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ORIGINAL ARTICLE

Relationship between dyslipidaemia and glycaemic status in patients with type 2 diabetes mellitus

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Abstract

The risk of coronary heart disease (CHD) is dramatically increased in diabetic patients due to their atherogenic lipid profile. The severity of CHD in diabetic patients has been found to be directly associated with glycated haemoglobin (HbA1c). According to the Malaysian Clinical Practice Guidelines on diabetes mellitus (DM), HbA1c level less than 6.5% reduces the risk of microvascular and macrovascular complications. Hence, this study aimed to determine the relationship between dyslipidaemia and glycaemic status in patients with type 2 DM (T2DM) patients in Hospital Putrajaya, a tertiary endocrine centre in Malaysia. This was a cross sectional, retrospective study of 214 T2DM patients with dyslipidaemia who had visited the endocrine clinic between January 2009 and December 2012. Significant correlations were found between fasting blood glucose (FBG) and HbA1c with total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL), non-high density lipoprotein cholesterol (non-HDL), LDL/HDL ratio and TC/HDL ratio; greater correlation being with HbA1c than FBG. In patients with HbA1c ≥ 6.5%, TC, TG, non-HDL and TC/HDL ratio were significantly higher than in patients with HbA1c < 6.5%. Non-HDL, LDL/HDL ratio, TC/HDL ratio and HbA1c were significantly lower in patients on statin treatment than non-treated patients ($p<0.05$). This significant association between glycaemic status and dyslipidaemia emphasises the additional possible use of HbA1c as a biomarker for dyslipidaemia as well as a potential indirect predictor of cardiovascular disease (CVD) risk in T2DM patients.

Keywords: diabetic dyslipidaemia, glycated haemoglobin (HbA1c), type 2 diabetes mellitus (T2DM), lipid parameters, fasting blood glucose (FBG)

INTRODUCTION

Diabetes mellitus (DM), a public health major concern, is a metabolic disorder due to failure of the pancreas to secrete insulin, insulin malfunction or both.[1] This is mainly related to chronic uncontrolled T2DM associated with atherosclerosis, diabetic nephropathy, neuropathy and retinopathy.[2] It has been estimated by World Health Organization (WHO) that in 2030, there would be a total of 2.48 million people with diabetes in Malaysia.[3]

HbA1c was established as the gold standard of glycaemic control in the Diabetes Complications and Control Trial (DCCT).[4] According to the Malaysian Clinical Practice Guidelines on diabetes, HbA1c level less than 6.5% can reduce the risk of microvascular and macrovascular complications.[5] It also can be used to predict the risk for diabetic complications, such as dyslipidaemia and cardiovascular disease (CVD).[1] Dyslipidaemia in DM is characterised by high triglyceride and decreased high density lipoprotein cholesterol (HDL) levels.[6] Previous studies have reported an association between HbA1c and various circulating lipid parameters.[1,7-9] This indicates that in addition to glycaemic control, HbA1c can be used as a potential biomarker for predicting dyslipidaemia in patients with T2DM.[1,3]

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MATERIALS AND METHODS

Subjects

The retrospective electronic data of 214 dyslipidaemic T2DM patients who had visited the endocrine outpatient clinic, Hospital Putrajaya from January 2009 to December 2012, were included in this cross-sectional study. Patients with blood disorders such as haemolytic anaemia and thalassaemia, abnormal liver function, nephropathy, neuropathy or retinopathy, alcohol abuse, hyperbilirubinaemia, high aspirin intake and uraemia were excluded from this study.

Laboratory measurements

Plasma glucose was analysed on UNICEL® DXC 800 (Beckman Coulter, Massachusetts, USA) by UV hexokinase method. TC and TG were analysed by enzymatic methods whereas low density lipoprotein cholesterol (LDL) and HDL were determined by homogenous, colorimetric assay on the same platform. Ion-exchange high performance liquid chromatography (HPLC) on the D10 BIORAD system (Biorad Laboratories, Hercules, California, USA) was used to measure plasma HbA1c.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 21.0. Spearman correlation test was performed to examine correlations between various parameters. Mann-Whitney and Kruskal-Wallis tests were used to compare medians of different parameters. The results were considered statistically significant when p-value < 0.05.

Ethics

Medical Research and Ethic Committee, Ministry of Health Malaysia ((NMRR-13-383-16156) and the Ethics Committee for Research Involving Human Subjects Universiti Putra Malaysia approved the study. The study was commenced once written permission was obtained from the Director of Hospital Putrajaya.

RESULTS

The demographic, clinical characteristics and biochemical data of the study population are shown in Table 1. No significant association was observed between demographic characteristics and HbA1c.

In univariate analysis (Table 2), statistically significant positive correlations were observed between various lipid parameters with FBG and HbA1c except HDL. However, the magnitude of correlation was stronger with HbA1c.

Diabetic patients were divided into 2 groups as per their FBG level (Table 3). The first group consists of patients with FBG value of < 7.0mmol/L and the second group consists of patients with FBG value of ≥ 7.0mmol/L. Patients with FBG value ≥ 7.0mmol/L had significantly higher level of TC, TG, LDL, non-HDL, LDL/HDL ratio and TC/HDL ratio as compared to patients with FBG value < 7.0mmol/L.

Patients were classified into 2 groups based on their HbA1c level (Table 4). The first group consists of patients with HbA1c < 6.5% and second group consists of patients with HbA1c ≥ 6.5%. The value of TC, TG, non-HDL and TC/HDL ratio were significantly higher in patients with HbA1c ≥ 6.5% than patients with HbA1c < 6.5%.

Table 5 shows the association between statin treatment and lipid parameters, HbA1c and FBG. Patients on statin treatment had significantly lower levels of non-HDL, LDL/HDL ratio, TC/HDL ratio and HbA1c compared to patients not on statin treatment.

DISCUSSION

In this study, the majority of the study population were Malay females. Predominance of females with diabetes concurs with other studies and is hypothesised to be due to the effect of hormones, lack of physical activities and increased ability of the body to store iron.[10] The high number of Malays with T2DM reflects the ethnic majority in Malaysia, whereby Malays constitute 63.1% of the population in Peninsular Malaysia.[11] Apart from that, lifestyle may also be a contributing factor.

Also noted were that the majority of patients were in the age group below 51 years old and were hypertensive. According to Clinical Practice Guidelines on the Management of Hypertension (2008),[12] hypertension is a common problem in diabetic patients and it is more prevalent in T2DM patients. However, only 29.4% of them were obese as compared to the study done in 2008 in Malaysia where 72% of diabetic patients were obese.[13] This difference could be due to restricted sample size in the present study. In this study, it was also found that 33.6% of the patients had other diseases such as gout, gastritis and osteoarthritis. These patients may have a constellation of risk factors that place them at increased risk of CVD at an early age.[14]

More than half of them were on statin

TABLE 1: Demographic, clinical characteristics and biochemical data of the study population

Variable	(N=214) n (%)		
Gender			
Male	83 (38.8)		
Female	131 (61.2)		
Age in years			
< 51	89 (41.6)		
51 - 60	67 (31.3)		
61 - 70	42 (19.6)		
> 70	16 (7.5)		
Ethnicity			
Malay	154 (72.0)		
Chinese	20 (9.3)		
Indian	40 (18.7)		
Co-morbidities			
Hypertension	145 (67.8)		
Obesity	63 (29.4)		
Cardiovascular disease	40 (18.7)		
Others:	72 (33.6)		
Acromegaly	1 (1.8)		
Asthma	7 (9.7)		
Benign Prostatic Hypertrophy	1 (1.4)		
Brain Tumour	2 (2.8)		
Chronic Kidney Disease	4 (5.6)		
Chronic Obstructive Airway Disease	4 (5.6)		
Cushings Syndrome	2 (2.8)		
Dementia	1 (1.4)		
Gastritis	11 (15.3)		
Gout	8 (11.1)		
Hyperthyroidism	7 (9.7)		
Hypothyroidism	5 (6.9)		
Osteoarthritis	10 (13.9)		
Parkinsons Disease	1 (1.4)		
Polycystic Ovary Syndrome	2 (2.8)		
Prolapsed Intervertebral Disc	2 (2.8)		
Rheumatoid Arthritis	2 (2.4)		
Renal Calculi	1 (1.4)		
Schizophrenia	1 (1.4)		
Statin/Anti-diabetic drugs			
Statin	126 (58.9)		
Insulin/Oral hypoglycaemic agents	194 (90.7)		
Biochemical data	Median (IQR)	Min – Max	Reference range
TC (mmol/L)	5.20 (1.53)	2.30 – 9.80	≤ 5.20
TG (mmol/L)	1.60 (1.10)	0.40 – 5.30	≤ 1.70
LDL (mmol/L)	3.10 (1.43)	0.80 – 8.10	≤ 2.60
HDL (mmol/L)	1.20 (0.40)	0.50 – 3.70	≥ 1.10
Non-HDL (mmol/L)	3.90 (1.50)	1.50 – 8.40	< 3.35
LDL/HDL ratio	2.65 (1.36)	0.41 – 16.20	< 3.0
TC/HDL ratio	4.33 (1.65)	1.54 – 10.67	< 4.0
HbA1c (%)	8.30 (3.43)	4.90 – 16.10	< 6.5
FBG (mmol/L)	8.27 (3.83)	2.95 – 27.63	< 7.0

total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), HbA1c (glycated haemoglobin), fasting blood glucose (FBG), interquartile range (IQR).

TABLE 2: Correlations between lipid parameters with FBG and HbA1c

Parameter	FBG		HbA1c	
	**r_s	p-value	**r_s	p-value
TC (mmol/L)	0.187	0.006*	0.192	0.005*
TG (mmol/L)	0.180	0.008*	0.232	0.001*
LDL (mmol/L)	0.149	0.029*	0.180	0.008*
HDL (mmol/L)	-0.036	0.605	-0.059	0.387
Non-HDL (mmol/L)	0.209	0.002*	0.231	0.001*
LDL/HDL ratio	0.135	0.048*	0.194	0.004*
TC/HDL ratio	0.185	0.007*	0.233	0.001*

*statistical significance at p<0.05; **Spearman correlation test (r_s)
total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), HbA1c (glycated haemoglobin), fasting blood glucose (FBG).

TABLE 3: Association between FBG and lipid parameters

Parameter	Normal FBG <7.0mmol/L (n=69)	High FBG ≥7.0mmol/L (n=145)	**z	p-value	Reference range
	Median(IQR)	Median(IQR)			
TC (mmol/L)	4.80 (1.35)	5.20 (1.80)	- 2.591	0.010*	≤ 5.20
TG (mmol/L)	1.40 (0.95)	1.70 (1.25)	- 2.778	0.005*	≤ 1.70
LDL(mmol/L)	2.80 (1.25)	3.30 (1.60)	- 2.397	0.017*	≤ 2.60
HDL(mmol/L)	1.20 (0.45)	1.20 (0.35)	- 0.507	0.612	≥ 1.10
Non-HDL(mmol/L)	3.70 (1.50)	4.00 (1.50)	- 2.866	0.004*	< 3.35
LDL/HDL ratio	2.43 (1.47)	2.73 (1.42)	- 2.335	0.020*	< 3.0
TC/HDL ratio	3.80 (1.60)	4.40 (1.73)	- 2.675	0.007*	< 4.0

*statistical significance at p<0.05; ** Mann-Whitney statistical test (z)
total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), fasting blood glucose (FBG), interquartile range (IQR).

TABLE 4: Association between HbA1c and lipid parameters

Parameter	Normal HbA1c <6.5% (n=30)	High HbA1c ≥6.5% (n=184)	**z	p-value	Reference range
	Median (IQR)	Median (IQR)			
TC (mmol/L)	4.60 (1.45)	5.20 (1.60)	- 2.122	0.034*	≤ 5.20
TG (mmol/L)	1.30 (0.73)	1.70 (1.20)	- 3.201	0.001*	≤ 1.70
LDL (mmol/L)	2.70 (1.25)	3.20 (1.50)	- 1.782	0.075	≤ 2.60
HDL (mmol/L)	1.15 (0.40)	1.20 (0.40)	- 0.131	0.896	≥ 1.10
Non-HDL (mmol/L)	3.30 (1.50)	3.90 (1.50)	- 2.394	0.017*	< 3.35
LDL/HDL ratio	2.45 (1.20)	2.70 (1.38)	- 1.587	0.113	< 3.0
TC/HDL ratio	3.79 (1.91)	4.37 (1.65)	- 1.980	0.048*	< 4.0

*statistical significance at p<0.05; ** Mann-Whitney statistical test (z)
total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), HbA1c (glycated haemoglobin), interquartile range (IQR).

TABLE 5: Relationship between statin treatment and lipid parameters, HbA1c and FBG

Parameter	Statin		**z	p-value	Reference range
	Yes (n=126)	No (n=88)			
	Median (IQR)	Median (IQR)			
TC (mmol/L)	5.00 (1.40)	5.30 (1.70)	- 1.409	0.159	≤ 5.20
TG (mmol/L)	1.50 (1.10)	1.70 (1.10)	- 1.288	0.198	≤ 1.70
LDL (mmol/L)	2.80 (1.50)	3.30 (1.38)	- 1.950	0.051	≤ 2.60
HDL(mmol/L)	1.20 (0.40)	1.10 (0.30)	- 1.549	0.121	≥ 1.10
Non-HDL (mmol/L)	3.70 (1.55)	4.10 (1.18)	- 2.229	0.026*	< 3.35
LDL/HDL ratio	2.50 (1.43)	2.80 (1.26)	- 2.502	0.012*	< 3.0
TC/HDL ratio	4.00 (1.64)	4.52 (1.45)	- 2.838	0.005*	< 4.0
HbA1c (%)	8.15 (3.10)	8.95 (3.85)	- 2.063	0.039*	< 6.5
FBG (mmol/L)	7.88 (4.29)	8.53 (4.34)	- 1.509	0.131	< 7.0

*statistical significance at p<0.05; ** Mann-Whitney statistical test (z)
total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), HbA1c (glycated haemoglobin), interquartile range (IQR).

treatment. Statin is a suitable first-line agent in familial hypercholesterolaemia, for primary and secondary prevention of CVD and coronary heart disease equivalents. It is most effective in reducing LDL level and has moderate effect in lowering TG and in elevating HDL.[15]

Although the majority of the patients in our study were on anti-diabetic drugs, only 32.2% and 14.0% achieved the target FBG < 7.0mmol/L and HbA1c < 6.5%, respectively. Almost similar results were found in the previous study by Chua *et al* (2011),[16] which showed 26.9% and 17.4% of the respondents achieved the target FBG ≤ 6.1mmol/L and HbA1c < 6.5%, respectively. This incidence could be due to non-adherence to or poor understanding of anti-diabetic medications.

In this study, HbA1c showed no significant association with gender and age, concurring with a study by Khan *et al* (2007).[17] Although there was also no significant association with ethnicity, interestingly Indians showed the highest HbA1c values compared to the Malays and Chinese. Indians are reported to be prone to DM due to several factors such as, high insulin resistance, genetics factors, diet, and inactivity.[18] A study done in the United States of America showed significant association between ethnicity and HbA1c whereby the mean HbA1c was higher in Hispanics (8.2%) than Blacks (8.1%) and Whites (7.6%). This difference, however, remains unclear but is hypothesised to be due to several factors such as red blood cell survival, the intracellular and extracellular environment and genetic determinants of haemoglobin glycation.[19] Future studies could look into the role of these factors in our multiethnic population.

With the exception of HDL, all lipid parameters were found to be significantly correlated with FBG and HbA1c, which is in agreement with findings of other investigators.[17] The stronger correlation of HbA1c than FBG with lipid parameters is supported by the previous study done by Khan *et al*[17] reporting higher correlation coefficients for HbA1c than FBG with TC, TG and LDL. Another study by Grant *et al*[20] reported stronger correlation coefficients for HbA1c than random plasma glucose (RPG) with TC, TG and LDL. Grant *et al*[20] suggested HbA1c as a better screening tool for both diabetes and CVD risk compared to RPG. Furthermore, smoking and medications can adversely affect FBG, which was not addressed in our study. On the other hand, measurement of HbA1c does not require a fasting state and is not affected by acute perturbations.[21]

We observed significant increases in all lipid parameters except HDL in patients with high FBG (≥ 7.0mmol/L) compared to normal FBG (< 7.0mmol/L). This finding concurs with the findings by Qian *et al*[22] reporting significant increase in TC and TG in impaired fasting glucose (IFG: FBG ≥ 5.6mmol/L and < 7.0mmol/L) than in normoglycaemic controls, whereas the HDL

level was significantly lower in IFG. In addition, patients with high HbA1c (≥ 6.5%) exhibited significant increase in TC, TG, non-HDL and TC/HDL ratio in comparison to patients with normal HbA1c (< 6.5%), which is consistent with the findings reported by Hammed *et al*.[2] The dysregulation of lipid and lipoprotein in hyperglycaemic state may be due to insulin resistance, which leads to hyperinsulinaemia, enhanced hepatic gluconeogenesis and reduces suppression of lipolysis in adipose tissue, leading to hypertriglyceridaemia and reduced HDL level.[23]

In the present study, HbA1c was found to be significantly associated with non-HDL, which can be obtained by subtracting HDL from TC.[23] Non-HDL provides a single index of all atherogenic, apoprotein B-containing lipoproteins, including LDL, VLDL, IDL, and lipoprotein (a).[24] Non-HDL is more reliable than LDL in predicting CVD risk. Firstly, LDL only can be applied in individuals with TG < 4.5mmol/L based on the Friedewald formula.[25] Secondly, LDL is normally not elevated in DM and only the small, dense LDL particles will be increased instead. However, this atherogenic and lipid poor small, dense LDL particles will not be raised in standard measurement.[24] Thus, a single LDL measurement will neglect the significant contribution of atherogenic cholesterol to CVD risk.[25] According to the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) [NCEP ATP III], the level of non-HDL should be targeted at < 3.35mmol/L.[26] The present study showed the median value of non-HDL in the study population was 3.90mmol/L, higher than the NCEP ATP III recommended value, suggesting an increased risk of developing CVD.

In this study, TC/HDL ratio was significantly associated with HbA1c whereas there was no association between HbA1c and LDL/HDL ratio. A study by Lemieux *et al*[27] revealed superiority of TC/HDL ratio over LDL/HDL ratio in predicting ischaemic heart disease risk. Diabetic dyslipidaemia is associated with elevated TG, reduced HDL and increased presence of small, dense LDL particles.[24] Individuals with high TG have more fraction of VLDL. Thus, the ratio of LDL/HDL may underestimate the magnitude of dyslipidaemic state in these individuals.[27] Aryal *et al*[25] classified diabetic subjects with TC/HDL ratio < 4 as low risk group of CVD. In the present study, the median value of TC/HDL ratio was 4.33, again pointing to an increased risk of CVD in these patients. This study shows that HbA1c is significantly associated with lipid parameters (non-HDL and TC/HDL ratio) known to have predictive value of CVD risk in T2DM patients.

In the present study, the diabetic patients were divided into two groups as per statin prescription. Patients on statin treatment exhibited significant lower levels of HbA1c, LDL/HDL ratio, non-HDL and TC/HDL ratio compared to patients not on statins. According to NCEP ATP III, statin is highly effective in lowering LDL, including small LDL particles, as well as IDL and VLDL remnants.[26] This combined action of lowering of LDL and triglyceride rich lipoprotein, results in efficacious lowering of non-HDL level in atherogenic dyslipidaemia or combined hyperlipidaemia. Although there was no significant association with LDL, patients on statin treatment showed lower median level of LDL than patients not on statins. The lack of statistical significance could be attributed to the different proportion between the two groups.

A study in Texas found a reduction of TC/HDL ratio and LDL/HDL ratio in dyslipidaemic patients on lovastatin treatment and predicted a decreased risk of first ischaemic heart disease event in these patients.[28] In this study, patients on statin treatment showed significantly reduced TC/HDL and LDL/HDL ratios. Both these ratios are valuable tools to evaluate CVD risk. The significant lower level of HbA1c in the statin-treated group as compared to the group not on statins suggests further prospective studies to evaluate it as an indirect marker of CVD risk prediction in diabetic dyslipidaemia. This is further supported by its correlation with lipid parameters (non-HDL and TC/HDL ratio) shown to be cumulative markers of CVD risk in diabetic dyslipidaemia.[25,27]

In summary, we found that there was no significant association between demographic factors and HbA1c. Both FBG and HbA1c were significantly correlated with all lipid parameters in this study except HDL. However, HbA1c showed stronger correlation than FBG. TC, TG, non-HDL and TC/HDL ratio were significantly associated with both FBG and HbA1c. The levels of non-HDL, LDL/HDL ratio, TC/HDL ratio and HbA1c were significantly reduced in patients with statin treatment compared to patients not on statin treatment. Thus HbA1c can be used as a biomarker in predicting dyslipidaemia in

T2DM patients in addition to glycaemic control. Furthermore, HbA1c being directly correlated with TC/HDL ratio and non-HDL, may be a potential indirect predictor of CVD risk in T2DM, though future prospective, cohort studies should be done in larger diabetic populations to further confirm this.

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