CHAPTER- II

REVIEW OF LITERATURE

2.1 HISTORY OF KIDNEY DISEASE
The significance of renal disease was recognized since Hippocrates made the association between bubbles in urine and kidney disease in 400 BC (Chadwick and Mann, 1950). Boerhaave and Cavelier (1733) and Rouelle (1773) reported that there is presence of more quantities of unknown soapy substance in urine. Fourcroy and Vauquelin (1797) isolated and crystallized the urea. They also demonstrated that the principle function of kidney is to “denitrogenize” the body by excreting urea in urine. Prevost and Dumas (1821) reported that in different animal species after bilateral nephrectomy there is significant rise of blood urea concentration. Wohler (1827) has synthesized urea, which is the first organic substance that belongs to animal kingdom was synthesized in laboratory. Christison (1839) described the modern perception of the uremic syndrome and Piirry (1847) coined the word uremia. Later Frerich’s (1851) described the clinical uremic syndrome. Picard (1856) developed a reproducible and sensitive method for measuring blood urea. Later Recklinghausen (1858) proved that the renal failure is a situation escorted by rise in blood urea concentration (Richet, 1988).

Bernard (1859) reported that uremic toxicity due to absorption of ammonium carbonate from gut. Bostock, Barlow and Rees (1833) proposed urea may be a retained product in kidney disease.

2.2 REVIEW OF GLOMERULAR FILTRATION RATE (GFR)
Glomerular filtration rate (GFR) assess kidney function. GFR decrease typically starts from the 40 years onward, around 1 ml/min per year (Rowe et. al., 1976). Some of the GFR estimation is normalized to body surface area (BSA) by using Dubois and Dubois formula (Dubois and Dubois, 1916).
GFR can be measured indirectly utilizing exogenous marker substances but these are inconvenient and costly. Serum creatinine is widely accepted endogenous marker for estimation of GFR which produces at a constant rate in every individual by non-enzymatic degradation of creatine in muscle (Levey et al., 1988). Creatinine synthesis varies based on their muscle mass (Forbes et al., 1976). Muscle mass depends on weight and gender (Cockcroft et al., 1976) and muscle mass decrease as age advances (Gallagher et al., 1997). In patients with cachexia also have very low creatinine excretion rate (Cocchetto et al., 1983).

Creatinine is filtered by the glomerulus and also secreted by tubular cells so that total creatinine clearance is equal to sum of GFR and tubular secretion when GFR is low. (Bauer et al., 1982). Ixkes et al., (1997) studies show that using drugs like trimethoprim and cimetidine will inhibit tubular secretion of creatinine and helpful in estimation of accurate GFR. When there is normal kidney function removal of creatinine by extra renal elimination is negligible, but due to lowering of GFR is reduced, the creatinine removal is by other ways such as degradation by intestinal flora (Hankins et al., 1981).

Various equations were developed during past few years as mentioned below
4. MDRD formula (1999) (Levey et al., 1999)
6. CKD-EPI formula(2009) (Levey et al., 2009)
7. Ix (equation D) (2011) (Ix et al., 2011)

Cockcroft and Gault, 1976 described the Cockcroft and Gault formula to estimate GFR and it overestimates the GFR because of tubular secretion to remove the contribution of tubular secretion the GFR is multiplied by 0.84 to obtain accurate GFR. This formula required body weight and it is not normalized to BSA.
Modification of Diet in Renal Disease (MDRD) formula was described by Levey et al., (1999) and it was derived from the clinical study of kidney disease patients and the GFR is less than 60 mL/min/1.73m² and it was derived using isotopically tagged iothalamate. In this study, some of the subjects have GFR value more than 60mL/min/1.73m² and MDRD equation underestimated the eGFR in this group and decreased precision which shows MDRD equation is not acceptable if GFR is more than 60mL/min/1.73m². In the year 2004 Mayo Clinic Quadratic equation (MCQE) derived based on ¹²⁵I-iothalamate clearance. In this study, the subject includes both healthy individuals and CKD patients it will give intermediate performance and MCQE never underestimate the normal GFR value (Rule et al., 2004). Levey et al., 2009 described the recent equation for estimation of GFR and it was developed by the CKD-Epidemiology Group (CKD-EPI). This study included most of the patients with GFR >60mL/min/1.73m². The CKD-EPI formula contains 8 equations for estimation of eGFR the each equation depends upon the patients is whether African American or Caucasian, male or female, and the Serum Creatinine is higher or lower value. CKD-EPI and MDRD gives similar results when eGFR is less than 50mL/min/1.73m². But in this method serum creatinine was measured by isotope dilution mass spectroscopy (IDMS) calibrated using serum creatinine.

The other alternative endogenous marker for estimation of GFR is Cystatin C. It is produced by nucleated cells with molecular weight of 13 KD. Cystatin C is freely filtered by glomerulus and not secreted, but reabsorbed within the tubules and metabolized completely (Randers et al., 1999). It does not depend on age, gender or muscle mass, and act as best marker of GFR in selected groups (Filler et. al., 2005).

The south India population study by Rajeshwari et al., (2011) estimated the renal function using CG and MDRD equations and noticed eGFR is lower in south Indian population compared to western and these equations required validation before using for kidney disease staging. The performance of CG, CKD-EPI and MDRD in relation to body size, GFR and age was reported by Wieneke et al., (2010) and they noticed that all three formulas are influenced by age and MDRD and CKD-EPI are influenced by GFR whereas CG is influenced by BMI and body weight and concluded that CKD-EPI gives best performance for GFR and its precision is near to MDRD.
The CG gives less GFR than MDRD and CKD-EPI in patients older than 69 years and three formula do not show any significant difference in staging of CKD patients with 59 to 69 years (Dharmarajan et al., 2012). These results also suggested the use of single formula consistently in a given patients to assess renal function over time. Huda et al., (2012) studied prevalence of CKD that is associated with risk factors in disadvantageous population and there study showed that no significant changes was observed in proportion of CKD whether CG and MDRD are used.

The study done by Teruel et al., (2007) reported that patients with advanced chronic kidney disease the classic CG equation is more accurate than the MDRD equation and classic CG equation have also shown similarity with arithmetic mean of the urea and creatinine clearances (CURCr). The other study reported the Mayo clinic quadratic equation (MCQE) is better formula to estimate GFR than the CG equation, MDRD equation is also accurate but it poorly predicted GFR because it overestimates low and underestimate high GFR so MCQE is a better predictor for GFR changes (Beauvieux et al., 2007). Whereas Fontsere et al., (2008) study reported MCQE proved inaccurate results in type 2 diabetic patients with normal renal function or hyperfiltration and there is no superiority of MCQE over the CG and MDRD.

The CG and MDRD formula when compared with inulin clearance in renal disease, it was observed that MDRD and CG formula have shown restrictions for proper GFR estimation (Botev et al., 2009). Poggio et al., (2005) demonstrated that GFR estimation calibrated serum creatinine is also a determining factor and they also concluded that MDRD is better formula for who have CKD. In healthy individuals, CG and MDRD formula shows association between measured GFR and measured serum creatinine.

The MDRD equation is more accurate in predicating the GFR in ESRD patients when compared to CG (Kuan et al., 2005). The CG and MDRD formula provided quite different eGFR in older people for estimating the renal function (Pedone et al., 2006). The GFR estimation by 24 hours creatinine clearance, MDRD and MCQE in older than 85 years was reported by both MDRD and MCQE equation provide different results compared with 24 hours creatinine clearance and shown that MCQE provides
suspiciously high GFR values (Vincenzo et al., 2010). Whereas the performance of CG and MDRD formula when compared with $^{51}$Cr-EDTA it was observed that both the formula has not shown accuracy but MDRD equation provided reliable GFR than CG formula for assessing kidney function (Froissart et al., 2005). The study done by Rigalleau et al., (2007) showed that Mayo clinic quadratic equation (MCQE) shown similar performance compared with MDRD in diabetic subjects but MCQE important advantage is it does not underestimate normal GFR.

Though numerous studies have been devoted to make use of predictive equations of eGFR. In our study we included three formula CG, MDRD and MCQE in two groups that are normal healthy individual and CKD patients and we also compared these three formula based on age wise.

2.3 REVIEW OF LIPID PROFILE AND LIPID PEROXIDATION IN CKD

Several studies have been conducted in CKD patients to know the alterations and potential consequences of CKD induced dyslipidemia. Many studies have also investigated markers of oxidative stress such as MDA and SOD and their role in atherosclerosis.

The earlier study by Bagdade et al., (1976) reported the result of renal transplantation, chronic uremia and hemodialysis on plasma lipids and lipoproteins. The study has shown there is an increase in Triglyceride (TG) level and cholesterol in both nondialysis and hemodialysis group. In kidney transplantation patients a significant rise of TG and cholesterol was noticed and finally concluded that alteration of lipoprotein metabolism in kidney disease patients is not affected by chronic dialysis and continued after transplantation. The peritoneal dialysis patients had risk for hyperlipidemia when compared with hemodialysis patients. Triglyceride turnover studies highlighted that the cause of lipidemia is due to impaired triglyceride removal rather than type of dialysis or lipid levels. This defect is corrected by increasing the efficiency of dialysis (Cattran et al., 1976). Rapoport et al., (1978) observed that HDL cholesterol was significantly decreased in hemodialysis patients and it was also observed that protein content of HDL reduced in parallel with cholesterol content.
The study done by Nobeck and Carlson (1981) observed that there was lipioprotein abnormalities found in uremia and it is present already in early stages of disease. It was also noticed that there was increased LDL cholesterol in males and finally concluded that degree of renal function and etiology will not influence the above factors. The hemodialysis process induces carnitine depletion, this depletion may have relationship to hyperlipidemia in uremic patients especially in long term hemodialysis patients and supplementation of aminoacids and carnitine stops depletion of carnitine and correct the hyperlipidemia in hemodialysis (Maebashi et al., 1983). Another study on Cholesteryl ester transfer protein (CETP) found to be low in hemodialysis patients when compared with control due to the presence of CETP inhibitors (Mendez et al., 1988). The CKD patients under hemodialysis showed increased triglycerides and Lp(a) level when compared to control whereas in continuous ambulatory peritoneal dialysis (CAPD) there was rise in cholesterol and triglycerides but their Lp(a) level were similar to control (Kandoussi et al., 1992). The ESRD patients both normotriglyceridemic and hypertriglyceridemic subjects showed abnormalities in size and composition of both LDL and HDL and these alterations were still high in hypertriglyceridemic patients (Joven et al., 1993). The abnormal lipoprotein in starting stages of CKD shows similar features of advanced stages in CKD with accumulation of apo-B lipoprotein (Samuelsson et al., 1994).

The total antioxidant capacity is increased in dialysis patients due to serum urate, but there was markedly reduced after hemodialysis and dialysis patients showed increased concentration of malondialdehyde and retinol and reduced concentration of ascorbic acid as compare to control (Jackson et al., 1995). Rousselot et al., (1997) studied antioxidant status of elderly people chronic kidney disease patients treated under continuous ambulatory peritoneal dialysis (CAPD) and found that there is a significant decreased plasma selenium and glutathione peroxidase activity whereas plasma thiobarbituric acid reactive substances (TBARS) in CAPD were not higher when compared with age match control non-CKD subjects. The study of relationship between oxidative stress and endothelial dependant vasodilation in CKD patients shown that there is increased oxidative stress markers and decreased antioxidants impairs the endothelial vasodilation function. They also notice that higher levels of deine conjugates, lipid hydroperoxide and oxidized glutathione (GS-SH) levels
(Annuk et al., 2001). The study done by Erdogan et al., (2002) estimated the carbonyl and malondialdehyde (MDA) levels in both peritoneal and hemodialysis patients. The values has not showed any significant difference when compared with control subjects. In both the peritoneal and hemodialysis group it was observed that there was twofold increment in serum total antioxidant activity and uric acid values. They suggested that raised endogenous and exogenous antioxidant levels in serum may prevent the free radical induced damage in CKD.

The LDL cholesterol apo-B and total cholesterol, are associated with drastic decline in renal function wherein TG, HDL cholesterol and apolipoprotein A (apo-A) were not shown. The association between dyslipidemia and rate of progression of kidney disease was even more pronounced in chronic glomerulonephritis (Samuelsson et al., 1997). The other study done by Hirano et al., (1999) demonstrated correlation between serum lipid level and renal function. They observed that serum lipid levels have correlation with creatinine clearance, proteinuria and age. Significant correlations were observed between the levels of TC, TG, phospholipids, LDL-C, apo C-II, apo B, and apo C-III with creatinine clearance, proteinuria and age. Significant correlation is also observed between levels of MDA, apo E/apo C-III apo B/apo A-I, with creatinine clearance, and age as well as between apo E levels with proteinuria and age.

The study done by Dumm et al., (2001) reported that there was an increased TG level in the plasma and erythrocyte membrane of hemodialysis patients and it was also observed there is an increase of plasma monounsaturated fatty acids and there is relative decrease of poly unsaturated fatty acids (PUFA). Baliga et al., (2002) studied lipid profile in transplant patients. Wherein, there was increase of LDL-C and TC levels but HDL-cholesterol level has not shown any significant change. Significant inverse correlation was observed between TG and TC levels and transplant duration. Nicotinic acid derivative Niceritrol has shown significant improvement of hyperlipidemia in CKD patients (Owada et al., 2003). The lovastatin was also corrected the increased TG, LDL-C, MDA and improved the total antioxidant and HDL-C levels this was observed after 3 months of lovastatin therapy (Argani et al., 2004).
Selvaraj et al., (2005) reported in CKD patients HbA1C percentage and plasma MDA were increased and found that MDA was significant determinant of HbA1C in CKD patients. They also observed that in vitro incubation of RBC with glucose and MDA will augment the pathway of glycation of hemoglobin. In other report Diepeveen et al., (2005) showed the effect of the initiation of hemodialysis and peritoneal dialysis therapy on lipoproteins and LDL oxidation. They noticed that in hemodialysis group after six months there is increased TC and TG whereas in peritoneal dialysis patients there is no significant change in lipoprotein profile. In both the group of dialysis in vitro copper induced oxidation of LDL is not seen after six months of treatment.

The effect of supplementation of Vitamin C, Vitamin E and reduced glutathione on copper ion induced lipoprotein oxidation in kidney disease patients was studied by Parameshwari et al., (2006). They found that the apo B level was drastically raised in transplanted patients in comparison to healthy individuals and CKD patients. In both the CKD and transplanted patients the values of TBARS formed oxidized LDL+VLDL lipoprotein fraction is higher. They concluded that oxidation of lipoprotein fraction can be prevented by supplementation with vitamin E and glutathione in CKD. Altaf et al., (2007) found that hemodilaysis patients have significant declined body mass index (BMI) and there was decrease in TC, LDL-C and HDL-C which explains malnutrition leads to inflammation and accelerates the atherosclerosis process and cardiovascular complications. Prakash et al., (2008) studied serum paraoxinase and protein thiols in CKD with oxidative status and lipid profile in CKD patients on conservative management and hemodialysis. They observed that there was increase of TC, TG, LDL-C, Lipid hydroperoxides and creatinine levels whereas HDL-C, protein thiols, albumin levels and paraoxanase activity were decreased when compared with control. The decreased paraoxanase activity is more in patients under chronic maintenance hemodialysis.

2.4 REVIEW OF ANEMIA PROFILE IN CKD

Jackson et al., (1995) studied hematological changes in hemodialysis patients and found that there was low grade hemolytic anemia which was due to nonbiocompatibility of dialysis membrane that leads to radical production. They also noticed that after hemodialysis there was increase in membrane lipid peroxidation,
increase in osmotic fragility and reduced membrane fluidity which were contributed to low grade hemolytic anemia. They suggested that supplementation of vitamin E will prevent these changes and it can acts as antioxidant. Vickers et al., (1998) studied the RBC count before and after dialysis at various time intervals i.e., at 2, 15, 30 and 180 min and had not found any changes in the number of circulating red blood cells (RBC) when compared to before dialysis samples. Małyszko et al., (1999) studied the before and after dialysis changes of Hb and RBCs count in ESRD patients under hemodialysis. They found that both these parameters did not differ significantly before and after dialysis. Butt et al., (1999) studied before and after dialysis changes of the reticulocytes count, RBCs count, Hb and Hct levels in ESRD patients under hemodialysis. They reported that the mean of Hb, Hct levels and RBCs count were slightly increased, while they found no changes in mean reticulocytes count after hemodialysis.

Han and kishimoto (1997) compared the RBCs count, haemoglobin (Hb) concentration, hematocrit (Hct) and RBCs indices levels before hemodialysis with normal healthy individuals. They concluded that the RBCs count, Hb, Hct and RBCs indices levels in ESRD patients were significantly decreased before hemodialysis when compared to the RBCs count, Hb, Hct level and RBCs indices levels of healthy subjects. Malyszko et al., (2001) assessed the RBCs count, Hb concentration in ESRD patients on regular hemodialysis and healthy controls. They found that the RBCs count, Hb concentration in ESRD patients were significantly lowered before hemodialysis when compared to the healthy subjects.

Yenicerioglu et al., (2000) measured the Hb and Hct values before, after and during hemodialysis in ESRD patients and found that the values were significantly higher after hemodialysis. Post-dialysis haemoglobin (Hb) is known to increase in correlation with pre-dialysis Hb that is a result of ultrafiltration of plasma volume during dialysis. Inagaki, et al., (2001) examined the effects of position on blood components analysis during hemodialysis. Significant decrease in Hematocrit was reported in hemodialysis patients. They concluded, the decrease in several hematological parameters during HD may not be attributable completely to
hemodialysis process, but may be due to supine position and subsequent haemodilution due to redistribution of water from the extra-to intravascular space.

Movilli et al., (2002) measured the degree of intradialytic and extradialytic variation of Hb and Hct in hemodialysis patients and noticed that the Hb and Hct levels raised significantly after hemodialysis sessions. The iron profile was studied by Hsu et al., (2002) and demonstrated that 62.6% of CKD patients have iron deficiency anemia where serum ferritin <100 ng/mL and transferrin saturation (TSAT) <20%. Whereas deficiency of iron is 25.8% when the serum ferritin is more than 100ng/ml and TSAT is less than 20%. Talwar et al., (2002) studied hematological profile in chronic kidney disease patients and the prevalence of anemia was 94% of which 60% had microcytic hypochromic anemia and also found that 62% patients have low serum ferritin and serum iron is below normal in 74%.

The Inter and post dialytic changes in Hb concentrations in non-anaemic hemodialysis individuals was studied by Minutolo et al., (2003). The study anticipated variations in inter dialytic fluid weight gain leads to incorrect measurements of Hb. The patients treated with hemodialysis are associated with decreased RBCs survival and increased haemolysis (Westhuyzen et al., 2003). The effect of the direct contact of the blood with the dialysis membrane in HD patients was studied by Olszewska (2004). They concluded that the dialysis membrane during hemodialysis causes a series of changes in blood cells. WBCs count and total lymphocytes number were decreased, neutrophils were stimulated and degranulated and platelets adhesiveness was increased. Interactions of granulocytes with the dialysis membrane stimulated the production of Radical Oxygen Species (ROS) and activated aerobic reactions triggering oxidative stress.

James et al., (2006) studied anemia due to iron deficiency and role of intravenous iron in CKD patients and reported that 68% were anemic and 28.4% had iron deficiency by the criteria of serum ferritin was less than 100ng/ml and TSAT less than 20%. Functional iron deficiency was 41% where serum ferritin is more than 100ng/ml and TSAT <20% and they concluded that iron deficiency was common in CKD patient and therefore reloading of iron stores in patients with CKD can be considered as part
of therapy for treating anemia in CKD population. Iron profile was studied by Malyszko et al., (2006) and reported the prevalence of functional iron deficiency to be 21% as indicated by 200 hemodialysis patients who had ferritin above 200ng/ml with transferrin saturation below 20%. This was also found to be associated with high hepcidin levels and inflammatory markers. Annear et al., (2008) noted that the prevalence of normocytic normochromic anemia which is the characteristic feature of EPO deficiency, was higher in CKD at stages 3-5 than in stage 1-2 groups. Ketut et al., (2005) studied morphology of 33 anemic CKD patients and reported that normochromic normocytic was 78.8%, slightly macrocytic was 21.2% and they have not found hypochromic anemia. Reza et al., (2009) reported normochromic normocytic being 80%, hypochromic microcytic 15% and macrocytic anemia 5% among 100 CKD patients.

The Hct level and Hb concentrations was measured before and after hemodialysis patients by Jaroszynski et al., (2006). Their results showed that Hb and Hct values were significantly increased after HD sessions. Sombolos et al., (2007), also assessed the Hb changes occurring at the beginning of high flux hemodialysis. They concluded that a 5% decrease in Hb was observed 5 min after the initiation of high flux dialysis with a zero ultrafiltration rate, and was primarily due to an increase in blood volume.

The hematological changes and RBCs membrane protein constitution in hemodialysis process was studied by Costa et al., (2008). The study has shown a considerable increase in RBCs count, Hb, Hct and RBCs levels, and significant decrease in spectrin. They concluded that HD process contributes to reduction in spectrin that is associated with reduction in RBCs deformation. Mohamed et al., (2008), performed the RBCs count, Hb, Hct, RBCs indices levels in chronic kidney disease individuals under hemodialysis and peritoneal dialysis before and after dialysis sessions. They found that all the haematological parameters increased insignificantly after dialysis sessions with exception of MCH, MCHC which were found to decrease significantly. They also added that duration of hemodialysis has not effect on haematological parameters, except of Hct levels and RBCs count that were significantly increased during HD process. Pereira et al., (2010), studied before and after dialysis changes of the RBCs count, Hb, Hct, RDW and RBCs indices in ESRD patients under
hemodialysis. They reported significant increase in Hb, Hct, MCHC values and RBCs count. There was no significant changes in values of RDW and MCH. However there was quite significant decrease of MCV value.

Rangel et al., (2010) studied the before and after dialytic changes of the Hb and Hct level in hemodialysis patients and found that the Hb and Hct values were significantly increased after HD sessions. The change in Hb concentration in patients undergoing hemodialysis was estimated by Geller et al., (2010). They found that the Hb values were significantly increased after HD sessions and concluded that after dialysis haemoglobin (Hb) increased in comparison with before dialysis Hb and hypothesized that as a result of ultra-filtration of plasma volume during dialysis. Suresh et al., (2012) studied hematological changes in chronic kidney disease and found that RBC count, haemoglobin, hematocrit and platelet were reduced significantly and also noticed negative correlation between serum creatinine and haematological parameters and concluded the degree of changes depends on the severity of kidney disease. In addition Alghythan and Alsaeed, (2012) reported that most of hematological parameters significantly increased after dialysis.

2.5 REVIEW OF CARDIAC MARKERS IN CKD
The creatine kinase MB and cardiac troponin in dialysis patients without ischemic heart disease was studied by Mary et al., (1997) and they concluded that expression of cardiac troponin I (CTnI) is not expressed by skeletal muscle whereas cardiac troponin T (CTnT) is expressed is more in skeletal muscle of chronic kidney disease patient so CTnI found to be a best marker of cardiac injury in CKD. Greg et al., (1998) reported that CTnI is a useful test for diagnosis of myocardial injury in cases with renal failure and elevated CTnI is also associated with increased short term mortality in kidney disease patients. They suggested that large scale trails requires to confirm the accuracy of CTnI in kidney disease patients.

The persistent increase of CTnT and CTnI values in end stage renal disease (ESRD) patients under hemodialysis was reported by Diana et al., (2000). They mentioned the increase was not always specific for coronary artery disease it may be due to minor myocardial damage and recommended blood sample should be collected before
dialysis because dialysis may alters the cardiac troponins. Marie et al., (2001) demonstrated that elevated levels of cardiac troponins are in association with cardiovascular risk factors such as ischemic heart disease and LVH in chronic hemodialysis patients. Marta et al., (2003) studied CTnI in hemodialysis patients and reported that serum CTnI is the best marker for cardiovascular disease in asymptomatic dialysis patients. Benjamin et al., (2003) studied CTnT and malondialdehyde level in hemodialysis patients and found the presence of Cardiac troponin T (CTnT) predicts prognosis in ESRD and the presence of CTnT is associated to uraemia, inflammation and oxidative stress.

Masato et al., (2003) studied the ratio between heart fatty acid binding protein and myoglobin and they noticed that the values of HFABP/ Myoglobin will be more useful marker for the estimation of volume overload and cardiac damage in hemodialysis persons when compared to HFABP alone. Jart et al., (2004) reported cardiac troponin T (CTnT) fragmented into small molecules and cleared by kidney in healthy individuals whereas impairment in renal function causes accumulation of CTnI fragments which may be the cause increase of serum CTnT in chronic kidney disease individuals. In hemodialysis patients clearance of BNP and NT-pro BNP was demonstrated by Hans et al., (2004). BNP is cleared dialyzer when using both low flux and high flux hemodialysis membranes whereas NT-pro BNP cleared by high flux but low flux membrane shows low clearance and increased post dialysis NT-pro BNP concentration. Nadia et al., (2005) reported that Troponin T is a promising tool for diagnosis of cardiovascular disease in ESRD because elevated levels were observed in ESRD patients who had poor survival rate and high risk of cardiac death. Rise of CTnT and CTnI in predialysis CKD patients without acute coronary syndrome was studied by Nasir et al., (2005) and observed that the rise is seen in early stages of CKD, including most of number from stage 3, and advanced stages of CKD is more common.

The study done by Andreas et al., (2005) shown that NT-pro BNP and BNP are highly influenced by renal dysfunction and noticed that mild to moderate renal dysfunction with the absence of severe left ventricular dysfunction (LVD) increases two folds increase of BNP and NT-proBNP whereas there is a four folds increase of
both markers in subjects with severe LVD with renal dysfunction. They concluded that adjusting cutoff concentration according renal dysfunction increases the predictive value of BNP and NT-pro BNP for left ventricular dysfunction. Toshiharu et al., (2005) studies shown that CKD is risk factor for occurrence of CVD in Japanese population and concluded that CKD group should be considered as high risk population for CVD and they require more intense preventive management of CVD.

The correlation and prognostic utility of BNP and NT-proBNP in renal dysfunction patients was demonstrated by Wendy et al., (2006). They found a strong correlation between the markers wherein BNP (> 175 pg/mL) and NT-pro BNP (> 1250 pg/mL) above certain levels clearly indicates patients to have high risk of mortality or cardiac dysfunction. Flores et al., (2006) studied CTn I in patients with CKD and suggested that using different cut off values are useful in detecting acute myocardial infarction (AMI) in CKD persons, decreasing the number of false positives, thus taking benefit of early therapies.

The B-Type natriuretic peptide concentrations is a predictor of nondiabetic chronic kidney disease as explained by Katharina et al., (2007). They found that increase in NT-proBNP and BNP concentration demonstrate an increase of risk for progression of the CKD to ESRD and it also assess the prognosis of CKD. Marta et al., (2007) reported that atrial natriuretic peptide (ANP), BNP and NT-pro BNP concentrations were higher in uremic patients with mild cardiac dysfunction than those with idiopathic dilated cardiomyopathy (DCM) without renal dysfunction and concluded that natriuretic peptide concentration depends upon GFR. Jochem et al., (2007) reported that in heart failure patients those who have severe anemia and renal dysfunction is associated with increased NT-proBNP and BNP level and also concluded that during interpreting the BNP and NT-pro BNP, factors like anemia and renal dysfunction should be taken into consideration.

The NT-pro BNP is dependent on GFR whereas BNP is independent of GFR and acts as appropriate biomarker for cardiac dysfunction in CKD (Rajat et al., 2008). The NT-pro BNP level in black hypertensive kidney disease patients was studied by Astor et al., (2008) and found that NT-proBNP level was associated with CVD and
mortality in blacks with hypertensive kidney disease along with significant proteinuria. Matthew et al., (2008) demonstrated that BNP can strongly predict the mortality in patients under long term dialysis and concluded that BNP level is higher in patients who are on dialysis with cardiovascular comorbidities and noticed that these are good predictors of death. Another study reported that NT-pro BNP more than 7200 ng/L act as cut off difference between persons with and without left ventricular dysfunction (Sascha et al., 2008).

The study done by Susan et al., (2008) found that NT-pro BNP and C-reactive protein (CRP) can independently predict all causes of mortality in nondialysis CKD population and may be useful in risk stratification. Montagnana et al., (2008) reported that CTnT and ischemia modified albumin (IMA) act as biomarker of myocardial injury that can be used in hemodialysis patients. During blood sampling and they found that IMA assess the long term risk but not for diagnosis of acute coronary syndrome immediately after hemodialysis. Leo et al., (2009) studies showed that all the ESRD patients have elevated levels of CTnT concentration and the elevation is highly prognostic of adverse events and found that CTnI is a better marker.

The left ventricular end diastolic wall stress is strong predictor of BNP in patients with CKD and ESRD and also mentioned anemia, obesity and heart failure type should be considered for interpreting BNP concentration in heart failure (Shinichiro et al., 2009). Kamyar et al., (2009) demonstrated that in long term hemodialysis patients, high interdialytic weight gain is associated with increased cardiovascular death and poor survival whereas patients with low fluid retention are associated with increased survival. The study done by Pelsers (2009) reported that heart fatty acid binding protein (HFABP) and liver fatty acid binding protein (LFABP) are useful markers for rapid detection and monitoring of renal injury and helpful in monitoring during patient treatment and also concluded that CKD is a risk factor for CVD so early detection by HFABP can stratify treatment and reduce death by CVD. Hafidh et al., (2009) reported that diagnostic efficiency of heart fatty acid binding protein (HFABP) and Cardiac troponin T (CTnT) for diagnosis of acute myocardial infarction (AMI) in CKD patients is limited because in CKD persons without (AMI) also there is raised HFABP and CTnT.
The presence of stable coronary artery disease determines plasma BNP levels in chronic hemodialysis patients. Plasma BNP value will be a useful marker in management of Hemodialysis patients (Shinichiro et al., 2009). Kang et al., (2009) measured CTnI in ESRD patients with sepsis and found that elevated CTnI level is associated with short and long term mortality. They concluded that elevated CTnI in those patients can be taken consideration and followed to prevent adverse outcome. Jacobs et al.,(2010) studies shown that there is significant relationship between natriuretic peptide and body composition assessed by bioimpedance. They found that cardiac troponin T (CTnT), natriuretic peptide and high sensitive CRP (hs CRP) were significantly related and concluded that there is a complex relationship between overhydration, malnutrition, inflammation and cardiac biomarkers in hemodialysis patients.

The NT-pro BNP level in hemodialysis patients was studied by John et al., (2010) and found that NT-pro BNP was not coherence with cardiac dysfunction and also registered that NT-pro BNP depends on factors associated with volume overload and malnutrition. Neeraj et al., (2010) demonstrated that most of ESRD patients had normal Troponin I (TnI) level but most of them have slight elevation in TnI by new generation assay. They concluded that hemodialysis treatment does not affect the levels of TnI and also mentioned low elevation remains unclear. The effect of renal dysfunction on BNP, NT-pro BNP and their ratio was studied by Pornpenet al., (2010). They observed that BNP and NT-proBNP values rise in renal dysfunction and the degree of change depends on left ventricular effusion force (LVEF) and gender. They also considered renal dysfunction based on stages, sex and LVEF for improving the diagnosis and monitoring efficiency of BNP and NT-proBNP.

The LVH is proved to be a strong predictor of the risk to dialysis in non-diabetic CKD, mostly in patients with less advanced renal dysfunction (Ernesto et al., 2011). Hiroyuki et al., (2011) observed the BNP level and cardiovascular risk in patients on chronic hemodialysis and noticed that left ventricular diastolic dysfunction is associated with increased BNP level and cardiovascular risk in hemodialysis patients. Increase of high sensitive CTnI and CTnT is common in CKD patients and the rise influenced by both cardiac and renal disease (Christopher et al., 2012).
Shihui et al., (2013) studied NT-pro BNP in CKD patients to find out relationship between renal function and NT-pro BNP. They concluded that with higher cut off value NT-proBNP detects chronic heart failure and predicts the mortality in old age associated with Chinese coronary artery disease in CKD patients.

2.6 REVIEW OF PROTEOMICS AND CKD

Most of the research focused towards urinary proteomics is to know the renal function in various diseases. Soggiu et al., (2012) studied urinary proteomics in type 1 diabetes patients by using two dimensional (2DE) electrophoresis followed by mass spectrometry and identified various proteins such as apolipoprotein E, a2-thiol proteinase inhibitor Tamm–Horsfall urinary glycoprotein, human complement regulatory protein CD59 and apolipoprotein A-I that are down regulated and up regulation of α-1B glycoprotein, α-1-microglobulin, retinol-binding protein 4 and zinc-α 2 glycoprotein. Finally they concluded that the urinary proteins can act as a prognostic biomarkers for kidney disease. Snell et al., (2009) studied urine proteomics using capillary electrophoresis and mass spectrum in diabetic kidney disease, diabetes and coronary artery disease revealed that fragments of collagen type I in urine can act as biomarkers.

The studies conducted by Alkhalaf et al., (2010) on validation of proteomic biomarkers in urine specific to diabetic nephropathy and found that urinary collagen fragments act as biomarker for diabetic nephropathy and concluded that it may act more specific biomarker. Papale et al., (2010) studied urine proteomics in diabetic nephropathy persons and found that ubiquitin and β2 microglobulin act as biomarkers and may involve in disease pathophysiolgy. Good et al., (2010) found that most of the biomarker peptides in the urine were products of proteolytic activity and also found the presence of extracellular proteases which may reflect the presence of the disease and its progression.

The Plasma proteome analysis of the critical limb ischemia (CLI) markers in diabetic individual with hemodialysis was studied by Hung et al., (2011) and they found that 50 differentially expressed proteins found in hemodialysis diabetic patients with CLI
when compared with hemodialysis diabetic without CLI and concluded that nearly half of the expressed proteins were in association with inflammatory responses.

Proteomic analysis in hemodialysis fluid done by Molina et al., (2005) revealed 292 proteins of which 70% are previously identified and half of the proteins were less than 40 kDa. Apart from them they also found 50 N terminal acetylated peptides during their study. Lin et al., (2012) studied plasma proteomics in long term hemodialysis survivors by using two dimensional gel electrophoresis followed by mass spectrometry and they found increase in vitamin D binding protein (DBP) and decrease in haptoglobin, hemopexin, apolipoprotein A-IV, clusterin, and altered isoforms of α1-antitrypsin, fibrinogen gamma and complement factors B and H.

Galli et al., (2007) studied proteomics in ultrafiltrate of hemodialysis patients and revealed that the ultrafiltrate contains pro-prealbumin, albumin, prealbumin (transthyretin), complement factors, α-1-antitrypsin precursor, Ig gamma chains and transferrin concluded that proteomics methods are effective tool for study of heterogeneous class of uremic toxins.

The plasma proteomics in uremic patients was studied by Pavone et al., (2011) by electrophoretic technique followed by mass spectrum and found that there is a carbonylation of protein and concluded that the carbonylation causes irreversible modification and altered protein structure and function which may leads to uremic atherogenesis. Proteomics is applied to the field of monitoring the absorption of proteins onto the hemodialysis membrane (Aoike, 2007). Mares et al., (2010) studied the blood dialyzer interactome using proteomics and revealed that lectin pathway of complement activation leads to hemodialysis induced inflammatory response.

Proteomic studies provide support to dialysis technologists and manufacturers and renders information for renal replacement therapy. Hallbauer et al., (2010) in his study shown that increasing pore size of hemodialysis membrane (low flux or high flux) will not show any effect on serum proteome composition. Urban et al., (2012) studied proteomics on protein absorption capacity of cellulose triacetate and Polysulfone-based helixone hemodialysis column and found that 22 low abundant
proteins concentrated in helixone membrane and 32 high abundant plasma protein were present on cellulose triacetate and concluded the difference is related to membrane material.

Cuccurullo et al., (2011) studied the proteomic analysis of peritoneal fluid in peritoneal dialysis patients and they identified 151 different proteins and concluded that osmolarity of dialysis solution is not altered by the protein qualitative composition but altered by quantitative difference and they found that four proteins which are related to inflammatory processes α1-antitrypsin, apolipoprotein A-IV, fibrinogen beta chain and transthyretin are under expressed in highest osmolar solution when compared with lower glucose concentrations.