent then it is called atypical anti-GBM disease. Around 8-12% of anti-GBM patients do not show anti-GBM Ab positivity.[2]

There are some diseases where histological findings may mimic anti-GBM disease such as Diabetes Mellitus, Fibrillary GN, Monoclonal Immunoglobulin Deposition Disorder (MIDD) etc.[3] These mimickers do not show strong deposition of antibody and presents with other typical clinical features of the respective disease. Usually, the younger patients show the whole constellation of Goodpasture's disease and the older patients show isolated organ damage-glomerulonephritis.[4]

Development of anti-GBM disease in Alport Syndrome after transplantation is well recognised. There are some medications that can induce anti-GBM disease such as alemtuzumab ipilimumab.[5,6] Now a day's treatment outcome is good if timely intervention can be initiated.[3]

Like all auto immune disease treatment option comprises two modalities removing the preformed antibody and stopping the production of antibodies with or without Renal Replacement Therapy.[1]

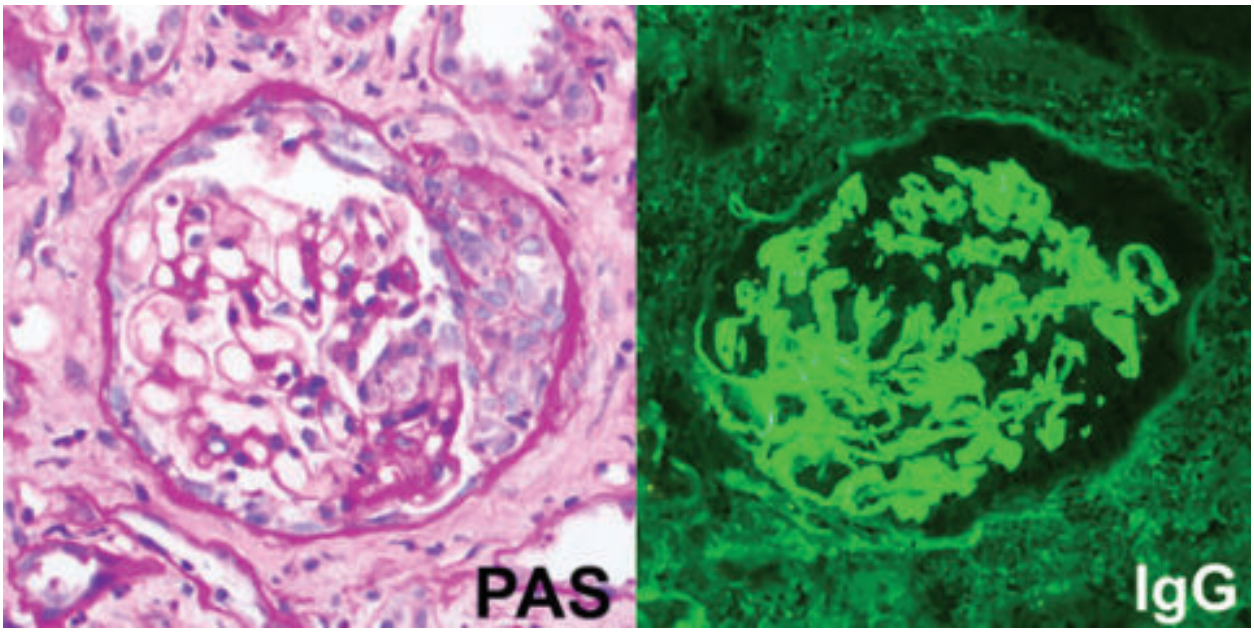

Fig.-1: *Representative picture of anti GBM disease with linear IgG deposition. PC: AJKD*

Discussion:

"Good Pasture Disease" this term was first used by the Australians Stanton and Tange in 1958. They credited the American physician Ernest Good Pasture who first described this condition in his paper in 1919.[2] Later on Good Pasture rejected the term by himself as it was thought that the published case in his paper was a case vasculitis .Very soon after that detection of anti-GBM Ab started and the first described case was by Wilson and Dixon.[2] However the eponym Goodpasture's disease persisted and was preserved for those who shows positive anti-GBM Ab and co-presentation of glomerular disease with lung disease.

The anti GBM disease is grouped under class 1 according to the revised international chapel hill consensus conference nomenclature of vasculitides on 2012.[6] It has got a bimodal age distribution with slight preponderance towards the third decade. It presents with a very aggressive form but if timely interventions can be given then ESRD is very rare.[1] Recurrence after remission is uncommon.

Although the inciting agent could not be established but there are some environmental factors related to lung haemorrhage like smoking, hydrocarbon inhalation etc.[1] Asians and whites has slight preponderance.

Patients with 100% crescents on biopsy or who require dialysis at presentation has a low kidney survival rate of 8% at 1 year of follow up.[3] In recent years there are increasing case reports of atypical anti GBM disease…where the biopsy shows typical IF findings but the clinical course is not aggressive and absent anti-GBM Ab.

In our case we have observed that our patient presented with RPGN without any lung findings, and his antibody is negative.

There are several case reports that shows cases with mild renal involvement without any lung involvement. In 2016 Nasr et al reported 20 cases who showed the similar features and was diagnosed as 'atypical anti-GBM disease'.[7] Notably these cases had very indolent course.

Pathogenesis: Deposition of auto antibodies leads to activation of complement and followed by inflammation and rupture of the GBM and fibrinoid necrosis. Leakage of pro-inflammatory plasma into the bowman's space causes parietal epithelial cell activation and crescent formation.[3]

There is different assumed mechanism of negativity of antibodies in some cases, these are mentioned below.[3]

Composition of the epitope/antibody: The Good pasture antibody is against the NC1 domain of alpha4 chain of type 4 collagen. But antibodies against the other chains like alpha1, alpha3, alpha5 chains of type 4 collagen is also possible and is difficult to detect.

Affinity of antibody: Serum anti-GBM antibody titre correlates with disease severity. Sometimes there are high affinity antibodies and these antibodies mostly traps into the kidneys with very low titre in the circulation. High affinity antibodies bind with GBM strongly and dissociates slowly. Thereby it becomes difficult to detect the antibody in the circulation.

Type of antibody: Nonspecific polyclonal antibodies in the plasma could alter the detection of antibodies. IgG1 is the most dominant subclass in typical anti-GBM diseases. Although IgG 1 and IgG4 are the dominant subclass in atypical anti GBM disease but IgG2 are reported frequently. IgG2 is a weak activator of the immune system. There are also different variants Ig noted in the pathogenesis of atypical Anti GBM disease like IgA, IgM mediated disease. These antibodies cannot be detected with conventional assay methods.

Test methods: There are several test methods like if, ELISA, chemo luminescence, radio immune assay, multiplex bead test, western blot, biosensor system. Elisa is more sensitive than IF assay. In our case we could not do the ELISA test.

With this previous explanation we can judge that atypical anti GBM diseases are becoming commoner and it need further clarification about the disease classification. Further research is needed to find out the disease process and disease progression in this type of atypical presentations of anti GBM disease.

a. Although this patient presented with RPGN like presentation but his anti-GBM Ab is negative. Most of the atypical anti-GBM cases presents with mild renal impairment with an indolent course.

b. This patient had crescentic GN but there was no pulmonary involvement.

Removal of the preformed antibody and inhibiting the production of antibodies remains the cornerstone of therapy in any antibody mediated renal disease.

For removal of preformed antibody, we used therapeutic plasma exchange, and for precluding further antibody we

have used steroid and cyclophosphamide. In this case there was no detectable antibody but still plasma exchange was done, as there are several ways of antibody production like there may be different class of antibody except IgG, antibody against the NC1 domain of alpha 1/2/4/5 but not alpha 3 chain. We had very less experience of treating atypical anti-GBM disease before, but we tried our best to save the remaining renal function of the patient but it was not successful, rather the patient developed different complications due to immunosuppression.

In his last follow up patients' creatinine was 3.5 mg/dl and urine output were satisfactory (1200 ml).

A subset of patients with biopsy proven anti-GBM disease may be seronegative due to false negative results. If the suspicion for anti-GBM disease is high based upon clinical presentation recommended treatment is like the classical Anti GBM disease.[9] Whether to treat patients who presents with dialysis dependent kidney failure without pulmonary haemorrhage is a more challenging decision, as there is very low likelihood of kidney response especially if there is 100% crescents. Other experts prefer a short trial plasmapheresis and immunosuppressive therapy, particularly among the following patients-

Whether to treat patients who presents with dialysis dependent kidney failure without pulmonary haemorrhage is a more challenging decision,as there is very low likelihood of kidney response especially if there is 100% crescents. Other experts prefer a short trial of plasmapheresis and immunosuppressive therapy, particularly among the following patients- 1. Patients with very acute disease in whom irreversible damage is unlikely, 2. Younger patients who are able to tolerate aggressive immunosuppression, 3. Patients whose biopsy shows focal crescentic glomerular damage associated with tubular injury & Patients with anti-GBM disease with ANCA positivity and features of systemic vasculitis.[9]

There are several treatment options in this disease-steroid, cyclophosphamide, mycophenolate mofetil, tacrolimus, rituximab can be used.[9] Finally renal transplantation can be done after 6 months of disease-free interval.[2]

References

1. Floege J, Johnson RJ, Feehally J. Comprehensive clinical nephrology E-book. Elsevier Health Sciences; 2010 Nov 8.
2. McAdoo SP, Pusey CD. Anti-glomerular basement membrane disease. Clinical Journal of the American Society of Nephrology. 2017 Jul 7;12(7):1162-72.
3. Bharati J, Yang Y, Sharma P, Jhaveri KD. Atypical anti-GBM disease. Kidney International Reports. 2023 Mar 21.
4. Silva N, Oliveira L, Frutuoso M, Morgado T. Anti-glomerular basement membrane disease: A case report of an uncommon presentation. J Clini Nephrol. 2019; 3: 061-065. https://doi.org/10.29328/journal.jcn.1001027
5. Meyer D, Coles A, Oyuela P, Purvis A, Margolin DH. Case report of anti-glomerular basement membrane disease following alemtuzumab treatment of relapsing–remitting multiple sclerosis. Multiple sclerosis and related disorders. 2013 Jan 1;2(1):60-3.
6. Sammartino C, Goodman D, Flanagan G, Hill P. Anti-GBM disease following CTLA4 blockade in a patient with metastatic melanoma. NDT plus. 2010 Apr 1;3(2):135-7.
7. Nasr SH, Collins AB, Alexander MP, Schraith DF, Hernandez LH, Fidler ME, Sethi S, Leung N, Fervenza FC, Cornell LD. The clinicopathologic characteristics and outcome of atypical anti-glomerular basement membrane nephritis. Kidney international. 2016 Apr 1;89(4):897-908.
8. Henderson SR, Salama AD. Diagnostic and management challenges in Goodpasture's (anti-glomerular basement membrane) disease. Nephrol Dial Transplant. 2018;33:196–202. https://doi.org/10.1093/ndt/gfx057
9. Kaplan AA, Appel GB, Pusey CD, Fervenza FC. Anti-GBM (Goodpasture) disease: treatment and prognosis. Plasmapheresis Plus Immunosuppressive therapy. 2007.Uptodate.

A 32-year-Old Man with Rheumatoid Arthritis Presented with Nephrotic Syndrome

Rahman GMH[1], Rana MS[2], Ahmed AS[3], Rahman HMM[4], Khan MAR[5], Islam MN[6]

Abstract:

Rheumatoid arthritis (RA) is a systemic inflammatory disorder characterized by joint inflammation, associated with autoantibody production. Renal involvement in RA may occur as a complication of treatment or can be related to the disease itself. Nephrotic syndrome is a rare renal manifestation in patients with RA. We are presenting a case of 32-year-old male with a history of seropositive RA who developed nephrotic syndrome. The patient presented with generalized edema, proteinuria, hypoalbuminemia, and hyperlipidemia. Renal biopsy revealed membranous nephropathy as the underlying cause of nephrotic syndrome. This case highlights the importance of recognizing nephrotic syndrome as a potential complication in patients with RA and the need for early intervention and multidisciplinary management.

(Bang. Renal J. 2023; 5(2): 76-78

Introduction:

Rheumatoid arthritis (RA) is an autoimmune disorder that affects primarily the joints. Extra- articular involvement may also occur, with appearance of rheumatoid nodules, pulmonary interstitial fibrosis, pulmonary nodules, pericarditis, mononeuritis multiplex, episcleritis and systemic vasculitis.[1] Renal findings in RA can be divided into three categories: 1. Serum amyloid A protein (SAA) related secondary amyloidosis; 2. Complication of treatment with disease modifying antirheumatic drugs (DMARDs), analgesics or non-steroidal anti-inflammatory agents (NSAIDs); 3. Renal disease related to RA itself or with an autoimmune predisposition.[2] The incidence of renal disease in RA is relatively low but it causes significant morbidity and mortality when present.[3] Abnormal renal manifestations of RA includes-isolated hematuria, isolated proteinuria, combined hematuria & proteinuria, chronic renal failure without hematuria & proteinuria.[3] Studies showed that kidney disease in RA patients has a wide spectrum. Renal histopathologic lesions are heterogenous and cannot be predicted with clinical and laboratory findings only. So, renal biopsy is essential for assessment of diagnosis and prognosis renal disease in RA.[7]

Case Presentation:

A 32-year-old male with the history of seropositive Rheumatoid arthritis (RA) for 5 years presented to the Department of Nephrology, Dhaka Medical College Hospital (DMCH) with the complaints of progressively increasing generalized edema, especially in the lower extremities, along with weight gain over the past four weeks. He reported no significant changes in joint symptoms or any recent infectious illnesses. He was treated initially with Methotrexate and low dose corticosteroid (prednisolone 5mg/day) for first 3 years, followed by tripple therapy (Methotrexate + Hydroxychloroquine + Sulfaslazine) for another 1 year and recently with Tofacitinib & low dose corticosteroid (prednisolone 5mg/day) for last 1 year. His treatment was adjusted according to DAS-28 based disease activity scoreOn general physical examination it was found that the was mildly anemic and edematous. His blood pressure was 150/90 mm of Hg. There were no other significant abnormalities in general and systemic examination. Laboratory investigations revealed that 24-hour Urinary Protein excretion of 8.57-gram, Serum Albumin 2.67 g/dL, Serum Cholesterol 340 mg/dL and Triglyceride 236 mg/dL. The patient's Serum Creatinine was 1.13mg/dL, Complete Blood Count revealed- Hemoglobin (11.7gm/dl), ESR-63mm in 1st hour, Total WBC count-9.89×10^9/L, Neutrophil-63%, Lymphocyte-30%, Platetet-500×10^9/L. Other laboratory findings include: SGPT-15U/L, Serum Uric Acid-8.9mg/dl, Urine R/M/E-Alb (++), RBC(1-2/HPF), pus cell (2-4/HPF).

1. GM Hafizur Rahman, Assistant Professor, Dept. of Nephrology, Dhaka Medical College, Dhaka.
2. Md. Sohel Rana, Resident Phase B (Nephrology), Dhaka Medical College, Dhaka.
3. Abu Saleh Ahmed, Associate Professor, Dept. of Nephrology, Dhaka Medical College, Dhaka.
4. Hossain Muhammad Mustafijur Rahman, Assistant Professor, Dept. of Nephrology, Dhaka Medical College, Dhaka.
5. Mohammad Ashikur Rahman Khan, Medical Officer, Dept. of Nephrology, Dhaka Medical College, Dhaka.
6. Md. Nazmul Islam, Professor & Head, Dept. of Nephrology, Dhaka Medical College, Dhaka.

Address of Correspondence: GM Hafizur Rahman, Assistant Professor, Dept. of Nephrology, Dhaka Medical College, Dhaka.
E-mail: hafiz.gazi@gmail.com, Mobile: +88 01712798618

Ultrasonography of KUB was normal. CXR PA revealed no abnormality.

Further work up included serological tests to rule out other causes of nephrotic syndrome such as Hepatitis B & C, HIV serology, ANA, c-ANCA, p-ANCA, C3, C4. All these tests were normal. Anti-PLA2Rab was negative (< 2 RU/ml). Which suggests that this is most likely not a case of primary Membranous Nephropathy.

The patient underwent a kidney biopsy where light microscopy revealed moderate degree of capillary basement membrane thickening with normal mesangial cellularity, patchy acute tubular injury, foci of tubular atrophy and interstitial fibrosis, mild arterial medial thickening. Granular deposit of IgG at glomerular capillary basement membrane zone was found in DIF, consistent with membranous nephropathy.

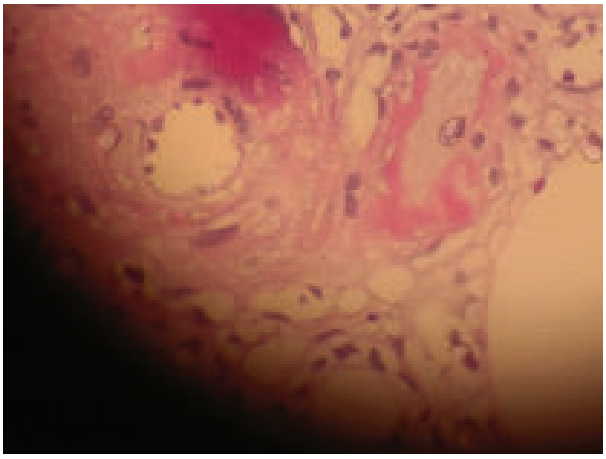

Fig. 1

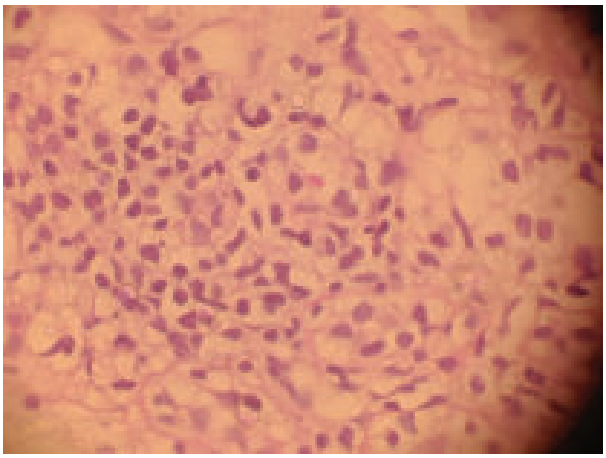

Fig. 2

Fig.-1 and 2: *Renal tissue showing mild foci of hyalinosis in the wall arteriols and mild medial thickening of arteries.*

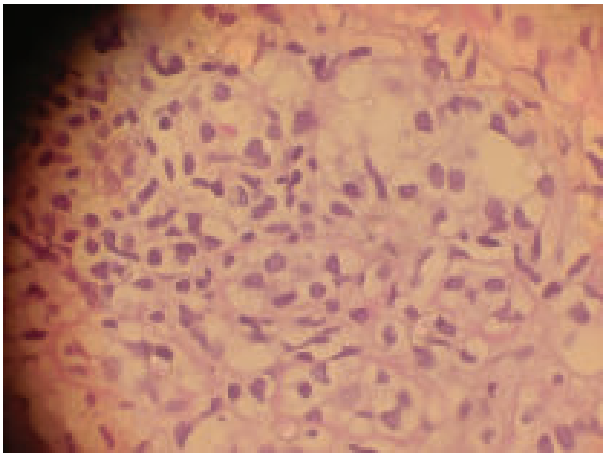

Fig.-3: *Renal histology showing tiny foci of interstitial lymphocyte infiltration along with tubular atrophy and interstitial fibrosis.*

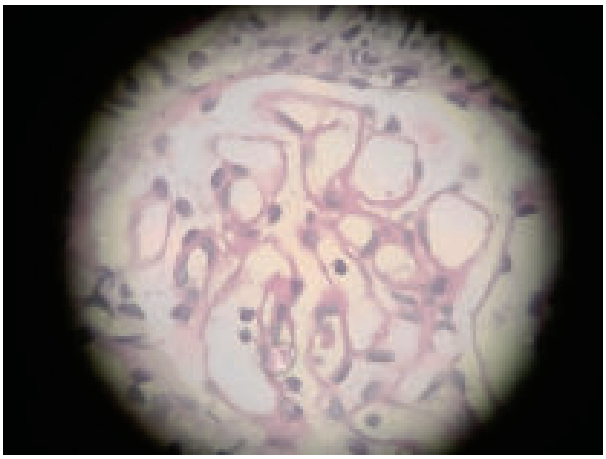

Fig.-4: *Glomeruli showing moderate degree of capillary basement membrane thickening with normal mesangial cellularity.*

Discussion:

The kidney can be frequently affected in the course of disease with RA. The scope of renal disease in RA encompasses well known entities such as amyloidosis, vasculitis & membranous nephropathy, but may be wider and include other forms of glomerulopathy and benign nephrosclerosis.[2] The associations between renal abnormalities and clinical data suggest that RA contribute to the renal damage caused by concomitant disease and often not related to the drugs used to treat RA.[2,10] In cases of proteinuria during treatment with DMARDs, membranous nephropathy is the first possible diagnosis which should be suspected. In cases of hematuria, mesangial proliferative GN, including IgA nephropathy, is strongly suspected. In cases of proteinuria in patients

with long-duration RA, amyloidosis should be the first diagnosis to be considered.[5] While it might seem reasonable to suspect the renal histological pattern from the clinical course, urinalysis, and renal functions of the patient, these relationships have not yet been established.[5] Renal lesions in RA are very diverse, and the patterns of drug treatments are

complex and varied within any large patient population, which makes the identification of causal relationships very difficult. Because membranous nephropathy and renal amyloidosis can be

detected only by histological examinations, a renal biopsy should be performed in cases with any continuing urinary abnormality or a worsening of renal function.[5]

Renal biopsy findings including light microscopy, electron microscopy & DIF of RA-associated

secondary membranous nephropathy is almost same as idiopathic MN.[6] Light microscopy cannot differentiate primary from secondary membranous nephropathy definitely.[8]

Immunofluorescent deposition of IgG4 is suggestive of IMN, while IgG1, IgG2 & IgG3 for secondary MN.[8] Treatment of secondary MN often includes removal of offending factors or treatment of primary diseases.[9]

This patient's histologic findings and direct immunofluorescence are consistent with primary or secondary membranous nephropathy. But as Anti-PLA2Rab is negative, we can consider this case as secondary membranous nephropathy due to RA. This case report illustrates the rare occurrence of nephrotic syndrome due to membranous nephropathy in a patient with rheumatoid arthritis.

The patient was advised RAAS blockade (Losartan potassium 50mg/day) as initial treatment of membranous nephropathy along with other medications for RA (Tofacitinib XR 11mg/day & Prednisolone 5mg/day) with advice for monthly follow up.

Conclusion:

Nephrotic syndrome can present as a challenging diagnosis in RA patients and its management requires a multidisciplinary approach involving rheumatologists and nephrologists. Early recognition and intervention are crucial for improving patient outcome and preserving renal function.

References:

1. Turesson C, Jacobsson L, Bergström U. Extra-articular rheumatoid arthritis: prevalence and mortality. Rheumatology (Oxford, England). 1999 Jul 1;38(7):668-74.
2. Boers MA, Croonen AM, Dijkmans BA, Breedveld FC, Eulderink F, Cats A, Weening JJ. Renal findings in rheumatoid arthritis: clinical aspects of 132 necropsies. Annals of the rheumatic diseases. 1987 Sep 1;46(9):658-63.
3. Sihvonen S, Korpela M, Mustonen J, Laippala P, Pasternack A. Renal disease as a predictor of increased mortality among patients with rheumatoid arthritis. Nephron Clinical Practice. 2004 Nov 17;96(4):c107-14.
4. Góis M, Carvalho F, Sousa H, Ferreira AC, Sousa J, Nolasco F. Renal involvement in rheumatoid arthritis: analysis of 53 renal biopsies.Port J Nephrol Hypert 2017;31(1):25-30
5. Makino H, Yoshinaga Y, Yamasaki Y, Morita Y, Hashimoto H, Yamamura M. Renal involvement in rheumatoid arthritis: analysis of renal biopsy specimens from 100 patients. Modern rheumatology. 2002 Jun 1;12(2):148-54.
6. Moroni G, Ponticelli C. Secondary membranous nephropathy. A narrative review. Frontiers in Medicine. 2020 Dec 3;7:611317.
7. Helin HJ, Korpela MM, Mustonen JT, Pasternack AI. Renal biopsy findings and clinicopathologic correlations in rheumatoid arthritis. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 1995 Feb;38(2):242-7.
8. Tesar V, Hruskova Z. Autoantibodies in the diagnosis, monitoring, and treatment of membranous nephropathy. Frontiers in Immunology. 2021 Mar 22; 12:593288.
9. Thomas M. Treatment of secondary membranous nephropathy. Nephrology. 2006 Apr;11: S170-1.
10. Rihova Z, Honsova E, Merta M, Jancova E, Rysava R, Reiterova J, Zabka J, Tesar

V. Secondary membranous nephropathy—one center experience. Renal failure. 2005 Jan 1;27(4):397-402.

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