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COMPARISON OF GLOMERULAR FILTRATION RATE IN DIABETIC NEPHROPATHY PATIENT WITH COMORBID HYPERTENSION AND MEDICATION ADHERENCE

Jimmy Chua[1], Yohanes Firmansyah[2], Joshua Kurniawan[1], Ernawati Su[3]
[1]Clinical Clerkship, Faculty of Medicine, Tarumanagara University
[2]General Practitioner, Faculty of Medicine, Tarumanagara University
[3]Departemen Ilmu Kesehatan Masyarakat, Fakultas Kedokteran Universitas Tarumanagara, Jakarta

Corresponding Author: Yohanes Firmansyah, MD, AIFO, Faculty of Medicine, Tarumanagara University
E-Mail: yohanesfirmansyah28@gmail.com

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Abstract

Background: Chronic Kidney Disease (CKD) is a global health problem with increasing prevalence and incidence of kidney failure, bad prognosis, and high treatment cost. The prevalence of CKD increases with the increasing number of elderly population and the incidence of diabetes mellitus and hypertension. Comorbidities of patient with CKD, according to Indonesian Renal Registry in 2018, are hypertension or uncontrolled blood pressure (51%) and type 2 diabetes mellitus (21%).

Methods: Cross-sectional studies of patients in "RT" Hospital Jakarta between 2018-2019. The independent variable in this research is hypertension comorbidities and medication adherence, whereas glomerulus filtration rate as the dependent variable. the correlation of cause and effect is tested with *Independent T-Test* and *Mann Whitney Test* as an alternative.

Findings: The research includes 26 respondents, with prevalence of hypertension in diabetic nephropathy patient of 17 (65,4%). Population of patient with diabetic nephropathy with hypertension comorbidities has lower glomerular filtration rate (GFR) compared with group of diabetic nephropathy patients without comorbid hypertension (14.4% vs 28.6%). Hypertensive patients with no routine treatment have average GFR of 8.5%, and hypertensive patients with routine treatment have GFR of 16.15%. Statistical test results with Mann Whitney shows that there are no meaningful difference in average GFR between the two groups (*p-value: 0.130*).
Conclusion: Blood pressure control and medication adherence can slow down the decline in renal function caused by complication of diabetic nephropathy, although there are no meaningful relation found in this research because of lacking in samples.

Keywords: *diabetic nephropathy; hypertension; prognosis*

INTRODUCTION

Kidney is an important organ which functions to keep blood composition by preventing waste from piling up and controls liquid homeostasis in the body, keeping electrolytes like sodium, potassium, and phosphate level stable, also producing hormones and enzymes that help in controlling blood pressure, producing red blood cell and keeping sturdiness of the bone. [1]

Chronic Kidney Disease (CKD) is a global health problem with high prevalence and incidence of kidney failure, bad prognosis, and high treatment cost. The prevalence of CKD increases with the increasing number of elderly population and the incidence of

diabetes mellitus and hypertension. Around 1 of 10 global population have CKD with certain stage. The result of systemic review and meta-analysis that's been done by Hill et al, 2016 shows that global prevalence of CKD is 13.4%. [1] According to Global Burden of Disease in 2010, CKD ranked 27th as a death cause in 1990 and raised into rank 18th in 2010 [2]. Whereas in Indonesia, kidney disease medication is ranked 2nd in BPJS medication expenses, following after heart disease. . [3]

Chronic kidney disease doesn't show any sign and symptoms in the beginning however it can be progressively progress to kidney failure. Kidney disease can be prevented and treated, with higher chance to get more effective therapy if it can be discovered early. [3–5]

According to Chronic Kidney Disease in the United States of 2019, more than 1 of 7 people have kidney failure, starting from stage 2 to stage 5, whereas in America, more than 37 million people have kidney failure. The incidence of CKD will significantly increase the rate of morbidity, mortality, duration of inpatient, and the burden of medical costs [6]. Divisions of Nephrology and Hypertension and General Internal Medicine found that the prevalence of chronic kidney failure of stage 2 to 5 had raised since 1988, as the consequence of hypertension (40%) and type 2 diabetes mellitus (25%) [7,8].

Indonesian Nephrological Association (Pernefri) in 2006 released data for chronic kidney failure patients in Indonesia in the amount of 12.5%/. The most common comorbidities of stage 5 chronic kidney disease patient, according to Indonesian Renal Registry in 2018, are hypertension or uncontrolled blood pressure (51%) and type 2 diabetes mellitus (21%). [9]

Comorbidities such as hypertension in type 2 diabetic patients have gained deep concern in order to delay the progression of kidney function decline. This study aims to compare the glomerular filtration rate of diabetic nephropathy patients with comorbid hypertension and medication adherence.

MATERIALS

METHOD

This observational analytic study with cross-sectional design was done at "RT" Hospital in January 2019 until May 2019. The samples that were included are diabetic nephropathy patients in "RT" Hospital in 2018-2019 that fulfilled the inclusion criteria. The estimated sample amount is 32 respondents with sampling method of *non-random consecutive sampling* The inclusion criteria for this study is type 2 diabetes mellitus patient with renal failure complication. The exclusion criterias are uremic syndrome, nephrotic syndrome, sepsis, urinary tract infection, post-streptococcal infection glomerulonephritis, type 1 diabetes mellitus and gestational diabetes. The independent variables are this study is medical adherence or controlled blood pressure. The dependent variable is glomerular filtration rate of diabetic nephropathy patient. The statistic test used for analysis are *Independent T-test* with alternative test of *Mann Whitney Test* to assess the significance between the 2 groups. This study was licensed by Tarumanagara University's Faculty of Medicine.

RESULTS

The study took place involving 26 respondents with 11(42.3%) male and 15(57.7%) female.

The prevalence of hypertension in diabetic nephropathy patients is 17 (65.4%). The mean body weight, height, and body mass index (BMI) were 64.15 (11.34) kg, 162.58 (9.29) cm, and 23.81 (3.27) kg/m2. The prevalence of obesity in diabetic nephropathy patients is 12 (46.2%). The mean albumin, HbA1c, random blood glucose concentration, fasting plasma glucose (FPG), urea and creatinine were 2.91 (0.54) g/dL, respectively; 7.82 (1.81) %; 210.19 (53.56) mg/dL; 144.77 (36.49) mg/dL; 111.73 (69.15) mg/dL; 3.55 (2.54) mg/dL. Glomerular filtration rate of 23.87 (14.86) % with progressivity status in the form of Deep Red (Highest Risk) of 11 (42.3%) respondents, Red (Very High Risk) of 8 (30.8%) respondents, Orange (High Risk) as many as 6 (23.1%) respondents, and Yellow (Moderately Increased Risk) as many as 1 (3.8%) respondents.

Table 1. Characteristics of Diabetic Nephropathy Patient in "RT" Hospital in Year 2018-2019

Parameter	N (%)	Mean (SD)	Med (Min – Max)
Age		69 (9,65)	68,5 (50 – 84)
Sex/Gender			
• Male	11 (42,3%)		
• Female	15 (57,7%)		
History of Hypertension			
• Yes	17 (65,4%)		
• No	9 (34,6%)		
Body Weight		64,15 (11,34)	61 (49 – 94)
Body Height		162,58 (9,29)	162 (147 – 182_
BMI		23,81 (3,27)	24 (17 -30)
Nutritional Status			
• Obese	12 (46,2%)		
• Overweight	6 (23,1%)		
• Normal	7 (26,9%)		
• Underweight	1 (3,8%)		
Albumin value		2,91 (0,54)	2,9 (1,7 – 4,0)
HbA1c value		7,82 (1,81)	7,4 (5,3 – 14,0)
Random Glucose Concentration value		210,19 (53,56)	207 (118-354)
FPG value		144,77 (36,49)	141,5 (52 – 254)
Ureum value		111,73 (69,15)	93 (32 – 296)
Creatinine value		3,55 (2,54)	2,60 (1,14 – 10,73)
Medication History			
Glomerular Filtration Rate		23,87 (14,86)	20,75 (4,00 – 55,40)
Progressivity Risk			
• Deep Red (Highest Risk)	11 (42,3%)		
• Red (Very High Risk)	8 (30,8%)		
• Orange (High Risk)	6 (23,1%)		
• Yellow (Moderately Increased Risk)	1 (3,8%)		
• Green (Low Risk)	-		

The result from analyzing the comparison of Glomerular Filtration Rate (GFR) of diabetic nephropathy patients with or without comorbid hypertension showed that the population of diabetic nephropathy patients with comorbid hypertension had lower GFR compared to the group without comorbid hypertension (14.4% vs 28.6%). Although there is a gap of 11.8% between the 2 groups, but there is no statistically significant difference between the 2 groups (p-value: 0.120). This is due to the lack of samples in this study. (Table 2)

Table 2. Comparison of Glomerular Filtration Rate (GFR) of Diabetic Nephropathy Patients with or Without Comorbid Hypertension

Parameter	Normalitas	Glomerular Filtration Rate of Diabetic Nephropathy Patient		Mean Rank	p-value
		Mean (SD)	Med (Min – Max)		
Hypertension	0,030	21,35 (15,06)	14,4 (4 – 52,10)	11,76	0,120
No Hypertension History	0,846	28,6 (14,08)	26,2 (9,80 – 55,40)	16,78	

The result from analyzing the comparison of Glomerular Filtration Rate (GFR) in diabetic nephropathy patients with good Medical Adherence or Without Medical Adherence showed a result contrary to the theory of the population of diabetic nephropathy patients who are not routinely seeking treatment has an LFG value of 23.29%, while those who routinely seek treatment have an average LFG value of 17.9%. This contradictory result is caused by the abnormal distribution of data in the group who routinely seek treatment, namely there is 1 respondent who has a very low LFG value that is 9.2% when compared to other respondents in the same group. On the other side, there can also be seen that in fact respondents who did not routinely seek treatment had the lowest LFG values which were worse than the respondents who regularly went for treatment (4.0% vs 9.2%). In the Mann Whitney statistical test there were no significant differences between the 2 groups (p-value: 0.799).

Table 3. Glomerular Filtration Rate (GFR) of Diabetic Nephropathy Patients Without or with Routine Treatment

Parameter	Normalitas	Glomerular Filtration Rate of Diabetic Nephropathy Patient		Mean Rank	p-value
		Mean (SD)	Med (Min – Max)		
No Routine Treatment/Uncontrolled	0,554	23,29 (15,94)	22,6 (4,0 – 55,4)	13,00	0,799
Routine Treatment/Controlled	0,033	24,29 (14,57)	17,9 (9,2 – 52,1)	13,87	

The analysis for diabetic nephropathy patients is further divided into 2 groups – group with comorbidity such as hypertension and without hypertension history. The group of respondents with hypertension is regrouped based on the history of routine treatment and the results showed that respondents with hypertension and no routine treatment had an average GFR of 8.5%. This number is far lower than the group of diabetic nephropathy respondents who routinely seek treatment with an average GFR of 16.15%. Mann Whitney statistical test results showed that there was no significant difference in average GFR between the 2 groups (p-value: 0.130). This meaninglessness is caused by the lack of samples in this study. (Table. 4)

Table 4. Comparison of Glomerular Filtration Rate in Diabetic Nephropathy Patients with Comorbid Hypertension and Medical Adherence in "RT" Hospital in 2018-2019

Parameter		Normalitas	Glomerular Filtration Rate of Diabetic Nephropathy Patient		Mean Rank/ Diff	p-value
			Mean (SD)	Med (Min – Max)		
Hypertension	No Routine Treatment/ Uncontrolled	0,253	14,3 (11,48)	8,5 (4,0 – 30,2)	6,00	0,130
	Routine Treatment/ Controlled	0,032	24,3 (15,8)	16,15 (8,2 – 52.1)	10,25	
No Hypertension History	No Routine Treatment/ Uncontrolled	0,992	30,78 (15,96)	30,1 (9,8 – 55,4)	6,55 (10,35)	0,547
	Routine Treatment/ Controlled	0,603	24,23 (10,63)	21,7 (15,1 – 35,9)		

DISCUSSION

Hypertension is the most common comorbidity in patients with chronic kidney failure (CKD) and diabetes mellitus. Hypertension will increase the risk of a decrease in kidney disease and increase the rate of cardiovascular (CV) morbidity and mortality. Diabetic nephropathy is the most common cause of CKD in populations with diabetes and its relationship to end-stage renal disease (ESRD) in the United States (US). The mechanism of hypertension in diabetic nephropathy is complex, starting with excess sodium retention, sympathetic nervous system (SNS) and activation of the renin-angiotensin-aldosterone system (RAAS), endothelial cell dysfunction (ECD), and increased oxidative stress. Non-pharmacological and pharmacological interventions become very important in the management of hypertension in diabetic nephropathy. [10,11]

The progression of diabetic nephropathy is divided into 5 stages – (1) Where the glomerular filtration rate increases to 40% above normal, this stage is reversible and lasts 0 - 5 years from the start of diagnosis. [12–14] At this stage *diabetic tubulopathy* occurs based on structural and

functional changes in the hypertrophied tubular epithelium, thickened tubular base membrane, mesenchymal epithelial transition, glycogen collision. At this stage there is diffuse and global glomerular hypertrophy and an increase in total volume and capillary size in the kidney, but albumin excretion is still normal but can still occur if the patient experiences poor metabolic control, fever, excessive exercise, stress. (2) Silent Stage which lasts for 5-10 years since the diagnosis of Diabetes mellitus is established. At this stage, microalbuminuria has occurred, whereas albumin excretion is around 30-300 mg / 24 hours. [15] Glomerular filtration rate is increasing and metabolic control is getting worse. (3) *Diabetes Incipient Nephropathy*, occurs after 10-15 years since diagnosed with Diabetes mellitus. Histopathologically, there is thickening of the glomerular basement membrane. At this time there has been an increase in blood pressure and the glomerular filtration rate is still high. At this stage, the deterioration process can still be prevented safely and quickly with good glucose and blood pressure control. (4) At this stage, diabetic nephropathy has manifested clinically, glomerular filtration rate has decreased below normal. This stage occurs 15-20 years after the patient is diagnosed with diabetes mellitus. In addition, other diabetes complications can already be found, such as retinopathy, neuropathy. At this stage, treatment management is done by controlling blood glucose, blood fat and blood pressure. (5) Kidney failure is characterized with a low glomerular filtration rate, and signs of uremic syndrome are found. At this stage, therapy that can be recommended is to do a kidney transplant. [12–16]

The population with diabetes has twice the risk of hypertension. Hypertension in type 1 diabetes mellitus usually occurs in patients with advanced microalbuminuria or nephropathy [10,17]. The prevalence of hypertension in normoalbuminuric type I DM patients varies; previous studies using the definition of hypertension with blood pressure of 160/95 mmHg showed a prevalence of hypertension of 19% [10,18,19]. Cross-sectional studies in Denmark involving more than 1700 diabetics and 10,000 controls show that in patients with type I DM without micro or macroalbuminuria, the prevalence of hypertension (above 160/95 mmHg) is similar to the general population (3.9% vs 4.4%). [10,17]. Subjects with type I DM in this study were younger than in the previous studies, which led to a lower prevalence or proportion of people with hypertension [10,11,19,20].

Hypertension in the population of type 2 diabetes mellitus usually occurs before the kidney disease. The common risk factors for glucose intolerance and hypertension, is obesity. One study explained, 58% of patients with newly diagnosed type II DM (without proteinuria) already had hypertension, with an incidence rate as high as 70%. Duration of diabetes does not increase the incidence of hypertension, even if accompanied by comorbid diseases such as impaired kidney function. Hypertension causes the development of kidney disease become quicker and contributes to the increase of the incidence of CV disease. [10,19,21,22]

Worsening kidney function also contributes to an increase in BP. The prevalence of hypertension in diabetic nephropathy increases at each stage of chronic renal failure, where it is close to 90% for the group of end-stage renal failure (ESRD) [10,23]. This is caused by a combination of metabolic and hemodynamic disorders, as well as genetic determinants which have an impact on the progression of decreased kidney function [19,24,25].

Various factors contribute to the increase in blood pressure in patients with diabetes and nephropathy. The main cause of hypertension is volume expansion caused by renal sodium reabsorption and peripheral vasoconstriction due to dysregulation of factors that regulate peripheral vascular resistance (Figure 1). The activation of RAAS, endothelin 1 (ET-1), reactive superoxide, and nitric oxide (NO) work together in increasing blood pressure. This pathogenic factor itself has a local non-hemodynamic effect that can accelerate the decline in kidney function and increase the risk of CV disease. [10]

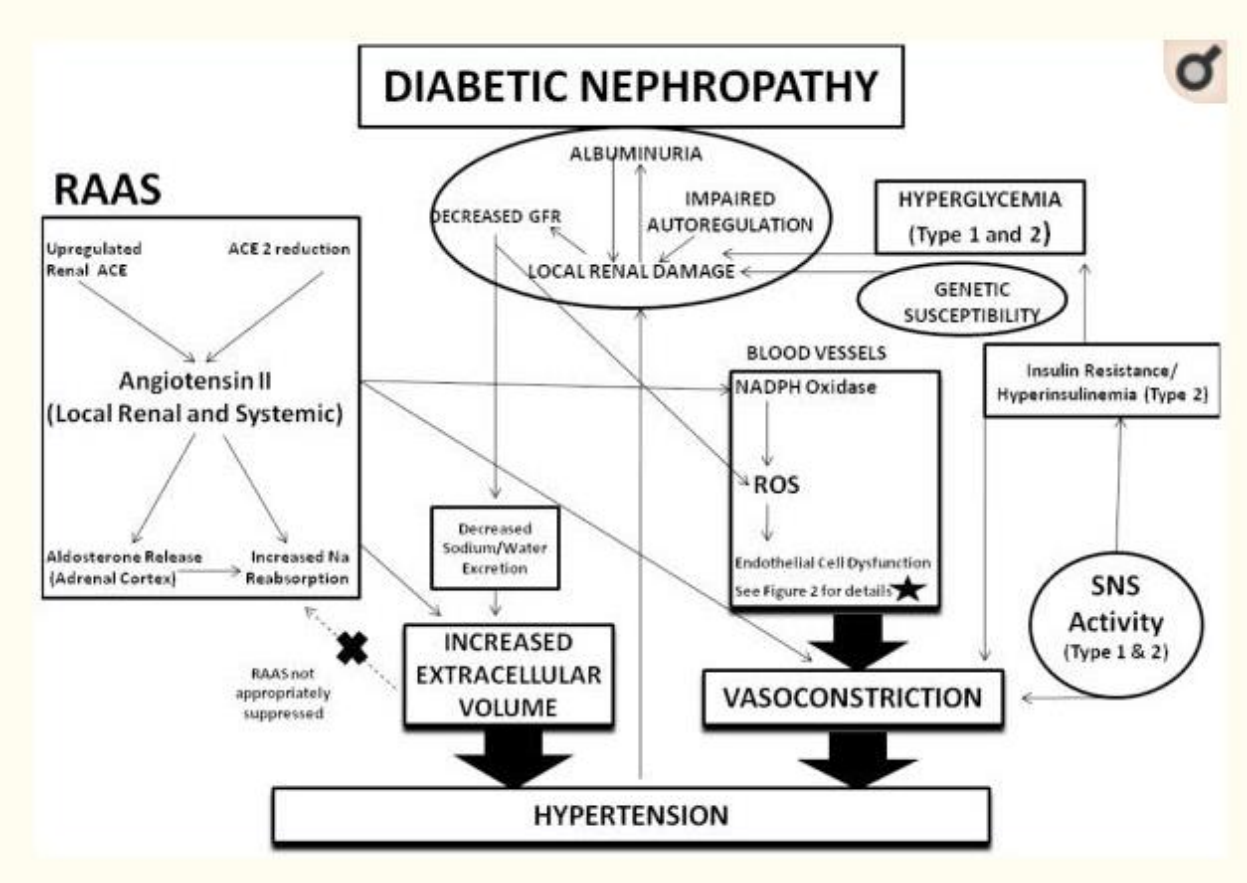

Figure 1. Pathogenesis of hypertension in diabetes and CKD which are mutlifactorial . [10]

The changes that underlie the occurrence of diabetic nephropathy include metabolic changes, activation of protein kinase C and non-enzymatic glycosylation. Inhibition of the transport of glucose in the blood can stimulate gluconeogenesis. One of the by-products of gluconeogenesis is the formation of ketone bodies, which can stimulate acidosis. Persistent hyperglycemia is also associated with glycation, glycoxidation, oxidative stress.

During the process, it can form early, intermediate, advance glycation products via the *Maillard* reaction, auto glucose oxidation and protein glycation. Excessive AGE accumulation, can cause toxic effects and become a major cause of diabetes complications, one of which is nephropathy. [14,26,27]

The auto glucose oxidation reaction of and protein glycation will produce reactive oxygen species (ROS). Excessive ROS will cause oxidative modification in cellular macromolecules such as in DNA, lipids, proteins, which ultimately leads to tissue damage. In addition, ROS also cause excessive inflammation because it will increase leukocyte recruitment. [14,26,28]

Activation of protein kinase C is associated with hyperglycemia, which can increase Diacyl-glycerol (DAG) which can increase the activity of protein kinase C. Activation of protein kinase C causes changes in function, such as increased vascular endothelial growth factors like TGF-β1, where TGF-β1 affecting the occurrence of diabetic nephropathy, by stimulating the formation of extracellular matrix components such as collagen-IV, proteoglycans. In addition, the expression of *plasminogen activator inhibitor-1* and *fibronectin* in the basement membrane, can cause permeability and hemodynamic changes in the vascular. [29]

Non-enzymatic glycolization is a reversible glucose binding reaction in proteins, fats and nucleic acids without enzyme reactions. This is also related to hyperglycemia, where glucose will become an irreversible bond with collagen and other proteins in blood vessels, and produce Advance glycocylation End products (AGE). Excessive AGE accumulation, can cause toxic effects and become a major cause of diabetes complications, one of which is nephropathy. [30]

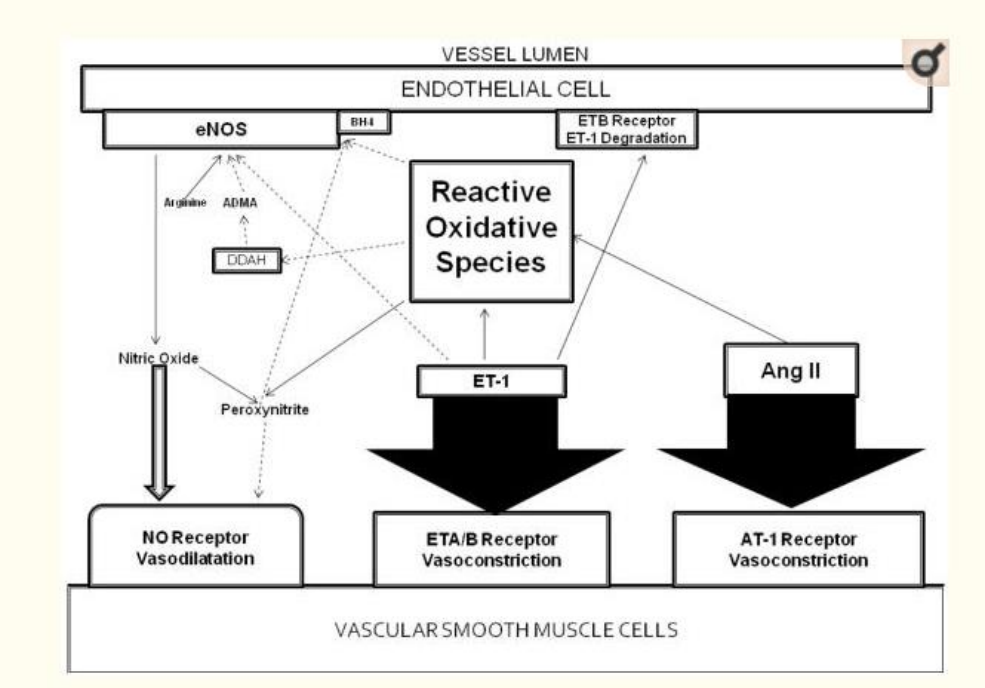

Figure 2. Pathogenesis and Pathophysiology of Vascular Vasoconstriction as Early Phase of Increased Blood Pressure [10]

CONCLUSIONS AND SUGGESTIONS

Conclusions

Blood pressure control and medication control supervision are important factors in preventing deterioration in kidney function due diabetic to nephropathy to increase the life expectancy of patients. The diabetic nephropathy group with hypertension and non-routine treatment had an average GFR of 8.5%. This number is far lower than the group of diabetic nephropathy respondents who routinely seek treatment with an average LFG of 16.15%. Although there was no significant difference in mean GFR between the 2 groups (p-value: 0.130), clinically it was found that the diabetic nephropathy group with comorbid hypertension who did not routinely seek treatment tended to have a lower LFG.

Suggestion

We recommend that prognostic scoring for hypertension at this productive age be used after further testing in the form of validity and reliability.

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