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Male and Female Differences in the High Density Lipoprotein (HDL) and Progression of Diabetic Disease in Coronary Heart Disease Patients

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Abstract

Coronary heart disease remains the major cause of morbidity and mortality in HDL cholesterol and diabetic patients among aged women compare to men. Whether or not this is true, it has not yet been well studied. The aim of this study was to examine the factors that are associated directly or indirectly in coronary heart disease patients by gender. We employed three different methods, which are logistic regression models, multiple linear regression models (MLR) and structure equation modeling (SEM) in order to know the associated factor of diabetes mellitus and high density lipoprotein (HDL). The statistical analyses revealed that there are partially significant differences due both to gender. Compared with male counterparts, diabetic women influence by body mass index, weight, the number of cigarette packs per year, total of cholesterol and high density lipoprotein except serum insulin level. There are four predictive factors which is influence by high density lipoprotein among male. The associated factors were height, body mass index, weight and total of cholesterol. The associated factors among female were height, body mass index and weight.

Keywords: HDL cholesterol, Diabetes, Coronary heart disease, BMI, Logistic regression and multiple linear regression

1 Introduction

Cholesterol levels are tremendously important measures for people with diabetes. High-density lipoprotein cholesterol (HDL-C) is a number that to be high because the higher it is, the lower chances of coronary heart disease (CHD), also called coronary artery disease. In fact, (HDL) cholesterol is positively associated with a risk of CHD. As defined by the US National Cholesterol Education Program [2], HDL cholesterol level of 60 mg/dL or greater is a negative (protective) risk factor (normal range 40 to 60 mg/dl). CHD is a condition in which a waxy substance called plaque builds up inside the coronary arteries. These arteries supply oxygen-rich blood to the heart [10]. Death from heart disease and the risk of stroke are 2 to 4 times higher for diabetic adults than for those without this condition [1]. Many people with diabetes have other conditions that increase their chance of developing CDH. One risk factor for heart disease and stroke are the family history of heart attack If one or more members in family had a heart attack at an early age (before age 55 for men or 65 for women), the possibilities of getting the diabetes are increase.

For men, a history of heart attack and cholesterol levels are increasing, the risk of CHD mortality more than a history of diabetes. But for women, that pattern is reversed, with prior diabetes increasing mortality risk more than a prior heart attack and cholesterol levels. The major cause of death for patients with incident heart attacks and high choleterol levels are coronary heart disease, but the patients with incident diabetes may increase their risk of death from coronary heart disease, stroke, cancer, kidney disease, infections, and other reasons [5].

1.1 Cause And Risk Factors

Coronary heart disease (CHD) starts when certain factors damage the inner layers of the coronary arteries [1, 2, 10]. These factors include smoking, high levels of certain fats and cholesterol in the blood, high blood pressure and high levels of sugar in the blood due to insulin resistance or diabetes. The major risk factor for CDH is unhealthy blood cholesterol levels. This includes high LDL (low-density lipoprotein) and low HDL (high-density lipoprotein) cholesterol. LDL is called “bad” cholesterol because it can build up in the wall of arteries. This narrowing can slow or block blood flow and increase the risk of heart disease. High LDL cholesterol is a major cause of heart disease. HDL is called “good” cholesterol because it helps remove the LDL (Bad) cholesterol from arteries.

Smoking doubles the risk of getting heart disease. Stop smoking is especially important for people with diabetes because both smoking and diabetes may narrow the blood vessels. Smoking also increases the risk of other long-term

are also considering the major factors of CDH. Blood pressure is considered high if it is at or above 140/90 mmHg over time. Patients with diabetes or heart disease consider to have high blood pressure when the pressure is defined at 130/80 mmHg or higher. While overweight or obesity refer to body weight that is greater than what is considered healthy for a certain height. The aim of this study was to retrospectively examine the possible gender differences between heart attack and the diabetes in coronary heart disease patients.

2 Materials and Methods

Study Area

This research was conducted in Kelantan, which is situated north-east of Peninsular Malaysia. Fig.1 (p.1828) shows the location of Kelantan.

Study population

We studied patients with coronary heart disease patients who attended the Family Health Clinic in Hospital Universiti Sains Malaysia (HUSM) Kubang Kerian, Kelantan in north-east Malaysia. A total of 289 eligible patients were selected. They were more than 30 years old and diagnosed to have coronary heart disease. Some of them, have been diagnosed with heart attack and type 2 diabetes mellitus. A total of 1995 registered coronary heart disease patients were registered, among which 289 met the inclusion/exclusion criteria (Table 2).

Table 1. Coronary Heart Disease Patients

Variable Name		Variable Description and Coding
1.	Choltot	Total cholesterol (mg/dl)
2.	Chd	CHD (0=no, 1=yes)
3.	Hdl	HDL cholesterol (mg/dl)
4.	Alcoh	Number of alcoholic drinks/week
5.	Bmi	Body mass index (weigh(kg)/[height(m)]^2)
6.	Ha	History of heart attack (0=no, 1=yes)
7.	Kcal	Kilo-calories of physical activity per week
8.	Procon	Proconvertin (%)
9.	Fib	Fibrinogen (mg/dl)
10.	Gender	Gender (0=female, 1=male)
11.	Diabetes	Diabetes status (0=normal, 1= diabetic)
12.	Med	Anti-hypertensive medications (0=no, 1=yes)
13.	Height	Height (cm)
14.	Weight	Weight (kg)
15.	Smoke	Smoking status (1=never, 2=former, 3=current)
16.	Pyrs	Number Pack-years of smoking
17.	Insulin	Serum insulin level (IU/ml)

Fig. 1. Location of Kelantan, Malaysia

Table 2. Inclusion and Exclusion Criteria

Inclusion Criteria
(1) Subject is diagnosed with coronary heart disease
(2) From Malaysia population
(3) Type 2 diabetes mellitus (as guideline WHO, 1999);
(4) Age range: 30-80 years
Exclusion Criteria
(1) Females who are pregnant
(2) Stroke patients
(3) Any other conditions as evaluate by the physician

3 Statistical Analyses

The data were analyzed with SPSS software (version 14). The distributions and frequencies were examined and all continuous variables was expressed as mean and standard deviation. Multiple logistic regression analysis was employed to evaluate the associated factors. All p values were two-tailed and α level of significance was set at 0.25. Mickey and Greenland (1989) [7] recommendation that 0.25 level be used as a screening criterion for variable selection in logistic regression. Multiple linear regression analysis with enter method was applied to HDL cholesterol (mg/dl). We also applied structural equation modeling (SEM) with the AMOS program 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.

4 Results

Table 3**.** Demographic and biochemical characteristics of the study population in adulthood.

Characteristics	Men (n= 186) Mean (SD)	Women (n=103) Mean (SD)	P value
Demographic			
Height, cm	172.7(6.4)	157.9(5.7)	<0.001
Body Mass Index, kg/m2	26.6(3.9)	26.0(5.5)	0.318
Weight, kg	79.5(12.6)	64.9(13.5)	<0.001
Kilo-calories of physical activity per week	1892.5(1914.6)	1645(1918.9)	0.295
Biochemical			
Total cholesterol	204.3(36.6)	217.3(38.0)	<0.001
HDL cholesterol	46.6(11.2)	58.9(15.3)	<0.001
Serum Insulin	22.9(51.2)	21.3(47.9)	0.804
Fibrinogen	328.2(63.8)	320.1(56.4)	0.289
Proconvertin (%)	118.1(26.5)	132.3(28.4)	<0.001

HDL = High-density lipoprotein.

The basic characteristics of the study population were expressed as mean or percentages with standard deviation (SD). Table 3 shows the comparison characteristic among men and women categories. A result of correlation test shows the significant statistical difference in height (<0.001), weight (<0.001), and total of cholesterol (<0.001), HDL (<0.001) and proconvertin (<0.001) but not in other characteristic among studied variables.

Logistic Regression Models Approach for Diabetes Mellitus

To explore the underlying association between diabetes mellitus and the selected explanatory variables, a set of logistic regression models is fitted in this section. Let us define the following dichotomous variables for the type 2 diabetes mellitus.

$Y = 0$ Having no type 2 diabetes mellitus

$Y = 1$ Type 2 diabetes mellitus

Then let us define the following model:

Model 1a : for male

$$G(X) = \beta_0 + \beta_1 Height + \beta_2 Bmi + \beta_3 Weight + \beta_4 Kcal + \beta_5 Smoke + \beta_6 Pyrs + \beta_7 Choltot + \beta_8 HDL + \beta_9 Insulin + \beta_{10} Fib + \beta_{11} Procon + \beta_{12} Ha + \beta_{13} Med$$

Table 4. Logistic regression model of the associated factors for diabetic disease (for the male results)

Dependent Variable	Independent Variable	Std. Coefficient Beta (β)	S.E	Adjusted OR*	95% CI for Adjusted OR	
					Lower	Upper
Diabetes Mellitus Disease	**Demographic and other factors**					
	Height, cm	-0.002	0.010	0.998	0.978	1.018
	Body Mass Index, kg/m2	-0.084**	0.062	0.920	0.815	1.038
	Weight, kg	0.042**	0.024	1.042	0.995	1.092
	Kilo-calories of physical activity per week	8.70×10^{-5}	8.39×10^{-5}	1.000	1.000	1.000
	Smoking	-0.338	0.313	.713	0.386	1.316
	Pack years	0.010**	0.006	1.010	0.997	1.022
	Biochemical					
	Total cholesterol	-0.004	0.004	0.996	0.989	1.004
	HDL cholesterol	-0.016**	0.013	0.985	0.960	1.010
	Serum Insulin	0.068**	0.020	1.071	1.029	1.114
	Fibrinogen	-0.002	0.002	0.998	0.993	1.003
	Proconvertin (%)	-0.001	0.005	0.999	0.989	1.010
	Diseases					
	Heart Attack	0.155	0.297	1.168	0.653	2.090
	Medication					
	Taking anti-hypertensive drug	0.373**	0.292	1.452	0.819	2.572
	Hosmer and Lemeshow Test		p -value 0.826			
	Area under the Curve		0.711 (95% CI: 0.635,0.787)			

*Note: Significant levels: **p < 0.25*, OR***:** *Odds Ratio*

Table 4 shows the variables in the final model of multiple logistic regression (for the male). In multivariate analysis, however, only six variables appeared as significant factors. It is clearly observed from the results that weight (OR =1.042, 95%CI=0.995, 1.18), number pack-years of smoking (OR =1.010, 95%CI=0.997, 1.022), serum insulin level (OR =1.071, 95%CI=1.029, 1.114) and taking antihypertensive medication (OR =1.452, 95%CI=0.819, 2.572) has been positively associated with the type 2 diabetes mellitus. High density lipoprotein (OR =0.985, 95%CI=0.960, 1.010) and body mass index (OR =0.920, 95%CI=0.815, 1.038), were negatively associated with type 2 diabetes mellitus. 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. This logistic regression model was fit based on a non-significant Lwanga and Lemeshow [11, 14] with p = 0.826 and good area under the curve (0.711).

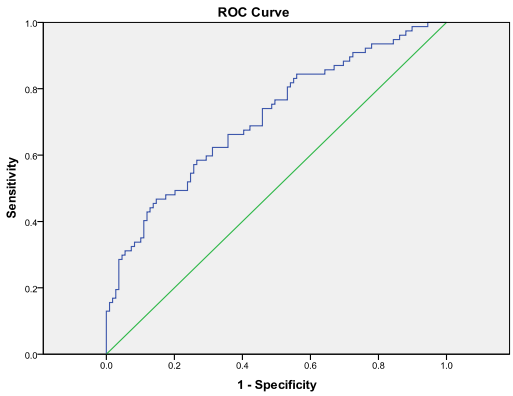

Fig. 2. ROC Curve

The area under the curve is 0.711 with 95% confidence interval (0.635, 0.787). Also, the area under the curve is significantly different from 0.5 since p-value is 0.000 meaning that the logistic regression classifies the group significantly better than by chance. The structure equation modeling for male can be summarizing as follows:

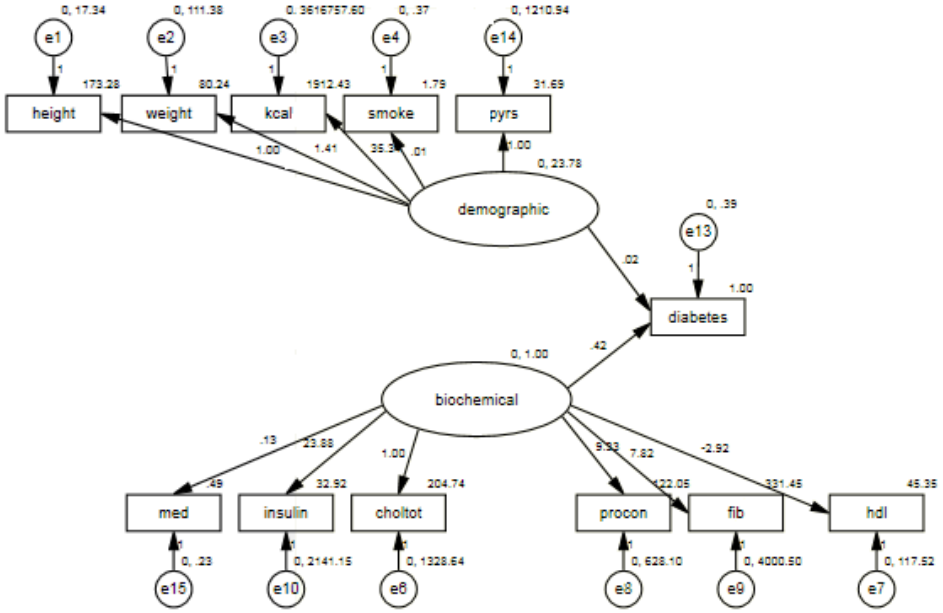

Figure 3 Hypothesized Path model for Male

From the reduced path model, we would note:

1. There are two major factors (demographic and biochemical) that contributed to diabetes mellitus type 2 among male patients.
2. Both of two factors have direct effect upon diabetes mellitus type 2

Model 1b : for female

$$G(X) = \beta_0 + \beta_1 Height + \beta_2 Bmi + \beta_3 Weight + \beta_4 Kcal + \beta_5 Smoke + \beta_6 Pyrs + \beta_7 Choltot + \beta_8 HDL + \beta_9 Insulin + \beta_{10} Fib + \beta_{11} Pr ocon + \beta_{12} Ha + \beta_{13} Med$$

Table 5. Final Logistic regression model of the associated factor for diabetic disease (for the female results)

Dependent Variable	Independent Variables	Std. Coefficient Beta (β)	S.E	Adjusted OR*	95% CI for Adjusted OR	
					Lower	Upper
Diabetes Mellitus Disease	**Demographic and other factors**					
	Height, cm	-0.008	0.022	0.992	0.951	1.035
	Body Mass Index, kg/m2	-0.236**	0.163	0.790	0.573	1.088
	Weight, kg	0.127**	0.073	1.136	0.984	1.310
	Kilo-calories of physical activity per week	2.31×10^{-5}	1.63×10^{-4}	1.000	1.000	1.000
	Smoking	0.699	0.643	2.011	0.571	7.087
	Pack years	-0.057**	0.035	0.944	0.882	1.010
	Biochemical					
	Total cholesterol	-0.011**	0.008	0.989	0.973	1.004
	HDL cholesterol	-0.050**	0.028	0.952	0.901	1.005
	Serum Insulin	0.097**	0.048	1.102	1.003	1.212
	Fibrinogen	0.001	0.006	1.001	0.989	1.013
	Proconvertin (%)	0.005	0.011	1.005	0.984	1.027
	Diseases					
	Heart Attack	-0.793	0.712	0.453	0.112	1.829
	Medication					
	Taking anti-hypertensive drug	0.100	0.649	1.105	0.310	3.944
	Hosmer and Lemeshow Test	p -value 0.061				
	Area under the Curve	0.868 (95% CI:0.785,0.951)				

*Note: Significant levels: **p < 0.25*, OR***:** *Odds Ratio*

Table 5 shows the variables in the final model of multiple logistic regression (for the female). In this analysis, only six variables appeared as significant factors. It is clearly observed from the results that weight (OR =1.136, 95% CI=0.984, 1.310) and serum insulin level (OR =1.102, 95% CI=1.003, 1.212) were positively associated with the type 2 diabetes mellitus. High density lipoprotein (OR =0.985, 95%CI=0.960, 1.010) and body mass index (OR =0.920, 95% CI=0.815, 1.038), number pack-years of smoking (OR =0.989, 95% CI=0.973 1.004), total cholesterol (OR =0.944, 95% CI=0.882 1.010), were negatively associated with type 2 diabetes mellitus. This logistic regression model was fit based on a non-

significant Lwanga and Lemeshow [11] with p=0.061 and good area under the curve (0.868).

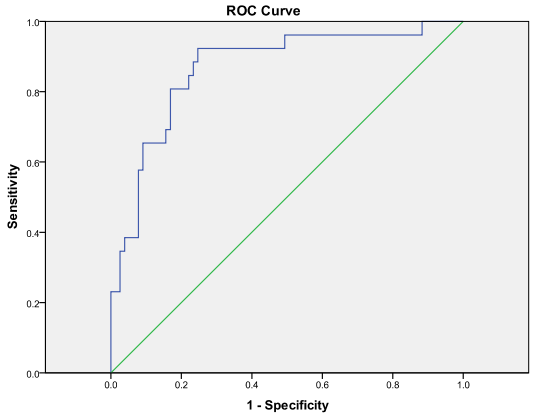

Fig. 4. ROC Curve

The area under the curve is 0.868 with 95% confidence interval (0.785 0.951). Also, the area under the curve is significantly different from 0.5 since p-value is 0.000 meaning that the logistic regression classifies the group significantly better than by chance. The structure equation modeling for female can be summarizing as follows:

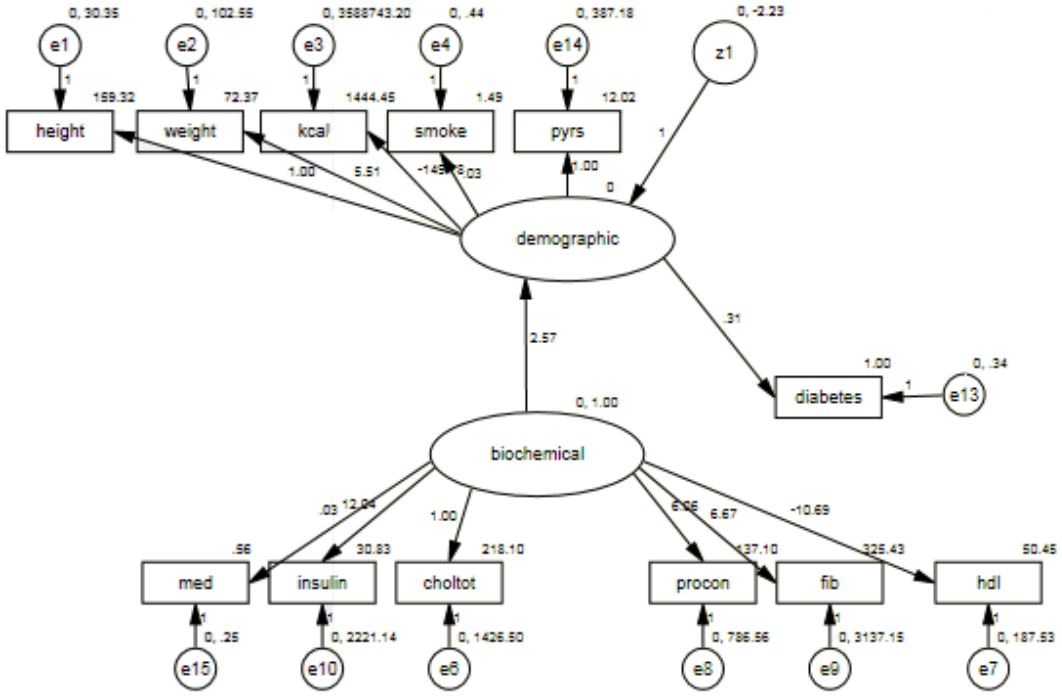

Fig 5. Hypothesized Path model for Female

From the reduced path model, we would note:

1. There is one major factor (demographic) that contributed to diabetes mellitus type 2 among female patients. Demographic factor has direct effect upon diabetes mellitus type 2.
2. Biochemical has no direct effect upon diabetes mellitus type 2, but has an indirect effect through demographic.

Table 6. Final model of the associated factor for HDL Cholesterol by multiple linear (MLR) regression (for the male results)

Dependent Variable	Independent Variable	Std. Coefficient Beta (β)	S.E	95.0% Confidence Interval for B	
				Lower	Upper
HDL cholesterol (mg/dl)	**Demographic and other factors**				
	Height, cm	0.410**	0.050	0.310	0.509
	Body Mass Index, kg/m2	0.931**	0.457	0.030	1.832
	Weight, kg	-0.593**	0.156	-0.901	-.285
	Kilo-calories of physical activity per week	2.15×10^{-4}	4.15×10^{-4}	-0.001	0.001
	Smoking	-2.122	1.778	-5.631	1.387
	Pack years	0.009	0.031	-0.052	0.071
	Biochemical				
	Total cholesterol	0.052**	0.023	0.007	0.097
	Serum Insulin	-0.021	0.016	-0.053	0.010
	Fibrinogen	-0.013	0.013	-0.039	0.012
	Proconvertin (%)	-0.040	0.032	-0.103	0.023
	Diseases				
	Heart Attack	-2.135	1.668	-5.428	1.158
	Medication				
	Taking anti-hypertensive drug	2.508	1.670	-0.787	5.803
	R 0.977				
	Adjust R^2 0.954				

*Note: Significant levels: *p < 0.05*

Table 6 shows the results of modeling relationship using multiple linear regression on HDL cholesterol (mg/dl). Total cholesterol, height, weight and body mass index were the main factors that associated in HDL cholesterol. It is clearly observed from the results that height ($\beta = 0.410$, 95% CL =0.310, 0.509), weight ($\beta = -0.593$, 95% CL = -0.901,-0.285), body mass index ($\beta = -0.931$, 95% CL = 0.030, 1.832) and total cholesterol ($\beta = 0.052$, 95% CL =0.007, 0.097) has been positively associated with the type 2 diabetes mellitus.

Table 7. Final model of the associated factor for HDL Cholesterol by multiple linear (MLR) regression (for the female results)

Dependent Variable	Independent Variable	Std. Coefficient Beta (β)	S.E	95.0% Confidence Interval for B	
				Lower	Upper
HDL cholesterol (mg/dl)	**Demographic and other factors**				
	Height, cm	0.545**	0.091	0.364	0.727
	Body Mass Index, kg/m2	1.955**	0.703	0.558	3.352
	Weight, kg	-1.332**	0.299	-1.926	-0.738
	Kilo-calories of physical activity per week	-0.001	0.001	-0.002	0.001
	Smoking	3.355	2.834	-2.275	8.985
	Pack years	-0.098	0.096	-0.289	0.092
	Biochemical				
	Total cholesterol	0.064	0.039	-0.014	0.142
	Serum Insulin	-0.035	0.030	-0.094	0.025
	Fibrinogen	-0.037	0.026	-0.089	0.016
	Proconvertin (%)	0.026	0.051	-0.076	0.127
	Diseases				
	Heart Attack	-0.458	3.176	-6.767	5.851
	Medication				
	Taking anti-hypertensive drug	2.146	2.906	-3.627	7.919
	R 0.977				
	Adjust R^2 0.955				

*Note: Significant levels: *p < 0.05*

Table 7 shows the results of modeling relationship using multiple linear regression on HDL cholesterol (mg/dl) for the female. Height, weight and body mass index were the main factors that associated in HDL cholesterol. It is clearly observed from the results that height ($\beta = 0.545$, 95% CL =0.364, 0.727), and body mass index ($\beta = 1.955$, 95% CL = 0.558, 3.352) were positively associated with HDL cholesterol and weight ($\beta = -1.332$, 95% CL = -1.926,-0.738) was negatively positively associated with HDL cholesterol.

5 Discussions

This paper examines the factors that are associated directly or indirectly with diabetes mellitus and HDL-C level among coronary heart disease patients by gender stratification. This analysis provides only a preliminary overview of the problem associated with the relationship with diabetes mellitus and HDL-C level.

In this paper, three different methods have been used: (i) logistic regression models (ii) multiple linear regression models (MLR) and (iii) structure equation modeling (SEM).
Findings from the present study indicate that there were no within gender differences for factors that associated with diabetes disease (see Table 4 and Table 5); it is surprising that in all these logistic regression models, it appears that factors height, body mass index, high-density lipoprotein, total cholesterol, weight, smoking and serum insulin were main significant factors that contributing to diabetes disease.

According to Beziaud et.al [4], current and past smoking are associated with a risk of diabetes mellitus essentially in men, but much less in women, and the relationship between fasting glucose and smoking appears different in men and women. No dose-relationship between the number of cigarettes smoked and diabetes mellitus was found. Smoking cessation is not associated with a reduced risk of diabetes. Results of linear regression shown in Table 6 (for male) reveal four significant factors that associated with HDL-C. Our data reconfirm that height, weight, body mass index and total cholesterol are correlated with HDL-C. In 2012, the study by Chung et. al [6] also showed the similar results. They also observed that three factors were including in final linear regression model for female. The factor include height, body mass index and weight were the main predictor of their case.

Brandon et al. [9] point out that there was a significant relationship between body mass index and HDL-C for the women and believed that Body mass index (BMI) is to be associated with coronary heart disease (CHD) risks. They noted that the women had higher HDL-C values than the men and the higher HDL-C were associated with lower body mass index. Many studies in the general population have shown that body mass index has high association with HDL-C. Our results also confirm that there is a strong association between HDL-C with body mass index. According to Makoto et al. [13], factors that were significantly associated with the risk of diabetes were: female gender (relative risk=0.57, 95% CI 0.33–0.96), BMI (per kg/m2) (1.11, 1.07– 1.16), baseline FPG (per mmol/l) (6.98, 5.92– 8.22) and current tobacco use (1.50, 1.15–1.95). Besides that, the inclusion of total cholesterol, HDL- cholesterol, triglyceride and systolic blood pressure, HDL-cholesterol and triglyceride were also significantly associated with the risk of diabetes (HDL-cholesterol [per mmol/l] 0.47, 0.29–0.76; triglyceride [per mmol/l] 1.11, 1.05– 1.18) Nobuko et al. [12 13] reported the Type 2 diabetes mellitus is closely related to life style factors, including diet, physical activities, alcohol and smoking, as well as obesity and a family history of diabetes.

In our case, when the subjects were group by gender, HDL-C was regressed on height, weight and body mass index (Table 7). Based on R^2 values, about 97.7% of the variation in the HDL-C is explained by the independent variables. This

regression equation appears to be very useful for making predictions since the value of the R^2 is closed to 1. Previous research has also revealed that total/HDL cholesterol ratios are two important coronary risk factors among diabetic patients. At this stage, the disease manifests itself in the form of high glucose, blood pressure and cholesterol levels. As a result of these conditions, people with diabetes are at risk for micro-vascular disease such as blindness, kidney damage and nerve damage and cardiovascular complications such as stroke and heart attack. Ample evidence support the important of HDL-C for coronary heart disease [3].

In conclusion, this study demonstrated that body mass index is strongly associated with diabetes mellitus and HDL-C among coronary heart disease patients. Hence, body mass index might be a valuable marker to be monitored in Type 2 diabetic patients

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Conflicts of Interest. The authors declare no conflict of interest.

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