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Hepatic fat content is a determinant of postprandial triglyceride levels in type 2 diabetes mellitus patients with normal fasting triglyceride

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Abstract

Postprandial hypertriglyceridemia is common in type 2 diabetes mellitus (T2D). Significant numbers of T2D patients who have normal fasting triglyceride (TG) have postprandial hypertriglyceridemia. The role of regional adipose tissue and adiponectin on postprandial TG responses in this group of T2D patients is unclear. This study aimed to examine the contribution of regional adipose tissue and adiponectin to the variation of postprandial TG responses in T2D patients who have normal fasting TG levels. Thirty-one Thai T2D patients who had fasting TG <1.7 mmol/L were studied. All were treated with diet control or sulphonylurea and/or metformin. None was treated with lipid-lowering agents. Mixed-meal test was performed after overnight fast. Plasma glucose, insulin, and TG were measured before and 1, 2, 3, and 4 hours after the test. Adiponectin was measured in fasting state. Visceral as well as superficial and deep subcutaneous abdominal adipose tissues were determined by magnetic resonance imaging, and hepatic fat content (HFC) was determined by magnetic resonance spectroscopy. Univariate and multivariate regression analyses of postprandial TG and regional adipose tissue and metabolic parameters were performed. The TG levels before and 1, 2, 3, and 4 hours after the mixed meal were 1.32 ± 0.40 (SD), 1.40 ± 0.41, 1.59 ± 0.40, 1.77 ± 0.57, and 1.80 ± 0.66 mmol/L, respectively ($P < .0001$). The area under the curve (AUC) of postprandial TG was positively and significantly correlated with fasting TG ($r = 0.84$, $P < .0001$) and log.HFC ($r = 0.456$, $P = .033$) and was inclined to be correlated with log.deep subcutaneous adipose tissue ($r = 0.38$, $P = .05$) and sex ($r = 0.326$, $P = .073$). The AUC of postprandial TG was not correlated with age, body mass index, waist circumference, log.superficial subcutaneous adipose tissue, log.visceral adipose tissue, hemoglobin A_{1c}, fasting glucose, AUC.glucose, log. fasting insulin, log.AUC.insulin, log.homeostasis model assessment%B, log.homeostasis model assessment of insulin resistance, and adiponectin. Only fasting TG ($\beta = .815$, $P < .0001$) and log.HFC ($\beta = .249$, $P = .035$) predicted AUC of postprandial TG in regression model (adjusted $R^2 = 0.84$, $P < .0001$). In conclusion, in T2D patients with normal fasting TG, the increase of postprandial TG levels is directly determined by fasting TG level and the amount of hepatic fat.

1. Introduction

Postprandial triglyceride (TG) levels can be increased in type 2 diabetes mellitus (T2D) patients, and the presence of which is associated with the development of atherosclerosis and macrovascular complications [1-4]. The elevated postprandial TG levels are also observed in subjects with metabolic syndrome who have no history of diabetes [5]. The pathogenesis of postprandial TG-induced atherosclerosis is unclear but may be associated with the development of oxidative stress and endothelial dysfunction [6-8]. Several studies have demonstrated the strong association between visceral adipose tissue (VAT) and postprandial TG levels in both nondiabetic and T2D subjects [9-11]. The positive association of VAT and postprandial TG is theoretically sound because VAT is metabolically active and highly sensitive to lipolysis; and as a result, free fatty acid drains directly into the liver through the portal circulation. Excessive free fatty acid flux into the liver causes overproduction of very low-density lipoprotein (VLDL) that results in the increase of TG levels. However, the study by Guo et al [12] has demonstrated that this might not be true.

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Visceral adipose tissue may be a marker for, but not the source of, substrate for TG production in centrally obese subjects. Given the strongly positive association of VAT and hepatic fat, it is possible that it is hepatic fat but not VAT that is associated with postprandial TG. In addition, the adiponectin levels that are inversely associated with hepatic fat content (HFC) may regulate postprandial TG metabolism. The increased amount of hepatic fat and the decreased adiponectin levels have been demonstrated to be independently involved in the development of fasting hypertriglyceridemia [13-15]; therefore, it is possible that either HFC or adiponectin or both may also contribute to the elevation of postprandial TG levels as well.

It is known that T2D patients with fasting hypertriglyceridemia have exaggerated and prolonged postprandial TG responses compared with those with normal fasting TG levels. However, exaggerated postprandial TG responses may also be observed in T2D patients who have normal fasting TG. Ahmad et al [1] reported that approximately 60% of newly diagnosed T2D patients who had normal fasting TG (<1.7 mmol/L) had postprandial hypertriglyceridemia (>2.3 mmol/L). This number was reported to be approximately 26% by Teno et al [2]. Why postprandial TG responses differ in patients who have similar fasting TG levels is uncertain, and it is unclear whether VAT or HFC or adiponectin contributes to this variation. The objective of this study is to examine the contribution of VAT, HFC, and adiponectin to the variation in postprandial TG levels in T2D patients who have normal fasting TG.

2. Materials and methods

Thirty-one Thai T2D patients (13 men, 18 women) were included in the study. The clinical characteristics of subjects are shown in Table 1. All were treated with diet control or sulphonylurea and/or metformin. Patients who were treated with insulin, thiazolidinedione, α-glucosidase inhibitor, or drugs that could interfere with lipid metabolism, which include statin, fibrate, nicotinic acid, glucocorticoid, protease inhibitor, estrogen, or androgen-related substance, were excluded. Only subjects who had normal (<1.7 mmol/L) or near-normal fasting TG levels were selected for the study. Patients who had >3-fold elevation of alanine aminotransferase or aspartate aminotransferase, serum creatinine >140 μmol/L, proteinuria in nephrotic range, or untreated hypothyroid as well as those who were pregnant, had history of regular alcohol intake, or were regularly involved in vigorous exercise were excluded.

Table 1
Clinical characteristics of subjects in the study

	N = 31
Age (y)	48.6 ± 8.6
BMI (kg/m^2)	26.3 ± 3.8
Duration of DM (y)	2 (0.08-25)
Waist circumference (cm)	89.1 ± 8.4
HbA_{1c} (%)	7.8 ± 2.2
Fasting glucose (mmol/L)	7.3 ± 2.6
Total cholesterol (mmol/L)	4.8 ± 0.7
Fasting TG (mmol/L)	1.3 ± 0.4
HDL cholesterol (mmol/L)	1.0 ± 0.3
LDL cholesterol (mmol/L)	3.1 ± 0.7
Adiponectin (μg/mL)	7.24 ± 3.98
HOMA%B	69.9 (10.1-334)
HOMA-IR	1.55 (0.6-4.3)
SSAT (cm^2)	91.0 (51.0-261.7)
DSAT(cm^2)	79.7 (14.1-235.7)
VAT (cm^2)	92.7 (57.3-191.7)
HFC (%)	8.7 (0-40.9)

Data are expressed as mean ± SD or median (range). DM indicates diabetes mellitus.

All came to our research unit at 8:00 AM with at least 12 hours of overnight fast and were instructed to avoid exercise as well as alcohol-containing beverage for at least 1 week before the study and continued until hepatic and abdominal fat was measured. Baseline characteristics that included age, body mass index (BMI), waist circumference, duration of diabetes, and all medications currently in use were obtained. Plasma glucose, insulin, and TG were measured before and hourly after the mixed-meal test for 4 hours. The mixed meal had a total energy of 470 to 580 kcal and consisted of 71 to 84 g carbohydrate, 16 to 30 g protein, and 13 to 16 g fat. The other blood tests that included adiponectin, hemoglobin A_{1c} (HbA_{1c}), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and total cholesterol levels were measured at a fasting state. Hepatic magnetic resonance proton spectroscopy (MRS) and abdominal magnetic resonance imaging (MRI) were performed within 1 to 2 weeks after the mixed-meal tests by using 1.5-T magnet (Sigma CVi, General Electric Medical Systems, Milwaukee, WI) to respectively measure hepatic TG or HFC and VAT and subcutaneous (SAT) abdominal adipose tissue.

2.1. Measurement of HFC

Measurements of HFC were obtained using MRS with the method described by Szczepaniak et al [16,17]. Coronal and axial slices through the right lobe of the liver were acquired; and a 27-cm^3 spectroscopic volume of interest was positioned, avoiding major blood vessels, intrahepatic bile ducts, and the lateral margin of the liver. After the system was tuned and shimmed, spectra were collected using a body coil for radio frequency transmission and signal reception. A PRESS (point-resolved spectroscopy) sequence was used for spatial localization and signal acquisition with the parameters interpulse delay repetition time = 3 seconds, spin echo time = 25 milliseconds, 16 acquisitions, and 1024 data points over a 1000-Hz spectral width. Only signals from a selected volume element were collected. Areas of resonances from protons of water and methylene groups in fatty acid chains of the hepatic TG were evaluated with a line-fit procedure. Signal decay due to spin-spin relaxation was calculated using

mean T_2 relaxation times for water and fat of 50 and 60 milliseconds, respectively, and the exponential relaxation equation $I_m = I_o \exp(-T_e/T_2)$, where I_m was the measured signal intensity (SI) obtained at the selected echo time of T_e, I_o was the SI immediately after the 90° pulse, and T_2 was the spin-spin relaxation time. Average T_2 relaxation times were used for these calculations instead of performing experiments to assess the relaxation times individually in each patient. Values provided by ^{1}H MRS denoted relative quantity of water and hepatic TG fatty acid chain protons in the volume of interest. To convert these results to absolute concentrations expressed as percentage fat by weight or volume, we used equations validated by Longo et al [18]. With these equations, a significant correlation was obtained between calculated HFC and the value measured by liver biopsy.

2.2. Measurement of VAT and SAT

The estimation of SAT and VAT areas was calculated from a single-slice MR image at the level of the umbilicus. The abdominal adipose tissue could be distinguished from other tissue types by its high SI on T1-weighted images. The abdominal adipose tissue compartments were defined according to the classification of Shen et al [19]. The VAT was bounded by the internal margin of the abdominal muscle walls and included the intraperitoneal, preperitoneal, and retroperitoneal adipose tissue. The SAT compartment included the adipose tissues outside of the VAT boundary and consisted of superficial and deep layer that was separated by the fascia superficialis. To measure the abdominal adipose tissues, the axial images obtained at MRI were transferred to the workstation (Advantage Workstation 4.0, General Electric Medical Systems). With the use of the cursor, a freehand region of interest (ROI) was drawn around the subcutaneous fat layer; and the mean SI ± SD of the adipose tissue was obtained from this ROI. The *threshold for adipose tissue* was defined as the mean SI ± 2 SD. The VAT area in centimeters was then measured by applying this threshold to an ROI drawn around the inner boundary of the abdominal wall muscles. Likewise, an ROI drawn around the external margin of the dermis was used to calculate the area of the total adipose tissue. An ROI drawn around the fascia superficialis was applied to indicate the combined area of deep subcutaneous adipose tissue (DSAT) and VAT, subtraction of which from the total adipose tissue area represented the superficial subcutaneous adipose tissue (SSAT) area. The DSAT area was obtained by subtracting the VAT area from the combined area of DSAT and VAT.

2.3. Biochemical analysis

Plasma insulin level was measured by immunochemiluminiscence method (Diagnostic Products, Los Angeles, CA) using automated machine with intra- and interassay coefficients of variation of 5.3% to 6.4% and 5.9% to 8.0%, respectively. Plasma glucose level was measured by hexokinase method. The HbA_{1c} was measured by turbidity technique (Cobas Integra 400 plus; Roche Diagnostic, Indianapolis, IN) with the reference range of 4.4% to 6.4%. Plasma TG, HDL, LDL, and total cholesterol levels were measured by enzymatic method (Dimension RxL, Dade Behring, New York, NY). Adiponectin was measured as total adiponectin by radioimmunoassay method (Linco Research, St. Louis, MO) with intra- and interassay coefficients of variation of 1.78% to 6.21% and 6.9% to 9.25%, respectively. Insulin resistance (homeostasis model assessment of insulin resistance [HOMA-IR]) and β-cell function (HOMA%B) were assessed by HOMA-2 model.

The study has been conducted in accordance with the guidelines in the Declaration of Helsinki. All subjects gave written informed consent before the beginning of the study, and the study was approved by the ethical committee of Ramathibodi hospital.

2.4. Statistical analysis

All values are presented as means ± SD or medians and ranges as indicated. Analysis of variance was used to test the differences of postprandial TG from fasting TG levels. The correlations between dependent and independent variables were tested with Pearson correlation, and variables with univariate correlation <0.1 were included in the backward stepwise multivariate linear regression models to evaluate its independent association. Data not normally distributed were log transformed before analysis. All statistical analyses were performed with SPSS version 13 (SPSS, Chicago, IL). The area under the curve (AUC) of postprandial TG levels was used as the dependent variable; and sex, age, BMI, waist circumference, adiponectin, HbA_{1c}, fasting glucose, AUC.glucose, fasting insulin, AUC.insulin, fasting TG, HOMA%B, HOMA-IR, VAT, SSAT, DSAT, and HFC were used as independent variables. The AUC was calculated by

Table 2
Univariate correlations of AUCs of postprandial TG and other parameters

	Correlation coefficient (r)	P
Sex	0.326	.073
Age	−0.205	.268
BMI	0.219	.237
Waist circumference	0.161	.388
SSAT[a]	0.194	.333
DSAT[a]	0.380	.050
VAT[a]	0.047	.816
HFC[a]	0.456	.033
HOMA%B[a]	0.069	.716
HOMA-IR[a]	0.137	.470
Adiponectin	−0.108	.564
Fasting TG	0.840	<.0001
Fasting glucose	−0.048	.797
AUC.glucose	0.157	.399
HbA_{1c}	−0.006	.974
Fasting insulin[a]	0.182	.328
AUC.insulin[a]	0.188	.311

[a] Log transformed before analysis.

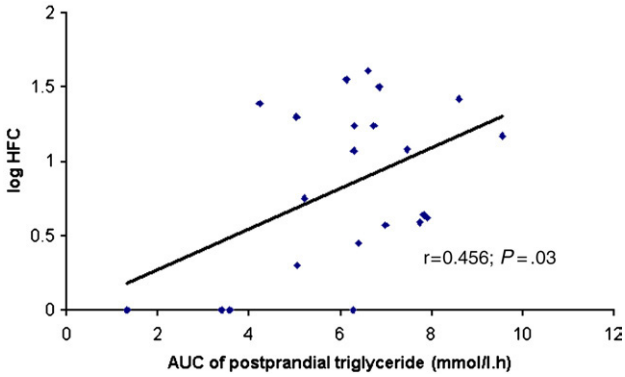

Fig. 1. The correlation of postprandial TG and HFC.

trapezoidal rule. A P value less than .05 was considered statistically significant.

3. Results

The clinical characteristics and biochemical data of 31 subjects are demonstrated in Table 1. About 50% of subjects had HbA_{1c} ≤7%, and all had normal or near-normal fasting TG levels at the time of study.

Serum TG levels were significantly increased from 1.32 ± 0.40 mmol/L at baseline to 1.40 ± 0.41, 1.59 ± 0.40, 1.77 ± 0.57, and 1.80 ± 0.66 mmol/L at 1, 2, 3, and 4 hours, respectively, after the test meal ($P < .0001$). Twenty-seven subjects (87%) had maximum TG responses at 3 or 4 hours. There were no sex differences of baseline characteristics and postprandial TG responses to test meal. As shown in Table 2, the AUC of postprandial TG (AUC.TG) was significantly correlated with fasting TG and log.HFC and was inclined to be correlated with log.DSAT and sex. The AUC.TG had no correlation with age, BMI, waist circumference, log.SSAT, log.VAT, fasting glucose, AUC.glucose, log.fasting insulin, log.AUC.insulin, HbA_{1c}, log.HOMA%B, log.HOMA-IR, and adiponectin. By backward multiple linear regression analysis and using AUC.TG as an independent variable, fasting TG ($\beta = .815$, $P < .0001$) and log.HFC ($\beta = .249$, $P = .035$) were the only variables that best fitted the model (adjusted $R^2 = 0.84$, $P < .0001$). The scatter plot of AUC.TG and log.HFC is shown in Fig. 1. The significant correlation between log.HFC and postprandial TG was demonstrated whether the latter was expressed as maximal TG responses ($r = 0.488$, $P = .021$), the maximal incremental responses from fasting TG levels ($r = 0.423$, $P = .05$), or the incremental AUC from fasting TG levels ($r = 0.454$, $P = .034$). However, log.HFC was not correlated with fasting TG ($r = 0.272$, $P = .22$) or adiponectin ($r = -0.166$, $P = .461$) in this study.

4. Discussion

Our study showed that in T2D patients who had normal or near-normal fasting TG, the postprandial TG responses were strongly determined by fasting TG levels and the amount of hepatic fat. The amount of VAT or adiponectin levels as well as the severity of insulin resistance, insulin secretion, or β-cell function and the level of glycemic control did not influence postprandial TG responses. Our study emphasized the important role of hepatic fat in predicting postprandial TG in T2D patients. The different amount of hepatic fat may partly explain why the magnitude of postprandial TG responses differs among T2D patients who have comparable fasting TG levels as observed in some studies [1,2].

The accumulation of hepatic fat has been shown to be associated with the overproduction of fasting TG particularly from large VLDL particles independent of VAT in both T2D and nondiabetic subjects [13,14]. It is hypothesized, although not confirmed in some studies, that the increased substrate flux from VAT is the major source of excessive TG availability in the liver, the presence of which is the driving force for the overproduction of fasting TG in T2D [12]. Furthermore, the study of postprandial turnover of intrahepatic TG by the use of ^{13}C MRS demonstrates that, although there is a rapid flux of dietary fatty acids in and out of the liver in postprandial state in both nondiabetic and T2D subjects, the magnitude of liver TG uptake and the rate of initial TG release are greater in T2D [20]. Therefore, the presence of excessive intrahepatic TG pool during postprandial state plausibly contributes to postprandial hypertriglyceridemia in T2D patients. To our knowledge, there are relatively few studies that specifically determine the association of hepatic fat and postprandial TG. Matikainen et al [21] recently demonstrated the direct relationship between hepatic fat and postprandial TG levels in Finnish male subjects. Adiponectin was also demonstrated to be inversely correlated with postprandial TG and hepatic fat in that study. However, only hepatic fat and fasting TG but not adiponectin were shown to be the significant determinants of postprandial TG in the regression model. Although the results of our study are somewhat similar to those of Matikainen et al, there are some points that are different and should be discussed. Firstly, the population in the study of Matikainen et al consists of both nondiabetic and T2D subjects, the combination of which may somewhat distort the results of the study because the postprandial TG handling and intrahepatic TG turnover may be different between nondiabetes and T2D [20]. Secondly, the study population in that study was selected by the amount of HFC into low (<5%) and high (>5%) HFC. Therefore, selection bias may occur; and subjects with higher HFC are prone to have higher fasting and higher postprandial TG. However, our study supports and extends the finding of Matikainen et al that the amount of hepatic fat is an independent factor associated with postprandial TG responses in T2D patients even in those who have normal fasting TG levels. This association is true whether postprandial TG is expressed as maximal TG response, maximal incremental TG response, or incremental AUC from fasting TG. Nevertheless, we found no association between HFC, fasting TG, and adiponectin in

our study, which is against the findings from several others [14,21,22]. This may be explained by the lower levels of fasting TG and the lower amount of HFC in our study population.

In contrast to other studies, VAT is not correlated with postprandial TG in our study. Why our finding is in contrast with others is unclear. Whereas the VAT area measured by MRI of our subjects is approximately 92 cm^2, such areas in the other studies are in the range of 126 to 154 cm^2 [9-11]. Therefore, the much lower amount of VAT in our subjects may possibly contribute. Although our study demonstrates the correlation of DSAT and postprandial TG in univariate analysis, such correlation disappears when multivariate analysis is applied, indicating that DSAT is not a significant factor for postprandial TG in this study. We cannot exclude β-cell function or insulin secretion as one of the determinants of postprandial TG in our study. It is known that insulin can inhibit TG synthesis; therefore, patients with insulin deficiency can present with postprandial hypertriglyceride. Because most T2D patients in our study were newly diagnosed, the inverse association of β-cell function and postprandial TG might not be demonstrated. In comparison with other studies, our study used diet with a much lower amount of fat than those previous studies. At present, there is no standard regimen of test meal particularly of the amount of dietary fat for evaluation of postprandial TG response [23]. We intended to use a lower amount of fat in the test meal to simulate the common diet in our Thai population. The concept of using high–fat load approach is that a large amount of fat can better challenge and bring out postprandial TG abnormality than a smaller amount of fat [24]. However, our study demonstrated that even with a much smaller amount of fat load, postprandial TG levels were significantly increased and that the relationship of postprandial TG and HFC could be demonstrated. It could have been that if a larger amount of dietary fat was used as challenge, these subjects would have more pronounced postprandial TG responses. Our study and the study of Matikainen et al [21] demonstrate that it might not be only the amount of dietary fat but the amount of HFC and the level of fasting TG that are important in determination of postprandial TG responses.

The limitation of our study is that we followed postprandial TG for only 4 hours, although several studies particularly those using high fat load demonstrated a peak of plasma TG at 6 to 8 hours [4,20,21]. We trust that the 4-hour postprandial period is adequate for the study of postprandial TG responses in our study because the studies that used moderate amount of fat load (~30 g) demonstrate a peak plasma TG at 4 hours [11,23,25]. The other limitation is that we did not measure other lipid components or lipoprotein subclasses in our study. However, because VLDL1 TG has been shown to be the major component of postprandial TG in T2D subjects with normal or near-normal fasting TG level [20,21], it is likely that it is postprandial VLDL1 TG that is associated with hepatic fat in our study. Furthermore, in the postprandial state, not only VLDL1 TG but also VLDL1 cholesterol and VLDL1 apolipoprotein B have been shown to be elevated in T2D subjects; and all are determined by the HFC [21].

In conclusion, our study shows that fasting TG levels and the amount of hepatic fat are the independent factors that control postprandial TG responses in T2D patients who have normal or near-normal fasting TG. Because the increase of hepatic fat can be observed in nondiabetic subjects particularly those with metabolic syndrome, it is therefore plausible that isolated postprandial hypertriglyceridemia may be one of the metabolic abnormalities in metabolic syndrome and associated with the increased cardiovascular risk in these patients.

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