

Effect of hypertriglyceridemia in dyslipidemia-induced impaired glucose tolerance and sex differences in dietary features associated with hypertriglyceridemia among the Japanese population: The Gifu Diabetes Study

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Keywords

Hypertriglyceridemia, Impaired glucose tolerance, Sex differences

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ABSTRACT

Aims/Introduction: The mechanisms underlying hypertriglyceridemia-induced impaired glucose tolerance in Japanese individuals remain unclear. We aimed to evaluate the effect of hypertriglyceridemia on glucose metabolism in comparison with that of increased low-density lipoprotein or decreased high-density lipoprotein levels and to elucidate the sex differences in hypertriglyceridemia-related dietary intake among Japanese individuals.

Materials and Methods: We randomly selected 898 (384 men and 514 women) participants aged 40–78 years in the Gifu Diabetes Study; those taking medication for dyslipidemia or diabetes mellitus were excluded. Serum levels of glucose metabolism parameters and the food frequency were measured cross-sectionally. The glycated hemoglobin was measured again after 5 years.

Results: Glucose metabolism parameters and the percentage of individuals with impaired glucose tolerance were significantly higher in the high triglyceride group in men and women. Similar trends were observed in the low high-density lipoprotein group, but only in men. Meanwhile, only the homeostasis model assessment of insulin resistance was higher in the high low-density lipoprotein group. In non-obese men, the percentage of energy intake from alcohol per total daily energy intake was significantly greater in the high triglyceride group. In obese women, the total energy intake was significantly greater in the high triglyceride group. At the 5-year follow up, the risk of elevated glycated hemoglobin levels with hypertriglyceridemia was increased in men.

Conclusions: Hypertriglyceridemia is a stronger risk factor for impaired glucose tolerance than increased low-density lipoprotein or decreased high-density lipoprotein. For dietary habits, increased daily alcohol energy intake in non-obese men and increased total energy intake in obese women were associated with hypertriglyceridemia.

INTRODUCTION

Hypertriglyceridemia is a dominant lipid abnormality in insulin resistance by inducing elevated levels of free fatty acids, which plays an important role in insulin resistance¹. Furthermore, hypertriglyceridemia has been reported to play an important

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role in glucose metabolism among individuals with normal glucose tolerance^{2–5}. Previous studies have also shown that hypertriglyceridemia is an independent risk factor for diabetes mellitus^{6–8}. However, the mechanisms underlying hypertriglyceridemia-induced impaired glucose tolerance and the risk for diabetes mellitus in Japanese individuals remain unclear.

Thus, the present study aimed to investigate the effect of hypertriglyceridemia on impaired glucose tolerance in comparison with that of increased low-density lipoprotein (LDL) or decreased high-density lipoprotein (HDL) cholesterolemia. We also aimed to elucidate the features of dietary intake associated with hypertriglyceridemia by sex among the Japanese population. Toward this goal, glucose metabolism and food intake profiles were cross-sectionally assessed among a randomly selected Japanese population. Glycated hemoglobin (HbA1c) level was also followed prospectively after 5 years to evaluate the change in glucose metabolism.

METHODS

Study protocol and participants

The present cross-sectional study used data from the Gifu Diabetes Study carried out in Gifu City, Japan. The Gifu Diabetes Study has been previously described in detail by Nonoyama *et al.*⁹ Briefly, a total of 2,260 men and 3,010 women aged 40–78 years were randomly selected from the Gifu residential registry in March 2005 through the personal information protection committee of Gifu City Hall. Of them, we initially evaluated 1,100 participants (452 men and 648 women) who agreed to participate in the current study after receiving our request by postal mail. After excluding 202 individuals who were taking medication for diabetes mellitus or dyslipidemia ($n = 195$) and without available blood sample data ($n = 7$), 898 (384 men and 514 women) Japanese individuals were included in the final analysis.

Between November 2005 and May 2007, the participants' serum levels of fasting plasma glucose (FPG), HbA1c, total cholesterol, LDL and triglyceride (TG) levels were measured after an overnight fast. All measurements were carried out in any one of the 35 participating medical institutions selected by the participants. The HDL level was calculated using the formula, "total cholesterol – LDL – TG / 5", except in cases where the TG level was ≤ 400 mg/dL. All participants underwent a 75-g oral glucose tolerance test (OGTT), except those with either a confirmed diagnosis of diabetes mellitus or receiving medical treatment. To derive the total energy intake per day, the participants' food intake profile including carbohydrate, protein, fat and alcohol intake was determined using a 169-item semiquantitative food frequency questionnaire developed by Shimizu *et al.*¹⁰ The questionnaire evaluated the average consumption rate for each of the foods and dishes listed, and their usual serving size for each item in the past 1 year before the study. The intake of nutrients and portion sizes were estimated using the frequency of ingestion and the Japanese Standard Tables of Food Composition¹¹, respectively. The reliability and

validity of the food frequency questionnaire, and the detailed calculation of nutrient intake have been described previously¹⁰.

The HbA1c was also prospectively re-examined at 5 years after the initial examination between 2010 and 2012. A total of 615 participants (242 men and 373 women) underwent the re-examination at any one of the 35 medical institutions.

Evaluation of glucose metabolism for serum lipid level, TG, LDL and HDL.

To elucidate the relationship between glucose metabolism and the fasting TG level, participants were classified into two groups according to the serum TG level as the normal TG group (<150 mg/dL) and the high TG group (≥ 150 mg/dL). Similarly, to elucidate the relationship between glucose metabolism and serum LDL or HDL levels, the participants were classified into the normal and high LDL (<140 vs ≥ 140 mg/dL) and the normal and low HDL (≥ 40 vs <40 mg/dL) groups, respectively. The following reference values were used to compare the data: homeostasis model assessment of insulin resistance (HOMA-IR) <1.6 for the evaluation of insulin resistance; homeostasis model assessment of β -cell function (HOMA- β) ≥ 40 for the evaluation of insulin secretion¹²; and FPG <110 mg/dL, 2-h post-glucose (2hPG) <140 mg/dL and HbA1c $<5.9\%$ for the evaluation of blood glucose levels. Normal values for OGTT were set at FPG <110 mg/dL and 2hPG <140 mg/dL according to the World Health Organization criteria.

Relationship between nutritional intake and serum TG levels

Participants were assigned into four groups as follows: (i) body mass index (BMI) <25 kg/m² and normal TG; (ii) BMI <25 kg/m² and high TG; (iii) BMI ≥ 25 kg/m² with normal TG; and (iv) BMI ≥ 25 kg/m² with high TG. The daily energy intakes of carbohydrate, protein, fat and alcohol evaluated through the food frequency questionnaire were compared according to sex in each group.

Relationship between HbA1c change after 5 years and serum lipid levels

The risk of increased HbA1c level after 5 years was compared between each classified group according to the TG, LDL and HDL levels. To follow up the glucose metabolism change in the participants, we used the HbA1c level rather than the 75-g OGTT results based on the recommendation of an international expert committee^{13–15}. This was also decided to lower participants' discomfort. A 75-g OGTT procedure involves fasting for >12 h, undergoing blood sampling four times, and abstaining from eating and drinking until the final blood sample is collected. In contrast, HbA1c measurements require only one blood sampling at any time of the day. Such consideration will allow us to achieve a relatively good rate of participation even after 5 years.

Statistical analysis

The characteristics of the participants were analyzed using Student's *t*-tests for continuous data, and χ^2 -tests for categorical

data. Logistic regression analysis was used to compare the glucose tolerance for each lipid level, with adjustments for age; BMI; alcohol intake; and TG, LDL and HDL levels. To investigate the relationship between various daily nutrient intakes and the serum TG levels with/without obesity, *t*-tests were used to compare between two categories, whereas Dunnett's tests were used to compare between four categories. All statistical analyses were carried out using JMP® version 11 (SAS Institute Inc., Cary, NC, USA).

Ethical considerations

This study was approved by the Ethical Review Committee of the Graduate School of Medicine, Gifu University (approval number: 17–107), and was carried out in compliance with the Declaration of Helsinki and the ethical guidelines for clinical research by the Ministry of Health, Labor and Welfare in Japan. Informed consent was obtained from all the participants before their participation.

RESULTS

Participant characteristics and differences according to sex

The BMI, alcohol intake, and TG and HDL levels were significantly different according to sex. The percentages of participants with abnormal OGTT results were also significantly different between men ($n = 130$, 34.0%) and women ($n = 120$, 13.4%). The characteristics of all the participants are described in Table 1.

Participant characteristics at each lipid level

The characteristics of the participants according to the lipid level are shown in Table 2. Of the 384 men, 94 (24.5%) and

290 (75.5%) had high and normal TG levels, respectively. Meanwhile, of the 514 women, 61 (11.9%) and 453 (88.1%) had high and normal TG levels, respectively. In both sexes, the mean BMI level and the percentage of participants with obesity were significantly higher in the high TG, high LDL and the low HDL groups than those in the normal TG (men 24.9 vs 23.3 [$P < 0.0001$], 43.6% vs 25.9% [$P < 0.002$]; women 24.0 vs 22.0 [$P < 0.0001$], 34.4% vs 15.7% [$P = 0.001$]), normal LDL (men 24.3 vs 23.3 [$P < 0.001$], 36.7% vs 25.7% [$P < 0.02$]; women 23.0 vs 21.7 [$P < 0.0001$], 24.4% vs 13.3% [$P = 0.002$]) and normal HDL (men 25.3 vs 23.3 [$P < 0.0001$], 50.0% vs 25.0% [$P < 0.0001$]; women 24.1 vs 22.2 [$P = 0.003$], 42.9% vs 16.9% [$P = 0.006$]) groups.

In men, the estimated daily alcohol consumption was significantly greater in the high TG group than that in the normal TG group (38.4 g vs 25.8 g, $P = 0.01$). However, in contrast to the TG groups, the estimated daily alcohol consumption was significantly higher in the normal LDL and HDL groups than that in the high LDL and low HDL groups (LDL 34.9 g vs 20.3 g [$P < 0.0001$]; HDL 29.9 g vs 18.4 g [$P = 0.005$]).

Glucose metabolism parameters including HOMA-IR, HOMA- β , 2hPG, HbA1c and the percentage of participants with impaired glucose tolerance evaluated through 75-g OGTT were significantly higher in the high TG group than those in the normal TG group in both sexes. However, only HOMA-IR and HbA1c were significantly different between the high and normal LDL group in both sexes. Meanwhile, there were significant differences in HOMA-IR, HOMA- β , 2hPG and percentage of impaired glucose tolerance evaluated by 75-g OGTT between the normal and low HDL group only in men, but not in women.

Table 1 | Characteristics of all the participants

	Total $n = 898$	Men $n = 384$	Women $n = 514$	<i>P</i>
Age (years)	58.5 ± 9.9	59.7 ± 10.2	57.6 ± 9.6	0.001
BMI (kg/m ²)	22.9 ± 3.1	23.7 ± 3.1	22.2 ± 3.1	<0.0001
BMI ≥25 kg/m ² (%)	23.2	30.2	17.9	<0.0001
Alcohol intake (g ethanol/day)	15.6 ± 28.9	28.9 ± 37.7	5.7 ± 12.8	<0.0001
0 g (non-drinker) (<i>n</i>)	310	73	237	<0.0001
0.1–19.9 g (<i>n</i>)	368	139	229	
20.0–39.9 g (<i>n</i>)	99	69	30	
≥40 g (<i>n</i>)	121	103	18	
TG (mg/dL)	106.1 ± 60.5	121.8 ± 69.7	94.4 ± 49.6	<0.0001
LDL cholesterol (mg/dL)	132.2 ± 31.0	130.7 ± 31.0	133.4 ± 31.0	0.2
HDL cholesterol (mg/dL)	63.2 ± 19.5	54.4 ± 16.5	69.8 ± 19.1	<0.0001
OGTT				
IFG or IGT or DM (<i>n</i>)	250	130	120	<0.0001
IFG or IGT or DM (%)	27.8	34	23.4	

Values are presented as mean ± standard deviation for continuous variables, and number or percentages for categorical variables. The *P*-value was estimated using *t*-tests for continuous variables, and χ^2 -tests for categorical variables. BMI, body mass index; DM, diabetes; HDL, high-density lipoprotein. OGTT, oral glucose tolerance test; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; TG, triglyceride.

Table 2 | Differences in the characteristics at each lipid profile

	TG			LDL			HDL		
	Normal	High	P	Normal	High	P	Normal	Low	P
	(<150 mg/dL)	(≥150 mg/dL)		(<140 mg/dL)	(≥140 mg/dL)		(≥40 mg/dL)	(<40 mg/dL)	
Men									
n	290	94		226	158		304	76	
Age (years)	60.0 ± 10.4	59.0 ± 9.7	0.41	60.3 ± 10.2	58.9 ± 10.2	0.18	59.8 ± 10.2	59.9 ± 10.3	0.9
BMI (kg/m ²)	23.3 ± 2.9	24.9 ± 3.2	<0.0001	23.3 ± 2.9	24.3 ± 3.1	0.001	23.3 ± 3.0	25.3 ± 2.9	<0.0001
BMI ≥25 kg/m ² (%)	25.9	43.6	0.002	25.7	36.7	0.02	25.0	50.0	<0.0001
Alcohol intake (g ethanol/day)	25.8 ± 34.5	38.4 ± 45.2	0.01	34.9 ± 42.0	20.3 ± 28.7	<0.0001	29.9 ± 35.3	18.4 ± 30.2	0.005
0 g (non-drinker) (n)	62	11	0.06	35	38	0.001	51	22	0.006
0.1–19.9 g (n)	108	31		71	68		107	32	
20.0–39.9 g (n)	50	19		46	23		57	12	
≥40 g (n)	70	33		74	29		89	10	
TG (mg/dL)	92.7 ± 27.9	211.5 ± 82.4		120.2 ± 81.1	124.2 ± 48.9	0.55	108.0 ± 51.8	155.7 ± 55.8	<0.0001
LDL cholesterol (mg/dL)	130.5 ± 31.6	131.4 ± 29.3	0.81	110.3 ± 19.9	159.8 ± 18.3		130.6 ± 31.6	133.1 ± 27.6	0.53
HDL cholesterol (mg/dL)	57.4 ± 16.2	44.7 ± 13.5	<0.0001	56.2 ± 17.7	51.9 ± 14.2	0.009	59.5 ± 14.3	34.1 ± 4.5	0.02
HOMA-IR	1.42 ± 1.34	2.04 ± 1.44	0.0002	1.44 ± 1.33	1.75 ± 1.46	0.03	1.48 ± 1.42	1.91 ± 1.22	0.003
HOMA-β	74.9 ± 70.6	92.7 ± 67.0	0.03	76.6 ± 79.4	83.2 ± 54.1	0.33	73.3 ± 68.2	96.2 ± 56.4	0.055
FPG (mg/dL)	94.1 ± 13.5	99.5 ± 17.2	0.007	95.0 ± 14.9	96.1 ± 14.3	0.45	95.3 ± 14.3	96.4 ± 16.1	0.008
2hPG (mg/dL)	128.2 ± 49.1	150.5 ± 60.8	0.002	134.7 ± 56.4	131.8 ± 47.7	0.58	129.3 ± 51.3	147.3 ± 55.9	0.11
HbA1c (%)	5.71 ± 0.50	5.93 ± 0.62	0.002	5.70 ± 0.53	5.85 ± 0.54	0.008	5.74 ± 0.51	5.86 ± 0.61	
OGTT									
Normal (n)	206	46	0.0003	143	109	0.58	211	40	0.01
IGT (n)	63	26		57	32		63	24	
IFG (n)	1	3		2	2		4	0	
DM (n)	20	17		23	14		24	12	
IFG or IGT or DM (%)	29.0	50.0	0.0004	36.4	30.6	0.28	30.1	47.4	0.006
Women									
n	453	61		301	213		493	21	
Age (years)	57.2 ± 9.7	60.0 ± 8.4	0.04	56.5 ± 10.6	59.1 ± 7.9	0.001	57.5 ± 9.6	58.3 ± 9.8	0.71
BMI (kg/m ²)	22.0 ± 3.0	24.0 ± 2.9	<0.0001	21.7 ± 2.9	23.0 ± 3.1	<0.0001	22.2 ± 3.0	24.1 ± 3.0	0.003
BMI ≥25 kg/m ² (%)	15.7	34.4	0.001	13.3	24.4	0.002	16.9	42.9	0.006
Alcohol intake (g ethanol/day)	5.9 ± 13.1	3.6 ± 10.5	0.12	6.6 ± 14.2	4.4 ± 10.5	0.04	5.7 ± 13.0	4.0 ± 7.3	0.3
0 g (non-drinker) (n)	211	26	0.03	134	103	0.16	228	9	0.6
0.1–19.9 g (n)	196	33		132	97		218	11	
20.0–39.9 g (n)	30	0		21	9		29	1	
≥40 g (n)	16	2		14	4		18	0	
TG (mg/dL)	80.3 ± 28.3	198.7 ± 48.9		83.5 ± 47.6	109.8 ± 48.3	<0.0001	92.1 ± 47.5	148.2 ± 65.2	0.0008
LDL cholesterol (mg/dL)	131.6 ± 30.7	146.6 ± 30.0	0.0004	112.7 ± 18.9	162.5 ± 18.8		133.3 ± 31.0	136.2 ± 30.5	0.67
HDL cholesterol (mg/dL)	71.9 ± 18.5	53.9 ± 15.6	<0.0001	72.2 ± 20.3	66.3 ± 16.6	0.0003	71.2 ± 18.0	34.8 ± 2.9	

Table -0002 (Continued)

	TG		LDL		HDL		P
	Normal (<150 mg/dL)	High (≥150 mg/dL)	Normal (<140 mg/dL)	High (≥140 mg/dL)	Normal (≥40 mg/dL)	Low (<40 mg/dL)	
HOMA-IR	1.26 ± 1.02	1.84 ± 1.58	1.25 ± 1.03	1.44 ± 1.21	1.29 ± 1.00	2.36 ± 2.47	0.06
HOMA-β	76.7 ± 48.9	91.4 ± 43.7	78.7 ± 48.1	78.1 ± 49.2	77.6 ± 48.4	97.9 ± 47.9	0.06
FPG (mg/dL)	90.9 ± 17.6	95.6 ± 19.1	89.9 ± 15.3	93.8 ± 20.6	91.3 ± 17.7	96.0 ± 18.8	0.23
2hPG (mg/dL)	113.8 ± 35.3	137.5 ± 48.5	114.1 ± 35.5	120.1 ± 40.7	115.8 ± 36.8	136.3 ± 55.0	0.11
HbA1c (%)	5.71 ± 0.60	5.98 ± 0.95	5.67 ± 0.65	5.84 ± 0.66	5.74 ± 0.65	5.89 ± 0.84	0.31
OGTT							
Normal (n)	356	36	238	154	379	13	0.34
IGT (n)	75	16	47	44	85	6	
IFG (n)	6	0	4	2	6	0	
DM (n)	14	9	10	13	21	2	
IFG or IGT or DM (%)	21.1	41.0	20.4	27.7	22.8	38.1	0.12

Values are presented as mean ± standard deviation for continuous variables and number or percentages for categorical variables. The P-value was estimated using t-tests for continuous variables and chi-square tests for categorical variables. 2hPG, 2-h post-glucose; BMI, body mass index; DM, diabetes; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment-insulin resistance; HOMA-β, homeostasis model assessment-beta cell function; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; TG, triglyceride.

Lipid profile and the risk for impaired parameters of glucose metabolism

Logistic regression analysis of the effect of TG levels on the risk of impaired parameters of glucose metabolism was carried out, after adjusting for age, BMI, alcohol intake, LDL and HDL (Figure 1a). The same analysis was also carried out for LDL (Figure 1b) and HDL (Figure 1c) levels.

Among the men in the high TG group, the odds ratios (ORs) were significantly greater for those with HOMA-IR ≥1.6 (OR 2.85, 95% confidence interval [CI] 1.56–5.24; P = 0.0006), FPG ≥110 mg/dL (OR 3.50, 95% CI 1.60–7.66; P = 0.002), HbA1c ≥5.9% (OR 2.55, 95% CI 1.46–4.49; P = 0.001) and abnormal OGTT values (OR 1.85, 95% CI 1.06–3.21; P = 0.03). Among women in the high TG group, the ORs were greater for those with 2hPG ≥140 mg/dL (OR 2.51, 95% CI 1.15–3.72; P = 0.02), HbA1c ≥5.9% (OR 2.07, 95% CI 1.15–3.72; P = 0.02) and abnormal OGTT values (OR 1.87, 95% CI 1.01–3.39; P = 0.045; Figure 1a).

In the high LDL group, the ORs were greater for those with HbA1c ≥5.9% (OR 2.30, 95% CI 1.41–3.77; P = 0.001) among men and for those with HOMA-β <40 (OR 2.04, 95% CI 1.18–3.55; P = 0.01), and HbA1c ≥ 5.9% (OR 1.53, 95% CI 1.02–2.31; P = 0.04) among women (Figure 1b). The glucose tolerance values did not significantly differ between the low and normal HDL groups (Figure 1c).

Nutritional intake and TG levels

The relationship between serum TG levels and various daily nutrient intakes was assessed in men and women with/without obesity. Among those without obesity, there was no significant difference in total energy intake between the high and normal TG groups in both sexes. Meanwhile, the percentage of alcohol intake per total energy intake was significantly greater in the high TG group than in the normal TG group among non-obese men (P < 0.05; Figure 2a). In obese women, total energy intake was significantly greater in the high TG group than that in the normal TG group (P < 0.05; Figure 2b).

Follow-up study

Of the 898 participants, the HbA1c levels were re-examined for 496 individuals (204 men and 292 women). The prospective change in the HbA1c level and its relationship with the lipid levels was followed up for 5 years; increased risks in the HbA1c levels induced by hypertriglyceridemia and hyper-LDL/lower-HDL cholesterolemia (Figure 3) were also assessed. The results of the 5-year follow up showed no significant differences in the HbA1c level for each of the lipid profile levels in both sexes. However, the 5-year ORs of increased HbA1c level were greater among men with hypertriglyceridemia than in those with hyper-LDL or lower HDL cholesterolemia.

DISCUSSION

The features and risks of hypertriglyceridemia-induced impaired glucose tolerance in Japanese individuals remain

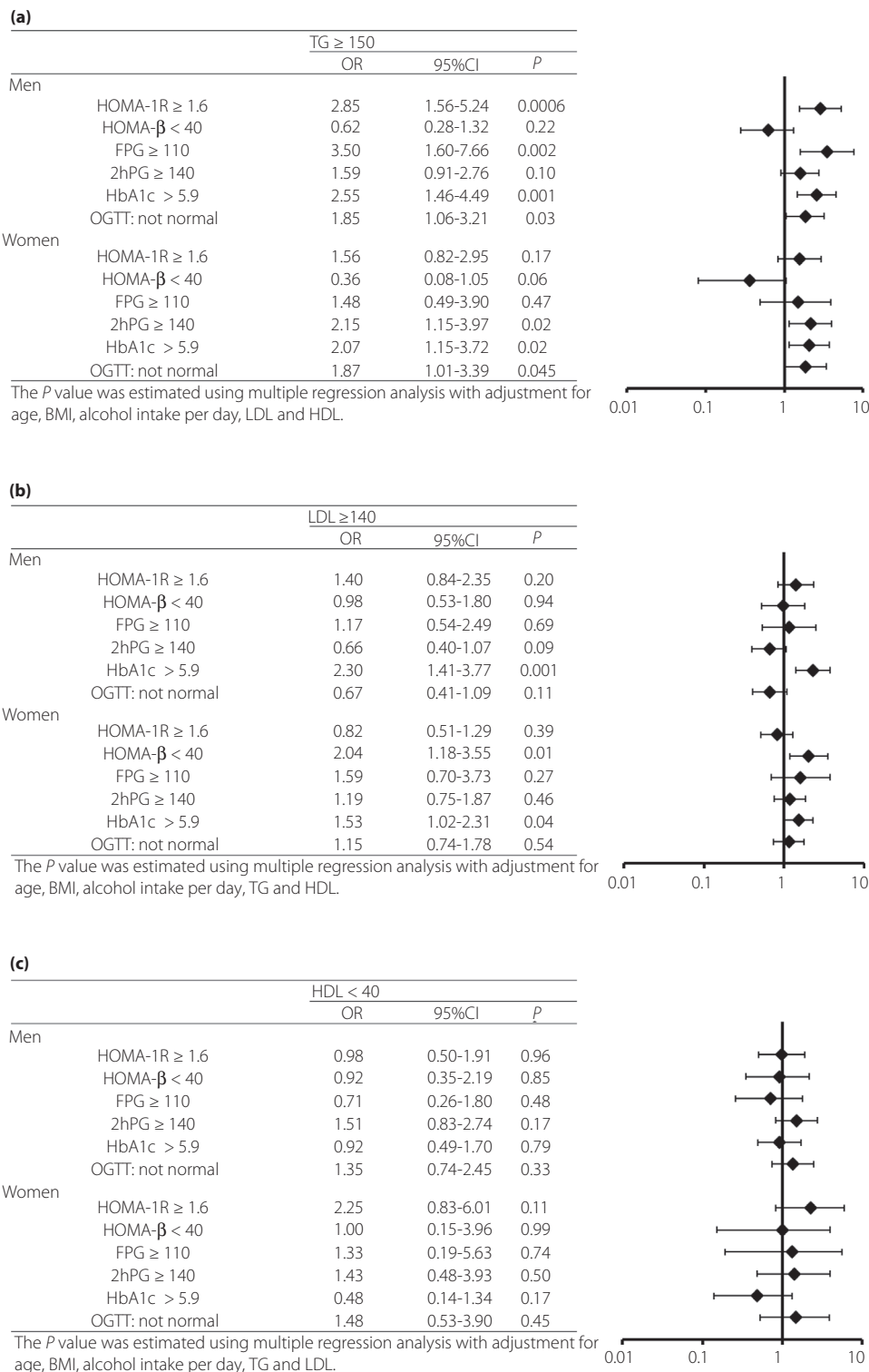


Figure 1 | Risks of impaired glucose tolerance according to the lipid profile. Adjusted odds ratios for impaired glucose tolerance with (a) hypertriglyceridemia, (b) increased serum low-density lipoprotein (LDL) cholesterol level and (c) decreased serum high-density lipoprotein (HDL) cholesterol level. The adjusted odds ratios of impaired glucose metabolism parameters (homeostasis model assessment of insulin resistance [HOMA-IR], homeostasis model assessment of β -cell function [HOMA- β], fasting plasma glucose [FPG], 2-h plasma glucose [2hPG], glycated hemoglobin [HbA1c], and oral glucose tolerance test [OGTT] results) were calculated using logistic regression analysis (adjusted for age, body mass index [BMI], and alcohol) for triglyceride (TG), LDL and HDL levels. 95% CI, 95% confidence interval; OR, odds ratio.

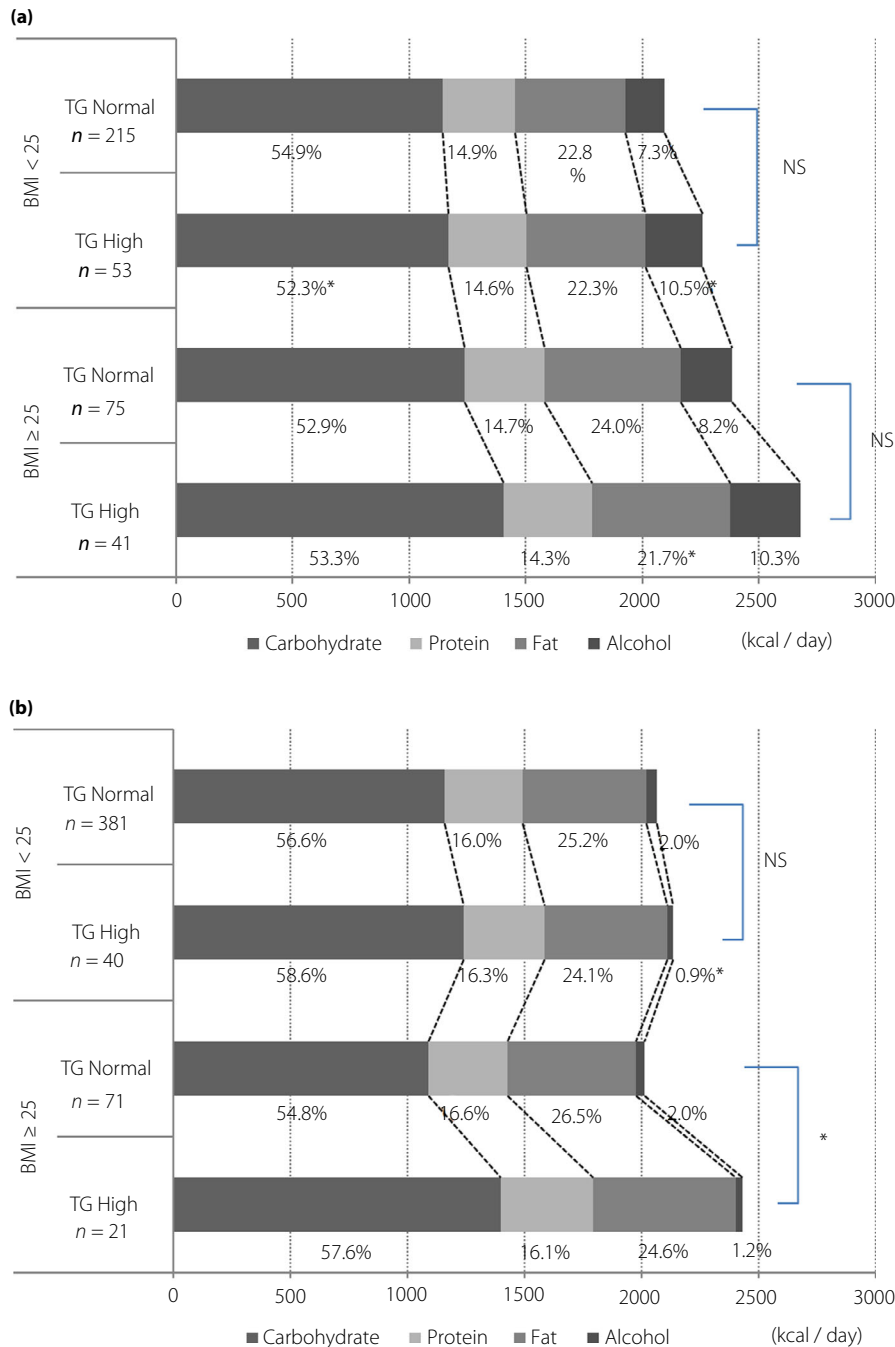


Figure 2 | Nutritional intake and serum triglyceride (TG; normal, serum TG level <150 mg/dL; high, serum TG level ≥150 mg/dL) levels with or without obesity in (a) men and (b) women. Total energy intake per day (kcal/day) is shown with bar charts, and the percentage intake of each nutrient (carbohydrate, protein, fat and alcohol per daily total energy intake) is shown as a number (%) in the graph. Student's *t*-test was used to compare two categories, whereas Dunnett's test was used to compare four categories. **P* < 0.05 by Dunnett's tests. BMI, body mass index; NS, not significant.

unclear. Three new findings were obtained in the present study. First, hypertriglyceridemia was associated with impaired glucose tolerance through increased insulin resistance and secretion, and it might exert a stronger effect than hyper-LDL or lower HDL cholesterolemia. Second, the risk for HbA1c

elevation after 5 years was higher in those with hypertriglyceridemia than in those with hyper-LDL or lower HDL cholesterolemia, but only in men and not in women. Third, with respect to nutritional features in the high TG group, the percentage of alcohol intake per total daily energy intake was

	OR	95%CI	P
Men			
TG \geq 150	1.85	0.73-4.51	0.19
LDL-cho \geq 140	0.74	0.34-1.57	0.43
HDL-cho $<$ 40	0.84	0.28-2.32	0.75
Women			
TG \geq 150	0.74	0.26-1.86	0.53
LDL-cho \geq 140	0.67	0.38-1.17	0.16
HDL-cho $<$ 40	0.82	0.17-2.92	0.77

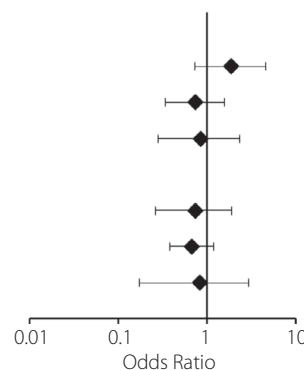


Figure 3 | Risks of glycated hemoglobin elevation after 5 years at each lipid profile. Adjusted odds ratios (OR) of increase in glycated hemoglobin after 5 years were calculated using logistic regression analysis (adjusted for age, body mass index and alcohol intake) for triglyceride (TG), low-density lipoprotein cholesterol (LDL-cho) and high-density lipoprotein cholesterol (HDL-cho) levels. 95% CI, 95% confidence interval.

greater in non-obese men, and total energy intake was greater in obese women.

Using a cross-sectional design, we showed that hypertriglyceridemia, rather than hyper-LDL/lower-HDL cholesterolemia, is significantly correlated with impaired glucose metabolism in the Japanese population. Particularly, HOMA-IR and HOMA- β were significantly increased in the high TG group compared with those in the normal TG group among both sexes. Although similar differences were seen between the high and normal LDL groups, and the low and normal HDL groups, these were very mild. Logistic regression analysis showed that the risk for increased HOMA-IR was significantly increased in men with hypertriglyceridemia. These results indicate that hypertriglyceridemia has the strongest effect on dyslipidemia-induced impaired glucose tolerance by increasing insulin resistance and secretion.

The present findings were consistent with those of previous studies from Italy and Mexico that showed that hypertriglyceridemia was associated with increased insulin resistance and secretion, even in individuals with normal glucose tolerance²⁻⁵. Moro *et al.*² showed a significant correlation between the plasma TG level and HOMA-IR value in participants with normal glucose tolerance. Bardini *et al.*³ also showed that hypertriglyceridemia increased insulin resistance by overstimulating β -cell function in individuals with normal glucose tolerance, but enlarged waist circumference. Furthermore, mildly elevated TG levels were found to be associated with increased HOMA-IR values, even in healthy children and adolescents with normal weight, in Mexico⁴. The present cross-sectional study clearly showed that hypertriglyceridemia induced impaired glucose metabolism by increasing insulin resistance and secretion among the Japanese.

With respect to insulin secretion, hypertriglyceridemia has been reported to be associated with increased insulin secretion and increased β -cell response in Italians² and Mexicans⁴. Conversely, hypertriglyceridemia-induced reduction in β -cell function was observed among patients with impaired glucose

tolerance in Italy³ and China.¹⁶ Ma *et al.*¹⁷ showed that TG level was an independent risk factor for β -cell dysfunction among Chinese patients with newly diagnosed type 2 diabetes. In the present study, we found that hypertriglyceridemia was associated with increased insulin secretion among both Japanese men and women, consistent with the report from Mexico, but in contrast to those from Italy and China. These results suggest that there are sex- and ethnicity-related differences in the mechanisms underlying modifications to insulin secretion, as proposed by Lin *et al.*¹⁸.

The results of the 5-year follow-up prospective evaluation showed that hypertriglyceridemia might increase HbA1c levels in men. In Mexico, Guerrero-Romero *et al.*⁶ showed that hypertriglyceridemia was an independent risk factor for the development of metabolic glucose disorders in young and middle-aged men and women in a 15-year follow-up study. In India, Ram *et al.*⁷ showed that hypertriglyceridemia and an enlarged waist circumference were strongly associated with the incidence of diabetes due to impaired glucose tolerance in men. In Japan, Kametani *et al.*⁸ followed-up 7,222 Japanese individuals (3,306 men and 3,916 women) with normoglycemia for 9 years, and confirmed the contribution of hypertriglyceridemia to the development of impaired fasting glucose and diabetes. However, they measured only fasting glucose level, and diagnosed impaired fasting glucose according to 110–125 mg/dL or diabetes mellitus as \geq 126 mg/dL following the 1997 American Diabetes Association criteria.

Despite the similarities in the present findings, to our best knowledge, this is the first study to show a hypertriglyceridemia-induced risk of HbA1c elevation among a randomly selected population of Japanese men through a prospective follow-up study. Compared with LDL or HDL, we found that high TG is the strongest risk factor for impaired glucose tolerance. We suspect that hypertriglyceridemia might have the most powerful effect on dyslipidemia-induced impaired glucose tolerance; however, this has not been thoroughly investigated previously. Recently, Sone *et al.*¹⁹ showed that serum TG level

is a leading predictor of coronary heart disease comparable to LDL in Japanese patients with type 2 diabetes, but not in diabetes patients in Western countries. Based on these findings, the present results of TG level being the most important factor for modifying insulin resistance and secretion in the Japanese population are reasonable. In the Japanese, slight impairments in insulin secretion occur even in those with normal glucose tolerance, and insulin secretion and sensitivity decrease in those with glucose intolerance.²⁰ Thus, hypertriglyceridemia-induced insulin resistance and insulin overproduction might strongly affect the progression of impaired glucose tolerance in Japanese.

From the cross-sectional survey, we found differences in food habits according to sex and obesity status among those with hypertriglyceridemia. Although the high TG group without obesity had a significant increase in alcohol intake percentage per daily total energy among men, the high TG group with obesity had a significant increase in total daily energy intake among women. Therefore, appropriate restriction of alcohol and energy intake should be recommended for non-obese men and women, respectively. Koppes *et al.*²¹ found a reduced risk of type 2 diabetes with appropriate volume of alcohol consumption, indicating the reliability of the present findings in non-obese men.

The present study had three limitations. The first is the number of participants; a sample size of 1,100 might not allow us to draw firm conclusions. The second is that the results might not generalize well to the entire Japanese population, as participants were randomly selected from the residential registry of only Gifu City, which might not be representative of all of Japan. However, we selected Gifu City as it is considered to be an appropriate model for a Japanese population study. Gifu City is located almost precisely in the center of Japan, and the population size/density/generation balance and economic size of Gifu City are reasonably comparable to average levels in Japan. The third is that our research design was not intended to show the mechanisms of hypertriglyceridemia-induced impaired glucose tolerance. Therefore, further research is required to identify the key factors in the development of insulin resistance in those with high TG. For example, a significant correlation between plasma adiponectin levels and insulin resistance related to the TG level was observed in Japanese individuals.²²

In conclusion, hypertriglyceridemia has a negative effect on glucose metabolism by increasing insulin resistance and secretion. Furthermore, such an effect was stronger than hyper-LDL or lower HDL cholesterolemia in the Japanese with dyslipidemia-induced impaired glucose tolerance. For dietary habits, increased daily alcohol energy intake among non-obese men and increased total energy intake among obese women were associated with hypertriglyceridemia.

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DISCLOSURE

The authors declare no conflict of interest.

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APPENDIX

The Gifu Diabetes Study Group (including current and former members with their affiliations at the time of their participation in this study) includes investigators Mayumi Yamamoto, Shino Oba, Yukio Horikawa, Chisato Nagata, Jun Takeda (Gifu University); Kayoko Adachi (Inaba Clinic); Kenzo Chimori; Yoshikazu Morimoto, Yasuyoshi Kimata (Yamada Medical Clinic); Hideo Hayashi (Hayashi Clinic); Maho Ishii (Sugiura Clinic); Midori Izai (Yasue Hospital); Keita Kamikubo (Kamikubo Clinic); Yoshinori Kanoh (Kanoh Internal Medicine Rheumatism and Diabetes Clinic); Toshihiro Kojima (Gifu Central Hospital); Takashi Komaki (Komaki Clinic); Joji Kosaka (Kosaka Clinic); Hiroyuki Maekawa (Sawada Hospital); Masanori Murayama; Eiji Suzuki; Kouji Yoshino (Gifu Prefectural General Medical Center); Masafumi Matsuda (Matsuda Clinic); Ikuo Matsui (Matsui Clinic); Shigehiko Ozeki (Ozeki Clinic); Shigeki Sakata (Joto Clinic); Hiroshi Sarui; Noriyuki Takeda (Murakami Memorial Hospital); Miyuki Sugimoto (Yamauchi Hospital); Rieko Totani (Totani Clinic); Hiroaki Wada (Wada Internal Medicine Clinic); Yuji Wada (Wada Clinic); Michie Yokoyama (Midori Hospital); Mitsuyo Araki (Araki Clinic); Eichi Goshima (Goshima Clinic); Hisashi Daido; Kotaro Nagai (Hashima City Hospital); Katsumasa Fushimi (Fushimi Clinic); Masahisa Kitada (Kitada Clinic); Makoto Hayashi (Matsunami General Hospital); Tatsuyuki Imai (Kaizu Medical Association Hospital); Noriko Kojima (Kojima Clinic); Mayumi Sato (Sato Clinic); Hiroshi Murase; Toshihiko Nagashima; Nobuyasu Noritake (Daiyukai General Hospital); Yoshiaki Noda (Noda Clinic); and Kazuhiro Ohmae (Oze Clinic).