Characteristics Predicting Dyslipidemia in Drug-naïve Type 2 Diabetes Patients

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Background: Plasma lipid concentrations are related to a variety of attributes in obese subjects, but these relationships have not been extensively examined in type 2 diabetes patients.

Methods: A cross-sectional survey was conducted on type 2 diabetes patients who had never been treated with antihypertensives, lipid-lowering agents, and oral antidiabetic drugs other than sulfonylureas. Statistical analysis was performed to search for the correlation between lipid profiles and various parameters.

Results: Among diabetic men, the plasma triglyceride (TG) level was positively correlated with the waist-to-hip ratio (WHR) and alcohol consumption, whereas high-density lipoprotein cholesterol (HDL-C) was negatively correlated with age and body mass index (BMI). Obese persons and alcohol drinkers were more likely to need pharmacologic treatment for dyslipidemia. Among diabetic women, the plasma TG level was positively correlated with WHR and the duration of diabetes since diagnosis, while HDL-C was negatively correlated with WHR and BMI. The necessity of treatment for dyslipidemia increased with the duration of diabetes.

Conclusion: We recommend a more intensive monitoring of lipid levels in drug-naïve diabetic patients who possess the characteristics of alcohol consumption or older age (men), long duration of diabetes (women), and higher BMI or WHR (both genders). [*J Chin Med Assoc* 2006;69(9):404–408]

Key Words: drug-naïve, dyslipidemia, predictor, type 2 diabetes mellitus

Introduction

Abnormal lipid metabolism is often present in patients with type 2 diabetes.[1,2] Furthermore, abnormality in the level of each of the major lipids has been independently associated with increased risk of cardiovascular disease.[2] The American Diabetes Association currently recommends measurement of plasma lipid levels annually for type 2 diabetes patients who are not being treated with lipid-lowering agents.[3] However, in our clinical practice, dyslipidemia has been observed more frequently in certain subgroups of diabetic patients, who would likely benefit from more intensive monitoring of plasma lipid levels. If we could predict from certain easily measurable parameters who is most likely to develop dyslipidemia, then it would allow us to target these at-risk groups for intensive lipid monitoring.

Plasma lipid concentrations are related to several anthropometric indices,[4–9] including waist circumference, waist-to-hip ratio (WHR), body mass index (BMI), and even skinfold thickness. Plasma lipids are also influenced by cigarette smoking, alcohol consumption, and physical activity. However, these associations have not been thoroughly examined in patients with type 2 diabetes. We therefore conducted this cross-sectional study to search for patient characteristics that might best predict higher plasma lipid concentrations. We also attempted to characterize patients who meet the criteria for pharmacologic treatment of dyslipidemia according to the guidelines of the

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Bureau of National Health Insurance (BNHI) in Taiwan.[10]

Methods

We conducted a cross-sectional survey of patients with type 2 diabetes who were enrolled in the diabetes case management program in Changhua Christian Hospital during the period from April 2002 to May 2004. The diagnosis of type 2 diabetes was based on the criteria established by the American Diabetes Association (ADA). Patients who had been taking antihypertensive medication, lipid-lowering agents, or oral antidiabetic agents likely to affect plasma lipid levels[11] (thiazolidinediones, metformin, alpha-glucosidase inhibitors) were excluded. Information pertaining to prior medication, duration of diabetes since diagnosis, and lifestyle factors (cigarette and alcohol use) was obtained through patient interview or review of medical records at the time of enrollment into the diabetes management program.

Blood pressure was measured during clinic visits using an automated sphygmomanometer, after patients had remained in a sitting position for at least 10 minutes. Hypertension was defined as systolic blood pressure (SBP) ≥ 130 mmHg and/or diastolic blood pressure (DBP) ≥ 80 mmHg.[12] Height was measured to the nearest centimeter. BMI was calculated as weight (kg) divided by height squared (m^2). Waist circumference was measured with the measuring tape positioned midway between the lowest rib and the iliac crest after the patient had exhaled normally.[13] Hip circumference was measured at the level of the symphysis pubis and the great gluteal protuberance.[14] Obesity was defined as BMI ≥ 27,[15] and abdominal obesity was defined as WHR ≥ 0.9 for men and ≥ 0.85 for women.[16] Eligibility for pharmacologic treatment of diabetic dyslipidemia was determined using the criteria established by the BNHI,[10] which include: (1) total cholesterol (TC) ≥ 200 mg/dL, or (2) low-density lipoprotein cholesterol (LDL-C) ≥ 130 mg/dL, or (3) triglyceride (TG) ≥ 200 mg/dL while either the high-density lipoprotein cholesterol (HDL-C) level is < 40 mg/dL or the TC/HDL-C ratio is > 5.

Blood samples were collected in the morning after an 8- to 12-hour fast. Levels of fasting blood glucose (FBS), glycosylated hemoglobin A1C (HbA1C), TC, HDL-C, LDL-C, and TG were determined in the hospital laboratory using standard methods.

Statistical analysis, including Student's *t* test, multiple regression and multiple logistic regression tests, was performed with SPSS version 10.0 (SPSS Inc., Chicago, IL, USA). A p value < 0.05 was considered statistically significant.

Results

In total, 408 subjects were included in this study. The mean age was 55.8 ± 13.9 years. There were 223 men (54.7%) and 185 (45.3%) women. The means and standard deviations of anthropometric indices and other attributes are shown in Table 1. The mean levels of TC, LDL-C, TG and HDL-C were 181.4 mg/dL,

Table 1. Anthropometric indices, physical factors, and lipid profiles by sex*

Baseline	Total (n = 408)	Male (n = 223)	Female (n = 185)	p
Age (yr)	55.8 ± 13.9	54.1 ± 13.7	58.0 ± 13.8	0.0046
DM duration (yr)	5.7 ± 6.8	5.6 ± 6.8	5.9 ± 6.7	NS
Drinking (yes)	19.4% (n = 79)	31.4% (n = 70)	4.9% (n = 9)	< 0.0001
Smoking (yes)	5.9% (n = 24)	8.5% (n = 19)	2.7% (n = 5)	0.0129
BMI	23.9 ± 3.4	23.8 ± 3.2	23.9 ± 3.8	NS
WHR	0.901 ± 0.069	0.913 ± 0.067	0.887 ± 0.069	0.0001
SBP (mmHg)	128.6 ± 18.3	127.0 ± 16.0	130.6 ± 20.6	0.0484
DBP (mmHg)	77.1 ± 10.5	78.0 ± 9.9	76.1 ± 11.2	NS
FBS (mg/dL)	159.0 ± 65.1	156.8 ± 58.8	161.5 ± 72.1	NS
HbA1C (%)	8.39 ± 2.32	8.44 ± 2.40	8.32 ± 2.24	NS
TC (mg/dL)	181.4 ± 39.0	174.5 ± 40.0	189.6 ± 36.1	< 0.0001
TG (mg/dL)	132.0 ± 89.6	137.6 ± 102.2	125.3 ± 71.4	NS
HDL-C (mg/dL)	50.0 ± 13.7	46.3 ± 12.7	54.4 ± 13.6	< 0.0001
LDL-C (mg/dL)	104.8 ± 29.7	101.4 ± 30.2	109.0 ± 28.7	0.0104

**Data are presented as mean ± SD. DM = diabetes mellitus; BMI = body mass index; WHR = waist-to-hip ratio; SBP = systolic blood pressure; DBP = diastolic blood pressure; FBS = fasting blood glucose; HbA1C = glycosylated hemoglobin A1C; TC = total cholesterol; TG = triglyceride; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NS = not significant.*

104.8 mg/dL, 132.0 mg/dL and 50.0 mg/dL, respectively. Plasma lipid levels other than TG were significantly higher in women than in men. Men were significantly younger and had lower SBP than women. There were no differences in FBS, HbA1C and BMI between men and women.

Table 2 shows the correlation between each of the measured lipids and various nonlaboratory attributes. Lower plasma concentrations of TC were associated with the male sex and nondrinkers. Nondrinkers also had lower TG levels. Plasma HDL-C had negative correlation, while plasma TG had positive correlation, with BMI and WHR. Table 3 shows the results of multiple regression analysis after controlling for age, the duration of diabetes since diagnosis, cigarette smoking, alcohol consumption, BMI, WHR, SBP and DBP in both genders. Among men, plasma TG level was positively correlated with WHR and alcohol consumption, whereas HDL-C level was negatively correlated with age and BMI, all with statistical significance. Among women, plasma TG level was positively correlated with WHR and the duration of diabetes since diagnosis, while HDL-C level was negatively correlated with WHR and BMI, all with statistical significance. In both men and women, no significant correlation with any factor was found for both TC and LDL-C levels.

Factors that predict eligibility for pharmacologic treatment of dyslipidemia are shown in Table 4 for men and Table 5 for women. Diabetic men who were obese (BMI ≥ 27) or who were alcohol drinkers were more likely to require pharmacologic treatment for dyslipidemia than the nonobese and nonalcohol drinkers (odds ratio [OR], 3.5–4.2). For diabetic women, the OR for requiring dyslipidemia treatment increased about 1.2-fold with each 1-year increase in the duration of diabetes. Overall, 29.4% of patients met the criteria (23.3% in men, 36.2% in women) for pharmacologic treatment of dyslipidemia.

Table 2. Correlation of lipid levels with anthropometric indices, sex, and lifestyle

Dependent variable	Explanatory variable	Estimate	*p*
Total cholesterol	Male sex	–18.18	< 0.001
	Nondrinker	–14.41	0.081
LDL-C	Male sex	–7.77	0.017
HDL-C	Male sex	–7.41	< 0.001
	BMI	–0.94	< 0.001
	WHR	–31.50	0.001
TG	Nondrinker	–67.51	< 0.001
	BMI	1.35	0.059
	WHR	260.48	< 0.001

LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; BMI = body mass index; WHR = waist-to-hip ratio; TG = triglyceride.

Table 3. Multiple regression analysis of relationship between anthropometric indices, physical factors, and lipid concentrations in men and women

Dependent variable	Men			Women		
	Explanatory variable	Coefficient	*p*	Explanatory variable	Coefficient	*p*
Cholesterol	—	—	—	—	—	—
TG	No drinking	–66.80	0.005	DM duration	2.04	0.012
	WHR′	29.08	0.008	WHR′	22.38	0.005
LDL-C	—	—	—	—	—	—
HDL-C	Age	–0.22	0.001	BMI	–0.70	0.012
	BMI	–1.31	< 0.001	WHR′	–4.54	0.003

TG = triglyceride; DM = diabetes mellitus; WHR′ = waist-to-hip ratio × 10; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; BMI = body mass index.

Table 4. Factors predicting eligibility for pharmacologic treatment of dyslipidemia in male diabetic patients*†

Guide of treatment	*n* (%)	Factor	OR	95% CI
LDL-C ≥ 130 mg/dL	28 (12.26)	Alcohol use	3.472†	1.174–10.309
TC ≥ 200 mg/dL	39 (17.49)	Alcohol use	3.922†	1.420–10.870
TG ≥ 200 mg/dL and TC/HDL-C > 5 or HDL-C < 40 mg/dL	20 (8.97)	BMI ≥ 27	4.238†	1.471–12.207

**Fulfilling any of the three criteria: n = 52 (23.32%); †factors are alcohol use, smoking, systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 80 mmHg, waist-to-hip ratio ≥ 0.9, body mass index ≥ 27; ‡p < 0.05. OR = odds ratio; CI = confidence interval; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride; HDL-C = high-density lipoprotein cholesterol; BMI = body mass index.*

Table 5. Factors predicting eligibility for pharmacologic treatment of dyslipidemia in female diabetic patients*†

Guide of treatment	*n* (%)	Factor	OR	95% CI
LDL-C ≥ 130 mg/dL	36 (19.46)	—	—	—
TC ≥ 200 mg/dL	63 (34.05)	—	—	—
TG ≥ 200 mg/dL and TC/HDL-C > 5 or HDL-C < 40 mg/dL	10 (5.41)	Duration of diabetes (>1 yr)	1.181	1.075–1.297‡

**Fulfilling any of the three criteria: n = 52 (23.32%); †factors are alcohol use, smoking, systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 80 mmHg, waist-to-hip ratio ≥ 0.9, body mass index ≥ 27; ‡p < 0.05. OR = odds ratio; CI = confidence interval; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride; HDL-C = high-density lipoprotein cholesterol.*

Discussion

The patients in this study had lower mean lipid values than previous studies,[9,17] with lower TC, LDL-C and TG, and higher HDL-C levels. Besides ethnicity, differences in anthropometric indices, blood pressure, and lifestyle factors might account for this finding. In this study, diabetic women had higher serum cholesterol but similar TG level compared with diabetic men. Previous studies also had the same finding.[17,18] While the higher HDL-C level among women might be attributed to gender difference alone,[4,5] the higher TC and LDL-C levels could also be related to the older mean age in the female group, since TC and LDL-C are positively correlated with age[4,7] and SBP.[19,20] Although men did not have higher plasma TG levels in this study, it might be accounted for by their younger age compared to women.[21]

Plasma lipid concentrations might be influenced by several factors. HDL-C is negatively correlated with WHR[7] and BMI,[4,8] and TG is positively correlated with WHR[7] and alcohol consumption.[6] TC is positively associated with alcohol consumption.[6] These associations were also observed in this study. Because there appeared to be notable gender differences in terms of these correlations, additional analyses were done separately for each gender. After separating the genders, there was no longer any correlation for TC and LDL-C levels with any of the factors we investigated. This partly concurs with another report in which LDL-C was not related to any of the investigated factors, including age, gender, glycemia, obesity, and smoking, whereas TC was related to age and smoking only.[4,5] Since the magnitude and strength of the associations between anthropometric measures and serum lipids tend to be greater among younger subjects,[6,22] the older mean age of our patients might be responsible for weakening these associations. With regard to TG level, because of the low prevalence of female alcohol drinkers in our study (4.9%) and in the Taiwanese population as a whole, it is not surprising that the correlation between TG level and alcohol consumption was observed only among men. Among women, however, TG is significantly associated with the duration of diabetes. This association has seldom received attention,[23] but it should nonetheless be taken into consideration when treating diabetic dyslipidemia.

According to the BNHI guidelines in Taiwan,[10] treatment with a statin is suggested if TC or LDL-C is higher than desired, whereas a fibrate is suggested for high TG combined with a low HDL-C. We therefore conducted a multiple logistic regression analysis with respect to age, duration since diagnosis of diabetes, anthropometric indices, blood pressure, and alcohol and tobacco usage to see which best predicted eligibility for pharmacologic treatment according to the BNHI criteria. We found that alcohol consumption predicted the requirement of treatment with a statin and obesity (BMI ≥ 27) predicted treatment with a fibrate in diabetic men. This finding agreed with a study that showed that BMI (≥ 27) was the best predictor for abnormal TG (≥ 200 mg/dL).[5] In female patients, the requirement for fibrate increased along with the duration of diabetes. The factors predicting need for treatment with antihyperlipid agents can be explained by the elevated TG levels frequently found among obese persons or alcohol drinkers. Overall, statin treatment is more often indicated in these patients than fibrate treatment.

There were several limitations in this study. The first was the sampling bias. Patients enrolled in the program may not be representative of all type 2 diabetes patients. Second, physical activity was not considered and the amount of alcohol and tobacco use was not quantified in our study. These 3 lifestyle factors were reported to be quantitatively correlated with plasma lipid levels.[4,6,7] Third, disorders that predispose to hyperlipidemia, such as hypothyroidism and nephrotic syndrome,[24] were not excluded in this study, and thereby might have introduced statistical bias. Fourth, the variability in the degree of glycemic control was not taken into consideration in the statistical analysis. Good glycemic control by itself might lower plasma cholesterol and TG levels and elevate HDL-C level.[7]

Finally, the accuracy of patients' medication history was subject to the reliability of the patients.

In conclusion, of the diabetic patients who were drug-naïve or who were treated with sulfonylureas only, about 1-third would require pharmacologic treatment for dyslipidemia. Female patients were apt to have higher levels of all major lipids. Alcohol consumption, BMI, WHR, and age were the most important factors associated with elevated plasma lipid levels in males. In consequence, men who were obese (BMI ≥ 27) or who were alcohol drinkers more frequently required lipid-lowering treatment. In female patients, BMI, WHR, and the duration of diabetes were more significantly associated with plasma lipid levels. Requirement for treatment with lipid-lowering agents increased with increasing duration of diabetes. For type 2 diabetes mellitus patients with lipid levels controlled by diet or sulfonylureas alone, we recommend a more intensive monitoring of lipid levels if they possess the aforementioned characteristics.

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