Apolipoprotein B Level in patients with Type 2 Diabetes who Achieved Goal of Low Density Lipoprotein Cholesterol and Non-High Density Lipoprotein Cholesterol

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Objective: *To demonstrate an apolipoprotein B (apo B) level in type 2 diabetic patients who achieved goal of low density lipoprotein cholesterol (LDL-c) and non-high density lipoprotein cholesterol (non-HDL-c). To identify the percentage of type 2 diabetes patients who achieved goal of apo B level.*

Material and Method: *A cross-sectional study was carried out from 1 October to 31 December 2008. Type2 diabetes patients who attended at diabetes clinics in the Phramongkutklao hospitals have determined the risk for develop cardiovascular diseases (CVD) and set up the goal for lipid level according to consensus statement from the American Diabetes Association (ADA) and the American College of Cardiology (ACC) foundation. Blood test for apo B will be done only the patients who achieved goal of LDL-c and non-HDL-c.*

Results: *133 of the 162 registered diabetic patients can achieve goal of lipid level. In this population, 9.7 percent (%) (n = 13) had a history of CVD. Apo B level in diabetic patients with and without CVD is 61.72 ± 12.63 and 67.2 ± 12.92 milligram per deciliter (mg/dL), respectively. Nearly ninety-eight percent of patients without cardiovascular diseases (CVD) have achieved apo B (< 90 mg/dL) goal, and 92.3% of patients with CVD have achieved apo B (< 80 mg/dL) goal. The two most commonly used lipid-lowering agents were statins and fibrates.*

Conclusion: *In patients with type2 diabetes who achieved goal of LDL-c and non-HDL-c have also achieved apo B level. Thus, apo B measurement in addition to reached LDL-c and non-HDL-c targets may be not necessary especially in diabetic patients who did not previous CVD.*

Keywords: *Apolipoprotein B, Type 2 diabetes*

Diabetes is identified as the coronary heart disease risk equivalents[1]. In addition to glycemic control, cholesterol-lowering treatment improves prognosis of diabetic patients[2,3]. According to National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP III) guideline, Low density lipoprotein cholesterol (LDL-c) and Non-high density lipoprotein cholesterol (Non-HDL-c) are the primary and secondary treatment goal of dyslipidemia, for diabetes patients, LDL-c should be < 100 and non-HDL-c < 130 mg/dL[4]. Recent data demonstrate that apolipoprotein B (apo B)is a better measure of circulating LDL particle number (LDL-P) concentration and is a more reliable indicator of risk than LDL-c, and there is growing support for the idea that addition of apo B measurement to the routine lipid panel for assessing and monitoring patients at risk for cardiovascular disease (CVD) would enhance patient management[5-15].

Apo B is the primary apolipoprotein of LDL-c, which is responsible for carrying cholesterol to tissues. One molecule of apo B is present in each of the atherogenic lipoprotein particles; therefore, the total apo B value indicates the total number of potentially atherogenic lipoproteins. Apo B measurement has many advantages. It does not require any fasting blood sample. It is a direct measurement. This means that there is no need for calculation from multiple parameters, which may introduce errors. The elevated cutoff point

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apo B more than 88 mg/dL was associated with increased cardiovascular risk[16].

Consensus statement from the American Diabetes Association and the American Colleage of Cardiology (ACC) foundation suggested LDL-c, non HDL-c, and apo B treatment goal in patients with cardiometabolic risk (CMR) and lipoprotein abnormalities. Patients with CMR were classified as the highest-risk or high-risk group. In highest-risk patients, including those with 1) known CVD or 2) diabetes plus one or more additional major CVD risk factors, suggested treatment goals with LDL-c < 70 milligram per deciliter (mg/dL), Non-HDL-c < 100 mg/dL, and apo B < 80 mg/dL. In High-risk patients, including those with 1) no diabetes or known clinical CVD but two or more additional major CVD risk factors or 2) diabetes but no other major CVD risk factors suggested treatment goals with LDL-c < 100 mg/dL, Non-HDL-c < 130 mg/dL, and apo B < 90 mg/dL. Other major risk factors (beyond dyslipoproteinemia) include smoking, hypertension, and family history of premature CAD[17]. However, not all studies agree about the important of apoB, in some studies, apo B did not outperform LDL-c and non-HDL-c a risk predictors[18-20]. Discrepancies between studies may be due to the inclusion of different proportions of subjects with CMR. In individuals with CMR, especially in type 2 diabetic patients, the discrepancies between apo B, LDL cholesterol, and non-HDL cholesterol are greater; suggesting that apo B may be a more useful risk predictor among these individuals[21].

In Thailand, the measurement of apo B is not available in routine laboratory and in Phramongkutklao hospital, we use the NCEP ATP III guideline for management patients with dyslipidemia, and we do not measure apo B in clinical practice.

The objective of the present study was to demonstrate an apo B level and the percentages of patients that achieved LDL-c and Non-HDL-c who also reached apo B goal.

Material and Method

A cross-sectional study was carried out from 1 October to 31 December 2008. A total of 162 type 2 diabetic patients were consecutively selected from among those seen at the diabetes clinic of Phramongkutklao hospital. The patients have determined the risk for develop cardiovascular diseases and set up the goal for lipid level according to consensus statement from the American Diabetes Association (ADA) and the American College of Cardiology (ACC) foundation[17].

Sample size (n) was calculated by the formula (see below). In the present study, we need total population at least 104 patients.

$$n = \frac{Z_\alpha^2 P(1 - P)}{d^2}$$

Note: 95 percent (%) confidence interval; $\alpha = 0.05$
$Z_\alpha = 1.96$
P = Prevalence of patients reaching LDL-c and Non-HDL-c targets who also apo B less than 90 mg/dL was 48 percent in the MERCURY II study [22]
d = margin of error (less than 5 percent) = 0.096

The diagnosis of diabetes mellitus was made according to the ADA criteria 1997[23]. The data were recorded on a case record form. The authors included: demographic data; pertinent parts of physical examinations; laboratory examinations; specific medications (including insulin, oral hypoglycemic agents, antihypertensive agents, lipid lowering agents and aspirin); and, diabetic complications verified by physician's reports.

Blood pressure was measured on the right arm after resting 5 minutes (twice, 30 seconds apart) using an automated blood pressure machine. Hypertension was defined as systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg, or was considered present if the patient was being treated with antihypertensive drugs. Height and weight were measured in light clothing and were used for Body Mass Index (BMI) calculation. Information on alcohol consumption, cigarette smoking, medication and history of diabetes were obtained through an interview.

Blood samples were obtained after an overnight fast (10-12 hours). Total cholesterol, triglyceride, high density lipoprotein-cholesterol (HDL-c), and apo B were immediately analyzed from total serum. Non-HDL cholesterol was calculated from subtraction of total cholesterol and HDL [non HDL-c = TC-(HDL-c)].

Total cholesterol and triglyceride were measured by commercial fully enzymatic methods (Roche Diagnostics, Basel, Switzerland). HDL-c was measured by a commercial direct method, without precipitation, using a-cyclodextrin sulphate, MgCl2, and polyethylene-glycol pretreated cholesterol esterase and oxidase to specifically measure HDL-c, even in the presence of the rest of lipoproteins (Roche

Diagnostics)[24].

We calculated LDL-c by Friedewald's formula[25] when triglyceride did not exceed 300 mg/dl. When triglyceride > 300 mg/dl, we measured LDL-c by ultracentrifugation in frozen serum stored at 2-8°C for no more than 96 hours. Apo B was measured by an immunoturbidimetric method (Tina-quant, Roche Diagnostics) using a calibrator whose apo B content is standardized against the WHO/IFCC reference standard SP3-07.

The protocol was approved by the ethical committee, and patients gave their informed consent.

Statistical analysis

Analyses were performed using the SPSS. Mean $\pm$ SD were determined for quantitative data, and frequencies were determined for categorical variables.

For continuous variables, and depending on normality distribution, Logistic regression was used if comparing two groups. All tests were two-tailed, and a p-value of ≤ 0.05 was considered significant.

Results

Complete demographic and plasma lipid concentration were available for 133 of the 162 registered diabetic patients. In this population, 9.7% (n = 13) had a history of CVD. Patient characteristics divided by history of CVD were showed as Table 1. Type2 diabetic patients with CVD had significantly higher percentage of retinopathy (61.5% vs. 21.0%, p = 0.003) and microalbuminuria (84.6% vs. 39.2%, p = 0.007) than the patients without CVD. The diabetes patients with CVD (vs. those without CVD) also had a higher percentage of used insulin (76.9 vs. 41.2, p = 0.023) and

Table 1. Patient characteristics divided by history of cardiovascular disease (CVD)

	Diabetes mellitus without CVD (n = 120)	Diabetes mellitus with CVD (n = 13)	Odds Ratio (95% CI)	p-value
Age year ($\bar{x} \pm$ SD)	64.86 $\pm$ 12.18	70.53 $\pm$ 11.80	1.044 (0.990, 1.102)	0.113
Weight (kg) ($\bar{x} \pm$ SD)	68.85 $\pm$ 19.26	70.11 $\pm$ 23.22	1.003 (0.974, 1.033)	0.832
Height (cm) ($\bar{x} \pm$ SD)	174.45 $\pm$ 152.12	161.75 $\pm$ 9.71	0.999 (0.988, 1.010)	0.834
BMI kg/m2($\bar{x} \pm$ SD)	27.61 $\pm$ 6.78	28.62 $\pm$ 3.57	1.021 (0.926, 1.127)	0.674
Waist Circumference (cm) ($\bar{x} \pm$ SD)	96.55 $\pm$ 17.99	104.64 $\pm$ 18.54	1.021 (0.984, 1.059)	0.268
Systolic BP mm/Hg ($\bar{x} \pm$ SD)	131.27 $\pm$ 15.92	138.62 $\pm$ 16.32	1.027 (0.993, 1.062)	0.121
Diastolic BP mm/Hg ($\bar{x} \pm$ SD)	73.66 $\pm$ 11.12	77.62 $\pm$ 10.05	1.034 (0.980, 1.090)	0.222
Sex				
- Female n (%)	48 (40.0)	7 (53.8)		
- Male n (%)	72 (60.0)	6 (46.2)	0.571 (0.181, 1.805)	0.340
Duration of diabetes (y) ($\bar{x} \pm$ SD)	10.59 $\pm$ 7.82	11.62 $\pm$ 5.71	1.020 (0.947, 1.093)	0.643
Diabetes complication				
- Retinopathy n (%)	25 (21.0)	8 (61.5)	6.016 (1.810, 19.999)	0.003**
- Microalbuminuria n (%)	47 (39.2)	11 (84.6)	8.543 (1.812, 40.271)	0.007**
Prior Myocardial infarction n (%)	0	13 (100.0)	1.00	1.00
Smoking n (%)	12 (10.0)	1 (7.7)	0.791 (0.090, 6.282)	0.791
HbA1c % ($\bar{x} \pm$ SD)	7.25 $\pm$ 1.39	7.48 $\pm$ 1.32	1.116 (0.759, 1.639)	0.577
Insulin used n (%)	49 (41.2)	10 (76.9)	4.762 (1.246, 18.202)	0.023*
Sulfonulureas n (%)	52 (43.7)	6 (46.2)	1.104 (0.350, 3.484)	0.865
Metformin n (%)	76 (63.9)	6 (46.2)	0.485 (0.153, 1.536)	0.219
TZD used n (%)	20 (16.8)	2 (15.4)	0.900 (0.185, 4.376)	0.896
Statin used n (%)	109 (91.6)	13 (100.0)	1.00	1.00
Fibrate used n (%)	11 (9.2)	1 (7.7)	0.826 (0.098, 6.964)	0.860
Ezetimibe n (%)	5 (4.2)	5 (38.5)	14.375 (3.434, 60.180)	< 0.01**
Anti-hypertensive drug n (%)	110 (94.0)	13 (100.0)	1.00	1.00

Analyze by Logistic regression, Odds Ratio (95% CI) = 95% Confidence Interval (CI) for the Odds Ratio, (*) indicated statistically significant p-value less than 0.05, (**) indicated statistically significant p-value less than 0.01 $\bar{x} \pm$ SD = Mean $\pm$ Standard Deviation, n (%) = Frequency (Percent)

Table 2. Laboratories profiles divided by history of cardiovascular disease (CVD)

Lipid level (mg/dL) ($\bar{x} \pm SD$)	Diabetes mellitus without CVD (n = 120)	Diabetes mellitus with CVD (n = 13)	Odds Ratio (95% CI)	p-value
Total cholesterol mg/dL	148.12 ± 19.87	128.69 ± 15.01	0.932 (0.922, 0.982)	0.002**
FPG mg/dL	138.73 ± 52.48	133.23 ± 44.79	0.998 (0.985, 1.010)	0.715
HDL-cholesterol mg/dL	49.98 ± 13.46	46.85 ± 16.94	0.982 (0.939, 1.027)	0.435
Triglyceride mg/dL	120.53 ± 48.34	101.23 ± 47.43	0.990 (0.975, 1.005)	0.171
LDL-cholesterol mg/dL	77.16 ± 14.45	65.85 ± 14.17	0.952 (0.916, 0.989)	0.012*
Non-HDL-cholesterol mg/dL	98.16 ± 15.99	86.92 ± 15.78	0.959 (0.926, 0.994)	0.022*
Apo B mg/dL	67.32 ± 12.92	61.72 ± 12.63	0.958 (0.908, 1.011)	0.116

Analyze by Logistic regression, Odds Ratio (95% CI) = 95% Confidence Interval (CI) for the Odds Ratio, (*) indicated statistically significant p-value less than 0.05, (**) indicated statistically significant p-value less than 0.01, $\bar{x} \pm SD$ = Mean ± Standard Deviation, n (%) = Frequency (Percent)

Table 3. Percentage of patients who achieved goal of lipoprotein

Lipid level (mg/dL) (mean ± SD)	Diabetes mellitus without CVD (n = 120) % achieved goal	Diabetes mellitus with CVD (n = 13) % achieved goal	Odds Ratio (95% CI)	p-value
LDL mg/dL				
- LDL < 70 mg/dL	37 (30.8)	7 (53.8)	2.617 (0.823-8.325)	0.103
Non-HDL mg/dL				
- Non-HDL < 100 mg/dL	62 (51.7)	10 (76.9)	3.118 (0.817-11.897)	0.096
Triglyceride mg/dL				
- Triglyceride < 150 mg/dL	93 (77.5)	11 (84.6)	1.597 (0.333-7.647)	0.558
HDL-C mg/dL				
Men: HDL-C > 40 mg/dL	58 (80.6)	4 (66.7)	0.483 (0.08-2.906)	0.426
Women: HDL-C > 50 mg/dL	18 (37.5)	1 (14.3)	0.278 (0.031-2.497)	0.253
Apo B mg/dL				
- Apo B < 80 mg/dL	107 (89.2)	12 (92.3)	1.458 (0.175-12.142)	0.727
- Apo B < 90 mg/dL	117 (97.5)	13 (100.0)	1.00	1.00

Analyze by Logistic regression, Odds Ratio (95% CI) = 95% Confidence Interval (CI) for the Odds Ratio, (*) indicated statistically significant p-value less than 0.05, (**) indicated statistically significant p-value less than 0.010, $\bar{x} \pm SD$ = Mean ± Standard Deviation, n (%) = Frequency (Percent)

ezetimibe (38.5% vs. 4.2%, p < 0.01). The lipid-lowering medications most used were statin (91.6% vs. 100%, p = 1.0; DM without CVD vs. DM with CVD) and fibrates (9.2% vs. 7.7%, p = 0.86; DM without CVD vs. DM with CVD).

Laboratories profiles divided by history of CVD were showed as Table 2. The diabetes patients with CVD (vs. those without CVD) had lower level of total cholesterol (128.69 ± 15.01 vs. 148.12 ± 19.87 mg/dL, p = 0.002), LDL-c (65.85 ± 14.17 vs. 77.16 ± 14.45 mg/dL, p = 0.012), and non-HDL-c (86.92 ± 15.78 vs. 98.16 ± 15.99 mg/dL, p = 0.022). Apo B level was also lower in diabetes patients with CVD (61.72 ± 12.63 vs. 67.32 ± 12.92 mg/dL, p = 0.116) but there is no statistically significant.

Percentage of patients who achieved goal of lipoprotein was showed as Table 3. All of the patients were achieved goal LDL-c less than 100 mg/dL and

non-HDL-c less than 130 mg/dL. The patients with CVD (vs. those without CVD) had a higher percentage of achieving the lipoprotein target (*i.e.* LDL-c < 70 mg/dL, non-HDL-c < 100 mg/dL, Triglyceride < 150 mg/dL, and apo B < 80 mg/dL) but there is no statistical significant. Nearly ninety eight percent of patients without cardiovascular diseases (CVD) have achieved apo B < 90 mg/dL, and 92.3% of patients with CVD have achieved apo B < 80 mg/dL.

Discussion

In this study, we found that patients with type 2 diabetes who achieved lipoprotein goal (LDL-c < 100 mg/dL and non-HDL-c < 130 mg/dL) have almost achieved apo B < 90 mg/dL. This result is inconsistent with MERCURY II study that patients reaching LDL-c and Non-HDL-c targets who also apo B < 90 mg/dL was less than 50 percent[22]. The reasons that may be explained, 1) population in MERCURY II study had more previous CVD than our study (62% vs. 10%) and 2) more patients with high baseline triglyceride > 200 mg/dL (32% vs. 0%). Plasma triglyceride > 176 mg/dL has effect to increment of small dense LDL-c and apo B[26, 27].

Limitations in this study, 1) the majority of patients in this study had no previous CVD, 2) almost patients were on treatment with statin, thus the result of this study can't be imply to all diabetic patients population.

Apo B measurement for assessing and monitoring patients at risk for CVD would enhance patient management especially in previous CVD patients or hypertriglyceridemic patients that achieved goals of LDL-c and non-HDL-c. In contrast, apo B measurement in addition to reached LDL-c and non-HDL-c targets may be not necessary in diabetic patients who did not previous CVD or low triglyceride level as our study.

HDL-c is another target for treatment of patients with diabetic dyslipidemia. HDL-c levels are a strong inverse predictor of cardiovascular events. This relationship was also observed among patients with LDL cholesterol levels below 70 mg/dL[28]. In this study, patients that achieved HDL-c goal were less about a half, whiles CVD patients were achieved HDL-c goal less than 40 percent. Strategy to raised HDL-c may be cardiovascular protection such quit smoking and aerobic exercise but inhibition of cholesteryl ester transfer protein (CETP) by torcetrapib therapy resulted in an increased risk of mortality and morbidity of unknown mechanism[29]. Further investigative studies

about fibrate, nicotinic acid, or any agents for HDL-c increasing are need in the future.

Conclusion

In patients with type2 diabetes who achieved goal of LDL-c and non-HDL-c have also achieved apo B level, thus apo B measurement in addition to reached LDL-c and non-HDL-c targets may be not necessary especially in diabetic patients who did not previous CVD.

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ระดับอโปไลโปโปรตีน บี ในผู้ป่วยเบาหวานชนิดที่ 2 ที่ควบคุมระดับไขมันแอลดีแอล และน็อนเอชดีแอลโคเลสเตอรอลได้ตามเป้าหมาย

ณัฐพล สถาวโรดม, อภัสนี บุญญาวรกุล

วัตถุประสงค์: หาระดับ apolipoprotein B (apo B) ในผู้ป่วยเบาหวานชนิดที่ 2 ที่ควบคุมระดับไขมัน Low density lipoprotein cholesterol (LDL-c) และ Non- high density lipoprotein cholesterol (Non-HDL-c) ได้ตามเป้าหมาย และหาร้อยละของผู้ป่วยที่มีระดับ apolipoprotein B (apoB) ได้ตามเป้าหมาย

วัสดุและวิธีการ: ทำการศึกษาแบบภาพตัดขวาง ตั้งแต่ ตุลาคม ถึงธันวาคม พ.ศ. 2551 ผู้ป่วยเบาหวานชนิดที่ 2 ที่มารับการตรวจติดตามในคลินิกเฉพาะทางโรคเบาหวาน โรงพยาบาลพระมงกุฎเกล้า จะได้รับการประเมินความเสี่ยง ของการเกิดโรคหัวใจ และหลอดเลือดเพื่อกำหนดเป้าหมายของระดับไขมันในเลือด ตามคำแนะนำของสมาคม โรคเบาหวาน และมูลนิธิโรคหัวใจแห่งประเทศสหรัฐอเมริกา ในผู้ป่วยที่ควบคุมระดับไขมัน LDL-c และ Non-HDL-c ได้ตามเป้าหมาย จะส่งตรวจ apo B เพื่อคำนวณร้อยละของผู้ป่วยที่มีระดับ apo B ได้ตามเป้าหมาย

ผลการศึกษา: ผู้ป่วยเบาหวานชนิดที่ 2 จำนวน 162 รายมี 133 ราย สามารถควบคุมระดับ LDL-c และ Non-HDL-c ได้ตามเป้าหมาย ร้อยละ 9.7 (จำนวน 13 ราย) ของผู้ป่วยเคยมีโรคหลอดเลือดหัวใจมาก่อน ระดับ apo B ในผู้ป่วย เบาหวานที่มี และไม่มีโรคหลอดเลือดหัวใจเท่ากับ 61.72 $\pm$ 12.63 และ 67.2 $\pm$ 12.92 มก./ดล. ตามลำดับ ร้อยละ 97.5 ของผู้ป่วยที่ไม่มีโรคหลอดเลือดหัวใจ มีระดับ apo B ได้ตามเป้าหมาย (ต่ำกว่า 90 มิลลิกรัมต่อเดซิลิตร) ขณะที่กลุ่มที่เป็นโรคหลอดเลือดหัวใจจำนวน 13 ราย วัดระดับ apo B ได้ตามเป้าหมาย (ต่ำกว่า 80 มิลลิกรัม ต่อเดซิลิตร) ร้อยละ 92.3 ยาลดไขมันที่ใช้มากสองกลุ่มหลัก ได้แกลุ่ม statins และ fibrates

สรุป: ผู้ป่วยเบาหวานชนิดที่ 2 ที่ควบคุม LDL-c และ Non-HDL-c ได้ตามเป้าหมาย ส่วนใหญ่ระดับ apo B จะได้ตามเป้าหมายเช่นกัน ดังนั้นการตรวจวัด apo B เพิ่มเติมจาก LDL-c และ Non-HDL-c อาจไม่มี ความจำเป็นในการรักษาภาวะไขมัน ในผู้ป่วยเบาหวานโดยเฉพาะผู้ที่ไม่มีเคยเป็นโรคหัวใจ และหลอดเลือดมาก่อน