ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 11, 2024

Traditional And Non-Traditional Risk Factors As ContributorsCKD: A Overview

Dr. RS. Meghasri[1],Dr. Binoy Varghese Cheriyan [2],Dr. Prakash Tigari,[3]Dr Rajitha.R[4]

1)[1] Dr R.S. Meghasri , Research Scholar, Saveetha college of Pharmacy, Saveetha Institute of Medical and Technical sciences, Saveetha University, Chennai, Tamil Nadu , 602105, India. meghasri229@gmail.com .

2)[2]*Binoy Varghese Cheriyan, Associate Professor, Department of Pharmaceutical chemistry, Saveetha college of Pharmacy, Saveetha Institute of Medical and Technical sciences, Saveetha University, Chennai, Tamil Nadu , 602105, India. lallybinoy@gmail.com . https://orcid.org/000-0003-0830-6816 .

3)[3] Dr. Prakash Tigari, Professor and Principal of Akshaya Institute of Pharmacy, Lingapura, Obalapura, Post, Tumkur, Karnataka, 572106, prakashtigari@gmail.com.

Corresponding Author * Binoy Varghese Cheriyan Associate Professor, Department of Pharmaceutical chemistry, Saveetha college of Pharmacy, Saveetha Institute of Medical and Technical sciences, Saveetha University, Chennai, 602105, Tamil Nadu,India. https://orcid.org/000-0003-0830-6816 lallybinoy@gmail.com

ABSTRACT:

Over the past few years, CKD has gained significant attention as a public forum. The professionals in medicine believe that diabetes and hypertension are the two most important CKD risk factors: cardiovascular disease s a primary factor contributing factor to morbidity and death in CKD. In stages three and four of CKD ,the risk CVD mortality doubles ,triples. The goal of the study is to report risk factors that are conventional, traditional, and non-traditional. The following are traditional risk factors: smoking, hypothyroidism, dyslipidemia, diabetes, hypertension, and testosterone, and the non- traditional risk factors include atherosclerosis, vascular calcification ,and anemia. To further lower the risk of CKD, we can summarize the connection between the illness and conventional and non-traditional cardiovascular risk factors.

Key Words :Chronic Kidney Disease, Cardiovascular disease,Vascular Calcification, Traditional and Non -traditional ,Glomerular Filtration Rate .

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 11, 2024

INTRODUCTION:

CKD is likely to rise in frequency world wide and rank fifth in terms of medical condition by 2040.[1] The term CKD refers to a group of non-communicable physiological illnesses that are connected to a progressive decline in GFR and compromised renal function. renal impairment linked to chronic renal disease can occur in five stages, ranging from moderate dysfunction to total failure.[2]

A patient with moderate to severe renal impairment usually has stage three or stage four CKD. Within stage three, there are two distinct types of renal impairment: 3A (GFR 45–59 ml/min/1.73 m2) and 3B (GFR 30-44 ml/min/1.73 m2). Stage four GFR ranges from 15 to 29 ml/min/1.73 m2.The final stage of CKD, end-ESRD, occurs when the body's kidneys are unable to sufficiently remove waste and extra fluid, necessitating dialysis or a kidney transplant.[3] Advanced CKD poses a heightened risk of mortality, with the likelihood growing CKD oescalating with age and certain concomitant conditions. Treatment has been shown to potentially delay CKD progression, avert complications and decrease (CVD risk. Due to nonspecific symptoms, CKD often goes undiagnosed until its advanced stage. [4]As shown in Table-1, GFR are used to categorize CKD. [5]

Table :1 Classification of CKD

Stages of CKD	GFR	Description
1	>90mL/min Proteinuria Or structural damage	Renal injury with a normal or elevated GFRbut additional signs of renal impairment
2	60-89mL/min Proteinuria Or structural damage	GFR slightly declining in conjunction withfurther renal disease symptoms
3a	45-59mL/min	modest decline in GFR
3b	30-44mL/min	With or without renal disease symptoms
4	13-29mL/min	Severer GFR Reduction
5	<15 mL/min	Renal failure and dialysis

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 11, 2024

Glomerular Filtration Rate:

The existence of Multimorbidity is the presence of two or more chronic conditions. According to a survey, out of 1.8 million patients, 23% of the general population is affected, withpeoplefromlowersocioeconomicgroupsbeingmoreaffected.[6]CKD is important. a factor in morbidity and death often linked to coexisting health issues that lead to adverse outcome When kidney function degrades, the risk of death rises considerably for people with diabetes mellitus, mostly because of cardiovascular issues. Diabetes and high blood pressure are key contributors to CKD and exacerbate both CKD and cardiovascular issues. Resolving modifiable risk factors can improve life expectancy and quality of life by lessening cardiovascular complications in CKD patients and slowing CKD progression to end-stage renal dysfunction (ESRD). [7]When it comes to their health, people with CKD usually have a far lower quality of life than people in general.

Complications related to CKD impact all body systems.[8]Malignant/accelerated hypertension, severe septicemia, poorly controlled chronic diabetes mellitus, HIV-associated nephropathy, and focal segmental glomerulosclerosis are the most prevalent diseases worldwide that lead to end-stage renal disease. Polycystic Kidney disease, specific in born metabolic abnormalities , and systemic lupus erythematosus(an autoimmune disease) are genetic causes of ESRD. The most frequently recognized cause of kidney transplantation is diabetes.[9]

CVD RISK FACTORS IN CKD

The notion of CVD risk factors was first presented in 1961 by the Framingham Heart Study group. They linked previously identified clinical conditions to the development offutureCVD.[10] In patients with CKD, risk factors are categorized as traditional or non-traditional **(figure:1)**.

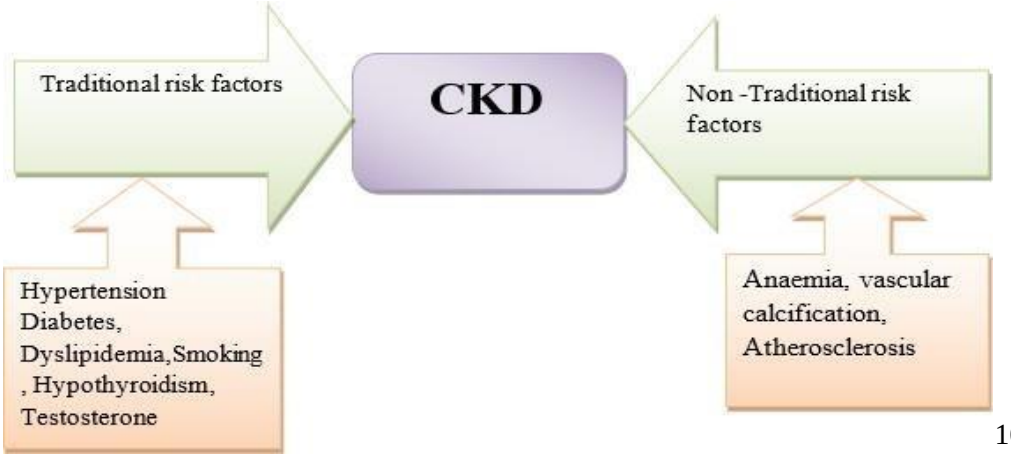


Figure 1: Risk factors for both conventional and non-traditional CKD and CVD in conjunction with renal disease.

OVERVIEW OF CVD IN CKD:

Chronic renal disease is the main cause of death and a contributing factor to CVD. [11]The risk of mortality due to CVD doubles in CKD stage and triples in stage four.[12] Evidence increasingly suggests that the presence of CKD results in distinct variations in the development and manifestation of CVD .

A team of experts from around the world detailed the existing understanding and its implications for patient treatment in critical domains like heart attack and coronary artery disease. Various cardiovascular illnesses, including congestive heart failure, cerebrovascular disease, atrial fibrillation, peripheral artery disease, and sudden cardiac death, were discussed in a clinical update conference called Kidney Disease Improving Global Outcomes (KDIGO).[13] Figure 2 Outlines the different forms of CVD that could impact individuals with CKD .An examination among hemodialysis patients in Cameroon revealed significant incidences of cardiac lesions, with findings including a high prevalence of left ventricular hypertrophy (60%), valvular calcifications (38%), cardiac failure (36%), and conduction abnormalities (33%).[14]

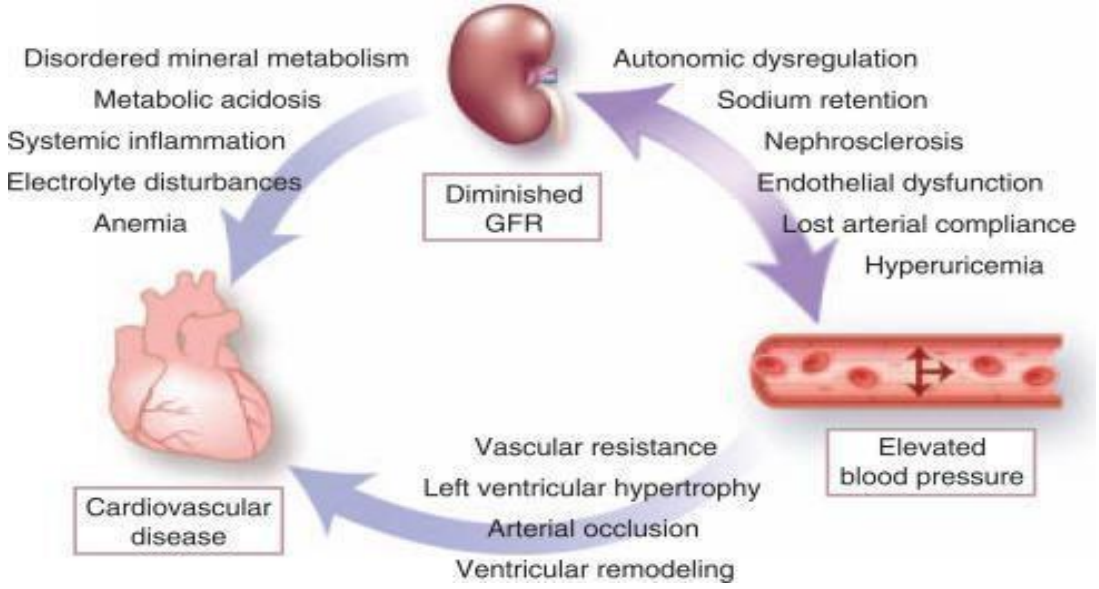


Figure 2: The dual effect of hypertension and CKD on cardiovascular risk . CKD or GFR: glomerular filtration rate.

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 11, 2024

TRADITIONAL RISK FACTORS:

Conventional cardiovascular risk factors are common in CKD patients, playing a substantial role in atherosclerotic vascular disease development even in early CKD phases. These risk factors not only impact the larger and smaller kidney vessels but also contribute significantly to the advancement of CKD and the attendant cardiovascular and cerebrovasular outcomes through hypertension , insulin resistance /diabetes, dyslipidemia and smoking. [15]

KIDNEY DISEASE WITH HYPERTENSION:

Hypertension ,which is the most significant cause of mortality worldwide and is thought to be a significant co-morbid risk associated with chronic kidney disease (CKD),is most frequently caused by CKD. Hypertension is prevalent in around 80-85% of individuals with CKD,with morepronouncedglomerularconditionsexhibitingagreaterincidenceofhighbloodpressure.The elevation of systemic blood pressure, irrespective of the underlying CKD cause,accelerates the decline in GFR,thereby establishing hypertension as a standalone risk factor for ESRD.[16] According to earlier studies, those with stage 2-3 CKD who have hypertension are more likely to experience new or recurring CV events.[17]

PATHOGENESIS OF HYPERTENSION IN CHRONIC KIDNEY DISEASE:

Patients with CKD have a complicated and diverse pathophysiology of hypertension that is frequently resistant to treatment.[17,18,19]The disease high blood pressure causes potential processes, including hormonal and neuronal alternations, that frequently work in concert to impair proper blood pressure regulation. The majority of the variables listed below (Figure 3) contribute to the development of hypertension in individuals with chronic renal disease.

DIABETES WITH CKD:

Diabetic kidney disease (DKD), previously known as In people with poorly diabetic nephropathy (DN), a controlled form of both type 1 and type 2 diabetes mellitus, is a leading cause of death.[20]DKD is marked by modifications to the structure and function of the kidneys, including mesangial expansion, glomerular sclerosis and thickening of the glomerular and tubular basement membranes.

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 11, 2024

Table2:Definition of albuminuria in diabetic kidney disease

Normoalbuminuria	<30 mg of urine albumin each day
Moderately increased albuminuria (Microalbuminuria)	Amount of urine albumin in a day: 30–300 mg Urine Albumin to Urine Creatinine Ratio: 30-300
Severely increased albuminuria (Macroalbuminuria)	Everyday urinary albumin amount: greater than 300 mg or Urine albumin to urine creatinine ratio: more than 300

It typically presents with persistent albuminuria, elevated blood pressure, declining elevated cardiovascular risks, glomerular filtration rate (GFR),and related mortality. As 2014,anestimated 380million individuals worldwide had diabetes, constituting 8.3% of the global population. Diabetes mellitus contributes to 30–47% ESRD cases worldwide, with approximately 54.4% of American type 1 diabetic patients eventually requiring renal replacement therapy (RRT).[21]

One of the most recognizable clinical indicators of DKD is albuminuria. Historically, the clinical progression of DKD typically involved the stages of early glomerular hyper filtration ,followed by microalbuminuria and macroalbuminuria ,leading to a decline in GFR, primarily observed among individuals with diabetes type 1 (figure 4).[22]However, recent research focusing on type 2 diabetes has shown that many DKD patients do not demonstrate the traditional stepwise progression described above.This challenges the conventional understanding of DKD's natural course, indicating that albuminuria in DKD represents a state that is both active and decaying as opposed to being a straight line. When macro albuminuria develops, GFR declines often and may eventually lead to ESRD.[23]

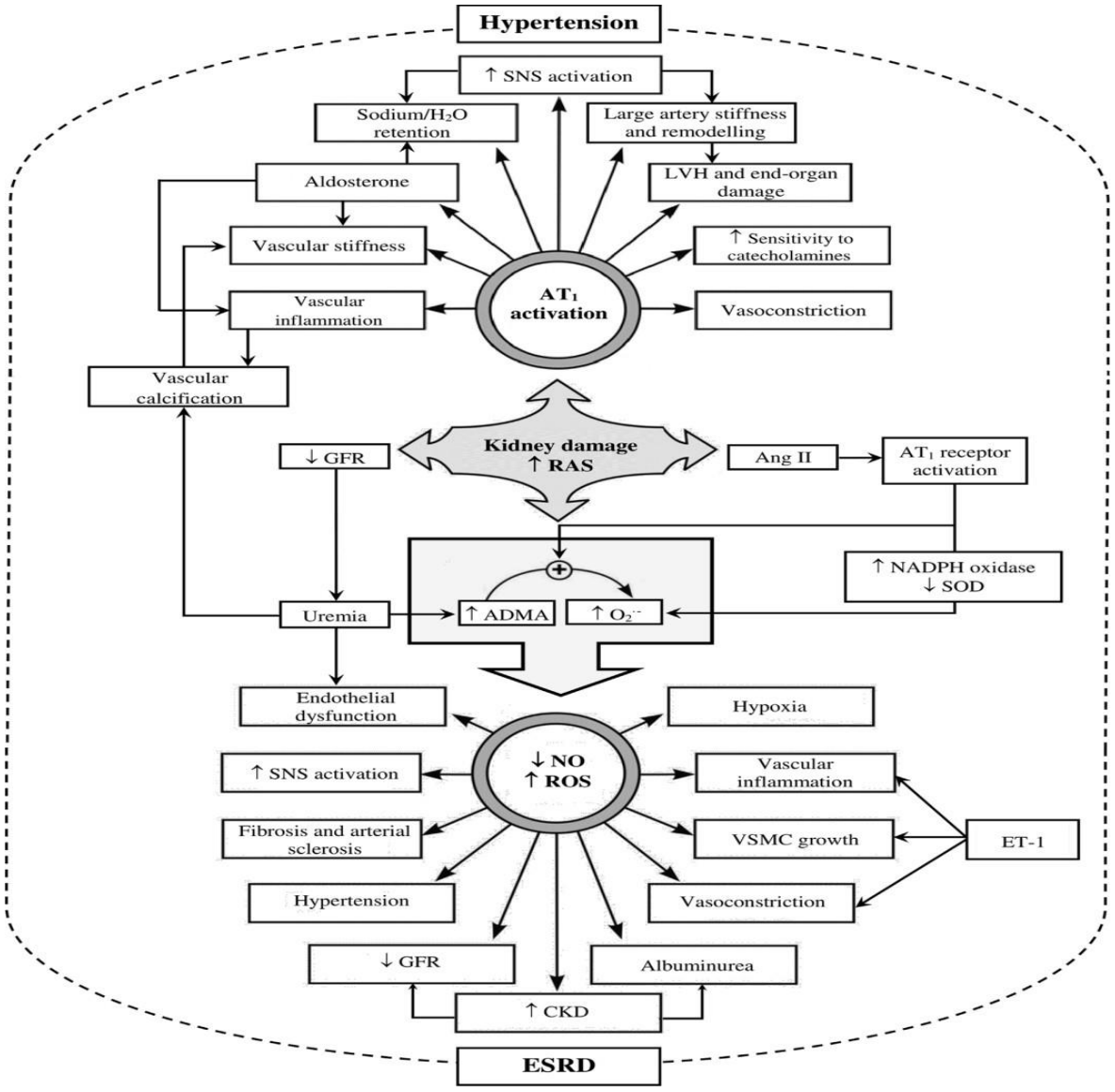


FIGURE 3. Schematic illustrating the renin-angiotensin system's function activation in end- stage renal disease, hypertension, and kidney damage progression. Angiotensin II (Ang II) levels rise when the renin-angiotensin system is activated., resulting in decreased glomerular filtration rate. This activation triggers ,and disruption of antioxidant- oxidant mechanisms, as well as height enedsympathetic nervous system activity. Reduced GFR leads to uremia, elevated endothelial dysfunction, oxidative stress, and asymmetric dimethylarginine (ADMA), and impaired nitric oxide signaling. These consequences can exacerbate sympathetic nervous system activation, vascular changes, inflammation, and systemic hypertension. Endothelin-1 receptor activation contributes to vasoconstriction, inflammation several effects, including salt retention, aldosterone release, inflammation, and vascular remodeling n, and hypertrophy. Chronic kidney disease can also induce vascular calcification, a key cardiovascular complication, further complicating CKD progressiontowardsend-stagerenaldisease.

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 11, 2024

CKDWITHDYSLIPIDEMIA:

Dyslipidemia, a recognized traditional risk factor generally associated with CKD populace, can be categorized as primary due to genetic anomalies directly impacting lipoprotein metabolism or secondary due to various conditions like diabetes mellitus, hypothyroidism, sepsis, autoimmune diseases, certain medications, liver disease, and CRI.[24,25]Patients with chronic renal insufficiency exhibit a distinct dyslipidemia profile compared to the general population, involving a lipoprotein classes across all stages of the condition. [26]

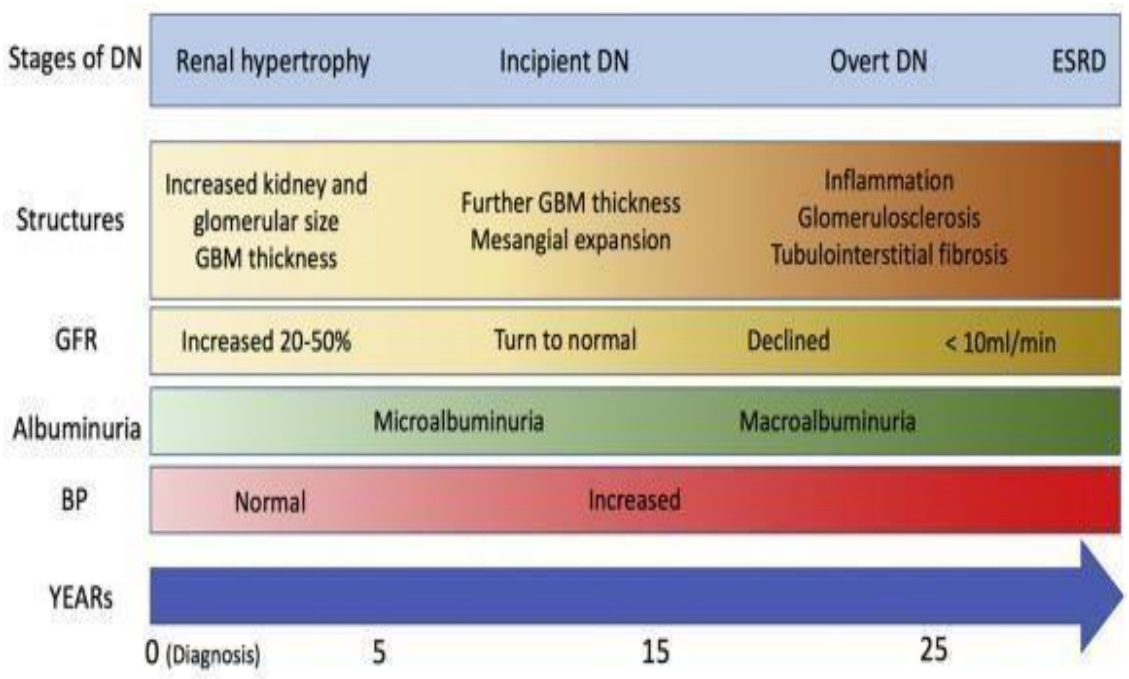


Figure4: Thenatural progression and renal alterations found in type 1 diabetes mellitus may not be the same as those seen in type 2 diabetic mellitus.Diabetic nephropathy ,ESRD, GBM, GFR ,and blood pressure(BP)are key factors in this context.

Richard Bright likely first observed hyperlipidemia in1836 while noting the "milky serum" of end-stage renal disease(ESRD)patients.[27,28]Subsequently,Baghdad and Samkels on identified hyper triglyceridemic as a hallmark of individuals under going hemodialysis, characterizing the dyslipidemia associated with CRI.[29]Dyslipidemia in CKD is defined by elevated levels of various lipids such as triglycerides, cholesterol, VLDL ,LDL ,and reduced concentration so HDL(Table:3).[30,31].An imbalance of lipids including triglycerides, and cholesterol, leads to

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 11, 2024

dyslipidemia[32].

Lipidsaretransportedtoorgansbylipoproteins,whicharemacormoleculesthatnetertheblood stream.[33,34]The degree of proteinuria and renal function both affect the lipid profile. impacting the balance of lipids that are crucial for organ transportation and are delivered by differing lipoproteins known as VLDL, LDL, and HDL depending on their densities.[35,36]

Moreover, the elevation of LDL in the blood stream is attributed to an elevated a polipoprotein B (apoB)/apoAI ratio.[37]Consequently, dyslipidemia progresses, potentially necessitating further lipid-lowering modifications for individuals with CKD.[38]

SMOKING: It is often recognized that smoking has harmful consequences on almost every organ, including the kidneys.[39]A substantial portion of the population is at risk for CKD, with around30.8millionsmok39A substantial portion of the population is at risk for chronic kidney disease (CKD), with around 30.8 million smokers. 39A substantial portion of the population is at risk for chronic kidney disease (CKD), with around 30.8 million smokers.

A substantial portion of the population is at risk for chronic kidney disease (CKD), with around 30.8 million smokers.[40]Regarding smoking, several human studies have demonstratedthatsmokingcigarettesexacerbatesendothelialdysfunction,oxidativestress,and glomerulosclerosis, all of which have a detrimental impact on the kidneys and the nervous system.

Furthermore, since, Tobacco smoking is associated with the development of albuminuria and has an impact on hemodynamic parameters such as blood pressure and peripheral vascular resistance another biomarker of cardiovascular disease, the co-occurrence of CKD and tobacco use may constitute an exceptionally high-risk state. Despite this, much Studies have been conducted in past on the connection between smoking habit and CKD progression, and little is known about the etiologic impact of smoking on CV risk and mortality in the context of CKD.[41]

Furthermore, in individuals Smoking enhances the development and progression of CKD in a synergistic manner with pre-existing CKD risk factors. Overall, the development of renal disease and new-onset CKD have been linked to smoking in a dose-dependent way. Quitting smoking has a significant positive impact on one's general well-being and quality of life in relation to health. Numerous pharmacotherapeutic strategies have been used to help people quit smoking without chronic

kidney disease .[42](Table 4) However, research has indicated that in order to reduce the danger of CKD linked to recent smoking onset, former smokers must abstain from smoking for more than 20 years, highlighting the long-lasting negative consequences of smoking.[43,44]

Table4:. Medication-assisted smoking cessation

.

	Dosing G	Renal Adjustment	Adverse reactions	Precaution
Bupropion	After three days, increase to 150 mg twice day from 150 mg once daily.	eGFR15–60: maximum 150mg daily AvoidineGFR ≤15	Nausea, constipation, insomnia ,headache, tachycardia, weight loss	Avoid in patients with a history of seizures, anorexia nervosa or bulimia, psychiatric disorder,suicidal thoughts/behaviour
Varenicline	Day 1–3: 0.5 mg every day Day 4–7: twice a day, 0.5 mg End of day 8: 1.0 mg twice a day Treatment should not take more than 12 weeks.	GFR≤30: 0.5 mg once day as a beginning dose; titrate as necessary to a maximum dose of 0.5 mg twice daily	headache, nausea, sleeplessness, and very vivid dreams	Prescription inhibitors of monoamine oxidase Stay away from mental illnesses and suicidal thoughts.
Nicotine Patch	: >10 cigarettes per day: 12 mg per day for six weeks, 14 mg per day for two weeks, and then 7 mg per day for two weeks	There is no specific adjustment recommen dation. Cautionin serious renal illness	Headache, irritated skin, and unusually vivid nightmares	Patients with angina or a recent heart attack (within two weeks) should avoid

HYPOTHYROIDISM:

Many large population-based studies have demonstrated that hypothyroidism is relatively common in kidney disease, affecting roughly 25% of individuals with moderate-to-advanced CKD.[45-47]Research has additionally shown an elevated incidence of hypothyroidism as renal function severity increases. Hypothyroidism was twice as prevalent in both people with

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 11, 2024

eGFR <30 ml/min/1.73 m2 and people with eGFR >60 ml/min/1.73 m2. 45, and every 10 ml/min/1.73 m2 drop in eGFR was associated with a 0.11 mIU/l rise in serum TSH and an 18% greater risk of hyperthyroidism.[47]It is still uncertain how precisely thyroid and renal illness are linked.

Nonetheless, several putative causes have been discovered, such as decreased cardiac output, modified intrarenal hemodynamics, decreased RAA Sactivity and generation, and enhanced tubuloglomerular feedback due to modifications to chloride channelexpression.[46]An analysis of CKD patients' TSH levels revealed a significant correlation between higher TSH levels (comparing >5.0 mIU/l with >10.0 mIU/L) and post-ESRD mortality, eventhough the TSH target recommendations specifically for this population have not yet been established.[48]

Testosterone:

Males are more likely than females to develop chronic kidney disease (CKD) and for it to proceed.[49]Althoughthereasonsforthissexdifferencearenotwell-established,sexhormones such as testosterone have been proposed as potential factors.[50]The apoptotic pathway mediated by Fas-FasL is suppressed in the presence of estradiol, and this is how testosterone may cause harm to renal tubule cells.[51]

NON-TRADITIONALRISKFACTORS ANAEMIA:

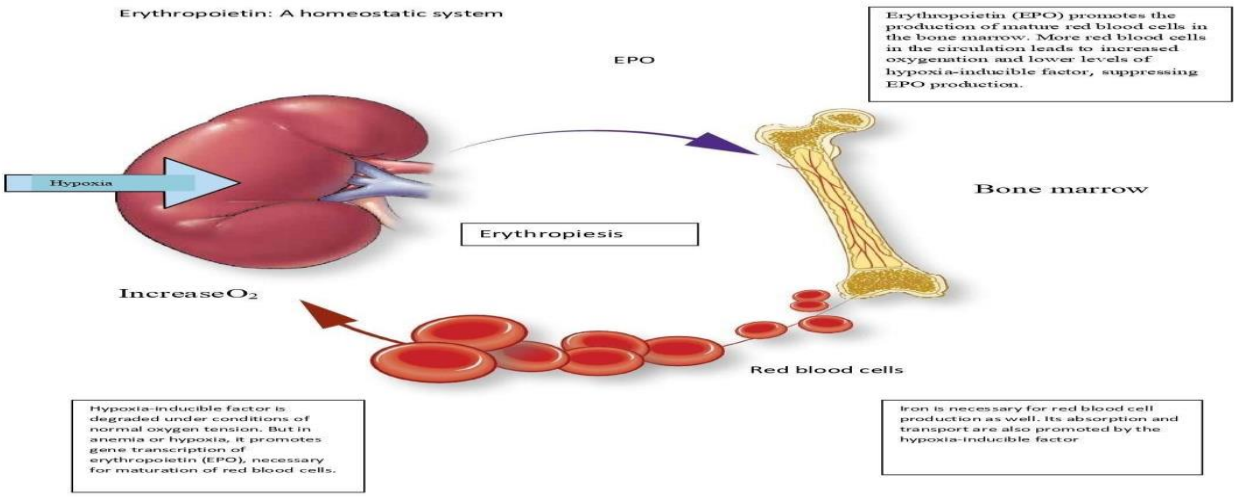
Patients with CKD have a high rate of morbidity and mortality, in addition to numerous additional CKD-related medical issues. Anemia, which frequently appears early in CKD and lowers quality of life, is one of the leading medical conditions affecting this population. It has demonstrated a high degree of predictive power for adverse outcomes, such as complications and cardiovascular mortality.[51]The World Health Organization defines anemia as having a haemoglobin concentration in adult males and non- menstruation females that is less than 13.0 g/dL, or less than 12.0 g/dL in women who are menstruating. [52] Anemia in chronic kidney disease is independently associated with the risk of death.[53]

Anemia is associated with adverse cardiac outcomes such as a heightened risk of myocardial infarction, coronary revascularization, and heart failure readmission. It is also linked to accelerated left ventricular hypertrophy progression, inflammation, increased myocardial and peripheral oxygen demand, higher rehospitalization rates, depression, fatigue,

impaired exercise tolerance, and stroke.[54] The decline in erythropoietin production due to decreasing GFR often underlies anemia in chronic renal disease, although various factors contribute to this complex process, including shortened red blood cell lifespan, deficiencies in folate and vitamin B12, insufficiencies in both absolute and functional iron, and the uremic milieu's suppression of erythropoiesis.[55]Erythropoietin is primarily produced by a specific population of peritubular interstitial cells located in the deep cortex and outer medulla of the kidneys.[56]

Erythropoietin is also produced by the parenchymal cells of the liver, albeit much less.[57] The rateofrenalerythropoietinsynthesisiscontrolledbytissueoxygenationratherthanrenalblood flow. Production increases as arterial oxygen tension and hemoglobin concentration decrease.[58] (Figure: 5)

Figure: 5 Erythropoietin



Vascular Calcification:

As per the definition in Health Science Descriptors, vascular calcification (VC) represents a condition where the tunica media and intima undergo calcification, leading to thickening and reduced elasticity in muscle arteries.[59] The term "VC" commonly denotes the calcification of these layers, although They differ from one another in some ways. Usually,intima

calcificationindicatesadvancedatherosclerosis,seeninatherosclerоticplaquewithinmajorarteries liketheaortaandcoronaryarteries.Ontheotherhand,mediacalcificationinvolveswidespreadminer al depositionalongelasticfibers This condition is frequently observed in patients with metabolic syndrome, diabetes, and CKD. VC is a common issue among CKD patients, and its prevalence is increasing as renal functionprogressively declines.[60]

Studies reveal that compared to patients without chronic kidney disease (CKD), those with renal disease have more severe and progressivecardiovascular calcifications. Complex mechanisms in CKD promote the development of VC. Kidney injury-related changes in iron, calcium, and phosphate levels upset the biochemical balance and impact vascular cell bone remodelling. The aetiology of VC in CKD and how it is related to changes in bone and mineral homeostasis are shown in Figure 6.Pulmonary hypertension(PH),an overlapping consequence in individuals with renalillness ,is more common in CKD patients with risk factors such as VC .[61]

FIGURE-6 Vascular Calcification

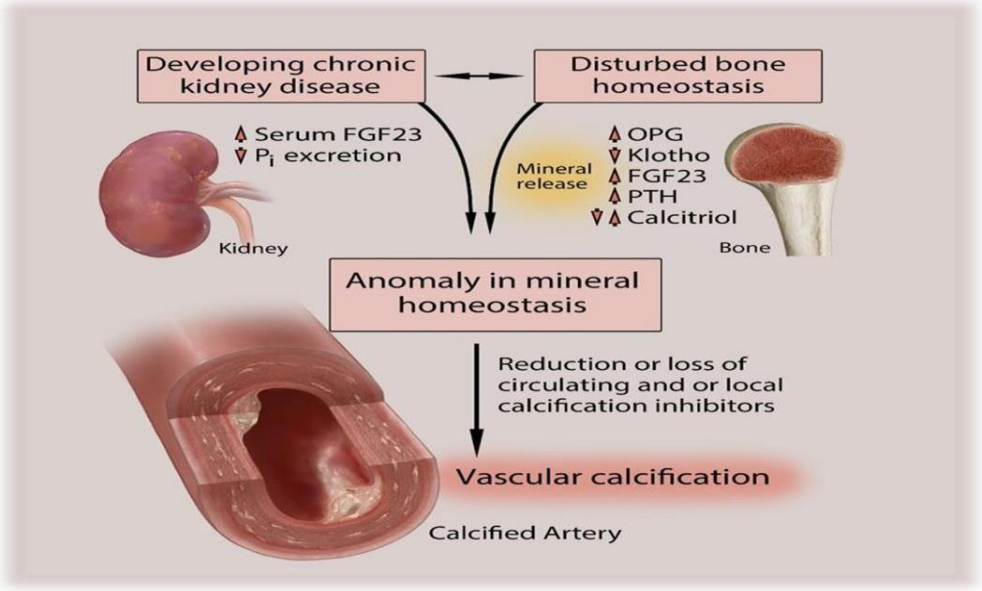


Figure:6.The pathophysiology of vascular calcification in CKD includes changes in mineral homeostasis and bone metabolism that are often observed and intricately linked. Declination of kidneyfunction causes increased levels of blood FGF23 and decreased excretion of organic phosphate, resulting in a clinical state that is mirrored by multiple biomarkers, including calcitriol, PTH, OPG, and Klotho. Changes in the serum and tissue levels of calcium,

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 11, 2024

phosphate, and magnesium are also brought on by the disturbed mineral homeostasis. These changes in turn lead to inflammation and other metabolic disorders that ultimately cause the reduced or complete loss of circulating and/or local calcification inhibitors such as fetuin-A, PPi, and MGP, which in turn causes vascular calcification.

This condition is frequently observed in patients with metabolic syndrome, diabetes, and CKD. VC is a common issue among CKD patients, and its prevalence is increasing as renal function progressively declines[60].Studies reveal that compared to patients without chronic kidney disease (CKD), those with renal disease have more severe and progressivecardiovascular calcifications. Complex mechanisms in CKD promote the development of VC. Kidney injury-related changes in iron, calcium, and phosphate levels upset the biochemical balance and impact vascular cell bone remodelling. The aetiology of VC in CKD and how it is related to changes in bone and mineral homeostasis are shown in Figure 6.Pulmonary hypertension(PH),an overlapping consequence in individuals with renalillness ,is more common in CKD patients with risk factors such as VC .[61]

Atherosclerosis: Cardiovascular disease is a significant complication of chronic kidney disease, with patients experiencing accelerated atherosclerosis. The onset of atherosclerotic lesions in early renal dysfunction stages and notable thickening of peripheral artery walls due to increased arterial media calcification have been observed.[62] The elevated cardiovascular disease risk in renal patients correlates with increased morbidity and mortality, with cardiovascular disease-related mortality progressively rising as renal function declines. Even a minor decrease in glomerular filtration rate during the second stage of chronic renal illness increases the risk of cardiovascular disease by two to three times; in dialysis patients, this risk is increased by 10 to 100 times when compared to the general population.[63]

CONCLUSION:

In summary, chronic kidney disease poses a significant public health challenge, with diabetes and hypertension emerging as primary risk factors. The relationship between conventional risk factors, such as smoking ,dyslipidemia, diabetes ,and hypertension and non-traditional risk factors such as atherosclerosis, vascular calcification, anemia, hypothyroidism, and testosterone imbalance plays a role in the advancement of CKD and its related cardiovascular complications.Cardiovasculardiseaseremainstheleadingcauseofmorbidityandmortalityin CKD patients, with a notably increased mortality risk in CKD stages 3 and 4. Understanding the intricate relationship between CKD and CVD is essential for enhancing patient outcomes.

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 11, 2024

Implementing management strategies that target modifiable risk factors can reduce the risk of CVD and slow the progression of CKD to ESRD, ultimately improving both survival rates and quality of life.

Addressing chronic kidney disease necessitates a thorough evaluation of risks, prompt identification, and timely intervention to control both conventional and unconventional risk factors. Implementing multidisciplinary methods that combine medical care, lifestyle adjustments, and tailored medication regimens based on individual patient characteristics is crucial for enhancing outcomes in chronic kidney disease patients. Additionally, continuous research is imperative to unveil the intricate mechanisms connecting chronic kidney disease and cardiovascular disease, paving the path for innovative treatment methods and better patient care. Dealing with the complex nature of chronic kidney disease and its heart-related complications requires collaborative efforts from healthcare providers, policymakers, and the wider community to enforce preventive measures, enhance patient education, and guarantee access to comprehensive healthcare services. By emphasizing early intervention and holistic management strategies, we can alleviate the challenges of chronic kidney disease and up lift the overall health and quality of life of affected individuals globally

REFERENCES:

1. K. J. Foreman, N. Marquez, A. Dolgert et al., "Forecasting life expectancy, years of life lost, and all- cause and cause-specifc mortality for 250 causes of death: reference and alternative scenarios for 2016- 40 for 195 countries and territories," Te Lancet, vol. 392, pp. 2052–2090, Article ID 10159, 2018.

2. Mousa Ghelichi-Ghojogh, Mohammad Fararouei, Mozhgan Seifand, Maryam Pakfetrat. Chronic kidney disease and its health-related factors: a case-control study. BMC Nephrology. (2022) 23:241-7. https://doi.org/10.1186/s12882-021-02655- w:24;1-7.

3. Abboud H, Henrich WL. Clinical practice. Stage IV chronic kidney disease. New Eng J Med 2010; 362: 56-65.

4. National Institute for Health Care and Excellence. Chronic Kidney Disease. NICE clinical guideline 73, 2008. Available on www.guidance.nice.org.uk.

5. Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 2012; 380:37–43.

6. Clare MacRae, Stewart W Mercer, Bruce Guthrie and David Henderson. Co-morbidity in chronic kidney disease: a large cross-sectional study of prevalence in Scottish primary care. British Journal of General Practice, March 202; e243-249.

7. Sullivan M, Rankin A, Jani B, et al. Associations between multimorbidity and adverse clinical outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. BMJ Open 2020; 10(6): e038401.

8. Olumuyiwa John Fasipe , Peter Ehizokhale Akhideno , Sampson Omagbemi Owhin , et al. The Co- morbidity Profile among Chronic Kidney Disease Patients in Clinical Practice: A Prospective Study. International Archives ofHealth Sciences. March 27, 2019; 46-51.

9. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J. Factors of risk in the development of coronary heart disease–six-year follow-up experience: the Framingham Study. Ann Intern Med. 2009; 55:33-50.

10)Sarnak MJ, Amann K, Bangalore S, et al. Chronic kidney disease and coronary artery disease: JACC state-of-the-art review. J Am Coll Cardiol 2019;74:1823–38. https://doi. org/10.1016/j.jacc.2019.08.1017; PMID: 31582143.

11) Charles A. Herzog, Richard W. Asinger, Alan K. Berger, David M. Charytan et al . Cardiovascular disease in chronic kidney disease.A clinical update from Kidney Disease: ImprovingGlobal Outcomes (KDIGO). Kidney International (2011) 80, 572–586.

12) Kaze FF, Kengne A, Djalloh AA, Ashuntantang G, Halle MP, Menanga AP, et al. Pattern and correlates of cardiac lesions in a group of sub-Saharan patients on maintenance haemodialysis. Pan Afr Med J. 2014; 17:3. DOI:10.11604/pamj.2014.17.3.3422.

13)Joachim Jankowski , PhD Jürgen Floege, MD Danilo Fliser, MD Michael Böhm , MD Nikolaus Marx , MD. Cardiovascular Disease in Chronic Kidney Disease Pathophysiological Insights and Therapeutic Options. Circulation. 2021;143:1157–1172. DOI: 10.1161/CIRCULATIONAHA.120.050686.

14) Omar Z. Amee Hypertension in chronic kidney disease: What lies behind the scene. Frontiers in Pharmacology.2022; 13 : 1-29. https://doi.org/10.3389/fphar.2022.949260

15)Muntner, P., He, J., Astor, B. C., Folsom, A. R., and Coresh, J. (2005). Traditional and nontraditional risk factors predict coronary heart disease in chronic kidney disease: Results from the atherosclerosis risk in communities study. J. Am. Soc. Nephrol. 16, 529–538. doi:10.1681/ASN.2004080656.

16) Campese, V., Mitra, N., and Sandee, D. (2006). Hypertension in renal parenchymal disease: Why is it so resistant to treatment? Kidney Int. 69, 967–973. doi:10.1038/sj.ki.5000177.

17) Townsend, R. R., and Taler, S. J. (2015). Management of hypertension in chronic kidney disease. Nat.

Rev. Nephrol. 11, 555–563. doi:10.1038/nrneph.2015.114.

18) Hamrahian, S. M. (2022). “Hypertension and cardiovascular disease in patients with chronic kidney disease,” in Approaches to chronic kidney disease (Springer), 281–295.

19)Gross JL, De Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T. Diabetic nephropathy: diagnosis, prevention, and treatment. Diabetes Care 2005;28(1):164e76.

20). de Boer IH, Rue TC, Cleary PA, Lachin JM, Molitch ME, Steffes MW, et al. Long-term renal outcomes of patients with type 1 diabetes mellitus and microalbuminuria: an analysis of the diabetes control and complications trial/epidemiology of diabetes interventions and complications cohort. Arch Intern Med 2011;171(5):412e20.

21) . Mogensen CE. How to protect the kidney in diabetic patients: with special reference to IDDM. Diabetes 1997;46(Suppl 2): S104e11.

22) . Retnakaran R, Cull CA, Thorne KI, Adler AI, Holman RR. Risk factors for renal dysfunction in type 2 diabetes: U.K. Prospective Diabetes Study 74. Diabetes 2006;55(6):1832e9.

23) Rader DJ, Hobbs HH. Disorders of lipoprotein metabolism. In: Gardner DG, Shoback D, editors. Greenspan’s basic and clinical endocrinology, 8th ed. McGraw Hilll; 2007. p. 333–54.

24). Mahley RW, Weisgraber KH, Bersot TP. Disorders of lipid metabolism. In: Kronenberg HM, Melmed Shlomo, Polonsky KS, Larsen PR, editors. Williams textbook of endocrinology, 11th ed. Sauders Elsevier; 2008. p. 1589–653.

25) Saland JM, Ginsberg HN. Lipoprotein metabolism in chronic renal insufficiency. Pediatr Nephrol. 2007;22:1095–112.

26) Joana Mesquitaa, Ana Varelaa, and JoseLuı´s Medinaa. Dyslipidemia in renal disease: Causes, consequences and treatment.Endocrinol nutr.2010;57(9):440-448.

27) Piecha G, Adamczak M, Ritz E. Dyslipidemia in chronic kidney disease: pathogenesis and intervention. Pol Arch Med Wewn. 2009;119:487–92.

28) Attman PO, Samuelsson O. Dyslipidemia of kidney disease. Curr Opin Lipidol. 2009;20:293–9.

29) . Cases A, Coll E. Dyslipidemia and the progression of renal disease in chronic renal failure patients. Kidney Int Suppl. 2005;(99):S87–S93.

30). Weiner DE, Sarnak MJ. Managing dyslipidemia in chronic kidney disease. J Gen Intern Med. 2004;19:1045–1052.

31) Diabetes Canada Clinical Practice Guidelines Expert, Committee; Mancini, G.B.J.; Hegele, R.A.; Leiter, L.A. Dyslipidemia. Can. J. Diabetes 2018, 42 (Suppl. S1), S178–S185.

32) Illingworth, D.R. Lipoprotein Metabolism. Am. J. Kidney Dis. 1993, 22, 90–97.

33) Barter, P. Lipoprotein Metabolism and CKD: Overview. Clin. Exp. Nephrol. 2014, 18, 243–246.

34) Lo, J.C.; Go, A.S.; Chandra, M.; Fan, D.; Kaysen, G.A. GFR, Body Mass Index, and Low High-Density Lipoprotein Concentration in Adults with and without CKD. Am. J. Kidney Dis. 2007, 50, 552–558.

35)Attman, P.O.; Samuelsson, O.; Alaupovic, P. Lipoprotein Metabolism and Renal Failure. Am. J. Kidney Dis. 1993, 21, 573–592.

36). Rosenstein, K.; Tannock, L.R. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update. Am. J. Kidney Dis. 2012, 60, 850–886.

37) Atar, D.; Jukema, J.W.; Molemans, B.; Taub, P.R.; Goto, S.; Mach, F.; CerezoOlmos, C.; Underberg, J.; Keech, A.; Tokgözo ˘glu, L.; et al. New Cardiovascular Prevention Guidelines: How to Optimally Manage Dyslipidaemia and Cardiovascular Risk in 2021 in Patients Needing Secondary Prevention? Atherosclerosis 2021, 319, 51–61.

38) . How Tobacco Smoke Causes Disease: the Biology and Behavioral Basis for Smoking-Attributable Disease: a Report of the Surgeon General. 2010.

39) . Cornelius ME, Wang TW, Jamal A et al. Tobacco product use among adults - United States, 2019. Morb Mortal Wkly Rep 2020;69:1736–42. https://doi.org/10.15585/mmwr. mm6946a4 118.

40) Michele Provenzano, Rafaele Serra, Ashour Michael , Davide Bolignano , Giuseppe Coppolino et. al Smoking habit as a risk amplifer in chronic kidney disease patients. Scientifc Reports .(2021) 11:14778 . https://doi.org/10.1038/s41598-021-94270-W.

41) Robin Lo, Yoko Narasaki,, Sean Lei, and Connie M. Rhee. Management of traditional risk factors for the development and progression of chronic kidney disease. Clinical Kidney Journal, 2023, vol. 16, no. 11, 1737–1750.

42) Jo W, Lee S, Joo YS et al. Association of smoking with incident CKD risk in the general population: a communitybased cohort study. PLoS ONE 2020;15:e0238111.https://doi. org/10.1371/journal.pone.0238111.

43) Ohkuma T, Nakamura U, Iwase M et al. Effects of smoking and its cessation on creatinine- and cystatin C-based estimated glomerular filtration rates and albuminuria in male patients with type 2 diabetes mellitus: the Fukuoka Diabetes Registry. Hypertens Res 2016;39:744–51. https://doi. org/10.1038/hr.2016.51.

44)Lo JC, Chertow GM, Go AS *et al.* Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. *Kidney Int* 2005;**67**:1047–52.

45)Rhee CM. The interaction between thyroid and kidney dis- ease: an overview of the evidence. *Curr Opin Endocrinol Diabetes Obes* 2016;**23**:407–15. https://doi.org/10.1097/MED. 0000000000000275.

46)Rhee CM, Kalantar-Zadeh K, Streja E *et al.* The relationship between thyroid function and estimated glomerular filtra- tion rate in patients with chronic kidney disease. *Nephrol Dialysis Transpl* 2015;**30**:282–7. https://doi.org/10.1093/ndt/ gfu303

47) . You AS, Sim JJ, Kovesdy CP et al. Association of thyroid status prior to transition to end-stage renal disease with early dialysis mortality. Nephrol Dialysis Transpl 2019;34:2095–10.

48)Neugarten J, Acharya A, Silbiger SR. Effect of gender on the progression of nondiabetic renal disease: a meta-analysis. J Am Soc Nephrol 2000;11:319–29.

49) Schlondorff D, Banas B. The mesangial cell revisited: no cell is an island. J Am Soc Nephrol 2009;20:1179–87.

50) . Verzola D, Gandolfo MT, Salvatore F et al. Testosterone promotes apoptotic damage in human renal tubular cells. Kidney Int 2004;65:1252–61.

51)Weiner D.E., Tighiouart H., Vlagopoulos P.T., et. al.: Effects of anemia and left ventricular hypertrophy on cardiovascular disease in patients with chronic kidney disease. J Am Soc Nephrol 2005; 16: pp. 1803-1810.

52) World Health Organization. *Database of anemia . Worldwide prevalence of anaemia 1993–2005* . <www.who.int/vmnis> ; 2009 [accessed 7.07.09].

53) . United States Renal Data System. Chapter 3. Morbidity & mortality in patients with CKD. www.usrds.org/2012/vie w/v1_03.aspx. Accessed June 9, 2016.

54)Geores Nakhoul, MD, , James F. Simon MD. Anemia of chronic kidney disease: Treat it, but not too aggressively. CLEVELAND CLINIC JOURNAL OF MEDICINE .2016;18:613-739. doi:10.3949/ccjm.83a.15065.

55) . Agarwal AK. Practical approach to the diagnosis and treatment of anemia associated with CKD in elderly. J Am Med Dir Assoc 2006; 7(suppl 9):S7–S12.

56)Bernhardt WM, Wiesener MS, Scigalla P, et al. Inhibition of prolyl hydroxylases increases erythropoietin production in ESRD. J Am Soc Nephrol 2010; 21:2151–2156.

57). Provenzano R, Fadda G, Bernardo M, et al. FG-2216, a novel oral HIF-PHI, stimulates erythropoiesis and increases hemoglobin concentration in patients with non-dialysis CKD. Am J Kidney Dis 2008; 51:B80.

58) Jelkmann W. Erythropoeitin: structure, control of production and function. Physiol Rev 1992; 72:449–489.

59) . Health Science Descriptors [cited 2012 december 07]; 1(1):[1 screen]. Available from: URL: http://decs.bvs.br/.

60) Temmar M, Liabeuf S, Renard C, Czernichow S, Esper NE, Shahapuni I, et al. Pulse wave velocity and vascular calcification at different stages of chronic kidney disease.