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Editorial

From the Desk of Editor-in-Chief

There are many medical journals publishing scientific articles for several years in Bangladesh.The articles are mainly in the subjects covering different arenas of medical science, published by different organizations and medical and post graduate medical institutes. The journals are usually published two or three times in a year. On the otherhand, specialist journals in different specialists are very scanty in Bangladesh. Moreover, the number of journals included in Exceptamedica, Pubmed, and other areas are few and far between.

In this circumstances, we are taking a very hard step to publish a nephrology journal from our hospital in January, 2024, initially two in a year followed by three in a year. We are not able to publish high ranking research at the begining but hope to popularize our readers within our country and spread to neighboring south Asian countries as well. We are sending the complimentary copies of the journal to the libraries of most of the medical college and other medical institutions in Bangladesh.

Kidney Foundation Hospital is a not-for –profit hospital established in 2002.The hospital started with a very meagre capital investment of US$1000.00.With dedication and hard work it is now one of the top hospital in Bangladesh for the patients with kidney disease and kidney failure.It is contributing in Clinical nephrology,academic activities and research. In 2013, the hospital awarded Joel,D.Copple award from International Federation of Kidney Foundation and in 2024 it obtained International recognition from International Society of Nephrology (ISN) for its outstanding contribution in nephrology, dialysis and transplantation in South Asian Region and also awarded Sherier Award.

The hospital is excellent in academic activities and research. We have ongoing PhD program from different hospitals at home and abroad. In order to strengthen our research we thought it is now high time to start publishing a journal. In the 1st volume and 1st issue of journal, we have included two original articles, three review and two case reports. I hope that the readers will find it useful. We have also included medcal quiz for nephrology trainees to justify their knowledge.
In the last section, we also included recent abstracts from Kidney Foundation Hospital and Research Inatitute published in different renowed journals in the world. We also welcome any comments from the readers about articles published or letters to the editors.

We invite the nephrologists, pediatric nepfrologists, urologists, renal histopathologists, radiologists and sonologists of medical colleges and institutes to submit their kidney-related research articles to the journal committee for publication. We accept both hard & soft copies of the articles. We go through the papers and if necessary, communicate the authors. We also thank all the authors for giving us opportunity to publish their research papers in this journal. We have tried our best to avoid erroneous information.

We like to add here that BJKD Journal and its editorial board accept no liability for any inaccurate and misleading information, opinion and statements. It is the responsibility of the individual author(s). We have mentioned the instruction for the authors in every issue. We request the contributing authors to follow the instructions for their manuscripts. We appreciate our Managing Director (MD), editors, members and advisors for their encouragement and also appreciate the contributors and reviewers for their participation. Last of all we welcome valuable suggestion, opinion, advice and constructive criticisms for improvement of the quality of the journal.

Original Article

Pattern of Biochemical Markers of Mineral Bone Disorder in the Patients on Maintenance Hemodialysis.

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Abstract

Introduction: Mineral and bone disorder in CKD (CKD-MBD) is associated with increased mortality and morbidity. It covers biochemical abnormalities, vascular calcification and bone fragility. This study was aimed to assess the biochemical markers of mineral and bone disorders in maintenance hemodialysis patients.

Methods: This hospital based cross sectional study was conducted at the department of Nephrology in a tertiary medical college and hospital. A total 129 maintenance haemodialysis patients were enrolled according to selection criteria.

Results: Mean duration of dialysis was 15 months. Most frequent causes of CKD were glomerulonephritis (GN), diabetes mellitus (DM) and hypertension (HTN). Mean iPTH was 351±202 pg/ml. According to iPTH level, patients were subdivided into three groups. Majority of the patients were in normal bone turnover groups (51.9%), 39.5% were in high bone turn over group and 8.6% in low bone turn over group. High turnover group of patients had hypocalcemia (34.38%) and 74.4% patients had hyperphosphatemia. Mean hemoglobin (Hb) was 9.76 gm/dl and majority of patients had Hb below 10gm/dl. There was a weak negative correlation between iPTH and Hb (P=.0004, R= -0.25)

Conclusion: In patients on maintenance hemodialysis, abnormalities of biochemical markers of mineral bone disorders were common. It can guide our treatment practice.

Key words: Chronic kidney disease, hemodialysis, mineral bone disorders, parathyroid hormone.

Introduction

Chronic kidney disease (CKD) is a worldwide public health problem that affects 10% to 16% of the world population with increasing prevalence and adverse outcomes in developed and developing countries (1,2).

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CKD is associated with mineral bone disease which starts early in the course of disease and worsens as the kidney damage progress (3) . Hyperparathyroidism occurs early in CKD and it is a challenge frequently encountered in the management of these patients. It is an adaptive and, in many cases, ultimately maladaptive process

that develops in response to declining kidney function, impaired phosphate excretion, and failure to bioactivate vitamin D. Dysregulation of calcium and phosphorous homeostasis lead to decreased renal phosphate excretion, increased serum phosphorous, elevated levels of the fibroblast growth factor 23 (FGF-23), and reduced synthesis of calcitriol, the active form of vitamin D. These changes result in increased synthesis and secretion of parathyroid hormone (PTH) and parathyroid hyperplasia, contributing to the development of a vicious cycle (4).

Secondary Hyperparathyroidism (SHPT) is a major complication of CKD, resulting from disturbances in the regulation of PTH, calcium, phosphorus, and vitamin D (5). Although hyperphosphatemia appears to be particularly important in the development of SHPT, the complication often occurs early in stage 3 of kidney failure.

PTH is a main regulator of calcium, bone and mineral homeostasis (6). It is a polypeptide containing 84 amino acids secreted by parathyroid glands. However, dysregulated homeostasis of parathyroid hormone, vitamin D, calcium and phosphorus are responsible partly in cardiac dysfunction in chronic renal failure patients (7) . Secretion of parathormone is moderated by alterations in concentration of calcium in the blood. In fact, reduced calcium concentration stimulates PTH secretion by the calcium-sensing receptors located in the parathyroid gland and it has various targets to increase serum calcium concentration(8). It is also a key stimulator of vitamin D production in renal tissue and its major physiologic regulator is circulating ionized calcium. The impact of PTH on intestinal cells, renal tissue, and also bone leads to maintain serum calcium levels within a narrow range. However, elevated levels of parathyroid hormone have been correlated with increased risks of congestive heart failure, cardiovascular mortality, hypertension and hypertrophy of left ventricle.

In Bangladesh, data regarding biochemical markers of CKD-MBD in ESRD patients are scanty. So, the present study was undertaken to estimate biochemical markers of CKD-MBD.

Materials & Methods

This was a cross sectional study which was conducted in the department of Nephrology, a tertiary Medical College & Hospital from February 2021 to August 2022. Total 129 patients with End stage renal disease (ESRD) on maintenance hemodialysis (8 - 12 hours per weekly for at least 3 months) were taken for this study. The study was started after receiving approval from Research Review Committee (RRC) of department of Nephrology and then ethical approval was taken from the Ethical Review Committee (ERC) of the Medical College. Selection of patient was done by purposive sampling according to inclusion and exclusion criteria. A written informed consent was obtained from all subjects after informing about study aim, objectives and procedure. Patients having acute infections, connective tissue disease, malignancy, recent fracture, Recent onset of ischemic heart disease, history of parathyroidectomy were excluded from this study.

All studied patients were subjected to full history taking, general and local examination, and laboratory investigations including complete blood count, serum albumin level, total Ca level, serum phosphate level and serum PTH level. The diagnosis of MBD among the studied patients was made according to laboratory indicators (serum PTH, serum Ca and serum phosphate).

On the basis of PTH level, CKD patients can be subdivided into three groups. Low turnover disease where iPTH level is <150 pg/ml, normal turnover where iPTH is 150-300 pg/ml and high turnover disease where iPTH is >300pg/ml. Blood samples were drawn from the arterial side of the vascular access before starting dialysis and prior to heparin administration, after a 48-h dialysis free interval. The patients' venous blood

(5cc) was collected by sterile disposable syringe with aseptic precaution. For estimation of Hb 2cc blood was collected in a tube mixed with anticoagulant. Rest of the blood was collected in another tube. All samples except iPTH were sent to clinical pathology department immediately after collection.

Intact PTH was measured by IMMULITE 2000 XPi which is a solid-phase, two-sited chemiluminescent enzyme-labeled immunometric assay using a Siemens Dimension Xpand plus (Siemens Health care Diagnostics, Deerfield, IL, USA) in the Referenced laboratory where 4cc blood was taken for each test.

Serum calcium, phosphorus, albumin was measured by standard laboratory methods using a BECMAN COULTER Clinical Chemistry Analyzer. Albumin was measured by Bromocresol green (1:1, 1000 microliter) which was incubated for 10 minutes at 37 degrees Celsius. Calcium was measured by Arsenazo 3(1:1,1000 microliter), incubated for 5 minutes and readings were taken after 1hour then turned into blue color. Phosphate was measured by ammonium molybdate (1:1, 1000 microliter). No blood specimen was preserved for future analysis and was discarded as per local standard protocol.

All collected information was stored in separate data record form. After checking all the data was analyzed by SAS Studio Version.

Statistical analysis

Data were collected, tabulated, and statistically analyzed with a personal computer using SAS Studio Version. Student's *t*-test was used for continuous quantitative parametric variables. Chi-squared test was used to compare between two groups or more regarding one qualitative variable. Pearson correlation test was used to assess the relationship between two continuous variables. *P* up to 0.05 was considered statistically significant.

Results

Total 129 hemodialysis patients were taken according to the selection criteria. Mean age was 43.96 years ranged from 18 to 76 years with male predominance 57.36%. Mean duration of dialysis was 15 months and mean BMI was 22.06 kg/m^2. Most frequent causes of CKD were glomerulonephritis (39.5%), diabetes Mellitus (34.1%) and hypertension (17.8%). Table III showing that mean Hb was 9.76 gm/dl where majority of patients' Hb was below 10gm/dl. Mean corrected Ca was 7.8 mg/dl and mean iPTH was 351.66 pg/ml. According to the level of iPTH, patients were subdivided into three groups where majority of the patients were in high bone turnover group which was 39.5% and 8.6% was low bone turnover. Table V showing that 105 patients had hypocalcemia among them 50 patients (39.06%) had normal turnover and then 45 patients (34.38%) had high turnover bone disorder where p value is statistically significant (0.0003). Majority of the patients (96 patients, 74.42%) had hyperphosphatemia (>4.5 mg/dl) where 47 patients (36.43%) had high turnover bone disorder which is also statistically significant (P <0.0001). Figure II showing that there is a weak negative correlation between Hb and iPTH.

Table I: Demographic variables of study patients (N=129)

Characteristics of patients	Findings (Mean±SD; n, %)	
Age (years)	43.96±14.82	Male- 47.66±14.68
		Female-38.98±13.61
Age groups(years)	Frequency (n)	Percentage (%)
<50	77	59.69
≥50	52	40.31
Gender		

Male	74	57.36
Female	55	42.64
BMI (Kg/ m^2)	22.06±2.55	
<18.5	12	9.30
18.5-24.9	109	84.50
≥25	8	6.21
Duration of dialysis (months)	15.48±9.50 (minimum 6 months -maximum 84 months)	
<12	35	27.13
12- 48	78	60.46
≥48	16	12.40

Table I showing that mean age was 43.96 years where there was male (74%) predominance. Majority of patients' BMI was normal range then underweight. Majority of patients' duration of dialysis was between 12 to 48 months.

Table II: Underlying cause of CKD (N=129)

	Frequency(n)	Percentage (%)
Glomerulonephritis	51	39.5
Diabetes mellitus	44	34.1
Hypertension	23	17.8
Obstructive uropathy	2	1.6
Polycystic Kidney Disease	5	3.9
Chronic pyelonephritis	4	3.1

Table II shows that the common causes of ESRD were glomerulonephritis, diabetes mellitus, hypertension.

Table III: Laboratory investigations findings of study patients (N=129)

Investigation findings	Mean±SD	Range
Hemoglobin (Hb) (gm/dl)	9.76±1.4	8.36-11.16
<10 gm/dl (frequency)	85(65%)	
≥10 gm/dl(frequency)	44(34.11%)	
Corrected Calcium (mg/dl)	7.8±0.9	4.94-10.90
Phosphate (mg/dl)	5.34±1.09	3.0-10.94
Albumin (gm/l)	35.98±5.1	30.88-41.08
Intact parathyroid hormone (iPTH) (pg/ml)	351.66±202	63-1033.40

Table III shows that mean Hb was 9.76 gm/dl where majority of patients' Hb was below 10gm/dl. Mean corrected Ca was 7.8 mg/dl and mean iPTH was 351.66 pg/ml ranging from 63 to 1033.40 pg/ml.

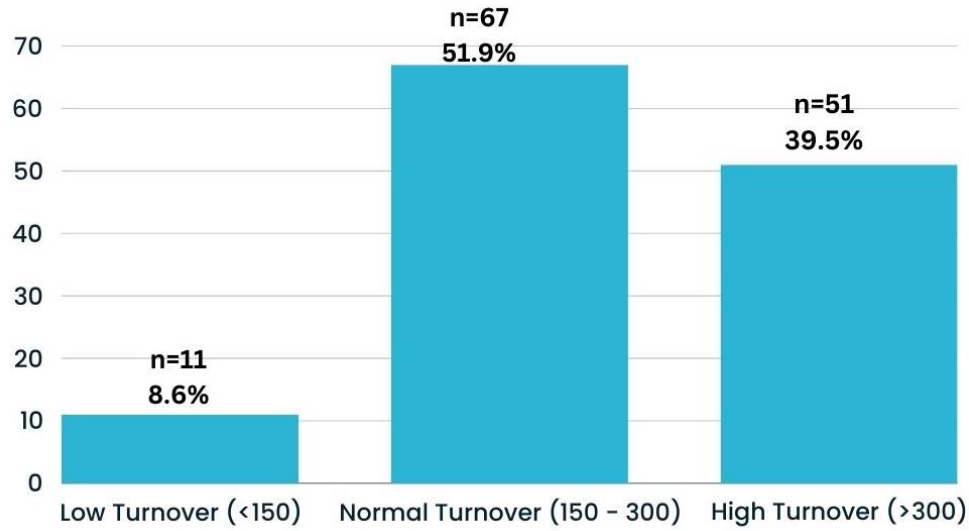

Figure I: Subdivision of study patients according to the level of iPTH (N=129)
Figure I shows that majority of the patients had normal turnover (51.9%) then high turnover (39.5%) bone disease.

Table IV: Distribution of Calcium, phosphate and iPTH (N=129)

Calcium (mg/dl)	Frequency (n)	Percentage (%)
<8.5	105	83.87
8.5-10.5	23	17.97
>10.5	1	0.78
Phosphate(mg/dl)		
<3.4	2	1.55
3.4-4.5	31	24.03
>4.5	96	74.42
iPTH (pg/ml)		
<150	11	8.6
150-300	67	51.9
>300	51	39.5

Table IV shows that among 129 hemodialysis patients, 105 (83.87%) patients had hypocalcemia (<8.5 mg/dl), 96 (74.42%) patients had hyperphosphatemia and 67 (51.9%) patients had normal turnover bone disorder.

Table V: Distribution of laboratory data (serum calcium, inorganic phosphate) of the studied patients (N=129) according to serum parathyroid levels.

Table of Calcium class by bone turnover				
Calcium class (mg/dl)	Bone Turnover			
	Low (n=11)	Normal (n=67)	High (n=51)	Total
<8.5	10(7.8%)	50(39.06%)	45(34.38%)	105

				(81.43%)
8.5-10.5	0	11(8.59%)	6 (4.69%)	17 (13.28%)
>10.5	1(0.78%)	6(4.69%)	0	7(5.47%)

P= 0.0003

Table of phosphate class by bone turnover				
Phosphate Class (mg/dl)	Bone turnover			
	Low(n=11)	Normal(n=67)	High (n=51)	Total
<3.4	2 (1.55%)	0	0	2(1.55%)
3.4- 4.5	5 (3.88%)	22 (17%)	4(3.10%)	31(24.03%)
>4.5	4(3.10%)	45 (34.88%)	47(36.43%)	96 (74.42%)

P<0.0001

Table V is showing that patients with hypocalcemia (105 patients), 50 patients (39.06%) had normal turnover and then 45 patients (34.38%) had high turnover bone disorder where p value is statistically significant (0.0003). Majority of the patients (96 patients, 74.42%) had hyperphosphatemia (>4.5 mg/dl) where 47 patients (36.43%) had high turnover bone disorder which is also statistically significant (P <0.0001).

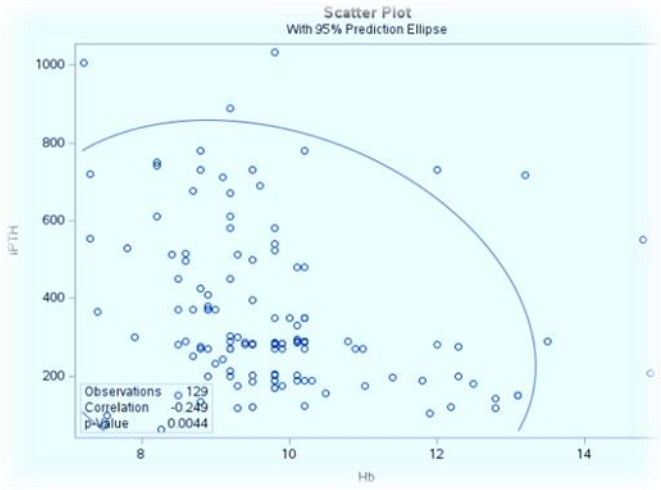

Figure II: correlation between hemoglobin (Hb) and Intact parathyroid hormone (iPTH) (N=129)

Pearson correlation test was done, showing a weak negative correlation between Hb and iPTH (r= -0.25, p= 0.004).

Discussion:

The biochemical marker of CKD-MBD vary from one patient to another and several factors may account for this variation (9). Most common disorders of bone in CKD are high-turnover bone disorders and low-turnover bone disorders (20). To separate these two diseases, measuring of Serum PTH is considered an adequate screening tool (9,10). For diagnosis of renal bone disease, bone biopsy being gold standard[11] but it's an invasive procedure with high cost

and for overall complexity has withdrawn it from clinical practice. To evaluate bone turnover in patients with CKD, measurement of serum markers serially is very important (12). Consequently, for assessing renal bone disease serum PTH level has taken leading position among the noninvasive tools (13). In 1986, Andress and colleagues[14] suggested that intact parathyroid hormone (iPTH) could be a good predictor of osteitis fibrosa in patients undergoing maintenance HD. The K/DOQI recommendation stated that PTH should be maintained in a target range of 150 to 300 pg/ml for CKD stage 5(9).

In this study, total 129 CKD patients on maintenance hemodialysis (MHD) were selected. Mean age of study patients was 43.96 ± 14 years majority (59.69%) of the patients was less than 50 years and 57.36% of them were male. Mean age among the males was 47.66±14 years whereas in case of female it was 38.98± 13 years. Sumon et al. also found male predominance which was 53% (15).

Mean duration of hemodialysis was 15.5 months which ranged from 6 months to 84 months. The mean BMI was 22.06±2.55 and similar range of BMI was observed by Al-Hiali et al (16). It was found that majority of the patients were normal and then underweight according to BMI, may be due to inadequate intake, malnutrition, systemic inflammation, influence appetite controlling hormones from reduction of renal clearance, insulin and insulin like growth factor resistance, metabolic acidosis etc. In previous study, no association was found between BMI and iPTH (17).

In this study, the most common etiology was GN (39.5%) followed by Diabetes Mellitus (DM) (34.1%) and Hypertension (17.8%). There is similarity to the findings of previous study that reported GN, DM and HTN as the most common etiology of CKD (18).

In our present study it was observed that the mean iPTH was 351.66± 202 pg/ml. According to laboratory criteria, on the basis of iPTH level, 39.5% (51) of patients had high turnover bone disorder and 8.6% (11) of patients had low turnover bone disease. Nearly 51.9% (67) of patients had maintained normal bone turnover. Agarwal found 39.4% of patients with high turnover bone disease in CKD 5 (19). In Egypt, Hasan et al. observed the prevalence of high turnover bone disease 28.1% and 27% patients had low-turnover bone disease (20). Jabber et al. found 60% of patients had high turnover bone disease (21). But in Nigeria, Sanusi reported 11.8% of patients with ESRD with secondary hyperparathyroidism (22).

In this study, the mean serum Ca was 7.8± 0.9 mg/dl among the patients and majority of the patients had hypocalcemia which was 83.87% though they are on supplement. They could be further subdivided into three groups. The first group included 105 patients with low serum Ca among 129 patients where 39.06% (50) patient had normal turnover and 34.38% (45) of patients had high turnover bone disorder, the second group included 17 patients with normal Ca where maximum patients had normal turnover bone disorder and third group included only 7 patients had high Ca level. In the first group with high PTH and low calcium levels, could be either undertreatment with vitamin D or poor drug compliance. In the first group, with high levels of both iPTH and Ca, it is likely that therapy with vitamin D was not effective and evaluation for the use of other vitamin D analogue and possible need of surgical intervention is to be considered.

In this study patients with low turnover disease had higher mean serum Ca levels compared with the both the high turnover group and normal bone turnover group. This was agreed in the study by Buargab et al (23).

The target serum level of iPTH was achieved in 67% of patients. Only 11% Of patients had serum Ca within target range. Hasan et al (20) found only 15% of patients had achieved iPTH within normal range and 28% of patients had normal serum Ca level.

Jabber et al. reported only 17.4% patents within normal iPTH range (21).

This study demonstrated hypocalcemia and hyperphosphatemia in 83.8% and 74.4% of patients respectively. In Nigeria where Onymekeihia found hypocalcemia and hyperphosphatemia in 71% and 79% of patients with CKD respectively which was studied by University of Benin Teaching Hospital (24). This similar type of report was found by Ile-Ife et al in Nigeria. Agarwal et al. [19]described hypocalcemia in 49.6% and hyperphosphatemia in 41.8%of patients in CKD stage 5. Whereas, La Clair et al.found hypocalcemia and hyperphosphatemia 28% and 50% in patients with CKD stage 5 (25). In comparison of both studies, it is found prevalence of hypocalcemia is lower in western data although both showed a high prevalence of hyperphosphatemia in CKD stage 5. However, in our study there is higher prevalence of hypocalcemia and hyperphosphatemia in comparison with the findings of Agarwal. In a recent study, Hasan et al. found prevalence of hypocalcemia and hyperphosphatemia 64% and 74% respectively (20).

This study also showed that control of anemia was not satisfactory as 65% of the studied patients had hemoglobin levels less than 10g/dl. Hyperparathyroidism is thought to contribute to renal anemia which might be reduced response to recombinant erythropoietin in patients with ESRD. We found a negative correlation between iPTH and Hb. In Egypt, Hasan et al. also found the negative correlation between iPTH and Hb (20).

Conclusion

From this study, we came to know that the abnormalities of biochemical markers are very common in chronic kidney disease on maintenance hemodialysis. These abnormalities are associated with sudden cardiac death, vascular calcification, bone fragility etc. So serial measurement of biochemical markers of bone mineral disorder in CKD especially on maintenance hemodialysis and adjustment of medication accordingly, will reduce mortality and morbidity in these patients.

Limitation of the study

It was a single center study with a relatively small sample size. In this study bone biopsy for bone histomorphometry was not done. Moreover, this study was conducted for a short period of time.

Recommendation

Multi-centered studies with large sample sizes are recommended to confirm the findings of this study.

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Original Article

Efficacy of Roxadustat versus Epoetin Alfa in Treating Anemia in Conventionally Erythropoietin Treated Maintenance Hemodialysis Patients in Bangladesh: A Randomized Controlled Trial

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Abstract

Introduction: Roxadustat is a hypoxia inducible factor prolyl hydroxylase inhibitor, introduced to treat renal anemia. Most patients in Bangladesh receive under dosed Erythropoietin Alfa due to financial constraints. The usual starting dose of Roxadustat has cost similar.

Methods: This is a single-center, open-label randomized controlled trial in a tertiary care center. 70 iron- replete patients on MHD receiving 5000 Epoetin alfa subcutaneously weekly were randomized at a 1:1 ratio to two arms – 70 mg Roxadustat orally thrice weekly and the usual EpoA. CBC and serum iron profile were checked at baseline and 12 weeks.

Results: Total number of patients were 70. Mean age was 49.4 years; 40% were male. Diabetes Mellitus (31.7%) and glomerulonephritis (21.7%) were the commonest cause of CKD. Baseline hemoglobin (Hb) was 7.59 and 7.7 gm/dl in the Roxadustat and the EpoA arms. Sex, mean age, duration of CKD diagnosis and HD, baseline transferrin saturation (TSAT) and serum ferritin did not vary significantly between the 2 arms. Analysis of Covariance showed that Roxadustat was associated with higher least squares mean increase in hemoglobin from baseline than EpoA (1.07 g/dl versus 0.11 g/dl respectively; $p = 0.006$). TSAT level fell significantly (49.2% versus 37.3%, $p = 0.003$), but the change did not vary significantly between the 2 arms ($p = 0.07$). Serum ferritin remained unchanged (1023.8 versus 1054.2; $p = 0.55$) over this period. Rate of hospitalization and mortality did not vary significantly between the 2 arms. Non-SAEs did not vary significantly between the 2 arms.

Conclusion: Roxadustat has shown to be at least of similar efficacy in treating renal anemia so far in this study.

Keywords: Roxadusta, epoetinalfa, anemia, maintenance hemodialysis.

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Introduction

Chronic kidney disease (CKD) is the irreversible loss of kidney function (1). It contributes to significant morbidity and mortality globally. Worldwide, the incidence of chronic kidney disease(CKD) is rising, the prevalence having reached 11% (2).

It is difficult to estimate the prevalence in Bangladesh due to the lack of sufficient high-quality data. However, a recent meta-analysis of the existing studies estimates the prevalence to be 22.48% (3). End Stage Kidney Disease (ESKD) is the most advanced stage of CKD, where life is incompatible without renal replacement therapy (RRT) (1). The economic burden of CKD, especially ESKD is massive, owing to its multitude of complications and RRT (2).

Anemia is one of the major complications of CKD. It is an independent risk factor for hospitalization, major adverse cardiac events (MACE), CKD progression and mortality in both non-dialysis and dialysis population (4). Various factors lead to anemia in CKD. Iron deficiency and lack of Erythropoietin (EPO) are the major ones. Therefore, iron correction and Erythropoietin Stimulating Agents (ESA) are the cornerstone of treatment of renal anemia. These factors become more pronounced in maintenance hemodialysis (MHD) patients(5, 6).

Recombinant Erythropoietin have been considered the standard of care in renal anemia for over 20 years(7). Newer treatment options are however emerging. Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF PHIs) are one such class of novel ESAs. In contrast to other ESAs, it works by stimulating the transcription of the EPO gene and increasing the level of endogenous EPO, rather than replacing it(8).

Roxadustat, a HIF PHI has been approved in several countries for correction of renal anemia in both dialysis dependent and independent CKD patients. It showed greater rise of hemoglobin compared to Epoetin alfa and non-inferiority to Darbopoetin alfa (9, 10). In addition, it also positively impacted iron profile by decreasing serum Hepcidin level, increasing intestinal iron absorption and increasing Transferrin saturation in dialysis patients (11).Since Roxadustat works on both fronts to increase the level of endogenous EPO and improve the iron profile, it could be a better alternative to conventional ESAs in CKD patients on MHD. It would lead to decreased pill burden, pricks, drug interactions and adverse reactions.

Bangladesh is a country with limited resources and even limited health care

spending, with a meager 2.8% of the gross domestic product (GDP) (16). With such a restricted health care budget, most health care related costs come from out of pocket, which is estimated to be more than 65% in several studies (17). The chronic and irreversible nature of CKD makes it an enormous burden on the patients, since they have to pay out of pocket. With more than 20% of the country's population living below the poverty line, following guidelines are not always an option for the health care providers, making it necessary to improvise and adapt according to affordability and availability (18). The treatment of renal anemia therefore differs from the prevalent guidelines. Patients likely to get treated for anemia are mostly ESKD patients on dialysis. Often the hemodialysis patients cannot afford ESAs and have to rely on periodic blood transfusions. Even when they can, most cannot afford the recommended dosage schedule of ESA. Most commonly used regimen is weekly subcutaneous administration of 5000 international units (IU) of Epoetin Alfa, which is an under dose (12-14). The cost of this prevalent under dosed regimen of Epoetin Alfa is similar to the usual adequate starting dose of thrice-weekly 70 miligrams (mg) of Roxadustat. Furthermore, the oral formulation makes it easier to store and administer, especially in remote locations.Therefore, if it can be made evident that moderately dosed Roxadustat is comparable in terms of efficacy to conventionally dosed Epoetin alfa in treating anemia in hemodialysis patients, it would be a good argument to use it routinely in a resource limited setting like Bangladesh.

Methods

This was a small single center, open-label, parallel group randomized controlled trial (RCT) done in the hemodialysis unit of a tertiary care hospital in Bangladesh, with an aim to compare the efficacy of thrice-weekly oral 70 mg Roxadustat to weekly subcutaneous 5000 IU Epoetin Alfa, along with comparing the iron status.

Trial design

Type of trial – Parallel group

Allocation ratio – 1:1

Blinding – Open label (Due to the difference in method of administration, blinding was not possible. Since the outcomes are all biochemical, we expect to minimize biases inherently associated with this design).

Inclusion Criteria

1. Patients receiving hemodialysis at least 2 times a week for at least 3 months.
2. Age ≥ 18 years.
3. Receiving weekly subcutaneous 5000 IU Epoetin Alfa.

4. Hemoglobin ≥ 7 gram/deciliter (gm/dl)
5. Ferritin ≥ 100 nanogram/milliliter (ng/ml) and Transferrin saturation (TSAT) ≥ 20%.

Exclusion Criteria

1. Known allergy to Roxadustat.
2. Any red blood cell or whole blood transfusion in the screening period.
3. Pregnant or breast-feeding females.
4. Females of child-bearing age, unless on contraception.
5. New York Heart Association Class III or IV congestive heart failure at randomization.
6. Acute coronary syndrome, stroke, seizure or a thrombotic/thromboembolic event (e.g. deep vein thrombosis or pulmonary embolism) within 12 weeks prior to randomization.
7. History of chronic liver disease.
8. Known causes of anemia other than chronic kidney disease (e.g. thalassemia, sickle cell anemia, pure red cell aplasia etc.).
9. History or suspicion of any malignancy, except if they are cured or in remission for ≥ 5 years.
10. Chronic inflammatory diseases (e.g. rheumatoid arthritis, systemic lupus erythematosus).
11. Any medical conditions that may confound the safety or efficacy of the drug.

Intervention delivered

Treatment arm – Received oral Roxadustat 70 mg (50 mg plus 20 mg tablet) 3 times weekly.

Control arm – Continued to receive subcutaneous Epoetin alfa 5000 IU weekly.

Criteria for rescue therapy

1. Red cell concentrate (RCC) transfusion was given in either group if hemoglobin fell below 7 gm/dl or rapid anemia correction was required to stabilize the patient's condition as deemed medically necessary by the investigator.Roxadustat or Epoetin Alfa was continued.
2. IV iron was administered if target Hb level was not achieved and Ferritin or TSAT values fell below 100 ng/ml or 20% respectively. Roxadustat or Epoetin Alfa was continued.

Criteria for discontinuing intervention

1. Patient's decision.
2. An adverse event that deemed to put the patient at undue risk by the investigator.
3. Severe noncompliance with the study protocol as determined by the investigator that could affect the validity of the data.
4. Pregnancy.
5. If a patient received an organ transplant during the study.

Prohibited concomitant medications

1. Any other investigational drug.
2. Any other erythropoietin analogue.
3. Iron chelating agents.
4. Androgens.
5. Dapsone.
6. Chronic doses of paracetamol > 2 g/day.

Sampling

After explaining the aims and objectives of the study along with its procedure, risk and benefits, 70 patients who provided informed, written consent were selected using the purposive sampling method. Total sample size was 70; 35 subjects in the treatment arm and 35 in the control arm. It was not calculated, rather adapted from a simulation study for external pilot randomized controlled trials, which reports that a sample size of 70 is desirable for good precision and minimum bias. Beyond a sample size of 70, there is less than 10% gain in precision when adding further participants (15).

Randomization

Randomization was done using a simple randomization technique. 70 sealed envelopes containing treatment cards (35 Roxadustat and 35 Epoetin alfa) were shuffled and randomly selected from for each patient.Prior to the initiation of the intervention, the envelopes containing the intervention were kept sealed.

Statistical Analysis

Computer based statistical analysis was carried out with appropriate techniques and systems. A descriptive analysis was performed for the demographic and clinical characteristics and results were presented as mean ± standard deviation for quantitative variables and numbers (percentages) for qualitative variables. Quantitative data were expressed as mean and standard deviation and qualitative data were expressed as frequency distribution and percentage. Statistical analyses were performed by using Statistical Analysis Software (SAS) Studio edition. The difference in means or percentages of different variables wascalculated using either the chi-square test for nominal variables or the Student t-test for numerical variables. For the analysis of outcomes, groups were compared using analysis of covariance (ANCOVA) method. An intention to treat principle was used. P-values less than 0.05 was considered significant.

Results

Total number of patients were 70, 35 in each arm. Mean age was 49.4 years; 40% were male. Diabetes Mellitus (31.7%) and glomerulonephritis (21.7%) were the commonest cause of CKD. The mean duration of diagnosis of CKD and time on

HD was about 6 years and 21.7 months respectively.

Baseline characteristics

Table I. Baseline characteristics of the Roxadustat and Epoetin Alfa arms

Variables	**Total (n = 70)**	**Roxadustat (n=35)**	**Epoetin Alfa (n=35)**	**p-value**
Demographic parameters				
Age, years[a,b]	49.4 (25 – 75)	48.6 (21 – 70)	50.1 (28 – 66)	0.57
Male, n (%)	28 (40%)	13 (37.1%)	15 (42.9%)	0.63
Education, n (%)[c]				
Below SSC	27 (44.3%)	14 (41.2%)	13(48.2%)	
SSC	6 (9.8%)	3(8.8%)	3 (11.1%)	0.78
HSC	13 (21.3%)	9 (26.5%)	4 (14.8%)	
Graduate	215 (24.6%)	8 (23.5%)	7 (25.9%)	
Income, n (%)[d]				
< 25k	27 (44.3%)	14 (41.1%)	13 (48.1%)	0.65
25-50k	23(37.7%)	12 (35.3%)	11 (40.7%)	
50-100k	8 (13.1%)	6 (17.7%)	2 (7.4%)	
> 100k	3 (4.9%)	2 (5.9%)	1 (3.7%)	
Cause of ESKD[c]				
DM, n (%)	19 (31.7%)	12 (35.3%)	1 (3.8%)	0.01*
GN, n (%)	13 (21.7%)	9 (26.5%)	10 (38.5%)	
Others, n (%)	28 (46.6%)	13 (38.2%)	15 (57.7%)	
CKD duration, months[e]	71 (±55.5)	64.3 (±52.9)	79.7 (±58.7)	0.3
HD Duration, months[e]	21.7 (±16.4)	20.8 (±14.3)	22.8 (±19)	0.65

[a]Data is expressed as mean (range)

[b]Unpaired T-test

[c]Fisher's Exact Test

[d]Chi-Square Test

[e]Data is expressed as mean (±SD)

*Significant

Table I shows the distribution of the baseline characteristics of the patients, divided into Roxadustat and Epoetin Alfaarms consisting of 35 patients each. Demographic parameters, such as age, sex, education and monthly family income, along with duration of CKD or duration on HD did not vary significantly between the 2 arms. However, there were more diabetic patients in the Roxadustat group (p=0.01).

Table II. Baseline biochemical parameters of the Roxadustat and Epoetin Alfa arms

Variables	**Total (n = 70)**	**Roxadustat (n=35)**	**Epoetin Alfa (n=35)**	**p-value**
Hemoglobin[a]	7.6 (±0.8)	7.6 (±0.8)	7.7 (±0.8)	0.55
Iron[a]	78.2 (±34.2)	76.3 (±33.9)	80.1 (±35)	0.65
Ferritin[a]	1023.8 (±563)	1090.6 (±560)	957.1 (±566)	0.33
TSAT[a]	49.2% (±22.4)	48.3 (±20.6)	50 (±24.3)	0.76

[a]Data is expressed as mean (±SD)

*Significant

Table II shows the distribution of the baseline biochemical parameters of the patients. There was no significant difference in serum hemoglobin, iron, ferritin and TSAT levels between the 2 arms.

Table III. Change in hemoglobin and iron status in the Roxadustat arm over 12 weeks

Variables	Baseline	12 weeks	Mean change[b]	p-value
Hemoglobin[a]	7.6 (±0.8)	8.6 (±0.8)	+0.93 (±1.2)	0.0002*
Iron[a]	76.3 (±33.9)	89.4 (±46.8)	+14.2 (±51.2)	0.14
Ferritin[a]	1090.6 (±560)	1098.7 (±547)	+22.9 (±86.9)	0.79
TSAT[a]	48.3% (±20.6)	34.1 (±18.8)	-13.5% (±23)	0.003*

[a]Data is expressed as mean (±SD)

[b]Paired T-test

*Significant

Table III shows the change in hemoglobin and iron status over 12 weeksof the patientsin the Roxadustat arm. Hemoglobin showed a significant rise of mean 0.93 gm/dl (p=0.0002) and TSAT showed a significant fall of mean 13.5% (p=0.0003). There was no significant difference in serum iron and ferritin levels between over the 12-week period in this arm.

Table IV. Change in hemoglobin and iron status in the Epoetin Alfa arm over 12 weeks

Variables	Baseline	12 weeks	Mean change[b]	p-value
Hemoglobin[a]	7.7 (±0.8)	7.8 (±1)	+0.01 (±1.1)	0.97
Iron[a]	80.1 (±35)	87.6 (±54.1)	+10.5 (±53.5)	0.33
Ferritin[a]	957.1 (±566)	1002.8 (±559)	+52.5 (±86.9)	0.55
TSAT[a]	50% (±24.3)	41.1 (±28.2)	-6.8% (±27.2)	0.22

[a]Data is expressed as mean (±SD)

[b]Paired T-test

*Significant

Table IV shows the change in hemoglobin and iron status over 12 weeks of the patients in the Epoetin Alfa arm. There was no significant difference in serum hemoglobin, iron, ferritin and TSAT levels between over the 12-week period in this arm.

Change in hemoglobin level between the 2 arms at 12 weeks

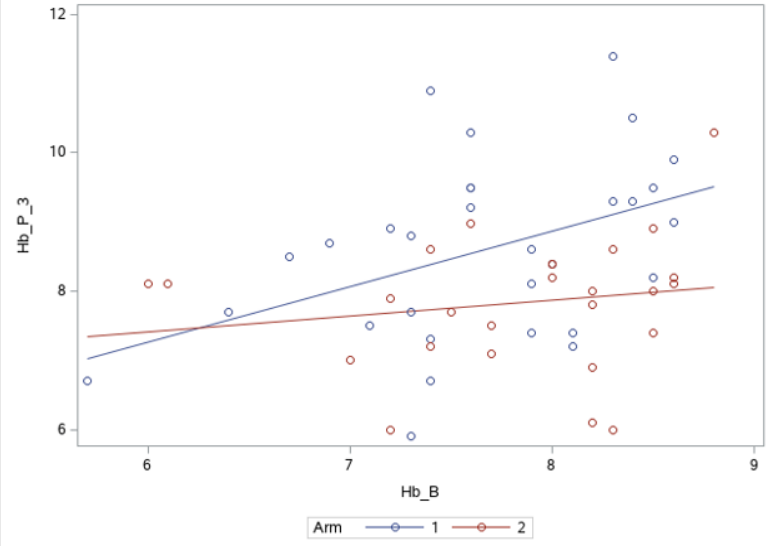

Fig. Analysis of Covariance showing the change in hemoglobin level from baseline (Hb_B) to 12 weeks (Hb_P_3). Blue represents Arm 1 (Roxadustat) and red represents Arm 2 (Epoetin alfa).

Figure 1 shows that Roxadustat was associated with higher least squares mean increase in hemoglobin from baseline over 12 weeks than Epoetin alfa (0.93 gm/dl versus 0.01 gm/dl respectively; p = 0.006).

Change in iron status between the 2 arms at 12 weeks

TSAT level fell significantly over the 12 weeks (49.2% versus 37.3%, p = 0.003), but the change did not vary significantly between the 2 arms (p = 0.07). Serum ferritin remained unchanged (1023.8 versus 1054.2; p = 0.55) over this period.

Mortality and morbidity

Six patients required hospitalization (4 in Roxadustat arm and 2 in Epoetin arm) and 5 patients died (2 in Roxadustat arm and 3 in Epoetin arm). Rate of hospitalization and mortality did not vary significantly between the 2 arms. One patient died of heart failure, rest of the 4 deaths occurred at home or at a different institute and it could not be

determined if it was an effect of the drugs. Dyspnea, fatigue, vertigo, chest pain and palpitation were the most common non-serious adverse events (SAE). Non-SAEs did not vary significantly between the 2 arms.

Discussion

Roxadustat, a HIF PHI, represents a novel approach to treating renal anemia. Unlike traditional erythropoiesis-stimulating agents (ESAs), Roxadustat acts by stimulating the transcription of the EPO gene, increasing endogenous EPO levels, and simultaneously improving iron profile by decreasing serum hepcidin levels, enhancing intestinal iron absorption, and increasing transferrin saturation in dialysis patients (11). While the efficacy of Roxadustat has already been proven in large trials and it has gained approval in most countries, there has been no studies in Bangladesh.The main goal for this small-scale limited duration trial was therefore to compare Roxadustat to the conventional Epoetin Alfa regimen.

The baseline characteristics of the study participants revealed a comparable distribution between the Roxadustat and Epoetin Alfa arms. Demographic parameters, including age, sex, education, and monthly family income, as well as the duration of CKD and hemodialysis (HD), were similar in both groups. Notably, there was a higher proportion of diabetic patients in the Roxadustat group. This difference may influence outcomes and needs to be considered in the interpretation of the results.

Biochemical parameters at baseline demonstrated no significant differences between the two arms. Both groups had similar levels of hemoglobin, iron, ferritin, and transferrin saturation, ensuring a balanced starting point for the intervention.

Over the 12-week study period, patients on the Roxadustat arm demonstrated a significant increase in hemoglobin levels compared to the modest change observed with Epoetin Alfa. This finding aligns with previous studies indicating Roxadustat's efficacy in raising hemoglobin levels in CKD patients, however the difference in change in hemoglobin levels was much higher than previously reported (9, 10). Since the study was not open-labeled, the circumstances of receiving a novel medication could have played a role in patient’s overall psychological well-being, prompting them to be more compliant with other medication and dietary advices.

The improvement in hemoglobin with Roxadustat was associated with a concurrent decrease in transferrin saturation, suggesting a potential impact on iron

utilization. However, this decrease did not significantly differ from the Epoetin Alfa arm.Iron parameters in both arms showed minimal changes over the study duration. While Roxadustat exhibited a numerical increase in serum iron levels, the difference was not statistically significant. This contrasted from prior studies, which mostly found an increase in serum iron and TSAT levels and consequent decreased need for rescue IV iron therapy (9,10,11).The lack of significant changes in iron parameters may suggest that Roxadustat's effect on hemoglobin is more related to its impact on EPO production than direct modulation of iron status in the Bangladeshi population.Serum Ferritin levels remained stable in both groups over the 12-week period. Previous trials found greater reduction of Ferritin levels in the Roxadustat treated patients (9,11). This could be due to the shorter duration of this study or a different effect in the Bangladeshi population.

The study reported a non-significant difference in adverse events and mortality between the two arms, similar to the larger trials (9,10,11). The observed events, such as dyspnea, fatigue, vertigo, chest pain, and palpitations, are commonly associated with CKD and its treatments. Further investigation is required to comprehensively assess the safety profile of Roxadustat compared to Epoetin Alfa in this population.

The study's limitations include the small sample size and open-label design, which may introduce bias, although efforts were made to minimize it through biochemical outcome assessment. Additionally, the relatively short 12-week follow-up period may not capture long-term safety and efficacy trends. Further studies with extended follow-up and larger sample sizes in this population are warranted to validate these findings.

Conclusion

In conclusion, this interim analysis suggests that Roxadustat is at least as effective as Epoetin Alfa in treating renal anemia in hemodialysis patients. The study provides valuable insights into the potential benefits of Roxadustat in resource-limited settings like Bangladesh, where cost-effective and easily administrable treatments are essential. However, long-term safety data and larger-scale trials are necessary to establish its place in clinical practice.

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Review article

Finerenone in Management of Patients with Diabetic Kidney Disease

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Abstract

Diabetic kidney disease is the most frequent cause of kidney failure, accounting for half of all cases worldwide. Standard-of-care treatment with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker is correspondingly low. Sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 receptor agonists, and a nonsteroidal mineralocorticoid antagonist are highly effective therapies to reduce kidney and cardiovascular risks in diabetic kidney disease.

Key words: Diabetic kidney disease, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, finerenone, hyperkalemia.

Introduction

Diabetic kidney disease (DKD) is a frequent and severe complication of diabetes. DKD refers to the development of CKD, defined by a sustained elevation of urinary albumin excretion (urine albumin-creatinine ratio >30 mg/g), a reduction in eGFR to <60 ml/min per 1.73 m^2, or both in a person with diabetes (1).

In 2021, >37 million Americans and 537 million people worldwide had diabetes. The worldwide number is predicted to rise to 643 million by 2030 and 783 million by 2045 (2).

DKD develops in approximately 30% of people with type 1 diabetes and 40% of those with type 2 diabetes, who make up the vast majority of diabetic individuals (≥95%) (3).

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Accounting for half of all cases, DKD is the most frequent cause of CKD leading to kidney failure worldwide (4).

Although the prevalence of other diabetic complications is falling, the number of diabetic patients with kidney failure is progressively rising (5).

Worldwide estimates indicate that nearly 700 million persons have chronic kidney disease. Chronic kidney disease is an important contributor to illness and is associated with a diminished quality of life and a reduced life expectancy (6)

Until recently, the only classes of medication that have been shown to slow a decline in kidney function were angiotensin-converting–enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs); however, most of

the evidence was generated in patients with type 2 diabetes.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors decrease glycated hemoglobin levels and have shown favorable effects on kidney and cardiovascular outcomes in large clinical trials involving patients with type 2 diabetes.(7)

Aldosterone plays critical physiological roles in maintaining normotension, eunatremia, and normokalemia.

However, overactivation of aldosterone and the renin–angiotensin–aldosterone system (RAAS) has also been implicated in the pathology of various cardiorenal disease states, including heart failure and hypertension.

Mineralocorticoid receptor antagonists (MRAs) have become key components of treatment strategies in these disorders.

Currently, the most used MRAs include spironolactone and eplerenone, both steroidal MRAs that bind to the mineralocorticoid receptor (MR) similarly to its natural ligand, aldosterone (8).

In patients with chronic kidney disease (CKD), MRAs reduce albuminuria when combined with angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) therapy; however, the risks include acute kidney injury (AKI), hyperkalemia, and hypotension (9).

KDIGO guidelines recommend a more conservative approach with this combination, noting a marked risk of hyperkalemia and declining kidney function in patients with eGFR less than 45 ml/min/1.73 m^2 (10).

Finerenone is a novel, non-steroidal MRA that may have unique utility in both albuminuric kidney disease and heart failure.

These effects have been shown to be mediated through potent anti-inflammatory and anti-fibrotic pathways. These benefits have been achieved with a lower risk of hyperkalemia when compared to steroidal MRAs like eplerenone and spironolactone (11).

Drug Characteristics and Mechanisms

Drug Characteristics

Spironolactone was developed using the chemical structure of progesterone and was the first MRA approved by the US Food and Drug Administration (FDA) in 1960 for edema related to cirrhosis, nephrotic syndrome, heart failure, idiopathic edema, essential hypertension, and cirrhotic ascites.

A more selective steroidal MRA, eplerenone, was approved by the FDA in 2002. These changes increased eplerenone's specificity for the MR and had a more favorable side effect profile with regards to gynecomastia, dysmenorrhea, and erectile dysfunction than spironolactone .

Finerenone is one of several non-steroidal MRAs that was developed using the chemical structure of a dihydropyridine channel blocker but optimized to create a bulky MR antagonist without any activity at the L-type calcium channel (12). Finerenone is both highly potent and has strong selectivity for the MR, overcoming significant barriers posed by previous generations of MRAs .

Mechanisms of Action

Despite spironolactone and finerenone binding the same ligand domain on the MR, these molecules have significant differences in their downstream signaling. First, finerenone appears to delay the nuclear accumulation of the MR–aldosterone complex more effectively than spironolactone . Second, finerenone may be more effective than spironolactone at blocking the recruitment of critical transcription cofactors. Spironolactone promotes a lesser but still significant recruitment of these transcription cofactors, while finerenone binding appears to impair recruitment of these cofactors and reduce the binding of existing MR–aldosterone complexes .

Finally, finerenone has bulky substituent groups that, when bound to the MR, leads to the formation of an unstable MR–ligand complex that cannot recruit cofactors (13).

Aldosterone also triggers a variety of pathogenic changes in the kidney, leading to proteinuria and impairment in kidney function. Patients with primary aldosteronism have higher rates of albuminuria than patients with essential hypertension, implicating aldosterone in proteinuric kidney disease (14).

In the glomerulus, aldosterone appears to have direct deleterious effect on the mesangium and on podocytes. Rats chronically infused with aldosterone demonstrated increased ROS via NADPH oxidase and podocyte foot process effacement. Treatment with eplerenone showed suppression of oxidative stress markers and prevented podocyte effacement (15).

Aldosterone infusion also triggers mesangial injury, cell proliferation, and matrix expansion via ERK/MAPK signaling pathway; these changes were again prevented through treatment with eplerenone (16).

Finerenone shows a similar kidney protective effect to steroidal MRAs. In a rat model of aldosterone-induced cardiorenal disease, treatment with finerenone provided protection from glomerular, tubular, and vascular damage, resulting in decreased proteinuria.

Finerenone also prevented endothelial cell apoptosis and smooth muscle cell proliferation in a murine model of vascular injury (17).

Clinical Trial Data in Humans

With regards to kidney outcomes, studies have shown that inhibition of the renin–angiotensin system, independent of changes in blood pressure, reduces the risk of major kidney events. Phase II Finerenone Clinical Trials After the safety and tolerability of different oral doses of finerenone were assessed and confirmed in healthy volunteers, a series of randomized clinical trials (RCTs) with finerenone began with the ARTS trial.

This phase 2a study enrolled participants with HFrEF and mild or moderate CKD (60 to less than 90 ml/min/1.73 m^2 and 30 to 60 ml/min/1.73 m^2, respectively) and showed that finerenone at a dose of 5 mg or 10 mg daily had larger reductions in NT-proBNP as compared to spironolactone 25 mg or 50 mg daily (11).

With success of the ARTS trial, the ARTS-DN trial was launched—a multicenter phase 2b RCT that evaluated the safety and efficacy of finerenone compared to placebo in reducing albuminuria in participants with diabetic albuminuria (urine albumin–creatinine ratio or UACR of 30 mg/g or higher) and mild-to-moderate CKD (eGFR of 30 ml/min/1.73 m^2 or higher) (18).

Phase III Finerenone Clinical Trials

Building on the aforementioned safety and efficacy data, the phase 3 FIGARO-DKD trial enrolled participants already on ACEi/ARB therapy with either stage 2–4 CKD (eGFR 25–90 ml/min/1.73 m^2) with moderately elevated albuminuria (UACR 30 to at most 300 mg/g) or stage 1–2 CKD (eGFR 60 ml/min/1.73 m^2 or higher) with severely increased albuminuria (UACR 300–5000 mg/g) (19).

The finerenone treatment group showed a decreased incidence of the kidney composite outcome (kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes) with a relative risk reduction of 15.6% .

Finerenone treatment was also associated with a 31% relative reduction in the UACR at month 4 of treatment. After 4 months, the decline in eGFR was also slower in the finerenone group (20).

The FIDELITY pooled analysis analyzed a population of 13,026 participants with a mean eGFR of 57.6 ml/min/1.73 m^2, median UACR 515 mg/g, and 48.3% of whom had very high KDIGO risk scores (eGFR less than 30; eGFR 30–44 and UACR 30 or greater; or eGFR 45–59 and UACR of 300 or greater).

At a median follow-up of 3 years, the finerenone treatment group showed a significant reduction in a composite outcome of time to cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization for heart failure (21).

The prespecified composite kidney outcome (time to onset of kidney failure, sustained at least 57% decrease in eGFR from baseline over at least 4 weeks, or renal death) occurred in 360 (5.5%) participants receiving finerenone and 465 (7.1%) participants receiving placebo (HR, 0.77; 95% CI 0.67–0.88; $P = 0.0002$). The component of sustained decrease in eGFR of at least 57% showed a 30% relative risk reduction, and the time to kidney failure component showed a 20% relative risk reduction. In the entire pooled analysis, the incidence of hyperkalemia leading to permanent discontinuation was 1.7% in the finerenone group and 0.6% in placebo (22).

The FIDELIO-DKD and FIGARO-DKD trials established therapeutic kidney and cardiac benefit among patients with diabetic nephropathy. The FDA approved finerenone in July 2021 for adult patients with CKD and eGFR greater than 25 ml/min/1.73 m^2 secondary to type 2 diabetes to “reduce the risk of kidney function decline, kidney failure, cardiovascular death, nonfatal heart attacks, and hospitalization for heart failure” (23).

In the past decade, significant advances have been made in the medical management of patients with type 2 diabetes mellitus. Notably, sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists have been demonstrated to reduce the risk of cardiovascular outcomes and CKD progression in patients with type 2 diabetes mellitus, including in patients with moderate-to-severe CKD.

The third-generation and newest-generation mineralocorticoid receptor antagonist, finerenone, is a nonsteroidal compound with balanced tissue distribution between the heart and kidney. On the basis of early studies, finerenone seems to be associated with a lower risk of hyperkalemia and has greater anti-inflammatory and antifibrotic effects within the kidney compared with its predecessors.

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Review article

Urinary Tract Infection in Renal Transplant Recipients

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Summary: Urinary Tract Infections (UTIs) are most common during the first year after renal transplantation and occur in about 25% of transplant recipients during that time. About 7% of renal transplant recipients will develop recurrent UTIs. However, it is associated with an increased risk of multiple antibiotic resistance, graft failure, and death. Post-transplantation risk factors for UTIs are: female gender, advanced patient age, longer time on dialysis before transplantation, recurrent UTIs before transplantation, polycystic kidney disease, DJ stent in graft ureter, urinary tract obstruction, etc. Routine urine examination as well as standard urine culture should be done. **Bacteriuria ≥ 10^{2-5} cfu/mL** is the cut-off value for immunocompromsed patients. Ultrasonography can be helpful and if negative, a non-contrast CT scan is the next step. Many experts recommend the screening for asymptomatic bacteriuria at 2, 4, 8, and 12 weeks after surgical transplantation. Nitrofurantoin may be used if the GFR is 30 mL/min or more. Simple cystitis is typically treated for 10 to 14 days. The optimal duration of antibiotic therapy for complicated UTIs is 14 to 21 days, although this can be extended. UTI prophylaxis is commonly used for the first 6 to 12 months post-transplantation. Trimethoprim-sulfamethoxazole is the most commonly used prophylactic agent.

Key words: Urinary Tract Infections (UTIs), renal transplantation, bacteriuria, fungal UTI, prophylaxis.

Introduction:

Urinary Tract Infections (UTIs) are most common during the first year after transplantation and occur in about 25% of transplant recipients during that time **(1)**. UTIs are one of the main causes of complications and hospitalization after kidney transplantation and seriously threaten successful transplantation outcomes (2,3). This infection can negatively impact transplant outcomes if not treated properly (4).

About 7% of renal transplant recipients will develop recurrent UTIs. Recurrent UTI is the two or more infections in six months or three or more infections in 12 months. Relapse refers to a recurrent UTI with the same organism that has not been adequately cleared. Re-infection is a recurrent UTI with the same or different organism, following clearance of the original UTI. However, it is associated with an increased risk of multiple antibiotic resistance, graft failure, and death. **(5)**

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Risk factors of UTIs:

Post-transplantation risk factors for UTIs are: female gender, advanced patient age, longer time on dialysis before transplantation, recurrent UTIs before transplantation, dose and duration of immunosuppression, polycystic kidney disease, co-morbidities, like DM, Foley's catheterization, DJ stent in graft ureter, deceased-donor graft, urinary tract obstruction and graft dysfunction. (6)

Some studies have reported that old age is a risk factor for post-transplant UTI. Increased incidence of BEP, bladder atrophy, impaired mobility, impaired immune system, poor personal hygiene are the proposed reasons behind the old age (7).

Around 80% of transplant recipients get infections within the first post-transplant year due to factors like potent immunosuppression, surgery and continuous exposure to nosocomial pathogens (8).

According to one study, the prevalence of UTI in patients who received a transplant from a deceased donor and those who received a kidney from a living donor was 70% and 28%, respectfully (9). The important reasons may be asymptomatic infection in the kidney donor and more immunosuppressive therapy in recipient.

Invasive devices, like indwelling urinary catheters and DJ stents are associated with an increased risk of UTI. Trauma to urinary tract during placement and contamination of the devices may be responsible. (10).

Anatomical abnormalities of urinary tract are one of the risk factors for UTIs in kidney recipients. The most common abnormalities leading to UTIs are BEP, ureteral obstruction, bladder dysfunction, urinary incontinence and vesicoureteral reflux (11).

Several studies have reported an association between period of acute rejection and UTIs. The rate of UTIs rises in patients who passed an acute rejection period with more immunosuppressive therapy. Nearly 60% of patients experience at least one infection during the first-year post-transplantation (12).

Pathogenesis:

Ascending urinary tract infection easily progresses to frank pyelonephritis due to short ureters and lack of an effective anti-reflux mechanism. Acute pyelonephritis is also related to the frequent graft rejection, acute kidney injury (AKI) with rising serum creatinine and recurrent UTIs. Morbidity and mortality from UTIs are increased in kidney transplant patients due to immunosuppression. In one study, first-time hospitalization for pyelonephritis was identified in 9.8% renal transplant recipients and in 0.2% control population (13).

Etiological pathogens:

UTI in posttransplant patients can be caused by viruses, bacteria, fungi and parasites.

The bacterial etiology of UTI in KT patients is similar to that of the general population. UTIs after KT is usually caused by Gram-negative microorganism (more than 70%). Escherichia coli and enterococci sp. are the most common pathogens (30 – 80%) (14). They mainly cause infection within 6 to 12 weeks post-infection. Klebsiella, Proteus and Pseudomonas are other Gram-negative bacteria that are frequently isolated. On the other hand, Gram-positive pathogens are less frequent like, Streptococci species, Staphylococcus saprophyticus (15).

In developing countries, like Bangladesh, mycobacteria tuberculosis is also a cause of UTI, reactivated by immunosuppressive medication.

Patients with DM are predisposed to fungal UTIs. Candida albicans is the most is the most common organism causing fungal UTIs. The fungus can aggregate as fungal balls to obstruct and result in hydronephrosis (16).

Common viruses causing UTIs are BK virus and CMV. Schistosoma hematobium is a parasite that may cause UTI in KT patients, often associated with renal stones and ureteric stricture. (17)

Classification of UTI:
UTI after renal transplantation are classified into acute simple cystitis, acute pyelonephritis or complicated UTI, recurrent UTI due to their different clinical presentation, management and prognosis. Asymptomatic bacteriuria (ASB) represents a frequent finding after renal transplantation. But ASB is considered to be a separate entity apart from UTI, as it is not necessarily a disease (18).

Clinical features:
Sometimes the diagnosis of a complicated UTI is difficult in renal transplant patients. Patients may be symptomatic or may have some non-specific symptoms, such as anorexia, nausea or fatigueness. Fever and graft tenderness is more likely to be due to UTI rather than acute rejection. Acute rejection is a strong differential diagnosis of UTI. Patients with acute rejection are more likely to have hypertension, rising serum creatinine and worsening proteinuria. All symptomatic UTIs in renal transplant patients are considered complicated UTIs. Symptoms of fungal cystitis or pyelonephritis are indistinguishable from those in bacterial infections (19).

Diagnosis:
Routine urine examination as well as standard urine culture should be done. Positive bacteremia is found in up to 9% cases **(20).**

Urine specimen collection for UTI:
There are at least 3 collection techniques for urine culture: 1. suprapubic aspiration, 2. straight catheter technique, and 3. clean-catch midstream urine (MSU) technique. Suprapubic collection is the best method to avoid specimen contamination in the distal urethra. Owing to patient discomfort and invasiveness this method is rarely practiced. Urine collection with a single straight catheter is the next best option. Due to possibility of introducing bacteria into the bladder, causing UTI, this technique is seldom used. The most common method of urine sampling for culture is via clean-catch midstream urine (MSU) technique. **(21)** In MSU technique the pre-collection cleansing procedures have been considered unnecessary in most adult populations as they do not decrease the risk of contamination from commensal bacteria.

Urine specimen preservation and processing:
Owing to the probable increase risk of growth of colony-forming units (CFU), urine specimens must be plated within two hours of collection, unless refrigerated or placed in a preservative. Preservation of the urine sample can be achieved with a boric acid solution or refrigeration for up to 24 hours. Samples that are left at room temperature for more than 4 hours have the risk of bacterial overgrowth of pathogenic and contamination organisms **(22).** Urine refrigerated for > 24 hours cannot be used for “Culture”.

Diagnostic growth of a urinary pathogen:

Urine routine examination: Significant pyuria is considered when urinary pus cell (WBC) is 10 per mm^3 or more (23).

Bacteriuria ≥ 10^5 cfu/mL: Qualitative urine cultures are done in blood agar and MacConkey agar media. For grown bacteria, biochemical identification tests and colony

count are done as per standard protocol. A positive result for UTI is considered when the bacterial counts are 10^5 cfu/mL of urine. This cut-off value remains the standard for diagnosis of UTI. (24) But up to 50% of UTI will escape diagnosis at this value.

Bacteriuria ≥ 10^{2-5} cfu/mL: This cut-off value is significant in **symptomatic** pyelonephritis, **symptomatic** cystitis in young women, children, male and immunocompromsed patients, e.g., renal transplant patients.

Fungi in urine: In patients without indwelling catheters, renal infection is documented with colony counts of 10^4 yeast colony forming units per milliliter (cfu/ml). In patients with indwelling catheters, colony counts of 2×10^4 to 10^5 cfu/ml is noted. A hematogenous renal candidiasis, renal involvement can be seen with any concentration of Candida in the urine. **(25**)
The techniques routinely used for the detection of bacteria, also detect Candida in urine. However, C. glabrata grows more slowly than other species and colonies may not appear for 48 hours.

Beta-D-glucan:
This is a rapid diagnostic test for invasive fungal infection. Beta-D-glucan is a cell wall constitute of Candida and other fungi (but not Cryptococci). This assay can detect intra-abdominal candidiasis 5 days earlier than traditional method. The sensitivity and specificity are 57 to 97% and 53 to 93%, respectively for diagnosis of invasive candidiasis. It has a good negative predictive value (80% or more), making it a potentially useful to prevent unnecessary use of anti-fungal drugs. False-positive results may occur from gram-positive infections (e.g., Strepto. pneumoniae), gut infection and some antibiotics (e.g., amoxicillin/clavulonic acid). (26)
The recommended cutoff value in single test result is more than 80 pg/m L or in 2 consecutive tests are more than 60 pg/m L. Two consecutive results within a week above this threshold are recommended to improve the diagnostic accuracy of this test. (27)
The galactomannan assay: This test can detect aspergillosis before symptoms appear, but sensitivity and specificity in solid organ transplant patients are lower than in hematological patients (28). A negative result does not rule out the diagnosis of IA and repeat testing is recommended.

Graft kidney biopsy: Clinical graft pyelonephritis is usually a contraindication to biopsy, but the presence of (asymptomatic) pyelonephritis on a transplant kidney biopsy appears to be a clinically significant finding. When histologic evidence of transplant pyelonephritis exists, treatment is indicated regardless of urinary abnormalities and of symptoms (29). Graft kidney biopsy also should be considered when UTI is suspected with acute graft rejection, which is more likely in the first six months of transplantation **(30).**

Imaging: Ultrasonography can be helpful as initial imaging. If the ultrasound is negative, a non-contrast CT scan is the next step. Contrast is potentially nephrotoxic and cannot be used safely in patients with high serum creatinine levels. Patients with polycystic kidney disease may have an infected cyst which may be difficult to identify. Such patients often have flank pain due to the infected renal cyst. In such cases, a CT-PET scan can be beneficial **(31).** Micturating cystourethrograms (MCU) can be helpful to identify reflux. Urodynamic study (e.g., uroflowmetry) will diagnose bladder dysfunction and outflow obstruction.

Treatment of asymptomatic bacteriuria in renal transplant:

Many experts recommend the screening for asymptomatic bacteriuria at 2, 4, 8, and 12 weeks after surgical transplantation. Treating asymptomatic bacteriuria during the first three months after transplantation remains an area of individual judgment by the transplant physicians.

Acute and recurrent graft pyelonephritis are significant risk factors for decreased long-term graft and patient survival. (32)

Treatment:

After Escherichia coli and Klebsiella pneumoniae, the next common pathogenic bacteria are Enterobacter, Pseudomonas aeruginosa, and Enterococcus. Patients with suspected UTI with a negative urine culture should be tested for *Corynebacterium urealyticum*, which requires special culture media for identification. Nitrofurantoin may now be used if the GFR is 30 mL/min or more. Simple cystitis is typically treated for 10 to 14 days. The optimal duration of antibiotic therapy for complicated UTIs is 14 to 21 days, although this can be extended. Infected cysts, prostatitis may need 4 to 6 weeks.

Current data indicate an increasing rate of multi-drug resistant (MDR) strains of urinary pathogens worldwide. The high incidence of MDR microorganisms is associated with increased mortality and graft failure and favors the recurrence of UTI (33). The rate of resistance of E. coli to trimethoprim-sulfamethoxazole (TMP-SMX) is nearly 70% in UTI occurring in first 6 months after KT. This resistance can be explained by its prophylactic use for Pneumocystis jiroveci pneumonia during the first 6 months of KT (34)

Urinary tract infection in renal transplant recipients. Transplant Proc.2007; 39:1016-7). Another growing problem is the current spread of carbapenem resistant Klebsiella pneumonia (CRKP). (35, 36).

Prophylaxis of UTIs in renal transplants:

UTI prophylaxis is commonly used for the first 6 to 12 months post-transplantation. The incidence of recurrent UTI in renal transplant recipients is 2.9 to 27% (37).

Recurrent UTI must be promptly investigated to rule out the existence of any anatomical or functional abnormalities, such as obstruction, strictures, stenosis, vesico-ureteric reflux, renal calculi, neurogenic bladder, complex cysts with meticulous exam including imaging of urinary tract, cystoscopy, cystogram, uroflowmetry and other urodynamic techniques, if necessary (38). Anatomical changes must be corrected, if possible, as this action has been associated with recurrent UTI resolution (39)

Knowledge of the etiology of previous UTI should be used to guide the selection of the empiric antibiotic regimen in the recurrent UTI. The duration of therapy is 6-week to 3 months (40,41). Trimethoprim-sulfamethoxazole is the most commonly used prophylactic agent, but there are concerns about increasing bacterial resistance. Cephalexin and norfloxacin prophylaxis has been used successfully in patients unable to take trimethoprim-sulfamethoxazole. At first current infection should be eradicated successfully according to C/S report. Low-dose prophylaxis should be taken at night like: nitrofurantoin 50mg, or cotrimoxazole 480mg or co-amoxiclav 250mg, etc. Prophylaxis should be for 1 year initially. Long term antibiotic may cause oral or vaginal candidiasis and this should be treated with anti-fungal drugs.

Management of fungal UTI in renal transplant:

Asymptomatic candiduria in the renal transplant patient does not need systemic antifungal treatment unless obstruction is

present or symptoms of local or systemic infection develop.
In low-risk patients with asymptomatic candiduria, removal of an indwelling urinary catheter will eradicate candiduria in many patients. If catheter is necessary, removing the existing catheter, a new one should be inserted. This will often eradicate candiduria transiently, but the
organisms will return within a short time. For eradication of Candida from the urinary tract, removal of obstruction in essential.

Patients with symptoms of cystitis or pyelonephritis, and in whom bacteria as well as Candida are found in the urine culture, should be treated with antibacterial drug initially. If no bacteria are present, treatment with an antifungal drug is appropriate. Eradication of the organism is more likely if the indwelling catheter is also removed. **(42)**

Oral fluconazole, excreted as active drug in the urine, is the drug of choice. A loading dose of 400 mg should be given, followed by 200 mg daily for 14 days. Many C. glabrata infections do not respond to fluconazole.

The possibility of drug-drug interactions should be kept in mind. Cyclosporine, tacrolimus, sulfonylurea anti-diabetic drugs, phenytoin, warfarin, etc may reach higher serum concentration levels with fluconazole. The other available azole agents, itraconazole, voriconazole, posaconazole are not excreted into the urine as active drug, which may or may not be effective in fungal UTI. **(43**)

The echinocandins (caspofungin, micafungin, and anidulafungin) have minimal or no excretion into the urine as active drug. Therefore, echinocandins are not recommended for the treatment of Candida UTIs except invasive fungal infection**. (**44)

In the patient with urinary tract obstruction with a fungus ball, irrigation through a PCN tube with amphotericin B is recommended, in addition to systemic antifungal treatment with fluconazole. Absorption of amphotericin B does not occur. Endoscopic removal of the fungus
ball is essential to eradicate the infection.

Treatment of invasive fungal disease:
Suspected invasive candidiasis (IC) not responding to broad spectrum antibiotics should be investigated with blood cultures and two consecutive beta-D-glucan levels in 2 to 5 days. If patient has multiple risk factors for IC, treatment should be started immediately with echinocandins without reports in hand. If the reports are suggestive of IC (beta-D-glucan result above 80 pg/m L,), echinocandin should be continued for at least 14 days after the first negative blood culture. Longer courses may be needed in presence of deep tissue infection or abscesses. If the reports are negative, anti-fungal should be discontinued.

Anidulafungin is free of interactions with other drugs such as prednisone, cyclosporin, tacrolimus, mofetil or sirolimus that are metabolized through the liver. Dosage adjustments are not required in renal impaired patients and in patients with severe liver disease. When compared to caspofungin, anidulafungin has a wider spectrum of action and lower toxicity profile (45).

Conclusion:
Urinary tract infection, particularly fungal UTI is associated with considerable mortality and morbidity in renal transplantation recipients. Several challenges exist in appropriate diagnosis and management of at-risk patients. Delay in treatment can negatively impact outcomes and increase health-care costs.

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Review article

Management of Cardiovascular Disease in Chronic Kidney Disease

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Summary: End-stage renal disease (ESRD) is a risk for premature death because of accelerated atherosclerotic cardiovascular (CV) complications. Many conventional as well as special CV risk factors operate in CKD. Low glomerular filtration rate (GFR) and high albuminuria are predictors of cardiovascular (CV) morbidity and mortality and also all-cause mortality. Acute MI in dialysis patients is associated with poor long-term survival. Significant improvement in hospital mortality has occurred in dialysis patients with (ST-elevation myocardial infarction) STEMI, but not with non-STEMI (NSTEMI). High hospital mortality with NSTEMI is due to atypical clinical presentations and lack of optimum management. This is an area of therapeutic nihilism- a strong idea that treatment is impossible to cure patients or many treatments are unnecessary, sometimes treatment may be harmful to the patients. Current guidelines recommend that acute coronary syndrome patients with CKD should be treated as aggressively as in patients without CKD.

Key words: Myocardial infarction, chronic kidney disease, dialysis, troponins.

Introduction:

Chronic kidney disease with and without albuminuria are tightly linked to cardiovascular disease. Albuminuria increases CV risk because of endothelial dysfunction. CKD is associated with generalized atherosclerosis with vascular calcification, occlusion and noncompliance and also left ventricular hypertrophy. End-stage renal disease (ESRD) is a risk for premature death because of accelerated atherosclerotic CV complications. Many conventional as well as special CV risk factors operate in CKD. Low glomerular filtration rate (GFR) and high albuminuria are predictors of cardiovascular (CV) morbidity and mortality and also all-cause mortality, known for long. (1).

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Physical inactivity is associated with albuminuria. Therefore, CKD patients are advised to be physically active. Avoiding smoking and taking balanced diets reduce cardiovascular morbidity and should be encouraged. However, in all CKD stages, too much protein restriction and protein-energy wasting (PEW) must be avoided. In dialysis patients, lower body mass index (BMI) and underweight is associated with poor prognosis (2).

Coronary artery disease (CAD) and CKD

Medical and interventional treatment of acute and chronic coronary diseases is more or less same between patients with CKD and patients without CKD. Patients with CKD should

receive a similar treatment with medicine and interventions with prognostic benefit (2)

Acute Coronary Syndrome (ACS)

ACS is a group of condition resulting from sudden severe sluggish or stopping blood flow to the cardiac muscle. The three traditional types of ACS are unstable angina (UA), acute non-ST-elevation MI (NSTEMI) and acute ST-elevation MI (STEMI). Acute MI in dialysis patients is associated with poor long-term survival. Significant improvement in hospital mortality has occurred in dialysis patients with STEMI, but not with non-STEMI (NSTEMI) mortality (3) High hospital mortality with NSTEMI is due to atypical clinical presentations, reluctant to do diagnostic tests and lack of optimum treatment. This is an area of therapeutic nihilism- a strong idea that treatment is impossible to cure patients or many treatments are unnecessary, sometimes treatment may be harmful to the patients. In patients with eGFR less than 45 mL/min, about three times patients present with acute MI as the initial presentation of coronary heart disease, rather than stable angina. Though CKD patients are less likely to receive appropriate therapy due to poor prognosis with acute MI, current guidelines recommend that acute coronary syndrome patients with CKD should be treated as aggressively as in patients without CKD (2)

Chronic Coronary Syndrome

CAD patients with CKD show more and larger plaques in comparison to non-CKD patients. Dialysis patients also show more calcified plaques in coronary arteries, in comparison to non-CKD patients where plaques are mostly non-calcified atheromatous (4) A low eGFR is associated with higher numbers of new intramural blood vessels and intraplaque hemorrhages (5). In CKD patients with CAD, asymptomatic (silent) angina is more common. The diagnostic approach to CAD in CKD patients is similar to the non-CKD patients, with lower accuracy of noninvasive testing, particularly in dialysis patients (6)

ECG should be done before first dialysis and then yearly or when acute coronary syndrome is suspected. Echocardiography should be done in all dialysis patients after they achieve "dry weight" on an interdialytic day. Detection of cardiomyopathy is also important, as carvedilol in such patients improves LV systolic dysfunction, decreases hospitalization, and reduces mortality. CKD patients with left ventricular ejection fraction (LVEF) below 40% should be evaluated for CAD, as in general population. For risk stratification and diagnosis of CAD, noninvasive tests (e.g., exercise treadmill testing, exercise echo, dobutamine echo, CT coronary angiogram, cardiac MRI, Myocardial Perfusion Scan or nuclear stress test) show less accuracy in patients with CKD and HD in comparison to invasive coronary angiography (7)

ESRD patients are less suitable for conventional exercise stress test because of limited exercise capacity and baseline ECG abnormalities. Presence of a resting (fixed anatomical) defect in coronary artery is predictive of cardiac death. But inducible myocardial ischemia by any cardiac stress test is predictive of acute MI and cardiac death (8)

Cardiac biomarkers

Plasma brain natriuretic peptides (BNP and NT-proBNP), cardiac troponins (cTnT, cTnI), and high-sensitivity CRP (hsCRP) are important biomarkers for the evaluation of heart disease in ESRD. Grossly BNP represents cardiac filling pressures (of the left and right heart), troponins represent myocardial cell death, and hsCRP represents inflammation.

Cardiac troponins (cTnT, cTnI):

Diagnosis of acute MI in patients with renal disease is difficult due to atypical presentation and chronically elevated troponin. The proposed mechanisms of higher troponin levels in CKD patients are: (a) reduced renal clearance, (b) LV hypertrophy and systolic dysfunction (CCF), (c) myocardial injury from uremia, circulating cytokines and acidosis, (d) HD-induced myocardial ischemia due to volume shift and hemodynamic change (HD-induced myocardial stunning (HIMS)). (9). Other non-cardiac causes of raised troponin I are sepsis, anemia, pulmonary thrombo-embolism and hypertensive crisis which may be present in kidney patients. Age above 60 years is a significant factor that can increase troponin I level (10)

A meta-analysis screened 2590 publications and investigated alternative cut-offs according to renal impairment. The manufacturer's upper reference level for troponin T is 14 ng/L. Based on meta-analysis, cut off values for troponin in renal impairment patients with MI was 42 ng for troponin I and 48 ng/L for troponin T. For dialysis patients, the cut off value of troponin T was 239 ng/L. A troponin I cut off value for dialysis patients could not be established (11). High-sensitivity troponin is elevated in almost all patients, and troponin-I in up to 30% of patients with HD, majority are transient (12). Patients with cardiac troponin above 5 ng/L should be retested at 3 hours. MI is ruled out at 3 hours if cardiac troponin are unchanged and remain below 99th percentile (13). For patients with ESRD and suspected ACS a dynamic rise in troponin levels of more than 20% within 9 hours should be required for a diagnosis of AMI, rather than simple fixed threshold levels (14).

N-terminal pro-brain natriuretic peptide (NT-pro BNP):

NT-pro BNP is a polypeptide that is secreted as BNP by cardiac myocytes in hypoxia induced cardiac dysfunction and excessive myocardial stretching from volume overload. Therefore, BNP and NT-pro BNP have been used as biomarker of heart failure in general population and in CKD patients. Yaqiong Wang et al. showed on 129 HD patients that NT-pro BNP is a predictive factor for volume overload in HD patients with or without low cardiac ejection fraction (EF) (15).

Coronary Angiogram (CAG)

CAG should be done in stable ESRD patients with inducible myocardial ischemia, unstable patients with acute coronary syndrome and patients with LVEF less than 40%. In CKD and dialysis patients with residual kidney function, fear of contrast induced nephropathy (CIN) may restrain use of coronary angiography. Acute kidney injury (AKI) after coronary angiography increases the risk of progression of CKD, ESRD, hospitalization and even mortality, but this fear should not discourage clinically mandated CAG. (16) Echocardiography is done before any CAG in CKD patients to diagnose valvular disease or cardiomyopathy, to assess volume status and LV function and to minimize exposure to radiocontrast media.

Coronary CT angiography is noninvasive, does not require catheter insertion into the coronary arteries and has similar accuracy to invasive coronary angiography. It is associated with a lower risk of AKI particularly in kidney transplant candidates. But coronary CT angiography may be inconclusive in dialysis patients because of tunica medial calcification that interferes with interpretation (17)

MRI is typically an adjunct to other imaging. The major advantage of MRI over other modalities is direct multiplanar imaging. MRI safety guidelines have been developed with an

extensive list of devices that are or are not MRI approved, and any devices in the patient need to be checked against this list. Although MR angiogram (MRA) can be performed with or without intravenous gadolinium contrast, contrast provides better images. Nephrotoxicity to gadolinium agents appears to be very uncommon and likely insignificant. (18). MRA with gadolinium had been contraindicated in patients with GFR below 30 ml/min because of the risk for nephrogenic systemic fibrosis or nephrogenic fibrosing dermopathy.

Medicine in Chronic Coronary Syndrome in CKD patients

According to current guidelines, drug therapy in chronic coronary syndrome (CCS) patients with CKD should not differ from therapy in non-CKD patients. But the renal- excreted drugs used in CCS should be used with caution, e.g. trimetazidine.

Coronary revascularization

CKD is an independent risk factor for death after coronary revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). (19). Compared with the medical treatment in CAD with CKD, the invasive treatment is associated with a significantly higher incidence of stroke, initiation of dialysis or death. (20). AKI immediately after coronary revascularization is associated with excess mortality. But mortality is lower in CKD5 and dialysis patients undergoing PCI or CABG in comparison to mortality with conservative treatment only. Dialysis patient survival after CABG is better than after PCI with stents (21) Mode of invasive treatment (PCI or CABG) should be chosen based on the general condition and life expectancy of the patients. PCI is less invasive and more appropriate in the most fragile and compromised patients (22). The preemptive coronary revascularization showed nearly 90 percent of 3-year cardiac event–free survival for patients waiting for renal transplantation. Optimal medical therapy may potentially reduce the benefit of prophylactic coronary revascularization (23).

Management of coronary heart disease in kidney transplant candidates:

High risk patients with central chest pain, past history of MI, multiple risk factors should be evaluated at first with 12 lead ECG and 2D echocardiography.

In case of typical symptomatic CAD, coronary angiogram should be done. If less than 75% stenosis is present, further intervention is not necessary and from cardiac point of view, patient is fit for renal transplantation. If more than 75% stenosis is present, further intervention is necessary, like CABG or PCI before renal transplantaton. If more than 75% stenosis with severe diffuse disease is present, further invasive intervention is not indicated. From cardiac point of view, patient is not fit for renal transplantation.

If CAG shows ambiguous/flow-limiting lesions, patient should be further evaluated by dobutamine stress echocardiogram. If report is positive, further invasive intervention should be considered, like CABG or PCI before renal transplantation. If report is negative, further intervention is not necessary and from cardiac point of view, patient is fit for renal transplantation

If patient has atypical chest pain, asymptomatic diabetes, previous MI, multiple risk factors without clean-cut diagnosis of CAD, at first dobutamine stress echocardiogram should be done. If the result is negative, from cardiac point of view, patient is fit for renal transplantation. If the result is positive, CAG should be done (24).

Heart failure in patients with CKD:
Heart failure in patients with CKD and CKD5D is due to maladaptive ventricular hypertrophy and fibrosis. Therefore, patients with CKD show an increased risk of heart failure and impairs the prognosis. SGLT2 inhibitors have shown benefit in both patients with heart failure and CKD and should be used in pre-HD CKD patients (25).

LVH occurs early in progressive CKD, due to hypertension and frequent nocturnal hypertension. Pressure overload results in concentric LV hypertrophy and volume overload manifests as eccentric LV hypertrophy. LVH is strongly associated with diastolic dysfunction, pulmonary hypertension and intradialytic hypotension. Left ventricular dilation (cardiomegaly) may be an end result of severe LVH, diffuse myocardial ischemia, recurrent volume overload and a high-output AVF. Cardiomegaly strongly predicts poor outcome.

Hemodialysis with hemodynamic changes can produce repetitive myocardial injury with left ventricular systolic dysfunction. This is called HD-induced myocardial stunning (HIMS). Obstructive CAD is not necessary for this pathological myocardial stunning. It is associated with increased 1-year mortality. Biofeedback dialysis (continuous modulating the conductivity of dialysate fluid for a desired end-dialysis result) or reduced dialysate temperature can help to reduce intradialytic hypotension and severity of HIMS. For decompensated heart failure in CKD, NT-proBNP is a better predictor of survival.

Treatment of CHF with in CKD
Based on left ventricular ejection fraction (LVEF), CHF are three types:
(a) HF with preserved EF (HFpEF): LVEF ≥50%,
(b) HF with moderately reduced EF (HFmrEF): LVEF ≥40% to 49% and
(c) HF with reduced EF (HFrEF): LVEF less than 40%.

Treatment of CHF with CKD are recommended largely based on data from the general population (Figure.1).

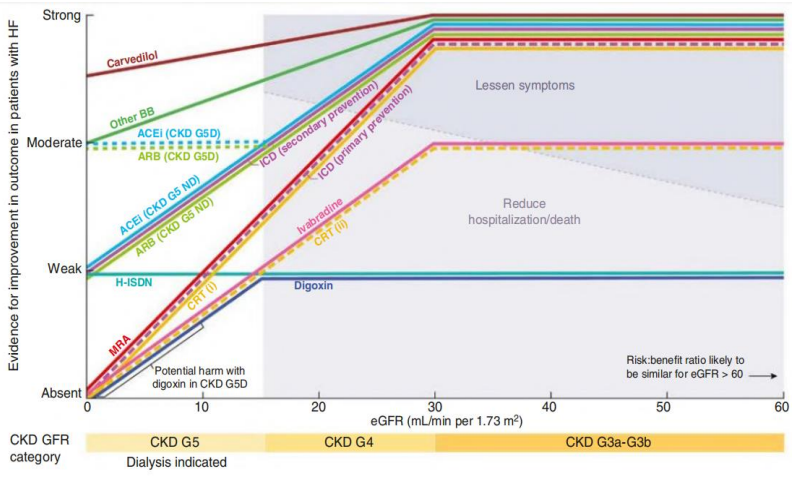

Figure.1 Positioning of therapies for CCF on the basis of ejection fraction (EF) and CKD staging. CRT, cardiac resynchronization therapy (biventricular pacemaker); H-ISDN, hydralazine and isosorbide dinitrate; ICD, implantable/internal cardioverter-defibrillator. (26)

SGLT2 Inhibitors

SGLT2 inhibitors cause glucosuria and osmotic diuresis along with weight loss and

natriuresis. In patients with diabetes, SGLT2 inhibitors significantly reduced cardiovascular morbidity and mortality. Patients with HFrEF have shown to reduce the hospitalization and cardiovascular death significantly with dapagliflozin or empagliflozin. These agents also reduce worsening or progression of CKD nephropathy. Clinical benefits have been seen in patients with eGFR as low as 20 mL/min. These agents are effective in patients with CKD 3 to 4. Therefore, dapagliflozin,
has recently been approved for use in patients with HFrEF and eGFR as low as 30 mL/min in presence or absence of diabetes. (27)

ACE Inhibitors/Angiotensin 2 Receptor Blockers

Solid data exist for the use of ACE-inhibitors in patients with CKD stage I–III plus heart failure with reduced ejection fraction (HFrEF). ACE-inhibitors reduce morbidity and mortality in patients with HFrEF. In case of ACE-inhibitor intolerance due to dry irritatve cough or angioedema, angiotensin receptor blocker (ARB) is recommended. (28)

Beta-Blockers

Treatment with beta-blockers is the main strategy for managing patients with HFrEF because of their ability to reverse the neurohumoral (adrenalin and nor-adrenalin) effects of the sympathetic nervous system with symptomatic and prognostic benefits. But they are underused mainly because of the misconception that hypotension and bradycardia may worsen the hemodynamic status of patients with HFrEF. Patients with CHF with CKD 3,4,5 and advanced CKD benefited from β-blocker therapy. Only three beta-blockers are FDA-approved to treat CHF: bisoprolol, carvedilol and metoprolol. (29)

Diuretics

Diuretics are indicated in patients with venous congestion and New York Heart Association (NYHA) II, as well as in patients with NYHA III and IV CCF. Patients can be treated with loop diuretics or thiazides, but patients with CKD stages 4 to 5 should receive either loop diuretics alone or loop plus thiazides diuretics. Patients should be monitored for hypotension, tinnitus, hypokalemia and hyponatrema. After cardiac decompensation, at least a low-dose diuretic should be continued.

Mineralocorticoid Receptor Antagonists (MRA)

Mineralocorticoid receptor antagonists (aldosterone antagonists e.g. spironolactone or eplerenone) reduce the aldosterone-mediated proinflammatory effects that are involved in the fibrotic remodeling processes. If patients with HFrEF (LV ejection fraction is 35% or less) are still symptomatic even after having ACE inhibitors or ARBs and beta- blockers, they should be treated with a MRAs. Special attention should be paid to the development of hyperkalemia, the risk of which is increased with severity of renal dysfunction. These agents are safe and effective in patients with CHF and CKD stages 1 to 3a (e GFR up to 50) but are contraindicated in CKD stages 4 and 5. A new selective nonsteroidal MRA, finerenone also blocks the damaging effects of the overactivated aldosterone system. It is equally distributed in myocardial and renal tissue. Finerenone reduced cardiac fibrosis and inflammation more than eplerenone in animal experiments.

Angiotensin Receptor Neprilysin Inhibitor (ARNI):

If patients are still symptomatic even after having treatment with a combination of ACE inhibitors/ARBs, beta-blockers, and MRAs, a new combination of angiotensin receptor neprilysin inhibitor (ARNI) should replace

ACE inhibitors or ARBs provided that kidney function permits. The sacubitril and valsartan combination has showed a reduction of hospitalization, cardiovascular mortality and all-cause mortality, and this benefit has been found in patients with eGFR up to 30 mL/min. Therefore, ARNIs are effective in patients with heart failure and CKD stages 1 to 3; in patients with CKD stages 4 to 5, no data are available. (30)

Standard dialysis prescription:

Incremental risk for all-cause mortality and cardiovascular death is associated with volume overload and weight gain between dialytic sessions. Uncontrolled hypertension in chronic HD patients may indicate that the target dry weight has not been achieved. Achieving the optimal dry weight may lead to good control of hypertension with minimum antihypertensive drugs. A standard dialysis prescription should consist of a high-flux dialyzer, a minimum treatment time of 4 hours per session, a blood flow rate of at least 250 ml/min, and a dialysate flow rate of 500 ml/min. The prescription is then adjusted to meet the target spKt/V of 1.4 per HD session for patients treated thrice weekly, with a minimum delivered spKt/V of 1.2. (31).

Valvular heart disease in CKD patients:

The prevalence of mitral and aortic valve calcification is significantly higher in CKD and dialysis patients in comparison to the general population. Asymptomatic dialysis patients with an aortic valve orifice area of <1.0 cm^2 are suitable candidates for valve replacement. The overall mortality is high, with in-hospital mortality about four times higher in CKD patients. In kidney transplant recipients, in-hospital mortality is 10 to 15%, and 2-year mortality rates are 60 to 62%. Overall, the prognosis of dialysis patients after valve replacement is poorer in comparison to non-dialysis patients. (32)

Atrial Fibrillation with CKD

Atrial fibrillation (AF) is the most common arrhythmia in advanced CKD, particularly in older patients initiating dialysis. It is an independent risk factor for development of ESRD in CKD. The prevalence of AF among dialysis patients is 15% to 20%, may be upto 40%, if episodes of paroxysmal AF are included. (33)

Treatment is anticoagulants, like warfarin. In observational studies, Hart RG et al. observed that the dose-adjusted warfarin was associated with a 76% relative risk reduction for ischemic stroke or systemic embolism among AF patients with CKD stage 3. (34). In acute MI patients with AF with no HD, warfarin treatment is associated with a lower risk for death, MI, and ischemic stroke. But KDIGO does not advise routine warfarin therapy in AF patients with dialysis for primary prevention of stroke. However, some experts suggested warfarin for secondary prevention of stroke. (35) Warfarin use in dialysis patients is also difficult due to fluctuation of PT INR and accelerated vascular calcification. In hemodialysis patients with AF, a reduced dose of rivaroxaban (10 mg daily) significantly reduce the composite outcome of fatal and nonfatal cardiovascular events and major bleeding complications compared with warfarin. (36)

Sudden Cardiac Death

The rate of cardiac arrest is 50% higher for HD than for PD patients at 3 months after dialysis initiation but is higher for PD patients at 3 years. The highest rate of sudden cardiac death occurs in the first 2 months after HD initiation. Strong predictors of sudden cardiac death are coronary heart disease, peripheral arterial disease, DM, elevated inflammatory biomarkers (e.g. sepsis), and reduced LVEF. Nearly 85% of all cardiac deaths and 34% of all-cause mortality in HD patients are attributable to arrhythmias. (37) Factors

contributing to the sudden cardiac arrest in ESRD patients include LVH, rapid electrolyte shifts, hyperkalemia, autonomic dysfunction and sleep apnea, and abnormalities in myocardium. Low-potassium dialysate (<2 mmol/L) doubles the risk for cardiac arrest. (38) The role that implantable cardioverter defibrillators (ICDs) may play important role in reducing mortality in CKD patients. Many guidelines recommend primary prophylactic ICD implantation if the ejection fraction is 35% or less. (39)

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Case Report

Iatrogenic Ureterovaginal Fistula after Hysterectomy

Sayed MA[1]

1. Dr. Md. Abu Sayed, FCPS (Urology), Assistant Professor of Urology, KFH&RI.

Abstract: The highest risk of intraoperative ureteral trauma is associated with hysterectomy, performed most frequently in complicated case or by unwary surgeon. The overall incidence of ureteral injuries varies in different studies between 0.5% and 10%. Ureterovaginal fistula following total abdominal hysterectomy with right salpingoophorectomy is reported in this case. Ureteral injury was not noticed during operation. Two weeks after the operation the patient noticed constant urine leakage from the vagina. A computed tomography scan revealed dilation of the right renal pelvis and the upper two thirds of the ureter due to an inflammatory fibrous mass at its lower part. Contrast medium outflow identified the site of urine leakage. The patient developed an iatrogenic ureterovaginal fistula, which was repaired successfully with a ureteroneocystostomy with psoas hitch over a double-J stent a month and a half later. Perioprative period was uneventfull and from 1st post-operative day, the patient noticed there was no urine leakage from the vagina. This paper highlights the problem of unnoticed ureteral injury during gynaecological surgeries, which, if overlooked, can develop into severe complications. Causes of ureteral injuries, prevention, and possible treatment options are also discussed.

Keywords: Ureter, vagina, injury, fistula, hysterectomy.

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IntroductionInjury of the ureter is a risk in any pelvic or abdominal surgery, including laparoscopy and ureteroscopy, and it also can be a result of penetrating or blunt trauma. The overall incidence of ureteral injuries varies in different studies between 0.5% and 10% (1-7).

Gynaecological surgery remains the most common cause of iatrogenic ureteral injuries. The incidence of ureteral injuries is 0.1–1.5%

in procedures due to benign diseases and rises to 5% in surgery of malignancies in gynaecology. About 30–45% of injuries are diagnosed intraoperatively, and 55–70% of injuries are diagnosed post-operatively. Among iatrogenic ureteral injuries in gynaecology, most occur in hysterectomy (54%), pelvic operations such as ovarian tumour removal (8%), and transabdominal urethropexy (8%) (1-3, 8-10). The leading cause of ureteral injury in laparoscopic surgery is vaginal hysterectomy (20%), resection of endometriosis (12.8%), oophorectomy (11.4%), pelvic lymphadenectomy (10%), sterilization (7.1%), and adhesiolysis and drainage of lymphocele (4.3%) (5). The experience of the surgeon plays a crucial role in the incidence of iatrogenic ureteral injury. Rates of ureteral trauma vary form 0.3% for experienced gynaecologists to 14% for those with little experience (3,6).

Case report

A 45-year-old woman with uterine myomas and right ovarian cystic lesion underwent a totalabdominal hysterectomy with right salpingoophorectomy at a district gynaecology department. Two weeks later she noted a urine leakage from the vagina, which is a symptom requiring careful evaluation in the post-operative period. On admission, pelvic examination revealed continuous urine leakage. A computed tomography (CT) scan revealed mild dilation of the right renal pelvis and the upper two thirds of the ureter due to an inflammatory fibrous mass (Fig 1) involving its lower part. Contrast enhancement identified the site of urine leakage. Considering the results of computed tomography, classic laparotomy with ureteral repair or ureteroneocystostomy was chosen as a method of treatment.

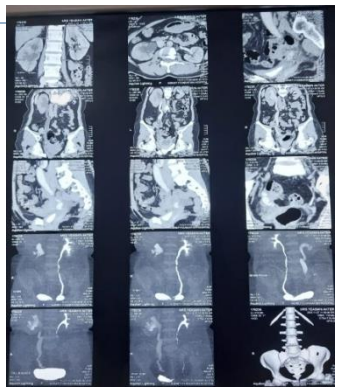

Fig 1: A computed tomography (CT) scan revealed mild dilation of the right renal pelvis and the upper two thirds of the ureter due to a mass lesion.

After one and half months, the patient was admitted to the urology department of Kidney foundation hospital and research institute and underwent a laparotomy with right ureteroneocystostomy. During the operation the right ureter was mobilized from surrounding tissues along the entire length up to the crossing with the right upper bladder artery. Intraoperatively, involvement of the ureter in a fibrous mass extending into the perivesicular space was revealed. The ureter

was cut at the most distal point to the fibrous tissue. The distal ureteral cuff was sewn and ligated with Vicryl 2/0 and left in the mass. A double-J stent 5Fr was inserted into the right kidney pelvis via the dilated proximal ureteral cuff. then the ureter was reimplanted in the right lateral bladder wall. Ureteroneocystostomy was made using the Lich-Gregoir technique over a double-J stent. The bladder wall was closed in 2 layers, and finally a transurethral catheter was inserted. The post-operative period was uncomplicated. After 14 days, the transurethral catheter was removed and the patient passed urine without leakage. The double-J stent was removed after 4 weeks. The follow-up after 3 months revealed no signs of left hydronephrosis on ultrasonography check.

Discussion

The mechanisms of ureteric injuries during operative procedures include crushing with a clamp, suture ligation, partial or complete primary transection, angulation, avulsion, or ischaemic necrosis following electrocoagulation. Significant complications after ureteral injury include renal insufficiency, ureteral strictures, vesicovaginal, and ureterovaginal fistulae. Ureteral fistulas to the genital tract in females may connect with the vagina or much less commonly with the fallopian tube or the uterus (7). Risk factors for the development of ureterovaginal fistula include endometriosis, obesity, pelvic inflammatory disease, as well as radiation therapy and pelvic malignancy. The main presentation of the ureterovaginal fistula is urinary incontinence despite the normal act of micturition (8). Incontinence usually begins between 1–4 weeks after surgery. Initially, the patient may experience flank pain, fever, and nausea due to the urinoma or obstructed kidney, followed by incontinence. Reviewed studies (9) considered ultrasonography, intravenous urography, retrograde pyelography, cystography, CT-urography, MRI, 3-swab test, and vaginal examination useful for the diagnosis of ureteral obstruction and ureterovaginal fistula. Cystogram may be useful to exclude a coexistent vesicovaginal fistula. The incidence of left-side ureteral fistula is 88.2% as compared to 11.7% on the right side (4,8). The probable reason is the fact that the operating gynaecologist usually stands on the right side of the patient; hence, the left-sided bleeding is controlled under obscured vision. The goal of the treatment of ureterovaginal fistula is the resolution of urinary leakage, prevention of urosepsis, and preservation of renal function. Early drainage of the affected upper urinary tract is essential (5). Immediate open surgical repair may be difficult; therefore, ureteral stenting or percutaneous nephrostomy are feasible options. Endoscopic management with ureteral stenting can promote closure of the fistula if initiated early. Persistent urinary leakage can be treated with percutaneous nephrostomy drainage, ureteral stent(s), and/or Foley catheter drainage. In more complex injuries treatment includes open surgeries and minimally invasive laparoscopic or robotic reconstructive surgeries, which involve ureteroureterostomy, ureteroneocystostomy, and ureteral replacement using ileal interposition or autografts. The majority of ureterovaginal fistulas develop due to injuries in the distal third of the ureter, below the pelvic brim, and can be repaired with ureteroneocystostomy. The Lich-Gregoir ureteroneocystostomy technique is most commonly used. There was no difference in outcome between refluxing and non-refluxing implantation in adults. In the majority of cases ureteroneocystostomy is combined with a psoas hitch manoeuvre or a Boari flap in order to cover a greater distance and facilitate tension-free anastomosis (5). In cases of bilateral or combined fistulas of

ureterovaginal and vesicovaginal fistula, management may require bladder reconstruction or urinary diversion.

Significant preventive measures for surgeons are as follows: 1) proper evaluation of surgical indications for hysterectomy and consideration of other treatment options; 2) experience using laparoscopic and laparotomy techniques, knowledge of all risks and benefits of each method; 3) knowledge of anatomical landmarks: location of blood vessels, nerves, ligaments, careful identification of the ureter; 4) knowledge of electrosurgery principles: depth, penetration, spread; 5) adequate exposure during operation: pneumoperitoneum, Trendelenburg position, bowel preparation, immediate control of bleeding, cautious tissue dissecting, intrauterine manipulator if needed; 6) preoperative recognition: cystoscopy with intravenous injection of indigo carmine or placement of ureteral stents; 7) strict monitoring in every case: temperature, passage of gas and stool, loin pain, vaginal leakage, serum C-reactive protein, and creatinine levels.

Conclusions

The morbidity associated with ureteral injury may be serious, resulting in prolonged hospital stay, suboptimal surgical outcome, secondary invasive interventions, decreased renal function and reduction of the patient's quality of life. The risk of ureteral complications after laparoscopic hysterectomy is comparable to open laparotomy. Surgical expertise, knowledge of pelvic wall anatomy, and careful identification and mobilisation of the ureter are the key measures to prevent injury. Early diagnosis is crucial to prevent long-term treatment. Endoscopic techniques are sufficient in the majority of early diagnosed cases. Nevertheless, more extensive reconstructive surgery is needed in ureteral injuries developing into renal insufficiency, urogenital fistulas, and severe ureteral strictures.

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Case Report

An Unusual Presentation of CAPD Peritonitis: Subcutaneous Emphysema

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1. Farnaz Nobi, Assistant professor of nephrology, KFH&RI, Bangladesh.
2. Mohammad Shakib Uz Zaman Arefin, Professor of nephrology, KFH&RI, Bangladesh.

Abstract:
We here report a case of CAPD peritonitis having a very unusual presentation, subcutaneous emphysema. Peritoneal effluent cultures yielded *Pseudomonas aeruginosa.* She was treated with intraperitonealamikacin, ceftazidime, vancomycin and intravenous meropenem but the infection persisted. She eventually required removal of catheter. Jugular venous catheter was inserted and haemodialysis started.
Since 2011, a total number of 478 patients received CAPD for ESRD at Kidney Foundation Hospital and Research institute. Among these patients the rate of peritonitis for the year of 2017, 2018, and 2019 was 1 episode per 32, 28 and 22 patient months respectively. However, this is the first case of subcutaneous emphysema presenting as a complication of CAPD.While free intra-peritoneal air is known to occur in peritoneal dialysis patient, dissection of this air into the abdominal wall mimicking the subcutaneous emphysema has not previously been reported in our center.

Keywords: CAPD peritonitis, *Pseudomonas aeruginosa,* subcutaneous emphysema.

Case Summary:
Mrs. X, a 66-year-old lady diagnosed case of ESRD due to CGN with HTN was on continuous ambulatory peritoneal dialysis for 10 months. She was reasonably well with good exchange three times daily.

Two months back she developed itching around catheter exit site for which she took azithromycin followed by flucloxacillin.
But itching persisted and she also developed abdominal pain during exchange for which she got herself admitted in Kidney Foundation Hospital.

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On general examination patient was afebrile with normal vital signs. On local examination, catheter exit site was dry, erythematous with no discharge. On palpation subcutaneous crepitation was felt around the exit site but tunnel track was non tender.
On x-ray imaging there was gaseous shadow occupying right lumbar region (Fig 1). Complete blood count revealed Hb: 6.7 g/dL, WBC: 7K, Platelet: 187 x 10^3 per cumm, CRP: 87 mg/L. Peritoneal effluent was clear

with 4/cmm cells, negative for AFB, Gene X-pert and culture yielded no growth. Then she was treated with intraperitoneal, topical antibiotic and oral antifungal. Inflammation subsided and crepitation resolved. She was doing well for one month. Then she again developed pain during exchange. At his time, it was associated with discharge from the exit site.

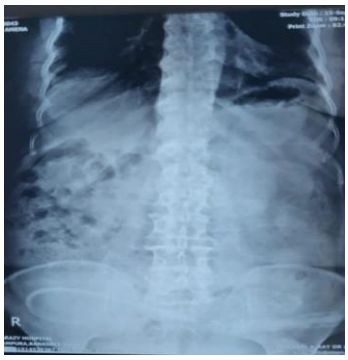

Fig1: X-ray abdomen erect posture showing gaseous shadow at right lumbar region.

Peritoneal effluent was clear with 1400 cells/cmm with growth of *Pseudomonas species* and *Staphylococcus haemolyticus*.

She was treated with injectable antibiotic for 14 days after consulting local doctor but didn't improve hence again admitted herself in our hospital. On examination patient was afebrile but erythematous lesion extended with no discharge or tunnel tract tenderness. Peritoneal effluent was still clear with no growth. She was also negative for QuantiFERON TB Gold. CAPD exchange was good but CRP was elevated persistently and repeat X-ray imaging revealed persistent gaseous shadow in right lumbar region.

Skin and abdominal wall ultrasonogram was done which showed air fluid collection around the tunnel suggestive of tunnel infection (Fig 2). Intraperitoneal and topical antibiotic was instituted but condition didn't improve.

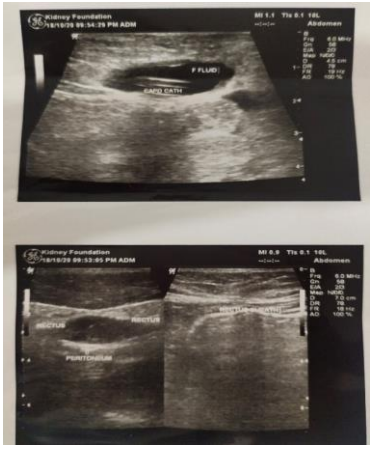

Fig2: Ultrasound scanning of abdominal wall and skin showing mild fluid collection appearing as branching, anechoic striations suggestive of CAPD exit site cellulitis with tunnel infection.

Eventually CAPD catheter was removed. Followed up imaging showed resolved fluid gaseous shadows. Patient started taking haemodialysis through JVC and later on AVF was constructed. Her general condition improved.

Discussion:

Peritonitis continues to be a leading complication of PD which accounts for 18% of the infection-related mortality in PD patients. The incidence of exit site infection in PD patients ranges from 0.05 to 1.02 episodes per patient-year. The incidence of exit site infections is seen anywhere between one episode in 27.3 patients' months to one episode in 41.9 patients' months [1]. The diagnosis of Tunnel Infection is mainly based on clinical suspicion and ultrasound examination. The extent of involvement of the subcutaneous PD catheter tract is a critical factor in the development of peritonitis [2]. Presentation of CAPD catheter related infection can be variable from erythema to purulent discharge or abdominal pain during exchange. Here we report the 1st case of CAPD peritonitis presenting with subcutaneous emphysema around the exit site.

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Medical Quiz

Nomany BMS[1]

Bakhtiare Md. Shoeb Nomany, Associate Professor of nephrology, KFHRI, Bangladesh.

Fig 1: Patient Profile

This 53-year-old gentleman was presented to nephrology OPD with occasional mild pain in his left loin for several years. Initially ultrasonogram was done that showed left sided hydronephrosis. CT urogram was done.

Question 1. Mention the abnormal findings of CT urogram.

Question 2. What is your radiological diagnosis?

Question 3. What may be the demographic and clinical features of the patient?

Question 4. How will you manage the patient?

Answer to the medical quiz:

Answer 1. Non-contrast CT urogram revealed marked dilatation of left pelvi-calyceal system with thinning of the cortex (Hydronephrosis) with abrupt narrowing at left upper ureter. Left ureter is delayed opacified with contrast. A small almost rounded fluid density area with thin wall and clear content (measuring about 10 mm x 9 mm) is noted in mid-reason of right kidney.

Answer 2. Impression: Left sided pelvi-ureteric junction obstruction (PUJO) and right renal cortical cyst (Bosniak type-I).

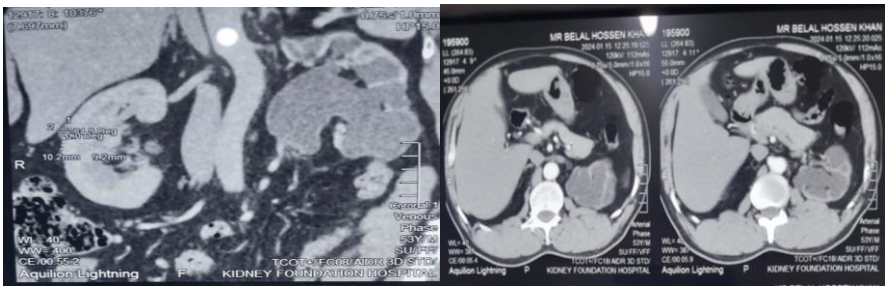

Fig 2: CT scan of KUB of the same patient.

Answer 3. PUJ obstruction occurs in 1 in 1500 live births. It is one of the most common causes of hydronephrosis that can be detected antenatally. It is more common in males (2:1), in the left kidney (1).

Up to 50% of infants have other urologic abnormality, such as contralateral PUJO, contralateral dysplastic and multicystic kidney, VUR, and contralateral kidney agenesis (1).

Older children can present with abdominal lump or with flank pain on and off that worsens after having plenty water or soft drinks or caffeine with brisk dieresis (Dietl's crisis). Hematuria may result from mild trauma, stone or UTIs. Hypertension can occur temporarily after pyeloplasy.

Answer 4. DTPA renogram with diuretic challenge can differentiate between significant obstruction requiring surgical correction and congenital dilatation of renal pelvis, requiring no surgery. Surgical management of PUJ obstruction is removal of aperistaltic portion of the ureter, allowing drainage from the affected kidney. The gold standard treatment is now laparoscopic or robotic pyeloplasty. Pyeloplasty is indicated for symptomatic patients (pain, infection, or stones) or for asymptomatic patients with >10% decrease in split renal function (2).

Endoscopic laser pyelotomy has inferior outcome compared with pyeloplasty (3).

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Information for the Authors about Writing Scientific Articles

Introduction

Many research workers are reluctant to publish their articles after completing the academic degrees. Sometimes they make an unacceptable delay in writing articles for publications in local or international journals. In many instances, the manuscript is written after several years, and many recognized journals do not accept the article for publication. Scientific articles must be published in time to make the research results acceptable to the professionals and to use the results by greater scientific community.

Guidelines for the Authors:

The Kidney Foundation Hospital and Research Institute Journal provides publication (six monthly) of articles in nephrology, pediatric nephrology, renal histopathology, renal imaging, transplant medicine and urology. The Journal welcomes the submission of manuscript that meets the general criteria of significance and scientific excellence. Papers must be submitted with the understanding that they have not been published elsewhere (except in the form of an abstract or as part of a published lecture, review, or thesis) and are not currently under consideration by another journal published by international research journals or any other publisher. The submitting (corresponding) author is responsible for ensuring that article's publication has been signed and approved by all the other co-authors.

Writing protocol of scientific article is different

Writing of the scientific article should be started as soon as the research has been completed. Actually, writing article is an art which has to be achieved by practice. There are some differences between writing thesis and research paper or research report. One may write a thesis of 160 pages but it may not be possible to publish a single article from that thesis in a peer reviewed journal having impact factor. On the other hand, more than one article may be prepared from some thesis having quality contents and data.

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Most clinical and scientific discovery is published in peer-reviewed journals. Peer-reviewed journals are those that utilize a process by which an author's peers (experts) in the respective contents evaluate the manuscript. The main objective of peer review is unbiased, independent and critical assessment of research papers by experts on the topic who are not involved in editorial office. Peer review helps editors to select the right article to publish in a journal. It also helps the author and the editor to improve the quality of the manuscript. Following peer reviewing, the manuscript is recommended for publication, revision or rejection.

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There are several types of articles written to publish in journals: a) Editorials, b) original article, c) review article, d) case report, and e) letter to the editors.

a) **Editorials:** It will be preferably written invited only and usually covers a single topic of contemporary interest.

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Nearly 85% submitted manuscripts by the novice researcher are rejected by a recognized journal. So, manuscript rejection should not invite frustration. After rejection by peer reviewers, the comments are usually sent to the author mentioning the problems and pitfalls in the manuscript which may guide the author to improve for next submission in another journal with greater chance of acceptance. For peer review manuscript publication repeated practice can improve the performance of the author.

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The reviewers usually follow the criteria for accepting the manuscripts: 1) timeliness, relevance, importance, and prevalence of the addressed topics; 2) appropriate, detailed, rigorous, and comprehensive study design to achieve the objectives; 3) thoughtful, focused, and up-to-date literature review; 4) sample size is sufficiently large; 5)

accurately constructed tables and figures; and 6) accurately and sufficiently described statistical analysis, 7) the text is grammatically correct, well-written, clear, straightforward and logical.

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The following are the main rejection criteria: 1) irrelevant, unimportant and insufficiently addressed problem; 2) use of inappropriate and insufficiently described populations or instruments; 3) text is poorly written and grammatically incorrect; 4) incomplete, inaccurate, or outdated review of the literature; 5) inaccurate, inconsistent and insufficient data presented; 6) inappropriate and insufficiently described statistical analysis; 7) small sample size or biased samples; 8) over-interpretations of study results; and 9) defective tables or figures.

Submission of completely prepared manuscript

Do not submit the partially prepared article. Read the article repeatedly before submission so that error(s) can be identified and corrected. Grammar, tense, and spelling mistakes are often a cause of rejection by reviewers. Despite the good content, these errors suggest that the authors have written the manuscript with less attention with incorrect findings. So, the manuscript should preferably be checked by a mentor before submission for publication. The articles have several sections: Title, Abstract, Introduction, Methods, Results, and Discussion.

Title:

Title should be attractive to the readers. Most of the readers take decision whether he/she will read the article or not by observing the title.

Abstract or summary

Abstract or summary of an article should contain 200-300 words. After reading the abstract the reader determines if the remainder of the article is worth reading. The abstract is a summary of the article allowing the readers to get a quick glance of the contents. It is better to submit structured abstracts containing back ground, objectives, methods, results and conclusion. The message in the abstract should be clean and precise to the readers.

Introduction

Introduction should be in present tense. The necessity of the present study is presented to the reader by describing the information reported in different studies. Introduction should cover the following points: a) significance of the topic, b) the knowledge gap in the available reports on the topic, 3) selection of some questions on the topic and discuss literature in support of the questions, 4) finding of justification, objectives and hypotheses. Don't try to review all available knowledge on the topic in introduction. Try to adhere to the topic strictly. Literature review is not your prime work and don't write too broad literature review. Describe the literature in such a way that rationale of the study is established. From the last few sentences of introduction, the readers should understand the knowledge gap on the present topic, the purpose and objectives of the study, possible outcome and implications of the study results. Last paragraph may be like this: "No systematic study on urosepsis has been carried out in the hospital. The purpose of the study was to find out bacterial causes of urosepsis in a tertiary care hospital and to observe the role of effective antibiotics in reducing mortality". In scientific article, 1st person language may be accepted such as 'we', 'our'. If any

abbreviation is used, it should be written in full with abbreviation in bracket at first, followed by abbreviations only in subsequent paragraphs.

Matereials and methods

The materials and methods (M & M) section is the heart of a scientific paper. After initial screening, the editors decide whether the manuscript should be sent for external review or not. Therefore, this section should be the most elaborated and detailed. M & M should contain the study question/hypothesis.

M & M should cover the explanation of the procedures in detail, the study design, place of study, the research population, inclusion and exclusion criteria which help the reader to understand the population used, sample size, sample collection procedure, data collection instrument/sheet, data management and data analysis.

Next paragraphs should be more detailed in describing the procedures. It is to be written in such a clean way that an appropriately trained researcher can be able to replicate the experiments. There should be complete transparency when describing the study. A researcher should be honest in doing research work and publishing scientific article.

Methodology section should cover the equipments and reagents used in the study, name of the manufacturing company and country, procedures done during the study with the instruments, the protocol used, the outcomes and the methods used for data analysis including the name of the test. Procedure of data collection, type of data collection (retrospectively or prospectively), place of data collection is also mentioned.

Approval from an appropriate ethical review committee should be included in methodology section. Example: under the subheading of "ethical issues" "informed written consent was taken from each participant and ethical clearance was obtained from the ethical review committee of the institute" should be mentioned.

Many editorial offices claim for the certificate of ERC and raw data for checking authenticity of the research work. If any research involves experiment with animals, a statement regarding kind handling of animal should be inserted as "animal experiment was carried out following the guidelines of international Animal Experimentation Ethics Committee (AEEC) and a clearance was obtained from AEEC".

Results

The results are actual statements of observations, shown in tables, figures, graphs and statistics.

Table should be constructed accurately and each table should stand alone and self explanatory. Tables should not have internal vertical and horizontal lines; data should not be in boxes in the table or a table should not be in one row or column. The title of the table should be just above the table. Inappropriately prepared table indicates that the manuscript is also prepared inappropriately.

Results should be written in past tense. In the text, all the results should not be shown in table; write the important points only with reference of table in parentheses. Example: Most (82%) of the isolated bacteria were resistant to ceftriaxone and ciprofloxacin (table-2); 35% were positive for ESBL gene (table-3; fig-2).

Write all means with standard deviation (+SD). Do not begin a sentence with digit, always spell out; and always spell out '1' as 'one". Example: "Seventy five percent of clinically suspected patients with renal cell carcinoma had microscopic hematuria."

All the figures should be numbered consecutively and should have a figure legend. Figure legend is the description of the figure and it should be just below a figure. Table number(s) should be different from figure numbers. If a manuscript has 5 tables and 3 figures, the tables will be numbered as table-1 to table 5. Similarly figure numbers should be figure 1 to figure 3.

Many formats for graphic presentation are acceptable, including graphs, charts, and pictures. Photograph should be clear, free of irrelevant background. Color photographs are preferred but need charges to publish in many journals. Digital figures (Scans or existing files and photographs) must be at least 300dpi.

All the tables and figures should be in separate sheets and photographs should be provided as separate files ('jpeg' or 'tif'). The editorial office decides where the tables and figures should be inserted in the published article. Some new researchers submit the raw figure and photographs without following instructions of the journal and it may be a cause of rejection of the article.

Don't ignore negative results

Negative and inconclusive results along with positive results should be mentioned. Do not suppress results which do not support your hypothesis and objectives. Example: suppose your study objective was "to find out renal complications like acute kidney injury (AKI) and proteinuria among the admitted COVID-19 cases." Many Covid 19 patients having pulmonary involvement and some having cardiac complications were observed. But you did not find any COVID-19 patient having acute kidney injury (AKI) and proteinuria during study period. In this case you may write as "although a good number of COVID-19 patients developed pulmonary and cardiac complications but none developed acute kidney injury (AKI) and proteinuria during study period."

Discussion

This section should cover the research results with interpretations only. Any additional results, not mentioned in the results section should not be discussed here. At first, the results should be presented and then discussed with relevant interpretations. Discussion should not simply be a repeat of the results section. Results can broadly be discussed in two ways: 1) comparison with other published reports on the same topic, where the research information is similar or different; 2) if other reports are different from the data, the reasons of such different results in other studies should be explained. In this connection all the possible hypotheses should be explained without biasness to support and establish the ongoing research hypothesis and objectives.

In discussion section, one of the major problems is making very strong statements or overestimating the significance of findings. The problem can be minimized by using soft words. Example: it is better to say: "It might be due to …" or "Observations of this study speculate …." or "Findings of the current study support…." or "these findings suggest…." rather than, "It is due to……" or "Observations of this study indicate…" or "Finding of the current study prove that…" or "this means that….". All no research findings are beyond the questions and criticisms. Therefore, word selection should be done carefully maintaining a sense of humbleness in writing discussion, like "might be" "suggests" "possibly" or "likely" to express the interpretations of results in a polite manner. These words actually express that some other explanations might also be there

besides what are mentioned here and thereby the criticisms about the research findings may be minimized.

Only discuss the ideas, concepts, or information covered by the research only without discussing any other irrelevant ideas, not covered by this topic. Carefully address all relevant results, not just the statistically significant ones, supporting the hypothesis only. In places where you have to give your opinion you may write "from the observations of the study on hemodialysis patients, the authors therefore speculate that" or "in our opinion, the sudden death of the hemodialysis patients might be due to….".

In any section of the article statement like "no research on this topic has been done in the country before or this is the first scientific paper or report on this topic in the country/world" should be avoided. This may be considered as over interpretation/overstatement.

Conclusion

Conclusion is not just a restatement of the research results, rather this is the final finishing, summary statements that reflect the flow and outcomes of the entire paper with the objectives. It should not contain any reference. Based upon the study findings, a statement about potential changes in clinical practice or future research opportunities can be added here. Conclusion paragraph should not be too long and should be covered in 3-6 sentences.

Acknowledgement

The researcher should acknowledge the supervisor or mentor of the research work, people who contributed in completing research by providing monitory fund by any funding agency, providing technical support, access to instruments and reagents which are not available in the department. The data collectors or nurses who were appointed on payment need not to be acknowledged.

How to cite references:

There are two referencing styles are commonly followed in scientific writing in biomedical research: Vancouver referencing style (1,2,3, etc) and Harvard referencing style (Faisal et al, 2018).

Citation of an article in a journal should be in modified Harvard style. Example: Nomany BMS, Rashid HU, Alam MR. Fasting Ramadan in Chronic Kidney Disease, Kidney Transplant and Dialysis Patients. Bangladesh Renal Journal, July 2023; 5(2):60-64. When citing in the text, introduction, discussion should be: "Muslims who have moderate to severe chronic kidney diseases and take regular medications may harm their health by fasting. (Nomany BMS et al, 2023)."In list of references it will appear as "Nomany BMS, Rashid HU, Alam MR. Fasting Ramadan in Chronic Kidney Disease, Kidney Transplant and Dialysis Patients. Bangladesh Renal Journal, July 2023; 5(2):60-64."

Citing of an Edited Book: Edited books are collections of chapters written by different authors. Their reference format is very similar to the book reference except instead of the author's name, the editor's name is used followed by '(eds.)' to distinguish them as an editor. The basic format is: Editor surname or last name (s), initial name (s). (eds). Title. Edition. Place of publication: publishers, Year Published. Edited Book. Example: Johnson R J, Floege J, Tonelli M. (eds.) Comprehensive Clinical Nephrology. 7th edition. Philadelphia, Pennsylvania: Elsevier, 2023.

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Online Journal Article example: Khan, AKM.' Corona virus in Bangladesh', Virology Journal [online], 2020. Available at: https:// www dmcj. com/reference-management/ reference-manager (Accessed: 15 June, 2020)

Authorship criteria

According to the authorship criteria of the International Committee of Medical Journal Editors (ICMJE), an author has to participate in all of the following three areas: "(1) conception of the reach idea OR data collection OR data analysis and interpretation of the findings, plus (2) drafting the manuscript OR critically reviewing it, plus (3) evaluation of the manuscript." For being author, it is not mandatory to be involved in the very beginning section of the research work, e.g., data collection. A co-author can participate from the data analysis and in the later part of the study. Friends, family members and funding agency cannot be the authors of a study.

Conflict of interest

Conflicts of interest have become a major concern and are getting more and more important for medical journals. Conflicts of interest undermine the credibility of submitted papers, their review process, and even the editorial decisions about acceptance or rejection of scientific articles. Example: If 'ABC' is a peer reviewed journal and someone of the editorial board of this journal becomes the author of a manuscript or any author having close relationship with the editor/reviewer submitted a manuscript for publication. Due to such types of relationship, there may be a chance of biasness for accepting the article for publication irrespective of its contents. This is a conflict of interest where the editor/reviewer plays a dual role.
Another good example of conflict of interest: if 'PQR' is an organization which sanctions funds for research. If any employee from this organization is the researcher and applies for fund or the researcher is close to the employee of the organization, there is a possibly of biased judgment regarding selection of protocol for granting fund. Financial conflict of interest may be associated with an increased chance of positive study outcomes by the authors. Studies sponsored by pharmaceutical

companies are more likely to have favorable outcomes to the sponsor.

Minimization or overcoming the conflict of interest

All types of conflict of interest should be disclosed by the researchers and the authors of a manuscript. For research funding, the researchers must submit financial disclosure forms at the time of proposal submission. Similarly, such declarations are also necessary when a manuscript is submitted for publication. Each financial interest and possible conflict of interest should critically be reviewed by an independent review committee for an unbiased judgment.

Length of the article

A scientific article should be up to 5000 words including end notes and references. The scientific articles should be written in a concise format and word count should usually be around 3000 words, excluding summary and references. Short communication, comments on a published paper should not be more than 2000 words including end notes and references.

Right of the editor:

The editor reserves the right to style and if necessary, shorten the material accepted for publication and to determine the priority and time of publication.

ABBREVIATIONS

Angstrom	A
body surface area	BSA
body weight	body wt.
centimeter	cm
celius	C
complement components	C1, C2, C3
Correclation coefficient	r
creatinine clearance	Ccr.
curie (s)	Ci
Equivalents	Eq
Fahrenheit	F
Glomerular fitration rate	GFR
inch	Inch
International Unit (s)	IU
Intramuscular	im.
intraperioneal	i.p.
intravenous	i.v.
inulin clearance	Cln
Kilogram (s)	kg
iter (s)	L
meter (s) or milli	m
microns (s) or micro	µ
milligram (s) per cent	mg/100ml
minutes (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
probanility	P
second (s)	sec
standard deviatation	SD
standard error	SE
standard error of the mean	SEM
ultraviolet	UV
unit (s)	U
volt	V
gram (s)	g
Grams per cent	g/100mi
half-time	tfl/2
hour (s)	hr


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