PUBLIC HEALTH RESEARCH

What Contributes to The Progression of Chronic Kidney Disease in Type 2 Diabetic Patients?

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ABSTRACT

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Introduction Chronic kidney disease (CKD) has emerged as a major medical illness that drew the attention of the community. This research focused on the prevalence of five contributing factors to the progression of CKD, namely blood pressure control, glycaemic control, lipid control, smoking and alcohol intake, and explored significant association between these variables. This was a cross-sectional study that examined the progression of CKD based on the worsening of CKD stages.

Methods This study was conducted among CKD patients with type 2 diabetes mellitus who attended Nephorology Clinic, UKMMC from April to May 2011. The progression of CKD was observed for 3 consecutive visits with 3 months intervals between the visits. Information regarding demographic data and social history were obtained through face-to-face interview, followed by case note review of the blood results. Data collected was analysed using SPSS version 19.0.

Results A total of 201 respondents were investigated, which included 39.3% (n=79) female and 60.7% (n=122) male. The mean age for the respondents was 66.9 years old (±SD 9.00). Among the respondents, 71.5% had poor glycaemic control; 59.7% had poor blood pressure control; 65.2% had poor lipid control; 19.9% smoked and 3.5% consumed alcohol. There was poor correlation, there were statistically significant association between systolic blood pressure control with the glomerular filtration rate (GFR) ($p=0.001$; $r=-0.229$). From this research, high systolic blood pressure was associated with low GFR, which indicated poor kidney function and resulted in progression of CKD.

Conclusions This study has clearly demonstrated that the control of blood pressure was essential in delaying the progression of CKD.

Keywords Chronic kidney disease - disease progression - risk factors - type 2 diabetes mellitus - blood pressure

INTRODUCTION

Chronic Kidney Disease (CKD) has emerged as a major medical problem and concern in the medical practices. It is related to various conditions or factors such as the underlying medical problems, management errors and the existing of unhealthy practices. This problem can only be curbed if an early detection and treatment are strengthened.

CKD is defined according to the presence or absence of kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for 3 months or more, irrespective of cause. Kidney damage is defined as pathological abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies. The glomerular filtration rate (GFR) can be estimated from calibrated serum creatinine and in this study; the estimating equation used was Modifications of Diet in Renal Disease (MDRD) Study equation. There are five stages in the classification of CKD based on the level of GFR.[1]

There are many causes of CKD. One of the important ones is diabetes mellitus. In Malaysia, the number of diabetics has increased by almost 80 percent in the last 10 years from 1996-2006.[2] Nephropathy develops in about 20-40% of diabetics and the improvement of survival rates in diabetic patients; it has emerged as a major health problem. The sign of early diabetic nephropathy is the presence of microalbuminuria (albuminuria 30-300 mg/day). This progresses to proteinuria (albuminuria > 300mg/day) and the decline in glomerular filtration rate (GFR).[3]

Study has also shown that type 2 diabetes is the primary cause of end-stage renal disease (ESRD).[4] Therefore, viable solutions such as early detection and control methods are urgently required to monitor and manage diabetes so that its progression towards CKD and finally ESRD could be slowed down.

An appropriate study is needed to explore the possible conditions or factors that facilitate the progression of CKD. Among the well-known factors which contribute to the progression of CKD are poor glycaemic control, hypertension, smoking, alcohol intake and hyperlipidaemia. [5,6,7,8,9,10] As there are not many studies done in Malaysia to understand this phenomena, this study examined all the possible factors that is responsible for the progression towards CKD and ESRD.

METHODS

This was a cross sectional study done in University Kebangsaan Malaysia Medical Centre. This research was approved by Research and Ethical Committee, Faculty of Medicine, Universiti Kebangsaan Malaysia (FF-126-2011).

There were 241 CKD patients with type 2 diabetes mellitus who came for follow up at Nephrology Clinic in UKMMC during the study period (April 2011- May 2011).

The sampling method adapted in this study was convenient sampling. The consent form was given to subjects to be filled up by them or their carers with the assistance of the researchers. The subject's demographic data and background history were obtained and a brief interview with respondents in order to acquire the past medical history and lifestyle practices. This was followed by case note review in order to obtain the patient's blood pressure, weight, HbA1c, serum lipid profile and renal profile on the latest 3 consecutive visits with an interval of 3 months. The progression of disease is determined by the worsening of stages of CKD based on GFR calculated from creatinine taken during the 3 consecutive visits. GFR was calculated by using Modification of Diet in Renal Disease (MDRD) equation which is

$$GFR = 186 \times [(\text{Serum Creatinine} \times 0.0113)^{-1.154}] \times (\text{age}^{-0.203}) \times F$$

Where F = 1 if male, and 0.742 if female

Table 1 CKD staging.

Stage	Description	GFR Level mL/min
1	Kidney damage with normal or higher GFR	> 90
2	Kidney damage and mild decrease in GFR	60 – 89
3	Moderate decrease in GFR	30 – 59
4	Severe decrease in GFR	15 – 29
5	Kidney failure (dialysis or kidney transplant needed)	< 15

In this research, the independent variables studied were blood pressure, HbA1c, serum lipid profile, renal profile, history of smoking and alcohol intake. Pearson correlation was selected for data analysis and a $p < 0.05$ was considered significant.

Statistical analysis

All statistical analysis of the data was carried out using 'Statistical Package for Social Science' (SPSS) version 19. All parameters were normally distributed. The parametric analysis of five factors (control of blood pressure, glycaemic and lipid; significant smoking and alcohol intake)

was done using Chi square test. Pearson's correlation was performed on continuous data of systolic blood pressure, diastolic blood pressure, HbA1c, triglycerides, cholesterol, cigarette pack-years of smoking and number of drinks for alcohol. Except pack-years smoking and number of drinks for alcohol, other parameters were calculated from average of three readings. Between all continuous parameters and the latest GFR, Correlation test was used. P value of less than 0.05 was considered significant.

RESULTS

A total of 201 respondents participated in this study. Of these, 60.7% were male and 39.3% were female. The respondents' age ranged from 34 to 87 years old. Majority of the respondents were Malays (53.7%) whereas Chinese and Indians were 37.8% and 8.5% respectively. Majority of the respondents had low to moderate educational level and 86.1% were married. (Table 2)

The overall percentage of patients suffering CKD progression was 21.39% with male 20.49% and female 22.78%. One out of five patients had worsening of their kidney function. It is decreased with age from 38.8% (45-54 years old) to 15.38% (75-84years old). Among the Malays it was relatively higher at 23.1%, followed closely by Chinese 22.4% and Indian 5.9%. Others sociodemographic characteristics were summarized in Table 2.

There was high prevalence of poor control of medical parameters namely glycemia, blood pressure and lipid. Poor glycaemic control was 71.5% whereas poor control of blood pressure and lipid is 83.1% and 65.2% respectively. Respondents who smoked significantly were 19.9% and 3.5% for significant alcoholic. Patients who smoke more than 10 cigarette pack-years classified as significant smoker whereby significant alcoholic means patients who consumed more than 15 drinks of alcohol weekly during the past year. (Table 3)

The proportion of CKD progression was relatively higher among those with poor glycemic, blood pressure and lipid control compared to those with the good control. The similar finding was also noted among those who smoked significantly compared to those who did not. However its difference was not statistically significant.(Table 4)

Further analysis was carried out using Pearson's correlation (Table 5). Latest GFR was used to correlate with average of three readings of Hb_{A1c}, systolic blood pressure, diastolic blood pressure, triglycerides and cholesterol. Quantity of smoking was represented by cigarette pack-years and alcohol intake by numbers of alcohol drinks. Although there was poor correlation, there was statistically significant association between systolic blood pressure control (p=0.001; r=-0.229) with the GFR (Figure 1). On the other hand, other parameters had no significant correlation with latest GFR.

Table 2 Sociodemographic background of study respondents (n=201).

		CKD progression		Mean±SD
Factors	Characteristics	Yes*=43 n(%)	No=158 n(%)	
Gender	Male	25(20.5)	97(79.5)	
	Female	18(22.8)	61(77.2)	
Age(in years)	>85	1(50.0)	1(50.0)	66.9±9.00
	75-84	6(15.4)	33(84.6)	
	65-74	13(15.3)	72(84.7)	
	55-64	16(29.1)	39(70.9)	
	45-54	7(38.9)	11(61.1)	
	<45	0(0.0)	2(100.0)	
Race	Malay	25(23.1)	83(76.9)	
	Chinese	17(22.4)	59(77.6)	
	Indian	1(5.9)	16(94.1)	
Education	None	5(13.9)	31(86.1)	
	Primary school	17(22.1)	60(77.9)	
	Secondary school	17(24.3)	53(75.7)	
	Pre-U/STPM	0(0.0)	5(100.0)	
	University/College	4(30.8)	9(69.2)	

Marital status	Married	38(22.0)	135(78.0)
	Divorced	0(0.0)	1(100.0)
	Single	2(40.0)	3(60.0)
	Widow/Widower	3(13.6)	19(86.4)

*Patients with CKD progression were those who showed worsening of CKD stages during their three latest follow-up in nephrology clinic, UKMMC

Table 3 Prevalence of various factors contributing to progression of CKD in type II diabetic patients

Factors	Good	Poor
Glycaemic control (n=201)	28.5%(n=57)	71.5%(n=144)
Blood pressure control(n=201)	16.9%(n=34)	83.1%(n=167)
Lipid control(n=201)	34.8%(n=70)	65.2%(n=131)
	Not Significant	Significant
Smoking(n=201)	80.1%(n=40)	19.9%(n=161)
Alcohol(n=201)	96.5%(n=194)	3.5%(n=7)

Table 4 Association between various factors and progression of CKD.

Factors	**CKD progression**				**X^2**	**p value**
	Yes (n=43)		No (n=158)			
	f	%	f	%		
Glycaemic control						
Poor[a]	33	23.1	111	76.9	0.739	0.39
Good	10	17.5	47	82.5		
Blood pressure control						
Poor[b]	36	21.6	131	78.4	0.016	0.90
Good	7	20.6	27	79.4		
Lipid control						
Poor[c]	31	23.7	100	76.3	1.154	0.28
Good	12	17.1	58	82.9		
Smoking						
Significant[d]	11	27.5	29	72.5	1.108	0.29
Not significant	32	19.9	129	80.1		
Alcohol intake						
Significant[e]	0	0.0	7	100.0	1.974	0.16
Not significant	43	22.2	151	77.8		

[a] Poor glycaemic control is when the HbA1c is more than 6.5%
[b] Poor blood pressure control is when the blood pressure is higher than 130mmHg(systolic) or 80 mmHg(diastolic).
[c] Poor serum lipid level control is when the total cholesterol exceeding 5.4mmol/L or triglycerides level exceeding 1.7mmol/L.
[d] Patients who smoke more than 10 cigarette pack-years.
[e] Patients who consumed more than 15 drinks of alcohol weekly during the past year, whereby one drink defined by wine (5 oz or 148 ml), beer (12 oz or 355 ml), and liquor (1.5 oz or 44 ml).

Table 5 Bivariate correlation between the parameters and latest GFR.

Parameters	GFR	
	r	p
HbA1c	0.027	0.7
Systolic blood pressure	**-0.229**	**0.001**
Diastolic blood pressure	-0.075	0.287
Triglycerides	-0.027	0.708
Cholesterol	-0.018	0.795
Cigarette pack-years	-0.047	0.719
Number of alcohol drinks	0.335	0.127

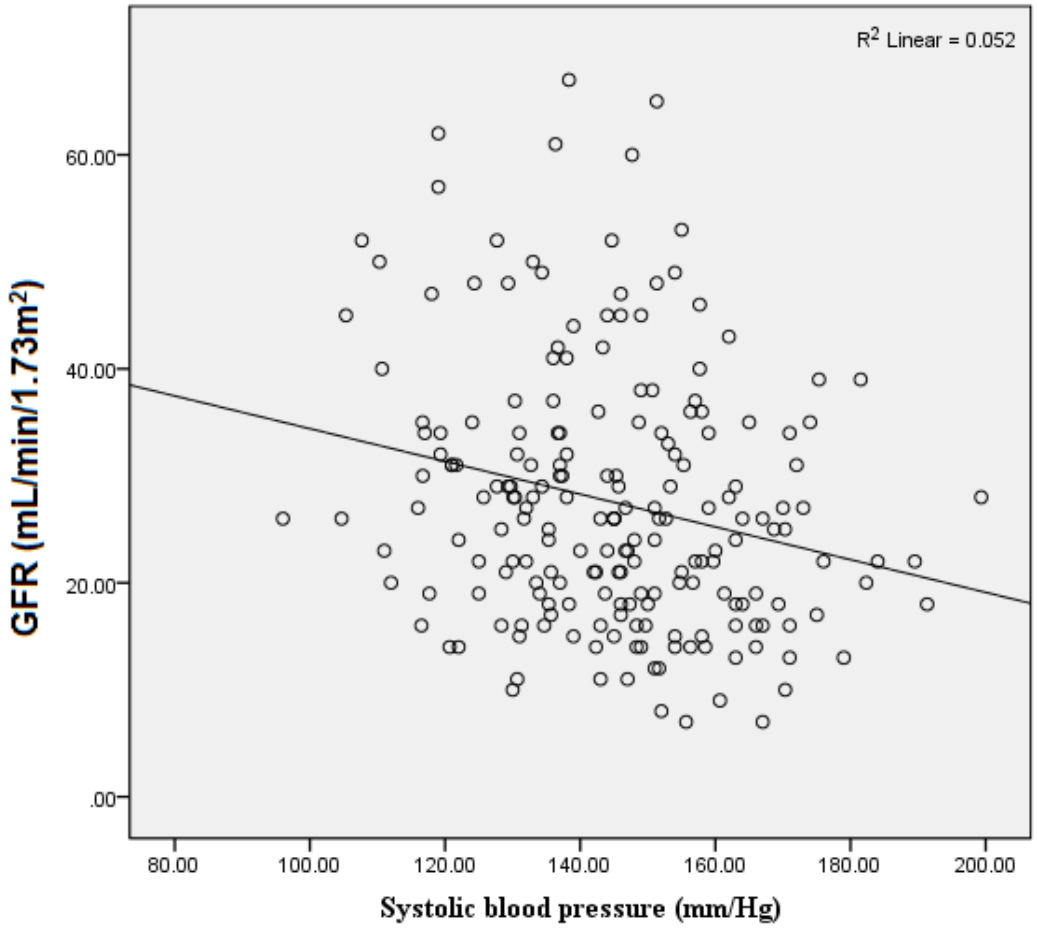

Figure 1 Scatter diagram shows correlation between systolic blood pressure and GFR.

DISCUSSION

High blood pressure has been well established to contribute to the pathology of disease, although our study failed to prove its role in the progression of CKD. Nevertheless, high systolic blood pressure was showed to be significantly correlated to low GFR, which indirectly depicts the importance of optimizing blood pressure control in CKD patients (p=0.001; r=-0.229). This result was supported by Marc A. Pohl et al in Irbesartan Diabetic Nephropathy Trial (IDNT), which also demonstrated presence of direct relationship between control of systolic BP and adverse renal outcomes among type 2 diabetic nephropathy patients, independent of baseline renal function.[11] Moreover, our study reveals that there was high

prevalence of poor blood pressure control in CKD patient with type 2 diabetic patients (59.7%). Elevated systolic blood pressure was evidenced to be a risk factor in catalysing renal impairment among patients with type 2 diabetes.[12] This indicated that an effective intervention in controlling blood pressure should be carried out in UKMMC.

The parameter used to determine glycaemic control in this study is glycated haemoglobin (HbA1c). Although there was no significant association between poor glycaemic control and CKD progression in our study which was in contrast to other study, the result was different in our study probably due to insufficient sample size and short duration of study.[6] However, our study revealed that there was high prevalence of poor glycaemic control in CKD patients with type 2 diabetes (71.5%). These results indicated that some interventions need to be taken so that blood glucose can be controlled since several study had stated that renal damage rarely occur when HbA1c is <7.5%[13,14]

The analysis results did not show any statistical significance between lipid control and progression of CKD. There were only 23.7% of respondents among poor lipid control that have progressive CKD. The result was not consistent with other studies probably due to the lipid profile of patients was calculated using the average of three laboratory investigation result in which some of the investigations were done many years ago. It may not give the true reflection of patients' lipid control. However, there was a high prevalence of poor lipid control in CKD patient with type 2 diabetic patients (65.2%). This figure drew our attention to improve patients' lipid control. There was evidence that lipid reduction by antilipemic agents might preserve GFR and decrease the proteinuria in diabetic patients.[14] Therefore, it is very crucial for patients to have a good lipid control.

Our study did not show any significant association between smoking with progression of CKD in type 2 diabetic patients. Among patients who had history of significant cigarette pack-years (≥ 10 pack-years), there were 27.5% of respondents with progression of CKD. Smoking had previously been associated with progression of CKD in various studies. In a study conducted by Telmer et al, prevalence of diabetic nephropathy was significantly higher among heavy smokers (>10 cigarettes a day for more than one year) than among non-heavy smokers (p<0.02) which was in contrast to our study.[16] Another study also demonstrated higher prevalence of nephropathy among patients who were or who had been cigarette smokers.[17] A study showed no significant impact of smoking on the rate of decline in GFR when patients were stratified into smokers and nonsmokers. However, when patients were stratified into heavy smokers (smoking ≥20 cigarettes a day) and non-heavy smokers (smoking ≤19 cigarettes a day and nonsmokers), heavy smokers had showed a significantly greater rate of decline in GRF.[4] In our study, we could not demonstrate a significant impact of smoking on the progression of CKD when patients were stratified into significant smokers (≥10 pack-years) and non-significant smokers (≤9 pack-years or non-smoker). This probably due to insufficient sample size (only 20% respondents are significant smoker) and short duration of study which failed to showed progression of CKD.

The result of this cross-sectional study did not show that alcohol intake is associated with an increase risk for CKD progression among patients with type 2 diabetes mellitus. There are relatively less studies done to demonstrate specifically the significance of alcohol intake in progression of either chronic renal disease or diabetic nephropathy. A case-control study done in several provinces of United States depicted significant increased risk of ESRD between persons who consumed more than two drinks per day compared to abstainers.[7] According to a prospective study of Australian adults involving 6259 adults ≥25 years of age, without a history of alcohol dependence has shown a significant association between high amounts of alcohol consumption with ESRD.[18] However, previous studies analysed western population only while in this study the alcohol intake were recorded from a multiracial population that consists of Malays, Chinese, and Indian. According to a study conducted on 562 consecutive attainders at an urban general practice, 70% of Chinese, 11% of Malays and 42% of Indians have used or are currently using alcohol and a vast majority of them were social drinkers.[19] Thus, even though some of the subjects consume alcohol but the majority of them were social drinkers and the amount and frequency of alcohol intake were not as high as in western culture. It was may be due to Islamic belief for Malays that prohibit alcohol consumption and different culture practice for Chinese and Indians races compared to westerners.

CONCLUSIONS

This study revealed there was poor control of glycaemic level, blood pressure and lipid level among CKD patients with type 2 diabetes mellitus in UKMMC. Thus, the patients should be educated properly from dietary aspects and the importance of compliance to medications to achieve a better control of these parameters. Although the development of end-stage renal failure as the end spectrum of chronic kidney disease is deemed to be unpreventable, the optimization of the health status of the patients is helpful in delaying its progression, thereby prolonging their lifespan.

Apart from that, this study supported the presence of relationship between blood pressure and low glomerular filtration rate (GFR), which had also been established in many other trials. Meanwhile, the necessity of modification of lifestyle such as smoking and alcohol cessation, besides dietary restriction of lipid and sugar intake should not be overlooked. Even though this study failed to reveal their role in hastening the deterioration of kidney function, this might be due to a number of limitations stated above.

Prevention is always better than cure. Hence, high risk population should be defined, so that intervention programmes can be targeted at them effectively. Health awareness campaign ought to be held in order to deliver knowledge to the public and aid in the control of the progression. Although aging is also correlated to the worsening of kidney function, other modifiable factors have to be emphasised and controlled to delay the onset of proteinuria and presence of other markers of kidney disease. Screening of high-risk groups might be needed so that treatment can be commenced immediately once a patient was diagnosed.

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REFERENCES

1. Andrew SL, Kai-UE, Yusuke T, Adeera L, Josef C, Jerome R, Dick DZ, Thomas HH, Norbert L, Garabed E. Definition and classification of chronic kidney disease: A position statement from kidney disease: Improving global outcomes (KDIGO). *Kidney International*; 2005. 67, 2089–2100.
2. Persatuan Diabetes Malaysia. 2011. Available at http://www.diabetes.org.my/article.php?aid=921 (Cited 7 July 2011)
3. Longmore M, Wilkinson I, Turmezei T, Cheung CK. Oxford Handbook Clinical Medicine, 7th edition, Oxford University Press, pg 306.
4. Kasper R, Christensen PK, Peter H, Lise T, Peter R, Henrik HP. Progression of nephropathy in type 2 diabetic patients. *Kidney International*; 2004. 66, 1596–1605.
5. Saleh JA, Yusuf H, Salawu FK. Prevention of diabetic nephropathy. *Nigerian Medical Practitioner*; 2008. Volume 53, Number 3, 28-32.
6. Nosadini R, Tonolo G. Relationship between blood glucose control, pathogenesis and progression of diabetic nephropathy. *Journal of the American Society of Nephrology*; 2004. 15: S1–S5.
7. Ritz E, Ogata H, Orth SR. Smoking a factor promoting onset and progression of diabetic nephropathy. *Diabetes Metabolism*; 2000. 26(supplement 4):54-63.
8. Ritz E, Stefanski A. Diabetic nephropathy in type II diabetes. *American Journal of Kidney Diseases*; 1996. 27:167-194.
9. Thomas V. Perneger, Paul K. Whelton, Ian B. Puddey, Michael J. Klag. Risk of End-stage Renal Disease Associated with Alcohol Consumption. *American Journal of Epidemiology*; 1999. 150;12: 1275-1281.
10. Waugh NR, Robertson AM. Protein restriction for diabetic renal disease. *Cochrane Database of Systematic Reviews*; 1997, Issue 4.
11. Pohl MA, Blumenthal S, Cordonnier DJ, De Alvaro F, Deferrari G, Eisner G, Esmatjes E et.al. Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the Irbesartan Diabetic Nephropathy Trial: Clinical implications and limitations. *Journal of American Society of Nephrology*; 2005. 16: 3027–3037.
12. Retnakaran R, Cull CA, Thorne KI. Risk factors for renal dysfunction in type 2 diabetes: UK Prospective Diabetes Study 74. *Diabetes*; 2006. 55: 1832–1839.
13. Fuller J, Shipley M, Rose G, Jarrett R, Keen H. Mortality from coronary heart disease and stroke in relation to degree of glycemia: The Whitehall study. *British Medical Journal*; 1983. 287: 867–870.
14. Warram JH, Scott LJ, Hanna LS, Wantman M, Cohen SE, Laffel LM et.al. Progression of microabuminuria to proteinuria in type 1 diabetes: Nonlinear relationship with hyperglycemia. *Diabetes*; 2000. 49: 94–100
15. Fried LF, Orchard TJ, Kasiske BL. Effect of lipid reduction on the progression of renal disease: a meta-analysis. *Kidney International*; 2001. 59: 260–69.
16. Telmer, S, Christiansen, JS, Andersen, AR. Smoking habits and prevalence of clinical diabetic microangiopathy in insulin-dependent diabetics. *Acta Medica Scandinavica*;. 1984. 215: 63–68

17. Christiansen JS. Cigarette smoking and prevalence of microangiopathy in juvenile-onset insulin-dependent diabetes mellitus. *Diabetes Care.* 1987.1: 146–149
18. Sarah LW, Kevan RP, Alan C, Jonathan ES, Robert CA et al. Alcohol consumption and 5-year onset of chronic kidney disease: the AusDiab study. *Nephrology Dialysis Transplant*; 2009. 24:2464-2472.
19. Maniam T. Drinking habits of Malaysians in general practice. *Medical Journal Malaysia*; 1994. 49(4):369-374.