INTRODUCTION

The large community of microbes residing in the intestinal tract (microbiome) constitutes a dynamic and symbiotic ecosystem that is in constant interaction with the host metabolism. Under normal conditions, the gut microbiome provides trophic and protective f unctions **(Nosratola et al., 2013) .**

Normal gut microbiota influences the well-being of the host by contributing to its nutrition, metabolism, physiology, and immune function **(Bäckhed et al., 2005).**

Disturbance of normal gut microbiota (dysbiosis) has been implicated in the pathogenesis of diverse illnesses, such as obesity, type 2 diabetes, inflammatory bowel disease, and cardiovascular disease **(Ramezani and Raj., 2014).**

Chronic kidney disease (CKD) and its treatment can significantly alter the biochemical milieu of the intestinal tract and, as such, may alter the structure, composition, and function of microbial flora. This may disturb the symbiotic relationship that prevails under normal conditions and lead to the production and absorption of proinflammatory and otherwise harmful

byproducts, and simultaneously limit the beneficial functions and products conferred by the normal flora. Such events can contribute to uremic toxicity, inflammation, and cardiovascular, nutritional, and other complications of CKD **(Nosratola et al., 2013).**

It is well documented that CKD patients have an extremely high risk of developing cardiovascular disease (CVD) compared with the general population, so much so that in the early stages of CKD patients are more likely to develop CVD than they are to progress to ESRD. Various pathophysiological pathways and explanations have been advanced and suggested to account for this, including endothelial dysfunction, dyslipidaemia, inflammation, left ventricular hypertrophy and cardiac autonomic dysfunction **(Hajhosseiny et al., 2012).**

The association between bacteria and atherosclerosis has been known for more than two decades **(Stoll et al., 2004).**

The focus has shifted from bacteria to its product, endotoxin, for its role in the development of atherosclerosis **(Wiedermann et al., 1999).**

In addition, certain intestinal bacteria can generate uremic toxins that are absorbed into the blood and are normally cleared by the kidney. Protein fermentation by gut microbiota results in the generation of different metabolites, including phenols and indoles**(Macfarlane , Macfarlane .,2012).** An elevated level of such metabolites are associated with vascular stiffness, aortic calcification, and higher cardiovascular mortality.

AIM OF THE WORk

To evaluate the role of gut microbiota mainly *lactobacillus acidophilus* in predicting the risk of cardiovascular complications among chronic kidney diseases patients.

Chronic kidney Disease

Introduction:

The definition and classification of chronic kidney disease (CKD) were introduced by the National Kidney Foundation (NKF) and Kidney Disease Outcomes Quality Initiative (KDOQI) in **2002**, and were subsequently adopted with minor modifications by the international guideline group Kidney Disease Improving Global Outcomes (KDIGO) in **2004**. **(Levey et al.,2005).**

These CKD guidelines shifted the concept of kidney disease from that of a rare life-threatening condition requiring care by nephrologists to that of a common condition with a range of severity meriting attention by general internists, and demanding strategies for prevention, early detection, and management **(Levey et al.,2009).**

The guidelines had a major effect on clinical practice, research, and public health, but also generated substantial controversy **(Eckardt et al.,2009).**

Defintion and staging of CHRONIC KIDNEY DISEASE:

According to KDOQI and KDIGO CKD is a group of disorders characterized by changes in kidney structure and function, which manifest in various ways depending upon the underlying cause and the severity of disease **(Levey et al.,2009).**

Risk factors for CKD include genetic and sociodemographic predispositions, or the presence of diseases which can initiate and propagate kidney disease.

Renal failure is the end-stage of CKD and is defined as severely reduced kidney function or treatment with dialysis. The term "end-stage kidney disease" (ESkD) generally refers to chronic kidney failure treated with either dialysis or transplantation. Acute kidney injury (AKI) may complicate CKD and hasten its progression **(James et al.,2010)**

CKD is usually asymptomatic in its early stages. Symptoms usually appear in later stages in association with complications. In addition to commonly recognized hormonal and metabolic complications such as anemia and hyperparathyroidism, CKD complications include increased risks for systemic drug toxicity, cardiovascular disease, infection,gastrointestinal complications, cognitive impairment, and impaired physical function **(Fink et al.,2009).**

Complications are usually occur at later stages, and may lead to death before kidney disease progresses to kidney failure. Complications may also occur from the adverse effects of interventions used to prevent or treat the disease.

According to the KDOQI and KDIGO guidelines that CKD is defined by the presence of structural renal damage or decreased kidney function for three or more months, irrespective of the cause **(KDIGO. Chapter 1.,2013) .**

The persistence of the structural renal damage or decreased function for at least three months duration is necessary to distinguish CKD from acute kidney disease. Kidney damage refers to histopathological abnormalities, whether established via renal biopsy or imaging studies, or inferred from markers such as urinary sediment abnormalities or increased rates of urinary albumin excretion. Decreased kidney function refers to a decreased glomerular filtration rate (GFR), which is usually estimated (eGFR) using serum creatinine calculated by one of several available equations.

Decreased GFR — GFR is generally considered to be the best index of overall kidney function, and decreasing GFR

is the hallmark of progressive kidney disease **(Hostetter et al.,1981).**

Measured GFR is variable in normal individuals by age and gender **(Wesson 1969)**,serum creatinine , dietary protein intake, and possibly by race-ethnicity, although the magnitude of racial variations are not well known. Based upon a clearance measurements in healthy people and in people with kidney disease, the widely accepted threshold defining a decreased GFR is less than 60 mL/min per 1.73 m2; ESKD is defined as a GFR <15 mL/min per 1.73 m2 or treatment by dialysis,renal transplantion.

According to **the KDIGO** measured GFR below this threshold should be considered part of the definition of CKD. GFR can be measured directly by using the clearance of exogenous filtration markers e.g inulin or iothalamate **(Stevens et al.,2006**).

In routine practice, therefore, individuals who have an eGFR below 60 mL/min per 1.73 m2 is defined as having CKD.

These individuals have a significantly increased risk cardiovascular mortality, ESRD, AKI and CKD progression in compared with those whose eGFR is 60 mL/min per 1.73 m2 or higher, even if the ACR is normal**(KDIGO. Chapter 1: 2013).**

GFR estimation — The various GFR estimating equations use serum creatinine along with combination of age, gender , race and body size as surrogates for the non-GFR determinants of serum creatinine, and provide more accurate estimates of measured GFR than serum creatinine alone . **(Stevens .,2009).**

Commonly used estimating equations are imperfect, providing GFR estimates that are usually lower than, and which can occasionally be widely disparate from, the measured GFR.

The Modification of Diet in Renal Disease **(MDRD)** Study equation is a frequently used GFR estimating equation in the US**(Stevens et al.,2007).**

However, the Chronic Kidney Disease Epidemiology Collaboration **(CKD-EPI)** equation is considered to be more accurate than **the MDRD** Study equation, especially at a GFR >60 mL/min per 1.73 m2, and is replacing the **MDRD** Study equation**(Earley et al.,2012).**

Both equations use age, gender, and race in addition to serum creatinine, and assign race as either black (eg, African American) versus non-black. Modifications of the equations for other geographical regions and racial-ethnic groups have been performed **(Teo et al .,2011).**

Cystatin C is an alternative endogenous filtration marker that may have advantages over creatinine for GFR estimation because it is less affected by race and muscle wasting, and because it is more predictive of subsequent cardiovascular disease and mortality **(Shlipak et al .,2013).**

Use of cystatin C and creatinine together enables more accurate GFR estimates **(Inker et al .,2011)**, and more accurate predictions of risk **(Shlipak et al .,2013).**

Kidney damage — Kidney damage includes pathologic abnormalities in the native or transplanted kidney. Kidney damage is identified in most of the cases by the presence of one of the following clinical markers:

●**Albuminuria** − In clinical practice, albuminuria is considered the most frequently assessed marker of kidney damage. Albuminuria means increased glomerular permeability to macromolecules**(Remuzzi et al .,2006).**

Albuminuria may reflect primary kidney disease or kidney involvement in systemic disease. In particular, albuminuria may represent endothelial dysfunction, such as can be seen with hypertension, diabetes,immune mediated diseases, hypercholesterolemia, smoking, obesity, and other disorders.

●**Urinary sediment abnormalities** − Urinary sediment abnormalities such as red blood cell casts or white blood cell casts may indicate the presence of glomerular injury or tubular inflammation.

●**Imaging abnormalities** − Kidney damage may be detected by the presence of imaging abnormalities such as polycystic kidneys, hydronephrosis, and small and echogenic kidneys and poor corticomedullary differention .

●**Pathologic abnormalities** − A kidney biopsy is examined by light or electron microscope may reveal evidence for glomerular, vascular, or tubulointerstitial disease.

●Kidney transplantation − Patients with a history of kidney transplantation are assumed to have kidney damage whether or not they have documented abnormalities on kidney biopsy or markers of kidney damage.

Staging of CKD :

The aim of CKD staging is to guide management, including stratification of risk for progression and complications of CKD. Risk stratification is used as a guide to inform appropriate

treatments and the degree of monitoring and patient education**(Levey et al.,2009)**.

In patients who are diagnosed as CKD using the criteria described above, staging of the CKD is done according to **(KDIGO. Chapter 1 .,2013)**.

- Six categories of GFR (G stages)
- Three categories of albuminuria (A stages)

Staging patients with CKD according to cause, GFR, and albuminuria enhances risk stratification for the major complications of CKD .

Cause of disease — Identifying the cause of kidney disease (eg, diabetes, drug toxicity,hypertension, auto-immune diseases, urinary tract obstruction, kidney transplantation, etc.) enables specific therapy directed at preventing further injury. In addition, the cause of kidney disease has implications for the rate of progression and the risk of complications .

It can be difficult to ascertain the cause of kidney disease. In clinical practice, CKD is most often discovered as decreased eGFR during the evaluation and management of other medical conditions.

GFR — The GFR (G-stages) follow the original CKD classification scheme :

- ●G1 − GFR >90 mL/min per 1.73 m2
- ●G2 − GFR 60 to 89 mL/min per 1.73 m2
- ●G3a − GFR 45 to 59 mL/min per 1.73 m2
- ●G3b − GFR 30 to 44 mL/min per 1.73 m2
- ●G4 − GFR 15 to 29 mL/min per 1.73 m2
- ●G5 − GFR <15 mL/min per 1.73 m2 or treatment by dialysis

Since the original KDOQI classification was published, stage 3 CKD (a GFR of 30 to 59 mL/min per 1.73 m2) has been subdivided into GFR stages 3a and 3b to more accurately reflect the continuous association between lower GFR and risk for mortality and adverse kidney outcomes .

Patients receiving treatment with dialysis are subclassified as GFR stage 5D to highlight the specialized care that they require.

Albuminuria — The three albuminuria stages follow familiar definitions of normal, moderately increased (formerly called "microalbuminuria"), and severely increased (formerly called "macroalbuminuria" and nephrotic range) albuminuria :

- ●A1 − ACR <30 mg/g (<3.4 mg/mmol)

- A2 − ACR 30 to 299 mg/g (3.4 to 34.0 mg/mmol)
- A3 − ACR ≥300 mg/g (>34.0 mg/mmol)

The addition of albuminuria staging to GFR staging is new since the original KDOQI classification scheme was published **(Levey et al.,2005).**

Albuminuria staging has been added because of the graded increase in risk for morbidity, mortality, progression of CKD, and ESRD at higher levels of albuminuria, independent of eGFR, without an apparent threshold value **(Levey et al.,2011).**

The increase in risk is significant for urine ACR values ≥30 mg/g, even when GFR is >60 mL/min per 1.73 m2, consistent with the current threshold value for albuminuria (≥30 mg/g) as a marker of kidney damage. An increased risk is also apparent with urine ACR levels between 10 and 29 mg/g ("high normal" albuminuria), suggesting that levels below 30 mg/g may also warrant increased attention.

Purpose for and implications of CKD staging —

The staging system for CKD is intended to aid clinicians in the management of patients with CKD by identifying those with the most severe disease who are, therefore, at greatest risk for

progression and complications. Staging according to cause, GFR, and albuminuria allows for a more complete description of risk for the major adverse outcomes of CKD.

Incidence of CKD — There are limited data concerning the incidence of new-onset CKD:

- The **Framingham Offspring study** consisted of 1223 men and 1362 women who were initially free of preexisting kidney disease **(Hallan et al.,2012).**

  After a mean follow-up of 18.5 years, 244 participants (9.4 percent) had developed kidney disease (defined as MDRD eGFR of <64 and 59 mL/min per 1.73 m2 for men and women, respectively).

  The development of CKD was associated with increased age, diabetes, hypertension, smoking, obesity, and a lower baseline GFR.

PREVALENCE OF END-STAGE RENAL DISEASE (ESRD) —

The prevalence of ESRD is increasing. The number of patients enrolled in the ESRD Medicare-founded program has increased from approximately 10,000 patients in 1973 to 615,899 as of