Introduction

Chronic Kidney Disease (CKD) is now recognized as a growing worldwide health epidemic that brings with it considerable morbidity even before the patient reaches end stage renal failure (ESRF). The United Kingdom (UK) incidence of new patients requiring renal replacement therapy has doubled over the past decade, to 101/million/year, and is projected to rise by 5–8% annually.Stage 3 CKD was defined as an eGFR of 30.0- 59.9 ml/min/1.73m^2, Stage 4 CKD as an eGFR of 15.0-29.9 ml/min/1.73 m^2 and Stage 5 CKD as< 15.0 ml/min/1.73m$^{2.}$ Early diagnosis in CKD presents an opportunity to delay, if not prevent, progression to ESRF. The evidence that early intervention can both delay progression and improve morbidity and mortality in the asymptomatic majority makes CKD an attractive proposition for screening. Moreover, the screening tools (eGFR calculation and urine analysis) are cheap and readily available ***(Annear et al., 2008).***

The benefits of screening at-risk populations, such as diabetics, hypertensives and patients with a family history of renal disease, are well established. By contrast, the feasibility and cost effectiveness of whole population screening remain unclear. Studies have shown that screening people with hypertension, diabetes mellitus, and the over 55 is an effective strategy in detecting patients with CKD, identifying 93.2% of all cases of CKD; on average 8.7 patients needed to be screened to identify one patient with CKD. The risk of progression to

ESRF among those detected was low, at 1–2% for CKD Stage 3, and 20% for CKD Stage 4. The higher prevalence of CKD among acute medical admissions compared with the general population makes the former group suitable for a systematic screening programme. Protocols could be established for initiating therapeutic interventions, including treatment of renal anaemia, avoidance of nephrotoxic drugs, optimizing control of blood pressure and blood glucose in diabetics, reduction of proteinuria using Angiotensin converting enzyme(ACE) inhibitors or angiotensin receptor blocking drugs, managing cardiovascular risk and arranging referral to nephrologists ***(Li et al., 2005; Hallan et al., 2006).***

Aim of the Study

The aim of this study is to investigate the incidence of chronic kidney disease stages 3-5 among medical admissions in Ain Shams University Hospital during 6 months follow up, taking in consideration the incidence of different causes of CKD among the patients.

1-Chronic Kidney Disease: 1a. Definition, 1b. Stages, Classification and 1c. Estimation of Glomerular Filtration Rate

Chronic kidney disease (CKD) has been recognized as a public health priority since the late 1980s. A dedicated, comprehensive, and systematic surveillance program that captures and tracks all aspects of CKD in those not yet receiving renal replacement therapy is fundamentally important for the ongoing assessment of the national CKD burden. ***(Hostetter and Lising,2003).***

Kidney disease is listed as the ninth most common cause of death by the National Center for Health Statistics. However, most patients are unaware of their declining kidney function until it is in its late stages. Progression of CKD, and its attendant comorbidity, can be slowed or potentially even halted with optimal medical care, with implications for increased lifespan, quality of life, and lower societal cost ***(Locatelli et al., 2008).***

1a. Definition of Chronic Kidney Disease:

Chronic kidney disease is defined primarily as an abnormality of kidney function or structure, as determined by laboratory tests, urinalysis or imaging tests which has been present for 3 or more months ***(Freedman and DuBose, 2007).***

Deaths of participants and losses to follow-up pose challenges for defining outcomes in epidemiologic studies. Several definitions of incident chronic kidney disease (CKD) were compared in terms of incidence, agreement, and risk factor associations. They used data from 14,873 participants in the community-based, multicenter, biracial Atherosclerosis Risk in Communities Study (1987–1999). The estimated glomerular filtration rate (eGFR) was based on serum creatinine at baseline and the 3 and 9 year follow-up visits. Hospitalizations were ascertained continuously. 4 definitions of incident CKD were compared:

1) Low eGFR (<60 mL/minute/1.73 m^2);

2) Low and declining (25%) eGFR;

3) An increase in serum creatinine (0.4 mg/dL) at 3 or 9 years follow-ups; and

4) CKD-related hospitalization or death.

From these definitions, they identified 1,086, 677, 457, and 163 cases, respectively. There was relatively good agreement among definitions 1–3, but definition 4 identified mostly different cases. Risk factor associations were consistent across definitions for hypertension and lipids. Diabetes showed weaker associations with definition 1 than with definition 4. Associations with gender differed in direction and magnitude

across definitions. Case definition can impact relative risk estimates for CKD risk factors ***(Bash et al., 2009).***

Kidney disease is characteristically asymptomatic, and is often not diagnosed until relatively advanced. Evidence is accumulating that CKD at any level is associated with poor outcomes. Long-term outcomes are impacted by conditions and risk factors that are present long before the initiation of dialysis. Given the modifiable risk factors identified in patients with CKD (anemia, hypertension, dyslipidaemia, abnormalities of calcium and phosphate, and nutritional deficiencies) it would seem that accurate identification of CKD in the populations would be important. The treatment of modifiable risk factors depends on accurate screening of high risk populations: thus, the need to identify those high risk populations at the appropriate time ***(Al-Ahmad et al., 2001)***.

There is an increasing awareness of the immense size of the patient group with kidney disease who do not require dialysis . The National Kidney Foundation sponsored Kidney Disease Outcomes Quality Initiative (KDOQI) working group proposed a set of guidelines regarding the definition, classification and evaluation of chronic kidney disease . Using large representative databases of both referred and non-referred patients, five stages of kidney disease have been defined. These stages correspond to the severity of kidney function loss and the prevalence of co-morbidities associated with kidney disease.

Importantly, the classification system describes the stages according to level of estimated glomerular filtration rate (GFR), not serum creatinine levels, and advocates for the use of estimated GFR values to be used in evaluation of all patients ***(Jones et al.,1998).***

The stages of CKD are defined by using ranges of estimated GFR, based on analysis of National Health and Nutrition Examination Surveys (NHANES) III data which examined the prevalence of abnormalities associated with kidney disease . The stages are defined currently using the best data available from these large population-based cohorts of patients.

Ib. Classification of Chronic Kidney Disease

Stage	Description	GFR ($mL/min/1.73m^2$)	Action*
	At increased risk	≥90 (with CKD risk factors)	Screening CKD risk reduction
1.	Kidney damage with normal or ↑ GFR	≥90	Diagnosis and treatment Treatment of comorbid conditions, slowing progression, CVD risk reduction
2.	Kidney damage with mild ↓ GFR	60-89	Estimating progression
3.	Moderate ↓ GFR	30-59	Evaluating and treating complications
4.	Severe ↓ GFR	15-29	Preparation for kidney replacement therapy
5.	Kidney Failure	<15 (or dialysis)	Replacement (if uremia present)

Shaded area identifies patients who have chronic kidney disease; unshaded area designates individuals who are at increased risk for developing chronic kidney disease. Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m^2 for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.* Includes actions from preceding stages. *Abbreviations: GFR, glomerular filtration rate; CKD, chronic kidney disease; CVD, cardiovascular disease*.

(National Kidney Foundation, 2002)

However, it is not worthy that three of the five stages of CKD (stages 3, 4 and 5) were defined and based on the absolute

threshold of eGFR(standardized to 1.73 m2 body surface area) without any requirement for concomitant evidence of 'kidney damage', such as proteinuria or adjustment for age and gender. These levels of eGFR, combined with the similarly selection of a time dimension (≥3 months) for their persistence to establish 'chronicity', became the 'gold-standard' for definition of a 'disease'. The abbreviated modification of diet in renal disease (MDRD) equation for deriving an estimate of true glomerular filtration rate (GFR) from values of serum creatinine quickly became the most widely used method for determination of eGFR, despite its lack of validation in subjects without CKD or across a wide spectrum of ages, body built, diet, ethnicity and geographic location ***(Coresh et al.,2005)***.

Because of inaccuracies, relative to true GFR, when eGFR is >60 ml/min/1.73 m^2 reporting of specific values of eGFR was recommended only when calculated values of <60 ml/min/1.73 m^2 were obtained, because of these limitations epidemiologists have used eGFR to estimate the overall prevalence rates of CKD, in its various stages, in representative samples of the general population ***(Levey et al., 2006)***.

According to the Disease Outcomes Quality Initiative DOQI estimate of (CKD) populations in the US, CKD stage 3 patients outnumbered those in the following stage (stage 4) almost 20-fold. The reported absolute numbers were 7.6 and 0.4 million for patients in stages 3 and 4, respectively. Such a huge

difference can either be due to a high mortality rate during the late periods of stage 3, so that only a minority of patients reach stage 4, or it is due to a very high mortality rate during stage 4. It should be indicated that stage 3 extends over a glomerular filtration rate (GFR) range (30–59) that is twice the GFR range of stage 4 (15–29).It could be indicated here that the CKD stage 5 patient count would also have been negligible compared to that of stage 4, as it is the case in fact in many developing countries, except for the availability of the renal replacement therapy (RRT). Such therapy has allowed for longer residence time within (dialysis) or after (transplantation) in this stage ***(Foley et al.,2005)***.

Specifically, KDOQI recommends evaluation of a patient for kidney disease only when GFR is 60 ml/min/1.73 m^2 in the presence of a risk factor. This somewhat recommendation leads to excessive use of health care resources, such as unnecessary close monitoring of substantial numbers of individuals. Their data indicate for most, if not all, screening populations evaluated that combining the albumin-to-creatinine ratio and eGFR substantially improves discrimination. Finally, the predictive importance of albuminuria in general is once again emphasized, but addition of albuminuria testing is not necessarily the only recommended modification of KDOQI guidelines.The study by Hallan et al. provides us much optimism that important modifications to the original KDOQI guidelines for staging of CKD could offer significant

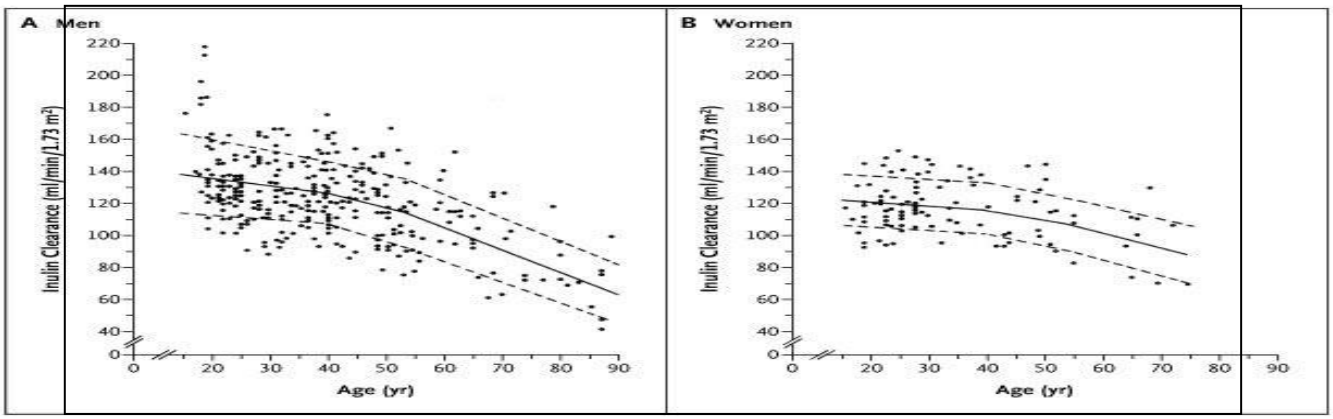
improvements in predicting progression to ESRD. The time has come to apply these modifications to the current guidelines ***(Hallan et al., 2009)***.

Ic.Estimation of glomerular filtration rate:

- *Measurement of GFR with Exogenous Filtration Markers**:***

In 1951, GFR was accepted as the best overall measure of kidney function. Normal values, which are related to age, sex, and body size, are approximately 130 mL per minute per

Normal Values for GFR in Men and Women



Stevens L et al. N Engl J Med 2006;354:2473-2483

and dashed lines represent the value 1 SD from the mean value of GFR per decade of age ***(Wesson,1969)***.

Furthermore, research studies have reported a measurement error of 5 to 20 percent (variation within a single clearance

procedure or between clearance procedures on different days). The variation is greater in the higher ranges of GFR on the absolute scale ***(Levey et al., 1993; Coresh et al., 1998)***

- *Estimation of GFR with Endogenous Filtration Markers:*

Urinary clearance of an endogenous filtration marker such as creatinine can be computed from a timed urine collection and blood sampling without the need for the administration of an exogenous marker. Nonetheless, timed urinary collections are susceptible to error, and 24-hour urine collections for the measurement of creatinine clearance are no longer recommended routinely to estimate the level of kidney function. The serum level of endogenous filtration markers can also be affected by factors other than the GFR, including tubular secretion or reabsorption, generation, and extrarenal elimination of the endogenous filtration marker ***(Stevens et al., 2005).***

- *Creatinine:*

Many studies support the similarity of creatinine clearance to GFR and its reciprocal relationship with the serum creatinine level. Creatinine is secreted by proximal tubular cells as well as filtered by the glomerulus; thus, the creatinine clearance exceeds the GFR. Tubular secretion of creatinine varies among and within individual persons, especially in those with a mild-to-moderate reduction in the GFR . The generation

of creatinine is determined primarily by muscle mass and dietary intake ***(Shemesh et al., 1985).***

Factors affecting Creatinine generation are: aging, female sex, race as it increase with Black and decrease with Asian and Hispanic, body built as it increase with musculin persons and decrease with amputated ones, with obesity there is no change, with chronic illness, malnutrition, inflammatory conditions(eg. Cancer, severe CVD disease, hospitalized patients) and neuromuscular disease decrease it also it is increased with ingestion of cooked meat and decreases with vegetarian diet which probably accounts for the variations in the level of serum creatinine observed among different age, geographic, ethnic, and racial groups. Extrarenal elimination of creatinine may be increased at low levels of GFR; this increase is mainly related to the degradation of creatinine by intestinal bacteria and can be affected by the use of antibiotics. The use of a single reference range for serum creatinine to distinguish between a normal GFR and an abnormal one can be misleading ***(Myers et al.,2006).***

- *Relationship of Serum Creatinine Level to Measured GFR in the Modification of Diet in Renal Disease Study:*

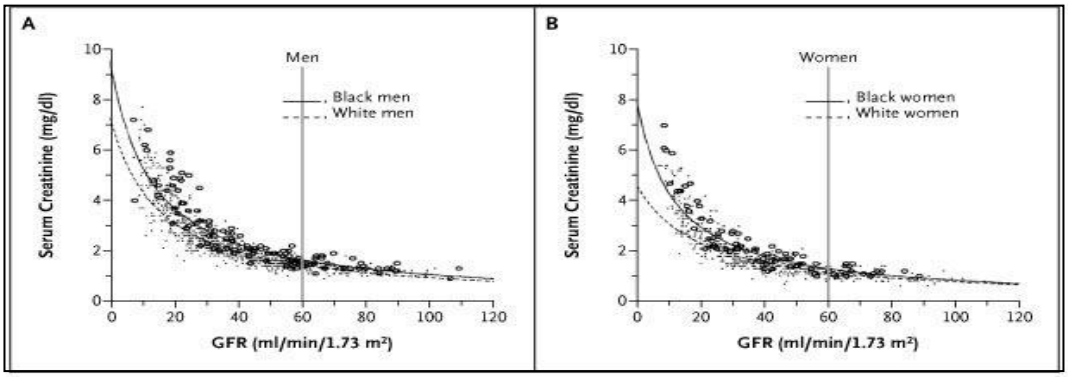


Figure 2: Shows the Relationship of Serum Creatinine Level to Measured GFR in the Modification of Diet in Renal Disease Study.

GFR was measured as the urinary clearance of [^{125}I]iothalamate Regression lines were computed from the relationship of the reciprocal of serum creatinine with GFR. When the GFR was 60 ml per minute per 1.73 m^2, the 95 percent confidence interval for the serum creatinine level was 1.3 to 1.5 mg per deciliter in white men (measured in 802) and in 1.4 to 1.8 in black men (measured in 113) and 1.0 to 1.2 mg per deciliter in white women (measured in 502) and 1.1 to 1.4 mg per deciliter in black women (measured in 84) . These levels are close to the upper limit of the reference range. Confidence intervals for serum creatinine levels were wider at lower levels of GFR. To convert the values for serum creatinine to

micromoles per liter, multiply by 88.4 ***(Levey et al.,2000)***. The sensitivity of serum creatinine (sCr) to identify CKD is low. As a result, many healthcare centers report estimated GFR (eGFR) with routine blood work. It aimed to determine the cost-effectiveness of automatic eGFR reporting compared with reporting sCr alone.eGFR reporting was dominant with a cost/effectiveness ratio of $16,751/quality-adjusted life year (QALY) *versus* $16,779/QALY for sCr reporting. Monte Carlo microsimulations in a hypothetical cohort of 10,000 patients demonstrated that: over 18 yr, an average of 13 fewer deaths, 29 fewer ESRD events, and 11,348 more false positive CKD (FP-CKD) cases occurred with eGFR reporting. A sensitivity analysis revealed that decreasing the FP-CKD quality of life by > 2% rendered sCr reporting more cost-effective than eGFR reporting. If FP-CKD reduced quality of life by 5%, the cost-effectiveness ratio for sCr reporting *versus* eGFR reporting would be $4367/QALY. A decision analysis suggests that reporting eGFR may be beneficial, but this limited benefit was reversed with virtually any reduction in quality of life caused by incorrect diagnosis of CKD ***(Den Hartog et al., 2009).***

- *Cystatin C*:

A nonglycosylated basic protein that is freely filtered by the glomerulus, is currently under investigation as a replacement for serum creatinine in estimating the GFR. After