

# Renal Function Decrement in Type 2 Diabetes Mellitus Patients in Cipto Mangunkusumo Hospital

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## ABSTRACT

**Aim:** to screen for reduction of renal function in type 2 diabetes mellitus (DM) patients based on various estimated Glomerular Filtration rate (eGFR).

**Methods:** 1283 newly registered type 2 DM patients were included in the study from the year 2003 until 2006. We calculated the eGFR by the Cockcroft-Gault (CG), Cockcroft-Gault adjusted for body surface area (CG-BSA), 4-variables Modification of Diet in Renal Disease (MDRD), and Chinese adapted MDRD (C-MDRD) methods based on serum creatinine. We also investigated the significant risk factors based on the method with the highest percentage of renal dysfunction.

**Results:** type 2 DM patients with serum creatinine  $\geq 2$  mg/dL (the abnormal limit in Indonesia) was only 5.8%, but the prevalence of patients with eGFR  $< 60$  mL/min was 36.1% (CG), 43.7% (CG-BSA), 13.2% (MDRD), or 22.8% (C-MDRD). We used CG-BSA to determine risk factors as the method with highest percentage of renal dysfunction. Significant risk factors for renal dysfunction based on multivariate analysis were history of hypertension ( $P=0.025$ , 95%CI 1.08-3.19), proteinuria ( $P=0.015$ , 95%CI 1.13-3.22), and diabetic retinopathy ( $P=0.001$ , 95%CI 1.43-4.20).

**Conclusion:** the use of eGFR is recommended to screen in type 2 DM patients than the use of mere serum creatinine. We advocate the use of CG-BSA method to increase the physician's awareness, as more subjects will fall within the ambit of CKD.

**Key words:** chronic kidney disease, DM type 2, estimated glomerular filtration rate.

## INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem.<sup>1-3</sup> It is recognized as an important condition due to its correlation with some factors. The first factor is the rapidly increased prevalence in all over the world. Screening surveys conducted in Australia, Japan, and European countries identify that the prevalence of CKD is about 6-11% among common population and it increases of 5-8% annually. CKD is more prevalent among the population with risk factors, i.e. 50-60%. Similar condition also occurs in developing countries.<sup>4,5</sup> The second factor associated with CKD is the extreme high cost for end-stage renal disease (ESRD).<sup>3-5</sup> Most patients in the world is unable to undergo hemodialysis or kidney transplantation because of such expensive cost.<sup>6</sup> Third, CKD increases the risk of cardiovascular disease.<sup>3-5</sup> This has been demonstrated by various study reports which indicate that there is correlation between decreased renal function and increased mortality risk of cardiovascular disease.<sup>3</sup> The fourth factor includes effective management that has been demonstrated to prevent disease progression.<sup>3-5</sup> Unfortunately, most patients with CKD have not been diagnosed early until they have more severe disease condition.<sup>6</sup>

Mass screening for CKD is expensive, inefficient and not effective. Currently, screening for any group with risk factors has been recommended.<sup>7</sup> One of population that has high-risk for CKD is patients with diabetes mellitus (DM).

The number of worldwide diabetic patients, particularly type-2 DM, has been increasing. Its complication has also increased, such as renal complication or diabetic nephropathy (DN). Moreover, DN has become the main reason for patients to have renal replacement therapy in the western countries (25-42%).<sup>8-11</sup> In Indonesia, the prevalence is also likely increase in patients with ESRD who have undergone renal replacement therapy.<sup>8,12,13</sup>

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As the other causes of CKD, there is also reduced glomerular filtration rate (GFR) in DN, a sign of CKD progression.<sup>7</sup> GFR is the parameter of renal function which determines CKD classification and treatment.<sup>14-16</sup> It is not easy to directly measure such parameter; therefore, most clinicians use estimated GFR based on serum creatinine level.<sup>15-17</sup> Two methods that most frequently used are the Cockcroft-Gault (CG) method and Modification of Diet in Renal Disease. In addition, there are also CG method adjusted to body surface area (CG-BSA), and Chinese adapted MDRD (C-MDRD). Such adaptation is considered as necessary, particularly due to different body size between the Asian and Western ethnic.<sup>15-18</sup> However, estimated GFR has not been performed as a routine although it has been frequently recommended.<sup>18</sup> GFR is also correlated to various risk factors, which should be noticed and controlled.<sup>19</sup>

This study was conducted in 100 newly diagnosed patients with type-2 DM at outpatient Endocrinology clinic, Cipto Mangunkusumo hospital in 2003. It showed prevalence of proteinuria as 37%. The study evaluated decreased renal function based on CG <60 mL/min and found 40% result.<sup>20</sup> However, the result based on MDRD, CG-BSA, and C-MDRD has not been known. Therefore, we consider that it is necessary to identify the profile of renal function in patients with type-2 DM by calculating estimated GFR and the affecting risk factors.

## METHODS

This study was a cross-sectional study by using secondary data (retrospective). During the study, there was data of 3802 new patients that had their first visit to Endocrine-Metabolic outpatient clinic in 2003-2006. From such data, 1283 newly diagnosed patients with type-2 DM were eligible, i.e. who had met the inclusion criteria and had no exclusion criteria.

**Inclusion criteria:** visit the outpatient clinic at Department of Endocrine Metabolic/Internal Medicine for the first time with diagnosis of type-2 DM during the period of January 2003–December 2006 and have a complete medical record of data needed in this study.

**Exclusion criteria:** have other concomitant disease that may cause CKD (except hypertension), such as kidney stones, congenital kidney disease, glomerulonephritis (based on history in medical record), having fever or infection, liver cirrhosis, history of amputation, having any drug treatment that may affect the serum creatinine level, such as cimetidin and trimetoprim, and creatinine serum level obtained by other than Jaffe-kinetic laboratory method.

The sample was selected by taking all of available medical record, i.e. data of every new patient that visit the outpatient clinic at Department of Endocrinology/Internal Medicine, Cipto Mangunkusumo General Hospital and data of eligible patients during the study period.

Based on the subjects' medical records, data of history, physical examination and laboratory test of serum creatinine level was evaluated. Data of lipid profile, urinalysis, urine examination of quantitative protein and retina examination was also examined to evaluate any diabetic retinopathy. All examinations should be performed in 3 month period of time since the date of patient's first visit to the outpatient clinic at the Department of Metabolic Endocrine/ Internal Medicine, Cipto Mangunkusumo General Hospital. Afterward, based on the result of serum creatinine level, the estimated glomerular filtration rate was calculated by using CG method, CG-BSA, MDRD, and Chinese adapted-MDRD.

**Table 1. Cockcroft-Gault formula and modified MDRD<sup>6,21</sup>**

Formula	Calculation
Cockcroft-Gault for male	$[(140 - \text{age}) \times \text{weight (kg)}] / 1.73 \text{ m}^2 \times \text{serum creatinine} \times 72$
Cockcroft-Gault for female	$[(140 - \text{age}) \times \text{weight (kg)} \times 0.85] / 1.73 \text{ m}^2 \times \text{serum creatinine} \times 72$
Modified MDRD for male	$186 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203}$
Modified MDRD for female	$186 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742^*$
Chinese modified MDRD for male	$175 \times \text{serum creatinine}^{-1.234} \times \text{age}^{-0.179}$
Chinese modified MDRD for female	$175 \times \text{serum creatinine}^{-1.234} \times \text{age}^{-0.179} \times 0.79$

\* (x 1.212 if the patient is Afro-American)

Notes: MDRD = Modification of Diet in Renal Disease

## Statistical Analysis

The prevalence was calculated for each estimated GFR method. Afterward, calculation was performed to obtain the odds ratio for estimated GFR with highest percentage (as screening for decreased renal function in a patient), and to obtain the risk factor of estimated GFR by using chi square test. Significant level of 5% was used in this study.

## RESULTS

### Baseline Characteristics

The subject characteristics are showed on table 2. The number of patients with creatinine  $\geq 2$  mg/dL was

**Table 2. Study subject characteristics (n= 1283)**

Variables	n	%	Median	Range
<b>Sex</b>				
Male	620	48.3		
Female	663	51.7		
<b>Age (years)</b>	1283	100	55	19-99
< 60 years	858	66.9		
≥ 60 years	425	33.1		
<b>Smoking Habit</b>				
Non-smoker	818	62.8		
Ex-smoker	304	23.7		
Smoker	161	12.5		
<b>History of DM in the family</b>				
Positive	619	48.2		
Negative	664	51.8		
<b>Hypertension History</b>				
Yes	493	37.4		
No	825	62.6		
<b>Duration of DM illness</b>				
≥ 5 years	341	26.6		
< 5 years	942	73.4		
<b>Control of Blood Glucose level</b>				
Controlled	249	19.4		
Uncontrolled	1034	80.6		
<b>Lipid Profile</b>	827	64.5		
Dyslipidemia	724	87.5		
No dyslipidemia	103	12.5		
Total Cholesterol (mg/dL)	819	99.0	218	53-656
Triglyceride (mg/dL)	791	95.6	154	37-1679
HDL-Cholesterol (mg/dL)	751	90.8	47	11-289
LDL-Cholesterol (mg/dL)	746	90.2	144	11-770
<b>Body Mass Index</b>	1283	100	24.6	14-54.8
< 25 kg/m <sup>2</sup>	687	53.5		
≥ 25 kg/m <sup>2</sup>	596	46.5		
Height (cm)	1283	100	157	102-187
Weight (kg)	1283	100	61	27-153
<b>Blood Pressure (mmHg)</b>				
Systolic pressure	1283	100	120	90-210
Diastolic pressure	1283	100	80	60-18
Systolic pressure ≥130	630	49.1		
Diastolic pressure ≥80	1003	78.2		
<b>Serum Creatinine level</b>	1283	100	1	0.1-15.2
< 2 mg/dL	1209	94.2		
≥ 2 mg/dL	74	5.8		
<b>Urinalysis</b>	897	69.9		
Proteinuria	387	43.1		
No proteinuria	510	56.9		
<b>Diabetic Retinopathy</b>	385	30.4		
Positive	144	37.4		
Negative	241	62.6		

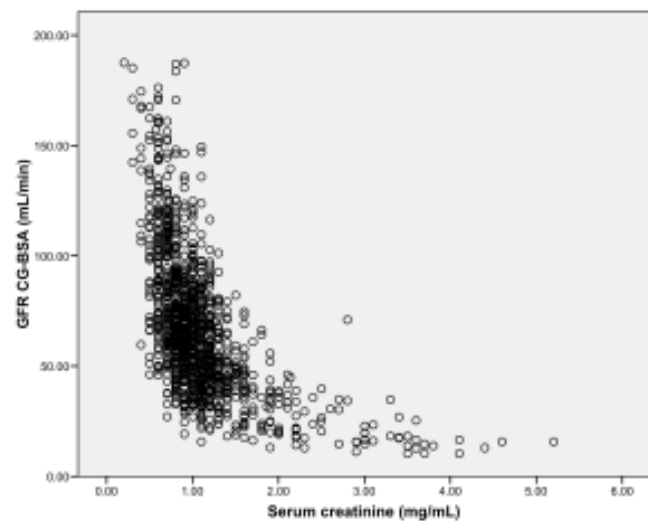
only 5.8%, while the percentage of patients who had decreased renal function (GFR < 60 ml/min) based on CG method, MDRD method and Chinese adapted MDRD method was 36.1%, 13.2%, and 22.8% respectively. The percentage was higher when the CG-BSA (43.7%).

Of 425 patients aged ≥ 60 years, 54.1% had decreased renal function based on CG method; while based on CG-BSA, there was 63% and 19.3%. when it was based on MDRD method. In contrast, there was only 7.5% patients who had serum creatinine level >2 mg/dL.

Table 3 demonstrates various risk factors and classification of GFR CG-BSA, the method that obtain the highest result for decreased renal function.

Based on classification of serum creatinine level and GFR CG-BSA as the method of highest percentage detection for decreased renal function, at serum creatinine level of 1-1.5 mg/dL, there was 47.1% patients who already had GFR <60 mL/min. (Table 4)

Figure 1 shows that the higher serum creatinine level, the lower GFR CG-BSA. This figure also indicates that there are quite many patients with serum creatinine level < 2 mg/mL but their GFR has decreased to < 60 mL/minit.



**Figure 1.** Correlation between GFR CG-BSA and serum creatinine level

### Risk Factors Correlated to Renal Function

Highest percentage of decreased renal function was found by CG-BSA calculation method and further analysis between such method and risk factors was performed (table 5). No test was performed on age and sex factors because both factors have been included as variables calculated in GFR formula.

### Multivariate Analysis

This study used logistic regression analysis as the multivariate analysis. Variables included in the multivariate analysis were all variables that has significant level of  $p < 0.25$ . The end result revealed variables that have significant correlation to decreased renal function includes history of hypertension, proteinuria and diabetic retinopathy.

**Table 3. Comparison of various variables in renal function < 60 and ≥ 60 mL/min**

Variables	GFR CG-BSA (mL/min)				Total
	< 60	%	> 60	%	
<b>Sex</b>					
Male	235	41.9	385	53.3	620
Female	326	58.1	337	46.7	663
<b>Age</b>					
≥60 years	268	47.8	157	21.7	425
<60 years	293	52.2	565	78.3	858
<b>Duration of DM illness</b>					
< 5 years	388	69.2	554	76.8	942
≥ 5 years	173	30.8	168	23.2	341
<b>History of DM in the family</b>					
Positive	301	53.7	318	44.0	619
Negative	260	46.3	404	56.0	664
<b>Smoking habit</b>					
Smoker	181	32.3	284	39.3	465
Non-smoker	380	67.7	438	60.7	818
<b>History of hypertension</b>					
Positive	245	43.6	235	32.5	480
Negative	316	56.4	487	67.5	803
<b>BMI</b>					
BMI ≥ 25	153	27.3	443	61.4	596
BMI < 25	408	72.7	279	38.6	687
<b>Systolic pressure</b>					
Systolic pressure ≥ 130	303	54.1	327	45.3	630
Systolic pressure < 130	258	45.9	395	54.7	653
<b>Diastolic pressure</b>					
Diastolic pressure ≥ 80	448	79.9	555	76.9	1003
Diastolic pressure < 80	113	20.1	167	23.1	280
<b>Dyslipidemia*</b>					
Positive	323	87.8	401	87.4	724
Negative	45	12.2	58	12.6	103
<b>Proteinuria<sup>^</sup></b>					
Positive	202	53.2	185	35.8	387
Negative	178	46.8	332	64.2	510
<b>Diabetic retinopathy<sup>#</sup></b>					
Positive	87	46.5	57	28.8	144
Negative	100	53.5	141	71.2	241
<b>Total</b>	561		722		1283
	(43.7%)		(56.3%)		

\*out of n = 827

<sup>^</sup> out of n = 897<sup>#</sup> out of n = 385

## DISCUSSION

This study found 13.2% prevalence of decreased GFR based on MDRD method in newly diagnosed patients with type-2 DM. Based on CG method, the prevalence was 36.1%; based on Chinese modified MDRD 22.8%, and based on BSA was 43.7%. A study

by Galastri et al in 2003 at Outpatient clinic of Metabolic Endocrine, Cipto Mangunkusumo hospital found prevalence of decreased estimated GFR by CG method CG <60 mL/min as 40%.<sup>20</sup> Razy et al found 30.7% (16 of n=52) patients with proteinuria who had decreased renal function based on creatinine clearance (GFR < 60

**Table 4. Classification of serum creatinine level and GFR CG-BSA**

Serum creatinine (mg/dL)	GFR CG-BSA (mL/min)				Total
	< 60	%	≥60	%	
< 0.5	1	0.2	32	4.4	33
0.5 – <1	148	26.4	457	63.3	605
1 – <1.5	264	47.1	225	31.2	489
1.5 – <2	75	13.4	7	1.0	82
2 – <2.5	29	5.2	0	0	29
≥ 2.5	44	7.8	1	0.1	45
<b>Total</b>	<b>561</b>	<b>43.7</b>	<b>722</b>	<b>56.3</b>	<b>1283</b>

**Table 5. Correlation between GFR CG-BSA method and risk factors**

Variables	p	Odds ratio	95%CI
Sex (male)	-	0.631	0.505-0.788
Age ≥ 60 years	-	3.292	2.583-4.194
DM illness > 5 years	0.002	1.470	1.146-1.886
History of DM in the family	0.001	1.471	1.178-1.836
Smoking habit	0.058	0.539	0.378-1.127
History of hypertension	<0.001	1.607	1.279-2.019
BMI >25	<0.001	0.236	0.186-0.300
Systolic pressure ≥130 mmHg	0.002	1.419	1.137-1.770
Diastolic pressure ≥80 mmHg	0.199	1.193	0.911-1.562
Blood glucose control	0.384	0.884	0.669-1.167
Dyslipidemia	0.860	1.038	0.685-1.574
Proteinuria	<0.001	2.037	1.555-2.668
Diabetic retinopathy	<0.001	2.152	1.413-3.279

mL/min).<sup>22</sup> Middleton et al in UK, by using MDRD method, found 27.5% prevalence of decreased renal function in patients with type-2 DM.<sup>23</sup> Coresh et al in United States shows 15.1% prevalence in patients with type-2 DM.<sup>24</sup> Such difference in prevalence might be caused by different method in examination and creatinine calibration.<sup>23</sup> However, overall, there was quite high prevalence of decreased renal function..

A study by Kong et al found 6% prevalence of patients with serum creatinine level ≥2 mg/dL. When the GFR calculation was based on MDRD, the prevalence of patients with GFR < 60 mL/min/1.73 m<sup>2</sup> was 15.8%.<sup>25</sup> Similar result has been found in this study. There was only 5.8% patients with serum creatinine level ≥2 mg/dL, but there was 13.2% patients with GFR <60 mL/min (MDRD method) – 43.7% (CG-BSA method). Galastri et al only found increased serum creatinine level in 2% patients; however, the percentage of patients with GFR <60 mL/min reached 40%.<sup>20</sup> This indicates that increased serum creatinine level is less sensitive in evaluating decreased renal function. Therefore, this parameter is

less ideal for renal function. In addition to the influence of many factors, a great GFR changes is necessary to increase serum creatinine level exceeding the normal limit.<sup>25</sup>

Early stage of CKD is usually asymptomatic which likely causes this disease regarded as mild illness.<sup>26</sup> The higher prevalence of patients with estimated GFR <60 mL/min compared to patients with serum creatinine ≥2 mg/dL indicates calculation of estimated GFR is important to remind the doctors on possibility that CKD has occurred. There are a lot of patients with CKD and patients at risk for CKD; therefore, doctors, including the specialist other than nephrologist, should be proficient in GFR estimating method.<sup>26</sup>

Calculating estimated GFR by direct note on laboratory test is one of methods that may increase doctors' awareness on CKD.<sup>27</sup>

The definition of decreased renal function in this study was GFR <60 mL/min. This number refers to study results that indicated an association of such value with increased risk of progression toward end-stage renal disease (ESRD) and mortality due to cardiovascular disease.<sup>27</sup> Go et conducted a longitudinal study on estimated GFR evaluation and demonstrated that there was a correlation between decreased GRF with risk of death, cardiovascular events and hospitalization. The correlation was obvious on GFR value <60 mL/min, and it sharply increased on GFR <45 mL/min.<sup>28</sup> Indeed, some studies found a correlation between increased serum creatinine level and mortality risk, risk of cardiovascular disease and cardiovascular events. However, because serum creatinine has no linear comparison with GFR, than it is better to use the estimated GFR.<sup>24</sup>

In this study, patients at outpatient clinic were participated. Therefore, we expect a more accurate calculation of estimated GFR, which is in accordance with the patients' characteristics that became study samples in preliminary studies resulting formula of GFR MDRD method.<sup>4,17</sup> Some literatures have shown the accuracy or MDRD method, particularly for patient in outpatient clinic with CKD.<sup>5,17</sup>

Zuo et al conducted a study about using various estimated GFR in Chinese patients who suffered from CKD. They compared the GFR measurements, i.e. by using Technetium (Tc) 99m, GFR CG method, GFR MDRD method 7 variables, and 4 variables. Overall, the accuracy and precision of the three estimation method are similar; however, the CG method has greater bias. One of factors that cause different results between various measurements is ethnicity. They suggested that a correction factor is necessary to calculate the GFR.<sup>29</sup> Our study did not compare the calculation of estimated

GFR with GFR measurement using inulin/contrast and the different result found needs further study. Ethnicity has become one of the causes and it may become a correction factor.

It should be noted that decreased renal function in patients with DM is not always accompanied by proteinuria. Our study found that the prevalence of patients with decreased renal function without proteinuria was 11.5% (CG), 12.3% (CG-LPB), and 7.1% (MDRD). A study by MacIsaac et al in patients with type-2 DM demonstrated that there could be a decrease of creatinine clearance without any increased proteinuria. The prevalence of patients with GFR < 60 mL/min and without proteinuria in the study by MacIsaac et al. was 39%.<sup>26</sup> The National Health and Nutrition Survey (NHANES) III found that there was no different rate of decreased renal function annually between micro- and macroalbuminuria group among the age group 60-79 years with GFR <60 mL/min. The pathogenesis has not been known and the other causes but DN has not been fully excluded.<sup>24</sup>

There has not any validation for estimated GFR in patients with type-2 diabetes in Indonesian population, particularly in patients with renal function disorder. This and the lack calibration of serum creatinine in accordance with the CCF laboratory, the place of MDRD study, has called for further studies on such aspect.

An observational study has indicated that smoking has enhanced the occurrence of microalbuminuria and the transition into macroalbuminuria.<sup>30</sup> The study did not found any correlation between smoking and decreased renal function. This might be due to less proportion of smoker in the study, i.e. only 12.5%. Moreover, the smoker and ex-smoker were categorized into one group in the study. A study on type-1 DM found that smoking cessation may delay the occurrence of DN, which similarly expected in type-2 DM.<sup>30</sup> However, it should be noted that in patients with type-2 DM with period of illness <5 years, there was only 11.6% smoker, in contrast to 13% smoker in patients with period of illness  $\geq$ 5 years

A study by Kuo<sup>27</sup> indicated that hypertension was an independent risk factor of CKD. Our study also found that history of hypertension had significant correlation to decreased renal function, and such result remained after multivariate analysis had been performed. In type-2 DM, hypertension frequently has multifactor causes and it is possibly as part of metabolic syndrome.<sup>30,31</sup> In this study, there was no significant correlation between hypertension and diastolic pressure. Later, after being analyzed by multivariate analysis, there was also no significant correlation either with diastolic or systolic

pressure. This might be caused due to single recording for blood pressure examination. When the correlation was evaluated for history of hypertension, it revealed significant result.

Dyslipidemia has no significant correlation in this study. Galastri et al<sup>20</sup> and Razy et al<sup>22</sup> also found similar results. Controversial result was found in various other studies. Current evidences indicate that dyslipidemia is the risk factor of CKD occurrence and progression. The MDRD study itself revealed that low HDL level correlated to rapid GFR decrease.<sup>32</sup> Such differences might be caused by incomplete data of lipid profile in the subjects of this study (only 64.5% had undergone examination) and some subjects were not newly diagnosed patients or already had treatment for their dyslipidemia disorder.

Razy et al found that patients with type-2 DM aged >45 years were likely having DN 1.15 times greater than aged <45 years.<sup>22</sup> A study by Kuo et al in Taiwan found that the prevalence of CKD in elderly ( $\geq$  75 years) was greater 17-25 times than the patients aged younger than 20 years old. Elderly is the main risk factor group for CKD.<sup>27</sup> A study by Tanaka et al in Okinawa, Japan, has also found increased prevalence of CKD in patients aged >60 years.<sup>33</sup> This was also found in our study. Based on CG-BSA method, we found that 63% patients aged >60 years in this study had already experienced decreased renal function. This is important considering that elderly patients are susceptible for cardiovascular complication from DM.<sup>34</sup>

A study by Kuo et al demonstrated that female had more frequent CKD, in contrast to other studies in Western countries, that it is more frequent in male patients.<sup>27</sup> Our study found that there was more female patients who had decreased renal function. Little has been known about the correlation between sex and decreased renal function. This may be correlated to different race/genetic associated with DN, environment factor and social factors.<sup>27</sup> However, a meta-analysis of 11 clinical trial on ACEI treatment in CKD patients did not find increased ESRD in male patients. In contrast, after being adjusted to baseline variables, such as blood pressure and proteinuria, the evidences indicated that female patients had higher risk. This may be due to menopausal state, which had not been calculated on female subjects in the study.<sup>32</sup>

Kong et al found a tendency of reduced body mass index along with decreased GFR.<sup>25</sup> Such condition was also found in our study. It is assumed that when CKD begin, there are some advanced changes in metabolism, especially increased circulating cytokines and hence it causes inflammation. Reduced clearance of waste

metabolic product and inflammatory cytokines may cause chronic inflammation, which can be worsen by malnutrition, catabolism and susceptibility against sepsis condition in patients with terminal renal failure.<sup>25</sup> Such finding is different from some study results in Western countries, which likely found decreased renal function in patients with body mass index  $\geq 25$ ; therefore, they proposed obesity as a potential risk factor for proteinuria.<sup>35</sup> The study by Galastri et al did not find any significant correlation between body mass index and DN.<sup>20</sup> While the study by Razy et al found significant correlation between obesity and albuminuria and significant correlation between albuminuria and creatinine clearance (odds ratio 13.867, CI 3.587-53.600).<sup>21</sup> Different result to this study may be due to different location of study, i.e. the study was performed at community health center or primary health care.

There was no correlation between blood glucose control and decreased GFR in this study. In other hand, this factor may have important role in DN development and it may interact with other risk factor causing enhanced progression of disease.<sup>30</sup> We assume that it may be because this study used various kind of laboratory test as the limit value and due to its cross-sectional study design.

Proteinuria does not only act as a marker of kidney disorder and disease severity, but it also has role in CKD progressivism.<sup>32</sup> Strong correlation between proteinuria and CKD may be found in a screening study by Iseki et al that found proteinuria as the strongest predictor of ESRD occurrence in 10 year period (odds ratio 14.9 CI 10.9-20.2).<sup>36</sup> Various studies has demonstrated strong correlation between proteinuria and CKD progressivism, without considering the cause of CKD.<sup>32</sup> In this study, we also found a correlation between proteinuria and decreased renal function, and remained after multivariate analysis. The study conducted by Galastri et al. did not find any correlation between both factors. This can be understood because most subjects in the study approximately had DM less than 4 years.<sup>20</sup> At initial stage of DN, indeed, there is glomerular hyperfiltration; therefore, the GFR will increase.

Galastri et al found a significant correlation between DN and diabetic retinopathy.<sup>20</sup> Razy et al also found similar result at the community health center (Puskesmas).<sup>22</sup> Our study also demonstrated a correlation between decreased renal function and diabetic retinopathy. This is important because diabetic retinopathy may increase the suspicion of renal dysfunction and early intensive treatment for DN has been proven that it may decrease the incidence of diabetic retinopathy.<sup>23</sup>

## Limitations

Cipto Mangunkusumo hospital is a type-C or tertiary hospital or central of referral. This may influence the patient selection that came to outpatient clinic at Cipto Mangunkusumo Hospital. The cross-sectional study design may cause that the causal-effect correlation between decreased renal function and risk factors can not be analyzed. However, such study design is well-applied, especially for disease with long onset and duration illness. Therefore, we compare the relative risk through odds ratio, i.e. the prevalence of disease in the group with and without risk.

This study only included patients with data that meet the inclusion criteria and without any exclusion criteria. This condition is frequently found in study field. In the United States, less than 1 of 4 patients with DM have HbA1c, lipid profile examination, and blood glucose level for at least once a year. It reveals that screening and better treatment are necessary in such patients.<sup>34</sup>

For more accurate GFR calculation by MDRD method, we need validation of examination method in measuring serum creatinine level, i.e. through calibration in CCF laboratory, i.e. at the place where MDRD was conducted..<sup>36,37</sup> Most sample in this study had examination at Clinical Pathology laboratory at Faculty of Medicine, University of Indonesia, Cipto Mangunkusumo Central General Hospital. When the test was not performed at the laboratory, the investigators asked the laboratory about the examination method and the test was excluded if there was any different technique used. Examination of serum creatinine level was performed at Clinical Pathology Laboratory, Faculty of Medicine, Cipto Mangunkusumo Hospital by using the technique of Jaffe kinetic reaction and it was calibrated continuously according to international standard prior to the examination. However, we did not know the comparison of its result with CCF laboratory.

## CONCLUSION

We found higher prevalence of decreased renal function in patients with type-2 DM based on estimated GFR compared to merely normal limit of serum creatinine level. Because some patients with GFR  $< 60$  mL/min still have serum creatinine level  $< 2$  mg/dL; therefore, we suggest that serum creatinine 2 mg/dL should better not be used for screening the decreased renal function in patients with type-2 DM. We recommend screening GFR in every patients with type-2 DM, by using estimation method, especially the CG-BSA method which will reveal more extensive result for patients with CKD and it may provide better prevention and treatment.

The risk factors of decreased renal function include history of hypertension, proteinuria and diabetic retinopathy.

## REFERENCES

1. US Renal Data System. 2005 Annual data report: International comparisons. *Am J Kidney Dis.* 2006;27(1 Suppl 1):S215-26.
2. Susalit E. Rekomendasi baru penatalaksanaan penyakit ginjal kronik. Naskah lengkap the 3rd Jakarta Nephrology and Hypertension Course and Symposium on Hypertension; 2003 Mei 9-11: Jakarta, Indonesia. Jakarta: PERNEFRI; 2003.
3. Suhardjono. Proteinuria pada penyakit ginjal kronik: mekanisme dan pengelolaannya. Naskah lengkap the 6th Jakarta Nephrology and Hypertension Course and Symposium on Hypertension; 2006 Mei 19-20; Jakarta, Indonesia. Jakarta: PERNEFRI; 2006.
4. Barsoum RS. Chronic kidney disease in the developing world. *N Engl J Med.* 2006;354(10):997-9.
5. El Nahas AM, Bello AK. Chronic kidney disease: the global challenge. *Lancet.* 2005;365:331-40.
6. Collins AJ, Couser WG, Dirks JH, Kopple JD, Reiser T, Riella MC, dkk. World kidney day: an idea whose time has come. *Am J Kidney Dis.* 2006;47(3):375-7.
7. Brown WW, Peters RM, Ohmit SE, Keane WF, Collins A, Chen SC, dkk. Early detection of kidney disease in community settings: the kidney early evaluation program (KEEP). *Am J Kidney Dis.* 2003;42(1):22-35.
8. Prodjosujadi W. Penatalaksanaan nefropati diabetik. In: Setiati S, Alwi I, Kasjmir IY, Aziza L, Lydia A, Syam AF, dkk, eds. Current diagnosis and treatment in internal medicine 2002. Jakarta: Pusat Informasi dan Penerbitan Bagian IPD FKUI; 2002. p. 21-8.
9. Gross JL, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T. Diabetic nephropathy: diagnosis, prevention, and treatment. *Diab Care.* 2005;28(1):164-76.
10. Vora JP, Ibrahim HAA. Clinical manifestations and natural history of diabetic nephropathy. In: Johnson RJ, Feehally J, eds. Comprehensive clinical nephrology. 2nd edition. Philadelphia: Mosby elsevier; 2003. p. 425-37.
11. American Diabetes Association. Nephropathy in diabetes. *Diab Care.* 2004;27(Suppl 1.1):S79-82.
12. Suwitra K. Penyakit ginjal kronik. In: Sudoyo AW, Setiyohadi B, Alwi I, Simadibrata M, Setiati S, eds. Buku ajar ilmu penyakit dalam. 4th edition. Jakarta: Pusat Penerbitan Ilmu Penyakit Dalam FKUI; 2006. p. 581-4.
13. Roesli R, Susalit E, Djafaar J. Nefropati diabetik. In: Suyono S, Waspadji S, Lesmana L, Alwi I, Setiati S, Sundaru H, dkk, eds. Buku ajar ilmu penyakit dalam. 3rd edition. Jakarta: Balai Penerbit FKUI; 2001. p. 356-65.
14. Stevens LA, Levey AS. Chronic kidney disease: staging and principles of management. In: Greenberg A, Cheung AK, Coffman TM, Falk RJ, Jennette JC, eds. Primer on kidney disease. 4th edition. Philadelphia: Saunders elsevier; 2005. p. 455-63.
15. National Kidney Foundation/Kidney Disease Outcome Quality Initiative (NKF/KDOQI). Clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. New York: NKF/KDOQI; 2002 [cited 2006 June 10]. Available from: <http://www.nkf.org>.
16. Schieppati A, Pisoni R, Remuzzi G. Pathophysiology and management of chronic kidney disease. In: Greenberg A, Cheung AK, Coffman TM, Falk RJ, Jennette JC, eds. Primer on kidney disease. 4th edition. Philadelphia: Saunders elsevier; 2005. p. 444-54.
17. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med.* 1999;130:461-70.
18. Verhave JC, Fesler P, Ribstein J, du Cailar G, Mimran A. Estimation of renal function in subjects with normal serum creatinine levels: influence of age and body mass index. *Am J Kidney Dis.* 2005;46(2):233-41.
19. Suhardjono, Markum MS, Prodjosujadi W. Pendekatan klinis pasien dengan penyakit ginjal. In: Suyono S, Waspadji S, Lesmana L, Alwi I, Setiati S, Sundaru H, dkk, eds. Buku ajar ilmu penyakit dalam. 3rd edition. Jakarta: Balai Penerbit FKUI; 2001. p. 295-306.
20. Galastri M. Nefropati diabetik dan manifestasi klinis pengunjug baru DM tipe 2 di poliklinik metabolik endokrin RSUPNCM [tesis]. Jakarta: Fakultas Kedokteran UI; 2003.
21. Ma YC, Zuo L, Chen JH, Luo Q, Li Y, Yu XQ. Modified glomerular filtration rate estimating equation for chinese patients with chronic kidney disease. *J Am Soc Nephrol.* 2006;17:2937-44.
22. Razy F. Prevalensi dan faktor risiko nefropati diabetik pada penyandang DM tipe-2 di pusat pelayanan kesehatan primer [Tesis]. Jakarta: Fakultas Kedokteran UI; 2002.
23. Middleton RJ, Foley RN, Hegarty J, Cheung CM, McElduff P, Gibson JM, et al. The unrecognized prevalence of chronic kidney disease in diabetes. *Nephrol Dial Transplant.* 2006;21: 88-92.
24. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: third national health and nutrition examination survey. *Am J Kidney Dis.* 2003;41:1-12.
25. Kong APS, So WY, Szeto CC, Chan NN, Luk A, Ma RCW, dkk. Assessment of glomerular filtration rate in addition to albuminuria is important in managing type 2 diabetes. *Kidney Int.* 2006;69(2):383-7.
26. MacIsaac RJ, Tsalamandris C, Panagiotopoulos S, Smith TJ, McNeil KJ, Jerums G. Nonalbuminuric renal insufficiency in type 2 diabetes. *Diab Care.* 2004;27(1):195-200.
27. Kuo H, Tsai S, Tiao M, Yang C. Epidemiological features of CKD in Taiwan. *Am J Kidney Dis.* 2007;49(1):46-55.
28. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med.* 2004;351;13:1296-305.
29. Zuo L, Ma YC, Zhou YH, Wang M, Xu GB, Wang HY. Application of GFR-estimating equations in chinese patients with chronic kidney disease. *Am J Kidney Dis.* 2005;45(3):463-72.
30. MacIsaac RJ, Watts GF. Diabetes and the kidney. In: Shaw KM, Cummings MH, eds. Diabetes chronic complications. 2nd edition. England: John Wiley & Sons; 2005. p. 21-47.
31. Shahab A. Why does DM increase the risk of cardiovascular disease? *Acta Med Indones-Indones J Intern Med.* 2006; 38(1):33-41.
32. Taal MW, Brenner BM. Predicting initiation and progression of chronic kidney disease: developing renal risk scores. *Kidney Int.* 2006;70:1694-705.
33. Tanaka H, Shiohira Y, Uezu Y, Higa A, Iseki K. Metabolic syndrome and chronic kidney disease in Okinawa, Japan. *Kidney Int.* 2006;69(2):369-74.
34. National Kidney Foundation. Guidelines for diabetes and CKD. *Am J Kidney Dis.* 2007;49(Suppl 2);S10-1.



35. Molnar M, Wittmann I, Nagy J. Prevalence, course, and risk factors of diabetic nephropathy in type-2 diabetes mellitus. *Med Sci Monit.* 2000;6(5):929-36.
36. Iseki K, Kinjo K, Iseki C, Takishita S. Relationship between predicted creatinine clearance and proteinuria and the risk of developing ESRD in Okinawa, Japan. *Am J Kidney Dis.* 2004;44(5):806-14.
37. Levey AS, Coresh J, Greene T, Stevens LA, Zhang Y, Hendriksen S, dkk. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med.* 2006;145:247-54.
38. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function-measured and estimated glomerular filtration rate. *N Engl J Med.* 354;23:2473-83.