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Letter to the Editor

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Understanding of Diabetic Dyslipidemia by Using the Anion-Exchange High Performance Liquid Chromatography Data

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To the Editor

Type 2 diabetes and dyslipidemia are cardiovascular risk factors which should be managed [1]. However, the precise lipoprotein profiles and the underlying mechanisms for diabetic dyslipidemia remain largely unknown. We previously developed an anion-exchange liquid chromatographic method (AEX-HPLC) which can measure cholesterol levels of triglyceride (TG)-rich lipoproteins such as very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL) and chylomicron (CM) in addition to low-density lipoprotein (LDL) and high-density lipoprotein (HDL) [2]. Here we compared lipoprotein profiles obtained by our previous studies using AEX-HPLC in young lean men [3], subjects with low Framingham risk score (FRS) [4, 5], type 2 diabetic patients without obesity and type 2 diabetic patients with obesity [6, 7].

The mean ± SD values of age, body mass index, HbA1c in in young lean men (n = 7) [3], low FRS subjects (n = 304) [4], type 2 diabetic patients without obesity (n = 194) [6], and type 2 diabetic patients with obesity (n = 5) [7] were 24 ± 2, 51 ± 8, 63 ± 13, and 60 ± 9 years old, 20.8 ± 2.2, 23.8 ± 3.0, 23.1 ± 2.0, and 29.5 ± 7.0 kg/m^2, 5.0 ± 0.2, 5.4 ± 0.5, 6.3 ± 1.0, and 9.1±2.1%, respectively.

HDL-cholesterol (HDL-C) in type 2 diabetes (49.9 ± 16.6 mg/dL (1.29 ± 0.43 mmol/L)), especially in type 2 diabetic patients with obesity (36.4 ± 5.3 mg/dL (0.94 ± 0.14 mmol/L)) was lower than young lean men (59.4 ± 10.1 mg/dL (1.54 ± 0.26 mmol/L)) and low FRS subjects (57.6 ± 14.7 mg/dL (1.49 ± 0.38 mmol/L)). IDL-C in type 2 diabetes was higher than other two groups, and IDL-C was higher in the order of type 2 diabetic patients with obesity (9.8 ± 3.0 mg/dL (0.25 ± 0.08 mmol/L)), type 2 diabetic patients without obesity (9.3 ± 4.6 mg/dL (0.24 ± 0.12 mmol/L)), low FRS subjects (7.3 ± 3.1 mg/dL (0.19 ± 0.08 mmol/L)), young lean men (4.3 ± 2.2 mg/dL (0.11 ± 0.06 mmol/L)). VLDL-C clearly showed higher values in the order of type 2 diabetic patients with obesity (27.3 ± 22.7 mg/dL (0.71 ± 0.59 mmol/L)), type 2 diabetic patients without obesity (20.1 ± 16.2 mg/dL (0.52 ± 0.42 mmol/L)), low FRS subjects (16.6 ± 12.8 mg/dL (0.43 ± 0.33 mmol/L)), and young lean men (4.0 ± 4.6 mg/dL (0.10 ± 0.12 mmol/L)). LDL-C and CM-C did not show the characteristic profile for diabetes.

According to accumulation of our previous AEX-HPLC data [3, 4, 6, 7], the characteristics in diabetic dyslipidemia is reduced HDL-C, and increased IDL-C and VLDL-C, which is further deteriorated by complication with obesity. Relative insulin deficiency due to insulin resistance increases activity and expression of hormone-sensitive lipase (HSL) in adipose tissue, which catalyzes the breakdown of TG, releasing free fatty acids (FFA) (Fig. 1) [8]. Insulin promotes apoB100 degradation, and hepatic insulin resistance causes reduction of apoB100 degradation [9]. Insulin resistance also induces an enhanced expression of microsomal TG transfer protein (MTP), a key enzyme involved in VLDL assembly [10]. In type 2 diabetes, increased FFA entry to liver, reduced degradation of apoB100 and enhanced expression of MTP may elevate hepatic production of VLDL. Relative insulin deficiency also decreases the activity of lipoprotein lipase (LPL), the rate-limiting enzyme of the catabolism of TG-rich lipoproteins such as CM, VLDL and IDL [11]. The formation of HDL is related with the catabolism of TG-rich lipoproteins by LPL [12]. Therefore, reduced LPL activity increases IDL and VLDL, and reduces HDL. The activity of hepatic TG lipase (HTGL), the enzyme that facilitates the catabolism of HDL, is correlated with insulin requirement [13]. In type 2 diabetes, low serum HDL-C may be partially due to an increased rate of clearance by HTGL [13]. LDL size and buoyancy are inversely proportional to HTGL activity [14], and patients with high HTGL have smaller, denser LDL particles, as compared with subjects with low HTGL activity [15]. Increased HTGL activity due

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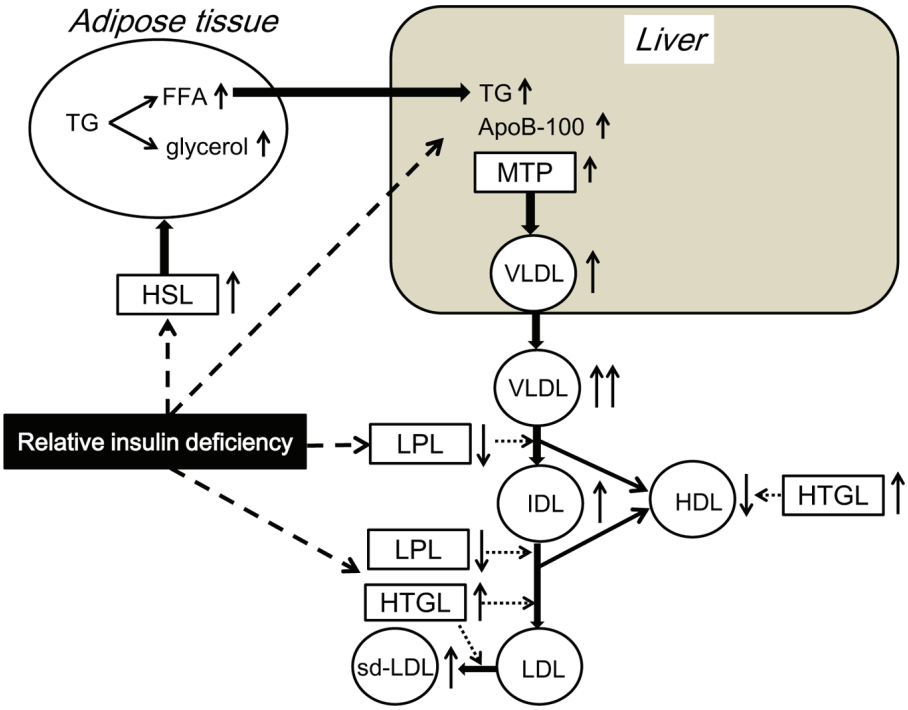

Figure 1. The underlying mechanisms for development of diabetic dyslipidemia. FFA: free fatty acids; HDL: high-density lipoprotein; HSL: hormone-sensitive lipase; HTGL: hepatic triglyceride lipase; IDL: intermediate-density lipoprotein; LDL: low-density lipoprotein; LPL: lipoprotein lipase; MTP: microsomal triglyceride transfer protein; sd-LDL: small dense LDL; TG: triglyceride; VLDL: very low-density lipoprotein.

to insulin resistance/relative insulin deficiency may increase small dense LDL, atherogenic lipoprotein, in type 2 diabetes.

In conclusion, accumulation of our previous AEX-HPLC data provided us the characteristics for diabetic dyslipidemia such as reduced HDL-C, and increased IDL-C and VLDL-C, which is further deteriorated by complication with obesity. Disturbed regulation in activity and expression of HSL, apoB100, MTP, LPL and HTGL due to insulin resistance/relative insulin deficiency may induce diabetic dyslipidemia.

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