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Original Research Paper

Internal Medicine

EVALUATION OF CAROTID INTIMAL MEDIAL THICKNESS AND ESTIMATED GLOMERULAR FILTRATION RATE IN CHRONIC KIDNEY DISEASE"

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KEYWORDS :

INTRODUCTION

Chronic kidney disease is characterized by a decrease in glomerular filtration rate and histological evidence of reduction in nephron population[1]. The clinical course is typically one of a progressive loss of nephron function leading to end stage renal disease. Kidney failure is the most common of the spectrum, but it represents only a minority of the total population affected by kidney disease.

The time between initial onset of disease and development of end stage renal failure may vary widely not only between different diseases with different histopathological findings but also in different patients with similar disease processes. The progressive nature of CKD and the final stage ESRD is putting a substantial burden on global and national health resources since all modalities of treatment are expensive.

There are multiple causes of kidney injury that lead to the final common pathway of end stage renal disease, and this syndrome is characterized by hypertension, anemia, nutritional impairment, neuropathy, renal bone disease, impaired quality of life, and reduced life expectancy. Increasing evidence acquired in the past decades indicates that the adverse outcomes of CKD such as renal failure, cardiovascular disease, and premature death can be prevented or delayed by early detection of CKD[3]. Earlier stages of CKD can be detected through laboratory testing only. Treatment of earlier stages of chronic kidney disease, as well as initiation of treatment of cardiovascular and other risk factors at early stages of CKD should be effective in reducing the rate of progression of CKD to ESRD.

In patients with CKD, the atherosclerotic cardiovascular disease is leading cause for morbidity and mortality[2]. Carotid intima-media thickness (CIMT) has been used as a marker for early atherosclerosis in patients. The increased incidence of CVD is the consequence of a high prevalence of both traditional risk factors, uremia-related and "new factors," such as infections (Herpes virus and Chlamydia pneumonia) and hyper homocysteinemia, oxidative stress, which increases Atherosclerotic risk among these patients.

According to the 1999-2004 National Health and Nutrition Examination Survey (NHANES), the prevalence of Chronic Kidney Disease among the USA population is 15.3%. It becomes apparent that the severity of CKD along with CVD severity in any population makes a very fatal combination for both patients and healthcare systems. Approximately 50% of patients with ESRD die from a major cardiovascular event, which indicates a cardiovascular mortality that is 30times higher in dialysis patients and 500 times higher in 25- to 34year-old ESRD patients than in individuals from the general population of the same age.

Studies have suggested that carotid intimal medical thickness can be used as a screening test as well as marker for atherosclerosis in cardio vascular disease .Non-invasive assessment of intima medial thickness of carotid arteries by B – mode ultrasonography is used widely in observational studies and trials as an indicational measure of generalized atherosclerosis. Increased intimal medial thickness of carotid arteries has been associated with disadvantageous levels of established cardiovascular risk factors, prevalent cardiovascular disease and atherosclerosis somewhere in the arterial system.

In this study the attempt to evaluate the association of increased intimal medial thickness with traditional and non-traditional cardiovascular risk factors in CKD patients was tried.

AIM

Study of the carotid intimal medial thickness and estimated glomerular filtration rate in patients with Chronic Kidney Disease

OBJECTIVES

Determine the stage of chronic kidney disease (CKD) depending on estimated glomerular filtration rate (eGFR)

To assess the carotid intimal medial thickness and estimated glomerular filtration rate in different stages of chronic kidney disease

To study the effect of cardiovascular risk factors on the grade of chronic kidney disease based on history and lipid profile of the patient.

To assess the carotid intimal medial thickness for detection of atherosclerosis in chronic kidney disease patients.

BACKGROUND :

Chronic Kidney Disease

Chronic kidney disease constitutes the entire spectrum of disease that occurs following the commencement of kidney damage. The introduction of CKD has enabled standardize current medical communication, ease appropriate population-based screening ,and encourage timely prevention and treatment of kidney disease.

Definition[4]

Kidney damage for > 3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by either

1. Pathological abnormalities; or Markers of kidney damage, including Abnormalities in the composition of the blood or urine, or abnormalities in Imaging test.
2. GFR < 60 ml / min / 1.73 m2 for > 3 months, with or without

kidney damage.

The GFR is considered the best measure of comprehensive kidney function. A GFR level below 60 mL / minute / 1.73 m2 represents loss of atleast one half of the adult level of normal kidney function. Normal GFR differs according to patient age, sex, and body size. The MDRD formula is a finer estimate of GFR than those derived from 24-h urinary creatinine clearance or the Cockcroft-Gault formula. The abbreviated MDRD formula takes into account age, gender, race, and serum creatinine.

The Abbreviated MDRD Formula[5]

eGFR = 186 × ([SCR/88.4]–1.154) × (age) –0.203 × (0.742 if female) × (1.210 if African-American)

where as eGFR = estimated glomerular filtration rate (ml/min/1.73m2),

SCR = serum creatinine concentration (mol/L), and age is expressed in years.

AGE

In young adults, the normal GFR is approximately 120 to 130 ml /minute / 1.73 m2 and declines with age.6 A decreased GFR in an elderly patient appears to be an independent predictor of adverse outcomes such as mortality and cardiovascular disease7,8. Because of the age-related reduction in GFR, the prevalence of chronic kidney disease increases with age; approximately 17 percent of persons older than 60 years have an estimated GFR of less than 60mL / minute / 1.73 m2.

Gender

Male gender has been accounted for as an important factor in the development of CKD[9].Gender-based genetic variability has been linked to differences in BP in both black[10] and whiteindividuals[11]. Males may be more susceptible to CKD, which would explain the higher proportion in renal replacement therapy programs. In contrast to testosterone, [12,13] Estrogens may attenuate CKD progression by lowering the cardiovascular stress response to adrenergic stimuli[14].

Staging Of Chronic Kidney Disease

As patients pass through the continuity of kidney damage, there are foreseeable complications, like the development of anemia, and an elevated parathormone levels and predictable management issues such as dialysis access preparation by either central venous catheterization in emergency or an arterio-venous fistula if elective. The NKF/KDOQI staging system[4] for CKD was developed to address this need.

Stage 1: Kidney damage (pathological abnormalities or markers of damage including abnormalities in blood or urine tests or in imaging studies) with normal or raised glomerular filtration rate (≥ 90 ml/min/1.73 m^2)

Stage 2: Glomerular filtration rate 60 – 89 ml/min/1.73 m^2 with evidence of kidney damage.

Stage 3: Glomerular filtration rate 30 – 59 ml/min/1.73 m^2

Stage 4: Glomerular filtration rate 15 – 29 ml/min/1.73 m^2

Stage 5: End-stage renal failure, glomerular filtration rate< 15 ml/min/1.73m^2

Early Kidney Disease – Stages 1 And 2

For stages 1 and 2, kidney damage is detected by a ratio of greater than 17 mg of albumin to 1 g of creatinine in men or greater than 25 mg of albumin to 1 g of creatinine in women on two separate (spot) if possible early morning urine tests. The main target in this group of patients becomes identification of whether renal function is likely to decline. The patients who at significant risk of progressing[19] include proteinuria >1 g/day[20], poorly controlled blood pressure, certain underlying diagnoses like diabetic nephropathy, should be timely evaluated and managed to decrease the risk of progression to End Stage Renal Disease (ESRD).

Stage 3 Ckd

Patients with stage 3 CKD have significant renal impairment and are probably the very group in whom renal failure is poorly recognised.[21]In patients with progressive renal failure, itis advisable to institute treatment to delay the need for dialysis. There is good evidence to support the efficacy of such measures in proteinuria patients.[22,23] The natural history of renal impairment in patients without proteinuria, however, is not clearly defined, and will depend at least in part on the underlying cause of renal damage. The large majority of these patients will not progress sufficiently to require dialysis.[24] However, patients with stage 3 CKD have substantially increased cardiovascular risk compared to patients with better renal function, with43–100% increased risk of cardiovascular events[25] and most of them will die as a result of cardiovascular disease before ever needing dialysis.[26] Increased cardiovascular risk appears to start increasing as GFR declines below 75 l/min/1.73 m2. [27] Management revolves around robust treatment of hypertension, particularly blockade of the renin-angiotensin system, to a blood pressure <130/80 mmHg (<125/75 mmHg if proteinuria >1 g/day is present), and treatment of other cardiovascular risk factors.

Stage 4 And 5

These patients have marked interference to normal physiology, causing complications such as renal anemia and renal osteodystrophy that require nephrologist management. These are also the stages at which preparations for dialysis and transplantation are required. Late referral of patients with advanced renal failure to nephrologists compromises the preparations for dialysis and subsequent survival of those patients[28] and is more costly than timely referral.[29]Even patients who are unsuitable for dialysis (or are unwilling to undergo it) will benefit from management of their anaemia and bone disease, and potentially from palliative care.[30]

Kidney failure is defined as a GFR below 15 ml / minute / 1.73 m^2, generally accompanied by signs and symptoms of uraemia, or as the need for initiation of renal replacement therapy for management of the complications of a decreased GFR. In the United States, approximately98 percent of patients begin dialysis when their GFR falls below 15 ml /minute / 1.73 m2. [31]

The number of patients with end stage renal disease is growing all over the world. About 20-30patients have some degree of renal dysfunction for each patient who needs renal replacementtreatment.[32] Diabetes and hypertension are the two most common causes of end stage renal disease and are associated with a high risk of death from cardiovascular disease.[33] Early detection and treatment often can prevent or delay some of these adverse outcomes.[34] However, opportunities for prevention may be lost because chronic kidney disease is not diagnosed or is treated insufficiently[35,36] due to lack of uniform application of simple tests for the detection and evaluation of the disease.[37]

Risk Factors For CKD

DIABETES

In the United States, diabetic nephropathy is the most common cause of kidney failure. It accounts for nearly 45% of all new cases of ESRD starting renal replacement therapy between 1996 and 2006.The underlying pathogenesis is intraglomerular hypertension. Its initial manifestation is micro

albuminuria with a normal or elevated GFR. Effective control of blood glucose and blood pressure especially in the renal glomerulus reduces the renal complications of diabetes.

Conscientious control of blood glucose has been conclusively shown to reduce the development of micro albuminuria by 35% in type 1 diabetes (Diabetes Control and Complications Trial)39 and in type 2 diabetes (United Kingdom Prospective Diabetes Study).[40]Other studies have indicated that glycemic control can reduce the progression of diabetic renaldisease.[41] Adequate control of blood pressure with a variety of antihypertensive agents, including angiotensin converting enzyme inhibitors, has been shown to delay the progression of albuminuria in both type 1 and type 2 diabetes[42,43] Recently, angiotensin receptor blockers have been shown to have Reno protective effects in both early and late nephropathy due to type 2 diabetes.[44]

Hypertension

Hypertension is the second most common cause of ESRD in the United States, accounting for 23% of incident ESRD patients between 1996 and 2000.[45] Hypertension is a well-established cause, a common complication, and an important risk factor for progression of renal disease. Controlling hypertension is the most important management to slow the progression of renal disease. Angiotensin converting enzyme inhibitors are specifically effective in slowing progression of renal insufficiency in patients with and without diabetes.[46] Angiotensin receptor blockers have a Reno protective effect in diabetic nephropathy, independent of reduction in blood pressure.[50]Non-dihydropyridine calcium channel blockers also have a role in slowing the progression of renal insufficiency in patients with type 2 diabetes. Early detection and effective treatment of hypertension to target levels is essential. Hypertension is the most common complication of CKD finally leading to ESRD. Hypertension is more difficult to control in patients with CKD. In one study, only 11% of CKD patients had BP levels lower than 130/85 mm Hg; 27% of these patients had a BP that was lower than 140/90 mm Hg; and 62% of them had a BP that was higher than 140/90 mm Hg.[48]

Proteinuria

Proteinuria, previously considered a marker of renal disease, is pathogenic and is one of the single best predictors of renal disease progression. Reducing urinary protein excretion slows the progressive decline in renal function in both diabetic and non-diabetic kidney disease. Angiotensin blockade with angiotensin converting enzyme inhibitors or angiotensin receptor blockers is more effective at comparable levels of blood pressure control than conventional antihypertensive agents in reducing proteinuria, decline in glomerular filtration rate, and progression to end stage renal disease.[49]

Dyslipidemia

Lipid abnormalities may be seen with even mild renal impairment and contribute to progression to end stage renal disease and increased cardiovascular morbidity and mortality. Hydroxy methyl glutaryl coenzyme A reductase inhibitors (statins) decreased proteinuria and preserved glomerular filtration rate in patients with renal disease, an effect not entirely explained by reduction in blood cholesterol.[50]

Obesity

Obesity has been associated with initiation and progression of glomerulonephritis.[52,53]Among NHANES III participants, the risk of either incident ESRD or kidney disease related death was independently a body mass index greater than or equal to 35 kg/m^2.[54] Obese people were more likely to have a decrease in estimated GFR.[55]

Cigarette Smoking

Cigarette smoking has been implicated in initiation as well as progression of CKD. The incidence of ESRD was increased by 5.9 times among heavy smokers (>15 pack years).56In another study, heavy smokers (> 20 pack years) had a risk of developing albuminuria three times that of non-smokers.[57] Smoking cessation alone may reduce the risk of disease progression by 30% in patients with type 2 diabetes.[58] Smoking increases the risk of cardiovascular events in men with kidney disease.[59]

Alcohol

Regular and heavy (> two drinks daily) consumption of alcohol might Also increase the risk of ESRD.[60]

Complications Of Chronic Kidney Disease

Anemia

Anemia of chronic renal disease is seen when the glomerular filtration rate falls below30-35% of normal and is normochromic and normocytic. This is primarily caused by decreased production of erythropoietin by the failing kidney,[62] other factors contributing to anemia include inhibitors of erythropoiesis, reduced RBC life span, platelet dysfunction, dropped iron intake, and secondary hyperparathyroidism. Anemia is an independent predictor of mortality and has also been associated with worsening of morbidity in CKD. Correction of anemia improves the quality of life, cognitive and sexual function, reversal of ST-T changes on ECG,and reversal as well as prevention of left ventricular hypertrophy, reduces the frequency of heart failure and hospitalization among patients receiving dialysis.[63],.The risk of coronary heart disease (CHD) increases when the anemia is not treated, and recent studies have indicated that anemia in patients with chronic renal failure may predispose to ischemic heart disease, heart failure, and premature death. Therefore, the risk of CHD may be intelligibly higher in people with renal insufficiency and concomitant anemia, when compared with people with renal insufficiency but without anemia and with people with normal renal function[64]. A significant proportion of patients have established cardiovascular complications on initiation of dialysis, raising the possibility of early correction of anemia as a possible interventional strategy for preventing cardiovascular co-morbidities among renal patients. It is thought that anemia can worsen the severity of heart failure and is associated with a rise in mortality, hospitalization and malnutrition. Anemia can also further damage renal function and cause faster progression to dialysis than is found in patients without anaemia[65]. Partial correction of anemia with recombinant human erythropoietin reduces left ventricular mass and volume. Complete correction of anemia may prevent progressive left ventricular dilatation in patients with normal left ventricular volumes. In the present work we aimed to consider the adverse effects of anemia in CKD .Whether anemia accelerates the progression of renal disease is not determined yet. Treatment of anemia with recombinant human erythropoietin may slow progression of chronic renal disease. Both National Kidney Foundation and European best practice guidelines Recommend evaluation of anemia when hemoglobin is <11 g/dl and consideration of recombinant human erythropoietin to maintain a target hemoglobin of >11 g/dl.[66] But when The United States Normal Hematocrit study evaluated 1,233 hemodialysis patients with clinical evidence of congestive heart failure or ischemic heart disease, the risk ratio (for death and non-fatal myocardial infarction) was 1.3 for the normal hematocrit group as compared to the low hematocrit.

Malnutrition

The prevalence of hypoalbuminemia is high among patients initiating dialysis, is of multifactorial origin, and is associated with poor outcome. Hypoalbuminemia may be a reflection of chronic inflammation rather than of nutrition. Spontaneous intake of protein begins to decrease when the glomerular filtration rate falls below 50 ml/min. Progressive decline in renal function causes decreased appetite, thereby increasing the risk of malnutrition.

Cardiovascular Disease

The prevalence, incidence, and prognosis of clinical cardiovascular disease in renal failure is not known clearly, but it begins early and is independently associated with increased cardiovascular and all cause Mortality.

Risk Factors Associated With Cardiac Disease[73]

Traditional
Age
Gender
Race
Smoking
Diabetes
Body mass index
Hypertension
Dyslipidaemia

CKD-related risk factors

Anaemia
Calcium phosphate
Cytokines
Electrolyte imbalance
Malnutrition
Hypoalbuminemia
Inflammation
C-reactive protein
Endothelial activation
Prothrombotic factors
Increased oxidative stress
Hyper-homocysteinemia
Advanced glycation end-products

Cardiac disease, including left ventricular structural and functional disorders, atherosclerosis, and arteriosclerosis is an important preventable and potentially treatable comorbidity of early kidney disease.[74] Patients with chronic kidney disease should be considered in the "highest risk" group for cardiovascular events[75] and appropriately managed.

Atherosclerosis of coronary arteries is the foremost cause of ischemic heart disease in patients with CKD, with acute myocardial infarction accounting for 20% of cardiovascular mortality. The coronary plaque in dialysis patients is considered a more advanced and complex lesion, characterized by greater degrees of medial thickening and calcification.

However, a significant number (27 -50%) of patients with ESRD who experience cardiovascular symptoms do not have large-vessel disease. In this case, micro vascular atherosclerosis, severe LVH and anemia are thought to be the etiological factors. Vascular remodeling is a pathological hallmark of CKD, affecting the large arteries as well as the coronary vessels of the heart. In part, this is due to medial calcification, which reduces compliance and manifests as an increase in pulse pressure with systolic hypertension. This process attributes to aortic stiffness, LVH and myocardial infarction, and matches the increase in cardiovascular morbidity and mortality in the CKD patient. In addition to the traditional risk factors, accelerated atherosclerosis characteristic to CKD involves the three related processes of vascular inflammation, oxidative stress and vascular calcification, all of which result in vascular remodeling. Oxidative stress has a central role in the pathogenesis of Atherosclerosis and CKD is associated with an imbalance of pro-oxidant over antioxidant systems, contributing to the increased atherosclerotic burden. Serum–C reactive protein (CRP) is a reliable marker of atherosclerotic complications. Both CRP and chromogenic factors, such as fibrinogen, are also elevated in patients with end stage renal disease, and are strong predictors of death and adverse cardiovascular events. Progressively reducing renal function itself is also associated with an inflammatory response, manifested by an increase in pro inflammatory cytokines in both early and progressive CKD. Increased levels of the proatherogenic cytokine,IL-6, are independently associated with carotid atherosclerosis and predict mortality in dialysis patients. Therefore, coronary angiography remains the gold standard for the detection of epicardial CAD, but complication rates tend to be higher among the CKD population due to the difficulty and variation in the modalities of treatment. These include contrast nephropathy, athero-embolism, bleeding complications and contrast induced pulmonary edema. In the pre-dialysis patient undergoing coronary angiography, the risk maybe enough to progress to ESRD as a result of the procedure.

Treatment Principles

1. Hypertension is both a cause and a complication of chronic kidney disease and should be laboriously controlled in all patients.
2. Treatment of co morbid conditions, interventions and management to slow progression of kidney disease, and measures to reduce the risk for CVD should begin during stage 1 and stage 2.
3. Evaluation and treatment of other complications of decreased GFR, such as anemia, malnutrition, bone disease, neuropathy, and decreased quality of life, should be undertaken during stage 3, as prevalence of these complications begins to rise when GFR declines to less than 60 ml/min per 1.73 m^2.
4. Preparation for kidney replacement therapy should begin during stage 4, well before the stage of complete kidney damage.
5. Initiation of dialysis and transplantation is usually seconded by the onset of uremic symptoms. Preparations for these treatments should begin when GFR declines to less than 15ml/min per 1.73 m^2 (stage 5) in end stage renal disease.

B Mode Imaging

Ultrasound imaging is done as "pulse echo techniques". An ultrasonic transducer is placed in contact with skin. The transducer repeatedly emits brief pulses of sound at a fixed rate called the pulse repetition sequencing. After transmitting each pulse, the transducer waits for the echoes from the interfaces along the sound beam path. Echo signals picked up by the transducer are amplified and processed into a format suitable for display. The distance to a reflector is determined from the arrival time of its echo. Thus d=ct/2 where d is the depth of the interface. T is the echo arrival time and c is the speed of sound in tissue[76]. The factor 2accounts for the round-trip journey of the sound pulse and echo. The equation mentioned above is called the range equation in ultrasound imaging. The speed of sound 1540m/s is considered inmost scanners when calculating and displaying reflector depths from echo arrival times. The corresponding echo arrival time is 13mcs/cm of distance of the reflector to create images pulses of image are transmitted along various beam lines. They are followed by reception and processing of the echo signals.

Imaging is done with transduces arrays where echo signals are taken by individual elements and are combined within a beam former into a single for each beam line. Following abeam former, echo signal processing for imaging consists of amplification of the signals; applying time gain compensation to counterbalance the effects of beam attenuation; applying nonlinear logarithmic amplification to reduce the wide range of echo signal amplitudes into a range that can be exhibited effectively into a monitor; demodulation which forms single spike like signal for each echo; and B mode processing. The B mode display is used in imaging[77].

Sclerotic and ageing changes in all cardiovascular stem of human is well reflected by the status and structure of *arteria carotis78*. This artery is well accessible by ultrasonic investigation is the main vessel supplying blood to the brain. Here by, ultrasonic investigation of *arteriacarotis*(AC) has been the target of numerous attempts. Findings in the structure of AC walls are very actual in anticipating of possible changes of coronary arteries, especially when there are no other symptoms of coronary ischemia[79]. AC wall structure and thickness are good indicators for calculation of risk for stroke and myocardial infarction. There are many associated

relations established between AC state from one side and diabetes, high blood pressure, early sclerosis overweight and other pathologies from the other. The main changes in AC can be observed in the wall structure, which in turn can bedivided into inner layer, contacting with blood (*intima*), middle layer of the wall (*media*) and outer layer (*adventitia*)[80].

Intima and media thickness (IMT) is proven to be one of the most informative parameters for differential diagnosis. Changes in thickness are visible well in advance of sclerotic plaque appearance, thus boosting early diagnosis of sclerosis. Sclerotic damage of vascular system manifests by thickening of *intima* layer which is thin for young and healthy persons. *Media* of the AC wall consists mainly from spiral fibres of muscles and is dependent on ability of arteries to support the blood flow and to react to stress factors. Ultrasonography of AC including measurement of *intima* and media thickness is a good modality for ischemic disease prediction, diagnosis and treatment control[81]. The main problem in diagnostics of the state of AC is insufficient precision of *intima* and media thickness measurements, since this shows all diagnostic reliability. Two layers are to be clearly separated because high blood pressure causes thickening (hypertrophy) of *media*, while arteriosclerosis causes hypertrophy of *intima*. For differential diagnosis therefore is very important clear differentiation of two layers as well as accurate measurement of absolute thickness.

Structure of carotid artery and acoustical model

Before ultrasonic investigation of structure of AC walls anatomical structure should be related to the acoustical model. Ultrasonic echography is based on reflection and scattering of incident ultrasonic pulses by changes of acoustical impedance of the object under investigation. Relation between anatomic and acoustic layers (changes in acoustic impedance) was established and possibility to measure thickness was proven. Since an ultrasonic transducer beam hits the artery from one side zones of *adventitia*, *media intima*, consequently causes reflections[82].

More convenient for thickness measurements are the AC wall on the other side from the transducer. Both walls can be measured simultaneously, or the high frequency transducer can be used near wall of artery. The farther wall has better reflections due to the interface blood-*intima-media-adventitia* acoustics impedance sequence. Since an ultrasonic transducer beam hits the artery from one side zones of *adventitia*, *media*, consequently causes reflections. More accessible for thickness measurements are the AC wall on the far side from the transducer. Both walls can be measured simultaneously, or the high frequency transducer can be effectively used near wall of artery.

Common Carotid artery (before it s bifurcation on its are usually used for carotid artery examinations. upper end) is accessible within about 10 cmalong the artery. Therefore, longitudinal variances of *intima-media* thickness can be measured or (with some assumptions) longitudinal information can be used for averaging of measurement results. Anyway, repeatable measurements raise the accuracy[83]. The general-purpose echographysystems are usually used for thecarotid artery examinations. It is because the 7 – 8 MHz linear scanning transducers are better useful for such investigations.

Both A and B scanning methods can be used for ultrasonic investigations. B scan is used more frequently, as it gives overall view of the artery and general assessment can be obtained for a longer segment of the vessel.

Median population values of *intima-media* thickness range between 0.5 – 0.9 mm. IMTis thickening with age with 0.01 to 0.3 mm per year. The axial resolution of a 7MHz transducer is about 0.3 mm in theory. If IMT is thinner than 0.3 mm, the two echo interfaces cannot be distinctly separated. If IMT is thicker than 0.3 mm, thickness can be measured better.

Overall thickness of *intima* and *media* layers is the most important diagnostic parameter. However, thickness of separate layers would be useful for pathological differentiation. Since boundary between *media* and *intima* isn t easily demarcated in terms of acoustic parameters, in most cases *intima-media* layer thickness is taken into consideration.

B-mode ultrasound is a non-invasive method of examining the walls of peripheral arteries and provides measures of intima-media thickness (IMT) presence of stenosis and presence of plaques. The IMT corresponds to the intima media complex, which is comprised of endothelial cells, connective tissue and smooth muscle and is the site of lipid deposition in plaque formation.

In healthy adults, IMT ranges from 0.25 to 1.5 mm and values above 1.0 mm are often regarded as abnormal. IMT has been proposed as a quantitative index of atherosclerosis of value in monitoring disease progression and the effects of treatment and as an endpoint in clinical trials. The validity of IMT for these purposes has been calculated by making comparisons of mean IMT in people with and without clinical evidence of Cardio Vascular Disease and discriminatory ability has been demonstrated. Epidemiological studies, which are less prone tobias inherent in clinical case series, have reported associations between a range of cardiovascular risk factors (smoking, blood pressure, elevated blood cholesterol) and IMT. Age is one of the most powerful determinants of IMT, with increases of from 0.01 to 0.02 mm per year and consequently may confound comparisons of IMT made between groups if appropriate age adjustment is not made[84].

Reported findings have demonstrated infrequent associations between IMT, risk factors and clinical disease and have also highlighted the importance of the presence and severity of arterial wall plaque as determinants of clinical cardiovascular events. Some of this variation in findings is likely to be due to the method of measuring IMT: mean bifurcation, mean bulb origin, mean common carotid, mean internal carotid, and also combinations of these. Correlations between these different approaches are reported to be very high. It has been suggested that measurement of IMT at the "common carotid artery alone, especially for studies of association of risk factors with carotid arterial disease, cohort studies or clinical trials, in that it, too, is associated with the status of coronary atherosclerosis" is a reasonable alternative to more detailed and technically difficulty measurement at other sites. However, plaque formation is not so common in the common carotid artery. Since thicker IMT bifurcation and bulb origin values tend to occur in people who also have plaques, it is possible that presence or absence of plaque, and not IMT at either the common carotid or bifurcation sites, is the more pertinent indictor of early atherosclerosis.

Comparison Studies

Margekar et al studies showed that the relationships of carotid intima-media thickness (CIMT) are a measure of subclinical atherosclerosis in CKD patients is a matter of debate. Hundred CKD patients were studied and compared with 50 subjects without CKD in the Department of Medicine, G.R. Medical College & J.A. Group of Hospitals, Gwalior (M.P.) India. In case group, majority were males (68%) were having age between 30-60 years (62%). Majority had stage V CKD (67%), 21% had stage III and 14% had stage IV CKD. Majority of the cases had CIMT between 0.9-1.0 mm (42%) followed by 0.7-0.8 mm (17%) as compared to 0.5-0.6 mm (42%) in control. Mean CIMT was significantly higher in cases (0.87 ± 0.24) as

compared to control (0.61±0.34) group.

Kumar S et al study showed that this was a prospective case control study of carotid intimal medial thickness in patients of CKD.

A total of 150 patients were enrolled. Out of total 300 cases, 114 (76%) patients of CKD and 113 (75.33%) control were male. CIMT in CKD patients was between 0.80 ± 0.28 mm and 0.64 ± 0.16 in control p=0.0001. CKD patients with diabetes were having mean CIMT 1.09 ± 0.22 mm in comparison to controls with diabetes having mean CIMT 0.63 ± 0.16 mm, p=0.0001. CKD patients with hypertension were having mean CIMT 0.76 ± 0.27 mm in comparison to controls having mean CIMT 0.62 ± 0.18 mm, p=0.0001. Mean CIMT was increased in all stages of CKD and there was no significant difference in CIMT in different stages of CKD. Patients having hypertension was having higher mean CIMT in comparison to patients having normal blood pressure, patient with diabetes had high mean CIMT as compared to mean CIMT of controls having diabetes Roumeliotiset al study is A case-control study involving 100 subjects made of 50 patients with CKD stages 2 and 4. The mean CIMT was higher in CKD population compared with controls (*P* < .001). Eighty-four percent of the study population was found to have thickened CIMT compared with 18% of controls (*P*<.001). Patients with CKD had significantly higher blood pressure and heart rate than controls. Cardiovascular disease was also more prevalent among patients with CKD as compared with controls.

PATIENTS AND METHODS

Place Of Study: The patients attending Internal medicine and nephrology department in Kamineni Institute of Medical Sciences, Narketpally.

Study Design: Single centre, Cross sectional study
Duration Of Study: 2 years (i.e. October 2019 to September 2021).
Sample Size: 60 cases over 2 years

Inclusion Criteria

Patients diagnosed with chronic kidney disease getting treated at Department of Internal Medicine and Nephrology at Kamineni Institute of Medical Sciences, Narketpally.

Exclusion Criteria

Patients with Nephrotic syndrome
Patients using statins
Patients on treatment with antiplatelets
Patients presenting with acute on chronic kidney disease
Patients with previous history of cardiovascular events

Procedure Of Data Collection :

CAROTID INTIMAL MEDIAL THICKNESS (cIMT) is checked in patients who are included in the study History of diabetes, hypertension, obesity , age, hyperlipidaemia, smoking and alcohol are to be asked.

The questionnaire is to be prepared according to the information asked.

Blood and urine samples for haemoglobin, hematocrit, fasting blood sugar levels, fasting lipid profile levels are to be taken into consideration Estimated glomerular filtration rate (eGFR) is calculated using MDRD formula as it is considered to be a better estimate of creatinine clearance than Cockcroft- Gault formula .

Carotid intimal medial thickness (cIMT) is calculated using B scan doppler ultrasonography of carotid vessels Abbreviated MDRD formula: eGFR = 186 x (serum creatinine/88.4) $^{-1.154}$ × (age) $^{-0.203}$ × (0.742 if female) × (1.210 if African/American) where

1. eGFR = estimated glomerular filtration rate (ml/min/1.73m2),
2. SCR = serum creatinine concentration (mol/L), and age is expressed in years

Conflict of interest : none

RESULTS

Population Characteristics

Among the 50 patients included in the study, 34(68%) were males and 16(32%) were females. Among 50 patients 21 were in 25-45 years age group, 25 were in 46- 65 age group, 4 were in >65 age group

Table 1: Age And Sex Distribution In Patients With Chronic Kidney Disease Patients (n = 50)

Age group in years	Total	Percentage	Male	Female
25-45	21	44	15	6
46-65	25	48	15	10
>65	4	8	4	0
Total	50	100	34	16

Table 2: Assessment Of Carotid Intimal Medial Thickness In Patients With Chronic Kidney Disease (n = 50)

Age in years	CIMT		Total
	<0.89 mm	>=0.89 mm	
25-45	6	15	21 (42%)
46-65	7	18	25 (50%)
>65	1	3	4 (8%)
Total	14	36	50

P value = 0.98
Correlation of CIMT with age is not statistically significant

Table 3: Evaluation Of Carotid Intimal Medial Thickness (CIMT) In Patients With Chronic Kidney Disease (n = 50)

Sex	CIMT		Total
	<=0.89 mm	>0.89 mm	
Male	8	26	34
Female	6	10	16
Total	14	36	50

P value = 0.3
The correlation of CIMT with sex is not statistically significant

Table 4: Evaluation Of Carotid Intimal Medial Thickness With Egfr(estimated Glomerular Filtration Rate) In Ckd Patients (n = 50)

eGFR (ml/min/1.73m2)	CIMT		Total
	<=0.89 mm	>0.89 mm	
61-90	5	1	6
31-60	7	11	18
5-30	2	24	26
Total	14	36	50

P value = < 0.0001

Correlation Of Cimt With Egfr Is Statistically Significant Educational Status:

In this study, 33 patients were illiterates, 7 patients had primary education, 8 Patients had secondary education, 2patients were college graduates.

Diabetes Mellitus In The Study Population:

Out of the 50 patients in the study, 29 patients had diabetesmellitus type 2 of which 20 (68.9%)patients were males and 9 (31.1%) werefemales.

Table 5: Evaluation Of Carotid Intimal Medial Thickness In Diabetics And Non Diabeticsin Ckd Patients(n = 50)

Glycemic status	CIMT		Total
	<=0.89 mm	>0.89 mm	
Diabetic	4	25	29
Non diabetic	10	11	21
Total	14	36	50

P value = 0.008
Correlation of CIMT with diabetes is statistically significant

Hypertension In The Study Population:
In this study, 33 (66%) patients were hypertensives out of which patients were 24 (72.7%) males and 9 (27.2%) patients were females

Table 6: Evaluation Of Carotid Intimal Medial Thickness In Hypertensives And Non Hypertensives In Ckd Patients
(n = 50)

Hypertensive status	CIMT		Total
	<=0.89 mm	>0.89 mm	
Hypertensives	6	27	33
Non hypertensives	8	9	17
Total	14	36	50

P value = 0.031
Correlation of CIMT with hypertension is not statistically significant.

Family History Of Cvd:
In this study, out of 50 cases, 4 (8%) patients have a positive family history of CVD, out of which 3 (75%) were males and 1 (25%) were females.

Alcoholism In The Study Population:
Among 50 patients, 28(56%) were alcoholics out of which 23 (96%) were male patients and 1 (4%) were female patients.

Table 7: Evaluation Of Carotid Intimal Medial Thickness Among Alcoholics And Non-alcoholics In Ckd Patients (n = 50)

Alcoholism	CIMT		Total
	<=0.89 mm	>0.89 mm	
Alcoholic	7	17	24
Non alcoholic	7	19	22
Total	14	36	50

P value is 0.57

Correlation of CIMT with Alcoholism is not statistically significant.

Smoking In The Study Population:
Out of the 50 patients, 16 (32%) patients were smokers. 16 (100%) were males and 0 (0%) were females

Table 8: Evaluation Of Carotid Intimal Medial Thickness Among Smokers And Non Smokers In Ckd Patients (n = 50)

Smoking	CIMT		Total
	<=0.89 mm	>0.89 mm	
Smokers	3	13	16
Non smokers	11	23	34
Total	14	36	50

P value is 0.31
Correlation of CIMT with smoking is not statistically significant

Table 9: Evaluation Of Hyperlipidemia And Egfr In Ckd Patients (n = 50)

eGFR (ml/min/1.73m2)	LDL		Total
	</= 130mg/dL	>130 mg/dL	
61-90	4	2	6
31-60	14	4	18
5-30	15	11	26
Total	31	17	50

P value is 0.38
Correlation of hyperlipidemia with eGFR is not statistically significant

Hemoglobin In The Study Population:
The mean haemoglobin in the study population is 8.06 gm/dL. Out of patients, 42 (84%) had haemoglobin less than 10 gm/dL.

Table 10 : Evaluation Of Carotid Intimal Medial Thickness With Anemia In Ckd Patients(n = 50)

Haemoglobin	CIMT		Total
	<=0.89 mm	>0.89 mm	
< 10 gm/dL	9	33	42
>/= 10gm/dL	5	3	8
Total	14	36	50

P value is 0.01

Correlation of Hemoglobin with eGFR isstatistically significant.

Table 11: Evaluation Of Carotid Intimal Medial Thickness With Body Mass Index In Ckd Patients (n = 50)

BMI(kg/m2)	CIMT		Total
	<=0.89 mm	>0.89 mm	
< 25	4	12	16
25.1 - 29.9	10	21	31
>30	0	3	3
Total	14	36	50

P value is 0.46

Correlation of CIMT with BMI is not statistically significant

DISCUSSION

Agecomparison:
This study is conducted on 50 patients admitted in the department of general medicine and nephrology of KIMS, Narketpally.

In this study, out of 50 patients 33 (66%) patients were males and 17 (34%) patients were females.

These findings were comparable to a study conducted on patients admitted in the hospital by Margekar et al. in which out of 100 patients, 68 (68%) were males and 32 (32%) were females.

In a study by Kumar S et al out of 150 patients, 114 (76%) were males and 36 (24%) were females. maximum number of subjects was in the age group 41-60 years in both cases (47.33%) and controls (47.33%). The mean age was 46.87 ± 14.23 years and 47.15 ± 14.12 years in cases and controls respectively In a study conducted by Roumeliotiset alout of 50 patients, 33 (63.5 %) were males and 17 (36.5%) were females.

CMC Vellore Study where 62% were males, probably reflect the faster decline in GFR in males

Age Distribution:
In the present study out of 50 patients, there were 21 (42%) patients each in the age group of 25 to 45years, and 24 (48%) patients each in the age group of 45 to 65 years and 5(10%) are in the group >65 years. The average age of patients is 50.16 years.

In a similar study by dhanapriya et al.,Among the 60 patients included in the study, 45 (75%) were males and 15 (25%) were females. Among 60 patients, 25(41.7%) were in 25 -45yrs, 30(50%) were in 45 -65 yrs, 5 (9.3 %) were in >65 yrs age groups.

In a study by Margekar et al conducted on 50 ICU patients the most common age group was 30-60 years (62%).

In a study conducted by Kumar S et al mean age of CKD was 46.87 ± 14.23 years The mean age in Roumeliotiset al, a study

conducted on two ICU patients was 60 ± 18 years.

Hinderliter et al studied 198 subjects and reported that the mean age of the study participants was 61 ± 14 years, with a range of 18 – 89 years. In 11 In 1 a similar study of Chhajed et al,8 higher prevalence of CKD among males (n=39 out of 70) with a mean age of 44.5 years (range 20-75 years) was reported

Family History Of Cvd

Family history of CVD was present 8% patients with male predominance.

In the study by Dhanapriya et al., of the 60, 16 (26.66%) patients were with family history of CVD, Of which 14 (87.5%) were males and 2(12.5%) were females.

Habits And CKD

Cigarette smoking was prevalent in 32%, alcohol consumption in 56%, which might have contributed to the faster progression of the disease in these patients whereas the CKD Registry of India Report, shows cigarette smoking was prevalent in 32%, alcoholconsumption in 6.4%. the study by Dhanapriya et al., Among 60 patients, 19(31.67%) were alcoholics.

Carotid Intimal Medial Thickness With CKD:

In this study the average egfr is 32.314 ml/kg/min/BSA.

In this study 18(36%) patients were in CKD stage 4 and 6 (12%)patients were in CKD stage 5.

In the study by Kumar S et al, majority of patients had stage V CKD (67%), 21% had stage III and 14% had stage IV CKD

Hinderliter et al nearly equal numbers had stage 3 (n = 86) and stage 4 (n = 88) CKD; 24 had stage 5 CKD

Hinderliter et al diabetes (30%), hypertension (99%), and CVD (42%) were common comorbidities

The mean carotid intimal medial thickness in this study was 0.8955, the right sided average carotid intimal thickness being 0.89 and the average left sided carotid intimal medial thickness being 0.9004.

The study is showing increased cimt compared to age matched controls. a study by Margekar et almean CIMT was significantly higher in Cases (0.87±0.24) as compared to Control (0.61±0.34) group (p<0.001)
In the study by Kumar S et al, Mean CIMT in CKD patients was 0.80 ± 0.28 mm

Hinderliter et al studied 198 subjects and reported that CIMT was significantly increased in the patient group (CIMT 0.86 ± 0.21 mm compared with the control group (0.63 ± 0.17 mm) Kumar S et al showed a strong correlation between CIMT and age (r=0.267 P - 0.001)

Roumeliotiset al showed that The CIMT was increased in patients with CKD compared with age-matched controls. This suggests that prevalence of carotid atherosclerosis is significantly higher in the CKD patients compared with controls.

Kuswardhani et al showed that CIMT was found to be correlated with age (R=0.538, P<0.001) In a similar study of Chhajed et al the mean CIMT in CKD patients significantly correlated with traditional risk factors including age (r = 0.605; P <0.001)1

In the present study, CIMT was well correlated with the stage of CKD i.e., eGFR p value- 0.0004 shows significant correlation.

Kumar S et al showed that the CIMT was not correlated with the stages of CKD, but it was significantly higher in the patient with CKD at all stages compared to healthy control.

Zhang et al showed IMT 0.83 in stage 2, 0.94 in stage 3 and 0.11 in stage 4 CKD patients.

There is no significant correlation of IMT with age, sex of the patients. Though we found diabetics, hypertensives, smokers and alcoholics have an increased IMT more frequently a significant correlation could not be found.

Pascasio et al. observed a large number of vascular plaques in uremia patients and concluded that the process of advance atherosclerosis might be started with the commencement of renal failure; he suggested that there are other factors than HD treatment to accelerate arthrosclerosis.

Damjanovic et al. evaluated IMT of 45 CKD patients found higher mean carotid IMT in HD than in control group; also showed positive correlation of IMT with certain risk factors for atherosclerosis (age, duration of dialysis and lipid parameters).

Shoji and Hojs et al shows only significant determinant of number of plaques and concluded that CKD patients had advanced atherosclerosis in the carotid arteries compared with normal subjects.

Savage et al noted more prevalence of plaque in carotid and femoral artery in HD and correlation between femoral artery plaque score and age of the subjects as well as correlation of age with IMT of carotid artery.

Kato et al showed a significant correlation of IMT with age in HD patients.

Papagianni et al showed a positive correlation of plaque score with age of the subjects.

Although there is altered lipid levels in CKD patients, no correlation were found with IMT in our study.

Patricia et al shows significant increase in IMT with elevated levels.

Maria et al showed increase in IMT with elevated total cholesterol levels.

Zancetti et al found no correlation with any of the lipid parameter

Diabetes Mellitus:

In this study, the total number of diabetes mellitus type 2 patients- 29 (58%)

Kumar S et al showed that the 55 cases of CKD were diabetes In the study of Chhajed et al there was a statistically significant difference of the mean CIMT in diabetic (0.93 ± 0.25) and non- diabetic patients (0.80 ± 0.14) (P ≤0.01) In the study by dhanapriya et al. Out of 60 patients, 30 (50%) had diabetes mellitus, of which were 22 (73%)were males and 8(26.6 %) were females.

Hypertension:

In the present study, 33(66%) patients were hypertensive.

Kumar S et al showed that the 93 cases of CKD were hypertensive
Study by dhanapriya et al. showed that 32 (53.33%) patients had hypertension, of which, 26(86.66%) were males and 6(13.33%) were females.

Triglyceride Levels:

In the present study the mean triglyceride level was 185.54

mg/dl showing that CKD patients have dyslipidemia when compared to an average patient.

Kumar S et al showed that the serum triglyceride levels were significantly ($p<0.0001$) high in patients (mean=154.48 ± 40.30) mg/dl in comparison with controls (118.04 ± 38.01) mg /dl

CHOLESTEROL LEVELS:

In the present study, the mean cholesterol was 160.2 mg/dl.

There is no significant correlation observed between altered lipid levels and e GFR.

Kumar S et al showed that the Serum Cholesterol levels were high in Chronic kidney disease (mean=211.16 ± 36.10 mg/dl) patients compared to control subjects (mean=194.32 ± 34.12), (P value=0.0001)

Roumeliotiset al showed that Lipid profiles were also found to be significantly impaired in the CKD patients compared with controls.

Body Mass Index:

In our study there is no significant correlation between BMI and IMT.

Hemoglobin

The average haemoglobin in this study is 8.064 gm/dL. Prevalence of anemia increased from Stage 2 to stage 4 and the correlation was statistically significant. This is consistent with the CKD Registry of India Report where anemia was present in 32.6% of Stage 3,

57.5% of Stage 4 and 83.2% of Stage 5 patients.

There is positive correlation between hemoglobin levels and IMT.

The key focus should be the early detection and prevention of progression of CKD at stages 1 and 2 using established and emerging therapies. Cardiovascular risk factoridentification and management may depend on CKD staging.

Special focus on non-traditional risk factors in CKD stages 3-5 may be appropriate in addition to traditional risk factor modification initiated in CKD stages 1 and 2.

Lastly, there is a need to disseminate information to primary care providers who may be key players in initiating and maintaining the most appropriate management strategies. For those with established CVD and CKD that require intervention, the increased risks must be considered and addressed To execute a change in the management of patients with CKD, medical students, healthcare professionals, and established physicians, need to be educated about the prevalence and consequences of CKD. The concept that CKD is a risk factor for cardiovascular disease, and needs to be managed should be emphasized.

Screening of the high risk individuals (those with hypertension, diabetes mellitus, cardiovascular disease and first degree relatives of patients with hypertension, diabetes mellitus or renal disease) will maximize the detection of CKD and benefit a large population of patients.

Limitations

The limitations of the study were that smaller sample size and urine output criteria were not included in the diagnosis of CKD because many patients were on diuretics at admission. Also preadmission normal baseline Sr. Creatinine were not available with many patients hence this study was limited to monitoring of patients from entry to the hospital and cannot be readily used to assess the status of patients on entry to the hospital. Lack of a ,,gold standard independent measure of GFR such as an inulin or radioisotope clearance, prevented from commenting on whether SrCreatinine correlated more accurately with a true decrease in GFR or not. Some biomarkers of poor cardiovascular outcomes regarded as nontraditional cardiovascular risk factor (inflammation, oxidative stress, sympathetic activation, hyper homocysteinemia) cannot be measured due to resource limitation. Most of the patients attending the centre of the study belong to the low socioeconomic and educational status and hence are not an accurate representation of the general population. Etiological diagnosis was not taken into account. B mode ultrasonography method liable to inter observer variation. Presence of atherosclerosis was not confirmed by angiogram. Hypoalbuminemia is a nonspecific marker of micro inflammation and is elevated in systemic lupus erythematosus, rheumatoid arthritis and liver diseases.This is a cross sectional study where follow up of the patients is not possible.

Further a large multicentric study is required to confirm these results.

Conclusion And Summary

High prevalence in traditional risk factors like diabetes, hypertension, smoking, age, alcohol, increased BMI was studied along with high prevalence in non-traditional risk factors like anaemia was studied.

More than half of the study population were illiterates Less than $1/10^{th}$ of patients showed positive family history Carotid intimal medial thickness is a strong predictor of cardio vascular disease in CKD patients and maybe usefully applied in this group of patients Association of carotid intimal medial thickness with diabetes mellitus in CKD patients is strong and maybe useful in this group of patients Association of carotid intimal medial thickness with a non traditional risk factor like anaemia is strong as was correlated in this study Association between carotid intimal medial thickness and dyslipidemia could not be established in this study Association of carotiod intimal medial thickness with hypertension, smoking, alcoholism and obesity could not be correlated in this study Identifying modifiable risk factors for the progression of cardiovascular disease may lead to targeted medical interventions in high risk groups

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