

Exposure and Factors Influencing the Progression of Diabetic Nephropathy Amongst Type II Diabetes Mellitus Patients in Seremban, Negeri Sembilan

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Abstract: The case of diabetic nephropathy often arises among people with type 1 or type 2 diabetes. The incident of diabetic nephropathy has increased dramatically in the last decade. Increasing case of diabetic nephropathy had worried to most of diabetic patient. A cross-sectional study was conducted and focused on two areas: modeling the applied logistic regression and to determine the factors that influence diabetic nephropathy mellitus using structural equation modelling in Seremban, Negeri Sembilan. Three hundred eighty three diabetic patients were selected from Seremban. Of those who had diabetes, 172 (44.9%) patients were female and 211 (55.1%) were male. Finding from the previous research, the earliest age to start diabetes mellitus is at 20 years old. Factors found to be significantly associated with diabetes mellitus on multivariate analysis were beta blockers (OR= 3.942, 95% CI= 0.422, 36.854), serum creatinine (OR= 1.057, 95% CI=1.023, 1.093), age (OR= 0.917, 95% CI=0.821, 0.97), blood glucose (OR= 1.564, 95% CI= 1.091, 2.241), gender (OR= 20.396, 95% CI= 0.963, 431.892). In this paper, we found that age, being male, taking Beta-blockers having blood glucose level and serum creatinine reported as influencing factors of type II diabetes mellitus.

Keywords: Logistic regression, SEM, diabetes mellitus, diabetic nephropathy.

I. Introduction

Diabetes mellitus (DM) type II is one of the major public health in the Asian-Pacific region due to the high medical and socioeconomic costs [1]. Diabetic nephropathy is much more common amongst diabetic patients. Previous research has been identified that diabetic patients have major risk factor for diabetic nephropathy. Based on the Diabetes Atlas, the highest number of people with diabetes would currently be in the European region with 48 million and Western Pacific Region with 43 million. However, by 2025, the greatest number of people with diabetes is expected to change in the South East Asia Region, with an estimated prevalence of 13.5% and in number with some 145 million people [2]. American Diabetes Association (ADA) examined the criteria for impaired fasting glycaemia (IFG) and recommended that the cut-point for IFG should be lowered to a fasting plasma glucose (FPG) ≥ 5.6 mmol/L (100 mg/dl) [3].

A study in 2006, has estimated that for the urban population in China, the direct medical costs of diabetes are US\$45 per year for someone without complications, meanwhile for people with complications it will up to US\$1694 per year [4]. Although DM type I remain the most prevalent form of the disease, it is likely that DM type II will be the predominant form within 10 years. DM type II has already been reported in from Japan, Pacific Islands, Hong Kong, Singapore, China, Malaysia, Korea and Australia. Among children in Japan, it is accounting for 80% of childhood diabetes; the incidence has almost doubled between 1976–1980 and 1991–1995 [5].

This rising trend is due to many factors such as ethnicity, strong family history of DM type II, age, high body mass index (BMI) scores and central obesity indicators (waist-to-hip ratio and waist circumference), low birth weight, and “Westernization” (adoption of lifestyle habits characteristic of the more industrialized countries) [6]. Second National Health and Morbidity reported that 3.4 million or 11.6% Malaysians are diabetes sufferers in 2010. The Indians are leading in DM type II by 19.9%, followed by Malays 11.9% and Chinese 11.4%. Malaysia has the most number of overweight and obese people in Asia, obesity is a main cause of diabetes 54% of the adult population are either obese or overweight, compared to only 24.1% 10 years ago.

High sugar intake (which also causes obesity) among Malaysians is one of the contributing factors to the high incidence of diabetes. Malaysians consume 26 teaspoons of sugar a day and are the eighth highest sugar users in the world. Amongst the 14 States in Malaysia, Negeri Sembilan, Malacca and Penang had the highest prevalence of DM type II of 15.3%, 15.2% and 14.9% respectively. The prevalence was higher in the urban at 12.2% (95% CI: 11.6-12.7) compared to the rural areas at 10.6% (95% CI: 9.9-11.1) [7]. DM can cause others serious illness and complications. Acute complications include diabetic ketoacidosis, nonketotic hyperosmolar

coma, cardiovascular disease, chronic renal failure, and diabetic retinopathy (retinal damage). One of the common disease closely related to DM type II is diabetic nephropathy. Diabetic nephropathy has become the leading cause of end-stage kidney disease worldwide. Diabetic nephropathy is a progressive rise in urine albumin excretion, coupled with increasing blood pressure, leading to declining glomerular filtration and eventually end stage kidney failure [8]. In people with DM type II, the nephrons (small units in the kidney) thicken and slowly become scarred over time. Then, the kidneys begin to leak and protein (albumin) passes into the urine. People who have more severe and long-term (chronic) kidney disease may have symptoms such as fatigue most of the time, general ill feeling, headache, nausea and vomiting, poor appetite and swelling of the legs.

II. Material And Methods

2.1 Study Area

This research was conducted in Seremban. Seremban is the capital of the Malaysian state of Negeri Sembilan

2.2 Study population

We studied patient with Diabetes Mellitus Type II who attended the Hospital Seremban. A total 383 eligible patients were selected. They were more than 22 until 88 years old and diagnosed to have Diabetes Mellitus Type II. Some of them have been diagnosed to have diabetic nephropathy

Sample size calculation for the first objective:

The sample sizes required at analysis stage are as follows.

Anticipated population proportion (p) = 0.057

Level of significance = 5% (0.05)

Absolute precision (Δ) = $\pm 5\%$

$$= \left(\frac{1.96}{0.05} \right)^2 0.057(1-0.57)$$

$$= 82.59 \approx 83 \text{ respondents.}$$

According to Lwanga and Lemeshow, [7].

In this case the response rate is estimated at only 75%, then add another 25% for data collection stage. So, we get $n = 82.59 + (0.25 \times 82.59) = 103.2 \approx 103$. Samples of 103 respondents are required at the analysis stage. For this analysis, we used 103 respondents.

Sample size calculation for the second objective:

In this study, we calculate the sample size with manual calculation, with the significance level (α) 0.05 and the power of study ($1-\beta$) of 80%. The detectable hazard ratio of the presence of prognostic factor relative to absence of prognostic factors was decided by the researcher and expert opinion by clinicians [5]. Two Proportions formula is given as follows:

$$n = \frac{p_0(1-p_0) + p_1(1-p_1)}{(p_0 - p_1)^2} (z_\alpha + z_\beta)^2$$

where:

P_0 = Based on literature review, P_1 = Based on expert opinion, $z_\alpha = z_{0.05} = 1.9600$

(one tailed) and $z_\beta = z_{0.20} = 0.8416$ (one tailed)

Table 1. Sample Size Calculation

No	Objective	* P_1	P_0	Type 1 Error	Power	Sample Size
1	Patients with Type II Diabetes Mellitus having a diabetic nephropathy[4]	0.39	0.22	5%	80%	114 patients
	Calculation	$n = \frac{0.39(1-0.39) + 0.22(1-0.22)}{(0.39 - 0.22)^2} \times (1.96 + 0.80)^2 = 108 \approx 109 \text{ patients}$				

After adding 10% estimated missing data, we get $n = 109 + (0.1 \times 109) = 119.90 \approx 120$ per group, which can be obtained as follows:

- i. Patients with Type II Diabetes Mellitus having a diabetic nephropathy = 120 patients
- ii. Patients with Type II Diabetes Mellitus which does not hasa diabetic nephropathy = 120 patients

Therefore, a total patient to be sampled is $(120 \times 2) = 240$ patients.

Table 2. Variable Description and Coding

Variable Name	Variable Description and Coding
1. Age	Age patient in years
2. Sex	Patient gender (female = 0, male = 1)
3. Serum	Serum Creatinine
4. Fasting Blood Glucose	Reading of level fasting blood glucose (mg/dL)
5. Beta Blocker	Taking Beta Blocker (0 = no, 1= yes)
6. Diabetes Nephropathy	(0 = no, 1= yes)

III. Statistical Analysis

The data were analyzed with SPSS software and SEM (Structural Equation Modeling). Multiple logistic regression analysis was employed to evaluate the associated factors and to determine all possible estimate risk. All *p* values were two-tailed and the level of significance was set at 0.25 based on Mickey and Greenland (1989) [5]. They recommend the alpha was set to 0.25 level and be used as a screening criterion for variable selection in logistic regression. Multiple logistic linear regression analysis with enter method was applied to Diabetes Nephropathy data. We also applied structural equation modeling (SEM) to investigate and estimate causal relations using a combination of statistical data and qualitative causal assumptions, while controlling for the effects of other variables included in the model and adjusting for measurement errors.

IV. Results

Logistic Regression Models Approach for Diabetes Mellitus

To explore the underlying association between diabetes mellitus nephropathy and the selected explanatory variables, a set of logistic regression models is fitted in this section. For the binary logistic regression approach we take the following dichotomous variables

$Y = 0$, Diabetic and having diabetic nephropathy

$Y = 1$, Diabetic with no diabetic nephropathy

Then we obtained the following model.

Table 3. Logistic regression model of the associated factors for nephropathy disease

Dependent Variable	Independent Variable	Std. Coefficient Beta (β)	S.E	Adjusted OR*	95% CI for Adjusted OR	
					Lower	Upper
Diabetic Nephropathy Disease	Demographic factors					
	Age (in years)	-0.086	0.057	0.917	0.821	1.025
	Sex	-10.384	4.023	20.396	0.963	431.892
	Biochemical					
	Serum Creatinine	0.056	0.017	1.057	1.023	1.093
	Fasting Blood Glucose	0.447	0.184	1.564	1.091	2.241
	Medication					
	Beta Blocker	1.372	1.141	3.942	0.422	36.854
	Hosmer and Lemeshow Test		p -value 0.886			
	Area under the Curve		0.954 (95% CI: 0.906, 1.00)			

Table 3 shows the final model of logistic regression. In this multivariate analysis, only five variables appeared as significant factors ($p < 0.25$). It is clearly observed from the results that age (OR = 0.917, 95% CI = 0.821, 1.025), patient's sex (OR = 20.4, 95% CI = 0.963, 431.9), has been negatively associated with the nephropathy

diabetes. Serum Creatinine level (OR = 1.057, 95% CI = 1.023, 1.093), betablocker (OR = 3.942, 95% CI = 0.422, 36.854), and fasting blood glucose (OR = 1.564, 95% CI = 1.091, 2.241) has been positively associated with nephropathy diabetes. Gardner and Altman (1989) [5] recommendation that 0.25 level be used as a screening criterion for variable selection in logistic regression. According to them, traditional level (such as 0.05) often fails to identify variables known to be important.

Diabetic nephropathy is the kidney disease that occurs as a result of diabetes (Amir et al., 2012). From multiple logistic regression, we can see that among male patients, the risk of developing diabetic nephropathy among male patients is 20 times higher compared to female. For the patient who is taking a beta blocker as a medication, the risk of developing diabetic nephropathy among patients who consume beta blocker is 4 times higher compared to patients who do not take the beta blocker. This logistic regression model was fit based on a non-significant Lwanga and Lemeshow [6, 13] with $p = 0.886$ and good area under the curve (0.954).

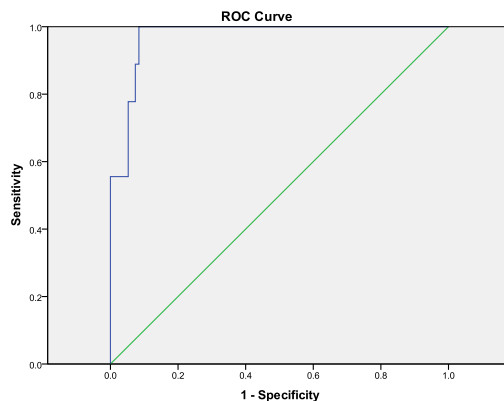


Figure.1 ROC Curve

We model the diabetic nephropathy case using structural equation modeling in order to determine or identify the relationship among variables. In the path diagram, kidney disease is predicted directly by sex, blood glucose, age and serum creatinine. In turn, sex is predicted by a beta blocker, and age is predicted by beta blocker and blood glucose. The path diagram also implies that the effect of beta blocker and fasting blood glucose on kidney disease are only indirect. They affect kidney disease only through their effects on sex, age and serum creatinine. Furthermore, some variables serve dual roles as predictors and outcome in the structural equation modeling diagram.

Structural Equation Modeling

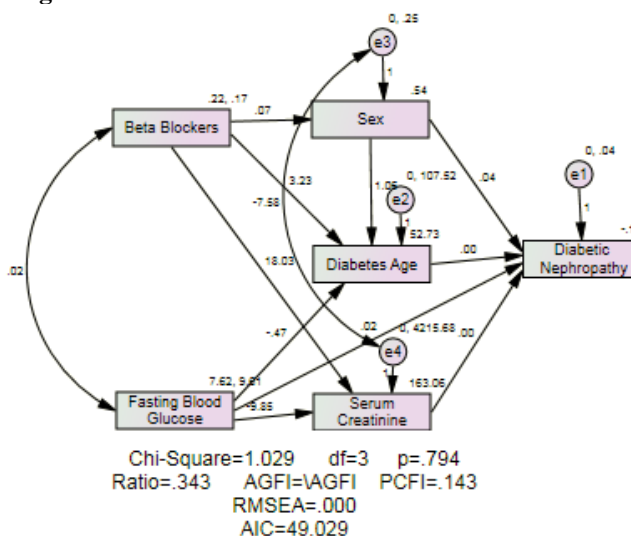


Figure 2. Structural equation modeling for diabetic nephropathy

Serum Creatinine

High serum creatinine level means the kidney is not well work. The normal measurement level of creatinine is 0.8 to 1.4 mg/dL. Male has higher serotonin level compared to male because male usually have

muscle mass. Blood test for creatinine is a simplest way to monitor the kidney function. From the previous research, female has found to be lower creatinine (0.6 to 1.2 mg/dL) than male, because they usually have less muscle mass. Creatinine based glomerular filtration rate is the best measure of kidney function since it account for age, bmi and sex. Usually, the measure of glomerular filtration rate declines when the kidney injured by disease. [Pradeep]. The American Diabetes Association and the National Institutes of Health recommend Estimated glomerular filtration rate (eGFR) calculated from serum creatinine at least once a year in all people with diabetes for detection of kidney dysfunction. [Pradeep]. Nayak et al., (2011) have found that serum creatinine level is associated with type II diabetes. In their study, they found that diabetic over 50 years of age were found to have higher mean serum creatinine values than the non diabetics.

Age and sex

Structural equation modeling shows that age and sex have a direct effect on kidney disease. A number of studies in humans have shown that diabetes nephropathy increasing with age and sex. The incidence of progression of nondiabetic renal is generally larger found in men compared to the woman. Many studies reported that the male sex is a risk factor for the development and rate progression of diabetic renal disease (Nayak).

Beta Blocker

Beta blocker has no direct effect upon kidney disease but has an indirect effect through diabetes, sex and serum creatinine. The function of beta-blockers is to slow the progression of diabetic nephropathy by lowering arterial pressure. Beta-blockers also block kidneys from producing a hormone called angiotensin II. In direct response to the action of angiotensin, it will result in diabetic nephropathy. From the structural equation modeling we can see that there is a connection between blood glucose with beta blocker. The purpose of beta blockers is to reduce the deleterious effects on blood sugar levels. Usually among the diabetics, beta-blockers may cause higher blood sugar levels.

Fasting Blood Glucose

From Figure 1.4, we have found blood glucose that has no direct effect upon kidney disease but has an indirect effect through serum creatinine. Several studies have shown that the glucose associated serum creatinine. Recent research by Gualano (2011) has suggested that creatine may be an option in helping to maintain healthy blood sugar levels. Studies show that maintaining better blood glucose can reduce the risk of getting diabetic nephropathy.

V. Summary and Conclusion

In this paper we examine the factors influencing the kidney disease. This paper provides an overview of the problem associated with the relationship with kidney disease. Finding from the present study using multiple logistics show that there are five significant factors that influence kidney disease. They are age (OR = 0.917, 95% CI = 0.821, 1.025), patient's sex (OR = 20.4, 95% CI = 0.963, 431.9), Serum Creatinine level (OR = 1.057, 95% CI = 1.023, 1.093), beta-blocker (OR = 3.942, 95% CI = 0.422, 36.854), fasting blood glucose (OR = 1.564, 95% CI = 1.091, 2.241) associated with nephropathy diabetes.

The results from structural equation modeling reveals that there are four factors that have direct effect upon kidney disease. Two factors have no direct effect upon kidney disease but has an indirect effect through serum creatinine, age and sex. Based on the goodness-of-fit indices shown in Figure 2, it can be seen that p value is not significant $p = 0.794$ (accepting the null hypothesis) and therefore the our model is well fit. The model fits the data well with $\chi^2 = 1.029$ with $df = 3$, $p = 0.794$. These two results are confirmed by both methods (multiple logistics regression and structural equation modeling).

We observed that diabetic nephropathy especially related to the type 2 diabetes. Pradeep (2010) point out that the diabetic nephropathy is the leading cause of chronic renal failure worldwide. It takes many years to develop in diabetic patients. Leaking of blood protein albumin into urine (microalbuminuria) cause the function of the kidney's filtering function begin to drop and resulting the body's retention of various waste. When a patient has developed the continual microalbuminuria, he or she possibly will be considered to have early sign for diabetic nephropathy. Early detection and taking an effective prevention step may help patient reverting to the standard level of microalbuminuria.

The process of kidney damage develops very slowly up to 15 to 25 years. The simplest way to monitor the kidney function by reading of urea nitrogen in blood and creatinine. Normal reading of blood urea nitrogen is around 7-20 mg/dL. Screening for diabetic nephropathy and monitoring the function of kidney is the best way to detect diabetic nephropathy at the earliest stage. Detection of diabetic nephropathy at the earliest can possibly prevent progression to the end-stage. People with type I and type II diabetes are at risk of diabetic nephropathy. The diabetic nephropathy risk is higher if blood glucose is poorly controlled. Besides that, people with higher

cholesterol level also have much more risk than others. According to Arora (2010), diabetes is the major cause of end-stage renal disease (ESRD). Traditional risk factors that have a strong relationship with ESRD are hypertension, hyperlipidemia and smoking. Albuminuria is known as the best predictor for ESRD while the other factors such as serum albumin, serum creatinine and hemoglobin level enhance the contribution of higher ESRD.

Evidence abounds that shows that controlling the blood pressure, and controlling the level of glucose can reduce the risk of developing nephropathy. Common treatment of diabetic nephropathy includes ACE inhibitors and ARBs. Both of two types of treatment perform an action by delaying the progression of nephropathy. They react by slowing down the progress of microalbuminuria. Once a year screening for microalbuminuria level will help us to identify the cause of nephropathy at the early stage. Controlling blood glucose and periodic treatment for diabetes will improve or slow the rate of progression of diabetic nephropathy. (American Diabetes Association, 2004)

References

- [1] Beatriz, A., Apodaca D., Shah, E., McCormack, V., Cosío, F.G. & Ruiz-Holguín, R. 2010. Prevalence of type 2 diabetes and impaired fasting glucose: cross-sectional study of multiethnic adult population at the United States-Mexico border, *Rev Panam Salud Publica* 28(3). Pp 174-181.
- [2] International Diabetes Federation. 2003. Diabetes Atlas. Executive Summary, 2nd edition. Brussels: International Diabetes Federation.
- [3] Genuth, S., Alberti, K.G., Bennett, P., Buse, J., Defronzo, R., Kahn, R., Kitzmiller, J., Knowler, W.C., Lebovitz, H., Lernmark, A., Nathan D., Palmer, J., Rizza, R., Saudek, C., Shaw, J., Steffes, M., Stern, M., Tuomilehto, J., Zimmet, P. 2003. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care*; 26:3160-7.
- [4] Shai I, Jiang R, Manson J.E, Stampfer M.J., Willett W.C., Colditz G.A. & F.B. Hu. 2006. Ethnicity, obesity and risk of type 2 diabetes in women: a 20-year follow-up study. *Diabetes Care*. 29(7):1585-90.
- [5] WHO. 2005. Type 2 Diabetes: Practical Targets and Treatments, Asian-Pacific Type 2 Diabetes Policy Group, Australia.
- [6] Van Dam R.M. 2003. The epidemiology of lifestyle and risk for type 2 diabetes. *Eur J Epidemiol*. 18(12):1115-25.
- [7] Letchuman G. R., Wan Nazaimoon W.M., Wan Mohamad W.B., L.R., Chandran, G.H. Tee, H., Jamaiyah, M.R., Isa, H., Zanariah, I., Fatanah, Y.A. Faudzi. 2006. Prevalence of Diabetes in the Malaysian National Health Morbidity Survey III 2006, *Med J Malaysia*. Vol 65 No 3 September 2010. 173-179.
- [8] Enyioha and Abdu Adem. 2005. Update in Diabetic Nephropathy. *Int J Diabetes & Metabolism* 13: 1-9
- [9] P.K. Dabla. 2010. Renal function in diabetic nephropathy. *World J Diabetes*. Vol 15; 1(2): 48-56
- [10] Gualano, B. 2011. Creatine in Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled Trial *Med Sci Sport*
- [11] American Diabetes Association. 2004. Nephropathy in Diabetes. *Diabetes care*. Vol 27. supplement 1. pp 579-583. [20 February 2013]
- [12] Nayak, B.S., Butche, D.M., Bujhawan S., Chang D., Chang S., Cabral-Samaroo D., Cadan S., Buchoon V., Budhram L., Boyce M., Teelucksingh S. (2011). Association of low serum creatinine, abnormal lipid profile, gender, age and ethnicity with type 2 diabetes mellitus in Trinidad and Tobago. *Diabetes Research and Clinical Practical*. Pp 342-347.
- [13] Amir, W.M.A., NorAzlida, A. Zalila, A. & Ariff, A. 2011. Modeling associated factors of HIV-infected tuberculosis (TB) patients using path model analysis. *World Applied Sciences Journal* 12(9): 1580-1584.
- [14] Amir, W.M.A., Norizan, M., NorAzlida, & A. Zalila. 2012. Influence of hypertension and diabetes Mellitus on family history of heart attack in male patients. *Applied Mathematical sciences*. 6(66): 3259-3266.