MAGNITUDE AND EPIDEMIOLOGY OF CKD IN INDIA

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Abstact : *Chronic kidney disease (CKD) is an important public health problem all over world including India. Prevalence of CKD is revealingly high and is also increasing. Further, even milder degree of CKD is an important cause of increased mortality. Treatment of CKD and its advanced stage, that is end stage renal disease (ESRD) is consuming a huge proportion of health resources in most other countries and in India it is beyond the reach of an average Indian. Thus assessment of magnitude is important for the prevention of CKD. Magnitude of CKD can be judged by the acceptance of patients on renal replacement therapy (RRT), incidence of CKD and/or ESRD or prevalence of CKD / ESRD. Due to various reasons, prevalence of CKD is the most viable way to assess magnitude of problem. Other criteria can only be extrapolated from this data. Further, prevalence of CKD can be hospital based or community based. Due to obvious advantages, community based data is most appropriate though difficult to study. In hospital-based data, there are variable reports about etiology of CKD. But, chronic glomerulonephritis, diabetic nephropathy, tubulointerstitial diseases were the three common causes of CKD. In one center, diabetes as cause of CKD has shown to be increased with time. In two community-based studies, prevalence of CKD was 0.16% and 0.78%, respectively, though the methodology was different in two studies.*

Chronic kidney disease (CKD) is an important public health problem all over world including India [1]. The word chronic renal failure (CRF) is changed to CKD by National Kidney Foundation (NKF), U.S.A as CKD is more acceptable name for understanding by the common man and also because at some stage person may have chronic kidney disease but kidneys are still functioning normally and NOT failed. Thus, now CKD is much more accepted terminology than CRF. NKF, USA has classified CKD into five stages (Table-1) [2].

Table-1 Stages of Chronic Kidney Disease

Stages	Description	GFR (ml/min/1.73m^2
Stage-1	Kidney damage with normal or high GFR	> 90
Stage-2	Mild ↓ GFR	60-89
Stage-3	Moderate ↓ GFR	30-59
Stage-4	Severe ↓ GFR	15-29
Stage-5	Kidney Failure	< 15 or Dialysis

Recently, this staging has been modified by KDIGO (Kidney Disease: Improving Global Outcome) in its meeting held recently [3]. Firstly, the treatment also needs to be included in staging. It means if patient is on dialysis, the word 'D' should be added after the stage. Like if patient with stage 4 is on dialysis, it should be labeled stage 4D. Secondly, all transplant patients have been included as a patient of CKD and word 'T' should be added with stage. Like a renal transplant patient in stage 2 should be labeled stage 2T.

Prevalence of CKD is revealingly high and is also increasing. While the annual population of United States is 1.3%, annual growth of end stage renal disease (ESRD) in same population is approximately 8%. Not only it is common, but it is also utilizing huge cost for its management. In can be estimated from the fact that 8% of US budget is being utilized for only 0.7% of ESRD population. Further, even milder degree of CKD is an important cause for increasing the mortality. Even increase in creatinine from 1 mg% to 1.5 to 2.0 mg% increases all causes mortality from 19% to 37%. Thus it is clear that CKD has become one of the important chronic non-communicable disease epidemics all over the world. It is also clear that treatment of CKD and its advanced stage, that is end stage renal disease (ESRD) is consuming a huge proportion of health resources in most of the country and in India it is beyond the reach of an average Indian. Thus, it is crucial that assessment of magnitude and prevention of CKD should become an important goal of the medical fraternity, government and public at large in any country, including India.

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MAGNITUDE OF CKD

Magnitude of CKD in any population can be judged in following ways

1.Acceptance rate of renal replacement therapy

One of the ways of assessing the magnitude of CKD is acceptance rate of ESRD on renal replacement therapy (RRT); maintenance dialysis and renal transplant. However, this method of assessing CKD may be more applicable in the countries where treatment is government funded. Otherwise, in the country like India, where treatment of CKD is not government funded in most of the cases, assessing the magnitude on the basis of acceptance rate for RRT will be underestimating the magnitude of CKD. This is because more than 80% patients of ESRD practically never get any form of RRT due to various reasons, of which at least one is cost involved in the therapy.

2. Incidence of CKD / ESRD

Second way of assessing magnitude of CKD is by way of assessing incidence of CKD/ESRD in the population. This method of assessing CKD is again possible in smaller countries where all the people's health status is known, not only once but also on a regular basis and data is approachable. In a country like India, where there is no general practitioner (GP) system and every one is free to choose his doctor, this type of information is not possible at present and may be difficult in future also.

3. Prevalence of CKD / ESRD

Another was of knowing the magnitude is by knowing prevalence of CKD/ESRD. This is the only way of knowing the disease magnitude related to CKD in India. Information regarding prevalence can be obtained in three ways; from the *whole community*, from a *sample representing the community* and from the *hospital based data*.

There are some studies from India regarding *hospital-based data* in relation to CKD. From our own hospital, between 87-98, out of 14796 new patients seen in nephrology outpatients, CRF was found in 47.8% cases [4]. Here it is important to note that this was CRF and not CKD. Many of the patients might be having CKD and in term of CKD prevalence, this will be underestimation. Further, from our own hospital, when we tried to compare the data from 87-98 and 98-2004, the prevalence of CRF increased from 47.8% to 58%

(Unpublished data). In another study done by us involving 48 hospitals representing all over India, prevalence of CRF was found to be approximately ~0.8% [5]. In another study from India, MK Mani [6] from Chennai in south India, while initiating a screening program in general and more so for diabetes and hypertension at community level in rural area (total population 25,000), reported a prevalence of chronic renal failure (CRF) of 0.16% and other renal diseases (short of CRF) in 0.7% cases. In this study, a preventive and social health worker (PSHW) travelled from house to house and a brief questionnaire related to renal illness were asked from each member of family. Urine was examined for albumin and reducing substance by using sulphosalicylic acid and benedict solution respectively. However, it is important to note that all subjects were not evaluated with blood tests for urea/creatinine and only those who had some abnormality in urine test/blood pressure and/or positive response to a questionnaire were subjected to blood test for urea/creatinine. Ideally speaking, this will not give true picture of CKD, though it may be practical solution in a community based screening program, where blood sample from every individual may not be a viable option.

The most definitive study so far from India is one done by our group in a *community setting*[7]. Four thousand nine hundred and seventy two (4972) subjects in community in urban area in city of Delhi were screened for urine examination, blood urea and creatinine estimation with a specific aim to find out prevalence of CRF. In addition, other information related to kidney disease, diabetes and hypertension was also collected, though it was not the primary aim of the study. Indian Council of Medical Research, New Delhi, funded this study. A thorough history and a detail physical examination including blood pressure measurement as per our questionnaire were done in each subject of the family of the age of 16 years and above. After this a fresh mid stream urine sample was examined for albumin and sugar using dipstick. Of the 4972 subjects evaluated, prevalence of CRF, defined as serum creatinine more than 1.8 mg% (Upper limit of our laboratory) persistent for more than three months in absence of any reversible factor, was found to be 0.79% or 7852 per million population (pmp). This figure is much higher than the figure in the study of Mani [6] because author had not screened the subject with serum creatinine estimation while we took blood sample in each subject for finding our prevalence of CRF. A 1998 report from the third cycle of the National Health and Nutrition Examination Survey (NHANES III), conducted from 1988 to 1994 in USA estimated that if we take serum creatinine > 1.7 mg% as cutoff for CRF (a value close to 1.8 mg%, what we had taken as cutoff for defining CRF in present study), then during the same period, CRF cases were 12 times more than ESRD cases [2]. Extrapolating this information, if we take ESRD patients to be 10% of CKD patients, from our own study, prevalence of ESRD comes out to be 785/pmp in India. There are many screening program on smaller scale are being conducted by physicians and nephrologist in different parts of India, however, there are no other peer reviewed data on the magnitude of problem of CKD in our country.

ETIOLOGY OF CKD/ESRD

The next issue related to CKD is cause of CKD. Again causes of CKD can be found out either in hospital or in community based studies. As discussed previously, there is only two community-based data on CRF in India. Dr. Mani 's study has not published in detail the etiology of CRF in his 0.16% of CRF patients in the community. Our own study was although not planned to study etiology of CRF, of the 0.79% patients of CRF, 41% were due to diabetes, 22% due to hypertension and 16% due to chronic glomerulonephritis (CGN). Thus, if we combine diabetes and hypertension, they constituted 63% of all cases of CRF in our study [7]. One may argue that etiology of hypertension as cause of CRF is controversial and many of other diseases causing CRF may be attributed to hypertension, as hypertension is a common early manifestation in many other diseases causing CRF. We classified hypertension as cause of CRF only if patient had long history of hypertension with evidence of other target organ damage in absence of other cause of CKD. As compared to community-based studies, if we compare hospital-based studies from India for the etiology of CRF/ESRD [8-10], the data is variable (Fig 1). This figure also compares these studies with the data from USRDS

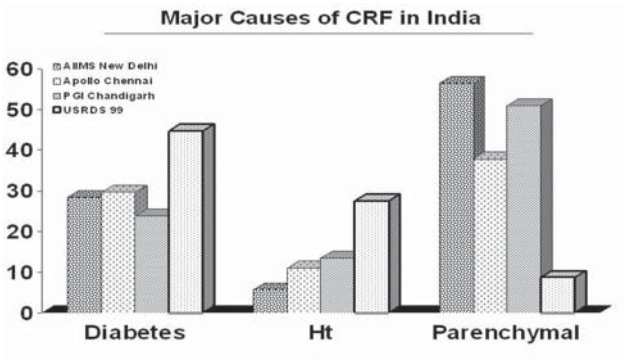

Fig.1 Causes of CRF in India.

(United State Renal data System) of 1999. Nearly 25% of all cases of ESRD in all these studies were due to diabetes and 6-13% were due to hypertension. However, we must realize that these studies are based on the data of tertiary care hospitals and do not represent community. For example in all these studies, mean age of patients was in early forties while in our community based study, mean age of patients of CRF was 59 years. There may be a bias in favour of younger persons attending hospitals. This can cause differences in etiology of patients of CRF attending hospitals as compared to patients in community. Further, if we see the CRF cases due to diabetes and hypertension only in one of these studies [10], the mean age of cases was nearly 50 years. Also, in the same study, in patients over 40 years of age, diabetes and hypertension comprised more than 55% of cases of CRF, the pattern nearly similar to as seen in our community based study. All this suggests that even in India, diabetes and hypertension are responsible for at least nearly 60% of all cases of CRF. With increasing problem of diabetes in India, the absolute number of diabetic CKD/ESRD is likely to be enormous in time to come.

If we compare our own two studies, one hospital based and one community based study (Table-2), there are few striking differences. Mean age of patients of CRF in community is much higher than in

***Table-2* Comparison of two studies of AIIMS**

	Out Patient Study	Community Study	P value
No of Cases of CRF	7165	37	
Mean age (Yrs)	37	59	<0.001
Males %	72%	48.6%	0.001
Diabetes %	28.4%	41%	0.09

hospital-based study and males are more common in hospital-based study. This may be due to bias of younger and male patients seeking/getting treatment in hospital setting. Further, diabetes is much more common as cause of CRF in community based study than hospital based study. In fact, we expect that community based study, though restricted to city of Delhi, is more representative than hospital based

study as bias will be much less in community based study, though in our study, generalization to other community of India may not be possible. This may leads to the presumption that even in India, diabetes is the commonest cause of CRF /CKD as against chronic glomerulonephritis, which was being considered a commonest cause few years back. Even while comparing our own data from outpatients between two time period, (1987-98 and 1999-2004) it was found that there was increase in diabetes as cause of CRF from 28.4% to 33.6% (Unpublished data) Fig.2.

Another source of information about etiology of CKD is the pilot

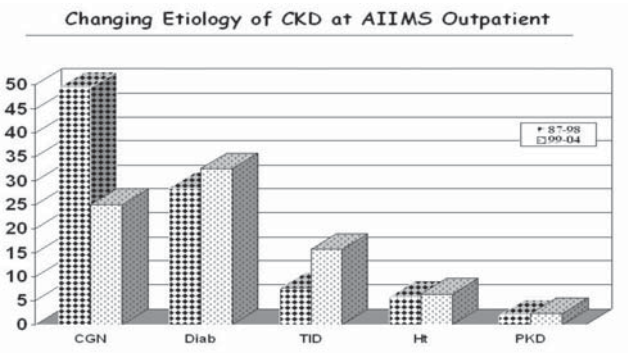

Fig.2 Changing Pattern of Etiology in Outpatient at AIIMS.

project started by Indian Society of Nephrology since June 2005, of which AIIMS was one of the member centers. This project was aimed at finding out many issues related to CKD in India, including spectrum of diseases causing CKD. It is to recall that it is also a hospital based data, though being done all over country at many centers. Till the data of 840 subjects being enrolled in this project from our center, males constituted 71% of these subjects and mean age was 47.3 years. Majority of patients were in stage CKD 3-5 groups. Diabetes mellitus as cause of CKD was seen most commonly in 29.7% patients followed by chronic glomerulonephritis and tubulointerstitial disease in 17.5% and 11.8% respectively. Thus, in this prospective hospital-based data from our center, diabetes was commonest cause of CKD. Similar are the results of pooled data of this registry from all over the centers (Unpublished), though at present it cannot be published.

In addition to these studies, there are many more centers who are doing screening program regarding CKD in India and a multicentric study is also being conducted for CKD in collaboration with Boston medical school on the lines of 'KEEP' but the details of these ongoing studies are not yet known.

To conclude, CKD and its late stage that is end stage renal disease is a major problem for India and with increasing diabetes burden, it is going to increase further. Managing whole population of these patients will be impossible for India, where many other issues demand more priority than CKD. However, the money invested at this time in establishing prevention program for CKD in India is definitely going to give results in years to come and ultimately on long-run will still be cost effective; the saved money can be utilized for other health care programs. But, in my opinion, it is going to be difficult to convey this idea and to impress upon the current policy makers/ political system of the country.

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Drug Profile

DEFLAZACORT

Pharmacodynamic Properties – Deflazacort is short acting oxazoline derivative of prednisolone; the drug offers potent anti-inflammatory & immunosuppressant actions with less side effects like diabetes, osteoporosis & lipid abnormalities.

Pharmacokinetic properties – Orally administered Deflazacort appears to be well absorbed and is immediately converted by plasma esterases to the pharmacologically active metabolite (D 21OH), which achieves peak plasma concentrations in 1.5 to 2 hours. Deflazacort is 40% protein-bound; its elimination plasma half-life is 1.1. to 1.9 hours. Elimination takes place primarily through the kidneys; 70% of the administered dose is excreted in the urine; remaining 30% is eliminated in the faeces.

Therapeutic indications - Deflazacort is indicated in wide range of indications, similar to corteosterioids such as, asthma & allergic disorders, rheumatoid arthritis, juvenile chronic arthritis, polymyalgia rheumatica, nephriotic syndrome, renal transplantation, neurological disorders.

Dosage & Administration: Deflazacort is a glucocorticoid derived from prednisolone, 6 mg of Deflazacort has approximately the same anti-inflammatory potency as 5 mg prednisolone or prednisone. For acute disorders, up to 120 mg/day Deflazacort may be needed; maintenance dose is - 3-18 mg/day.

In hepatic impairment, the dose should be adjusted to the minimum effective dose. *Renally impaired patients*, no special precautions are necessary. In *children*, the indications are the same as for adults; alternate day administration may be appropriate; dose of Deflazacort usually lies in the range 0.25-1.5 mg/kg/day. **Deflazacort withdrawal:** Deflazacort shows less HPA axis suppression; hence the only can be easily withdrawn with less risk of withdrawal symptoms. Once, a daily dose equivalent to 9 mg Deflazacort is reached, dose reduction should be slower to allow the HPA-axis to recover.particularly if more than 73 week therapy is given.

Contraindications : *Systemic infection* unless specific anti-infective therapy his employed; *hypersensitivity* to deflazacort or any of the ingredients; patients receiving *live virus immunization.*

Special warnings : (a) **Adrenal suppression** : Withdrawal must always be gradual to avoid acute adrenal insufficiency, being tapered off over weeks or months.

b) **Anti-inflammatory/immunosuppressive effects and infection** : Suppression of the inflammatory response and immune function increases the susceptibility to infections and their severity. The clinical presentation may often be atypical and serious infections such as septicaemia and tuberculosis may be masked and may reach advanced stage before being recognized.

Special precautions : The following clinical conditions require special caution and frequent patient monitoring is necessary: (a) *Cardiac disease* or congestive heart failure (except in the presence of active rheumatic carditis), hypertension, thromboembolic disorders. Glucocorticoids can cause salt, water retention and increased excretion of potassium; dietary salt restriction and potassium supplementation may be necessary; (b) *Gastritis or oesophagitis, diverticulitis, ulcerative colitis* if there is probability of impending perforation, abscess or pyogenic infections, fresh intestinal anastomosis, active or latent peptic ulcer; (c) *Emotional instatbiliy* or psychotic tendency and epilespsy; (d) Previous *corticosteroid-induced* myopathy; (e) *Liver failure;* (f) *Hypothyroidism and cirrhosis*, which may increase glucocorticoid effect; (g) *Ocular herpes simplex* because of possible corneal perforation;

Pregnancy : Deflazacort does cross the placenta; caution should be exercerised

Lactation: Corticosteroids are excreted in breast milk, no data are available for Deflazacort.

Fluid and electrolyte disturbance: Sodium and water retention with hypertension, oedema and heart failure, potassium loss, hypokalaemic alkalosis, are less with the drug.

Drug interactions: The same precautions should be exercised as for other glucocorticoids; it is recommended to increase the maintenance dose of Deflazacort when liver enzyme inducers, are co-administered, e.g. rifampicin, rifabutin, carbamazepine, phenobarbitone, phentoin, primidone and aminoglutethimide. For ketoconazole which inhibit liver enzymes, reduction in dose is required; in patients taking estrogens, corticosteroid requirements may be reduced. The efficacy of coumarin anticoagulants may be enhanced by concurrent corticosteroid therapy. The renal clearnance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication. Antacids may reduce bioavailability; leave at least 2 hrs between administration of deflazacort and antacids.