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ORIGINAL ARTICLE

Casual serum triglyceride as a predictor of premature type 2 diabetes mellitus: an 8-year cohort study of middle-aged Japanese workers

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Abstract
Background The utility of casual serum triglyceride (TG) as a predictor of type 2 diabetes mellitus (DM) is unclear, especially during the most productive years.
Methods Participants were 3271 workers (913 men and 2358 women, age 20–57) without DM at baseline. They underwent consecutive annual medical check-ups for 8 years. The association between newly diagnosed DM and casual serum TG level was determined by classifying the participants into 4 groups according to casual serum TG level at baseline: below 50 mg/dL (group A), 50–100 mg/dL (group B), 100–150 mg/dL (group C), and ≥150 mg/dL (group D). The effects of casual serum TG level in combination with sex, obesity, or serum glucose level on newly diagnosed DM were also evaluated.
Results A total of 222 newly diagnosed type 2 DM cases with a mean age of 50 years old were observed during the follow-up period, i.e., 10/406 in group A, 66/1534 in group B, 58/712 in group C, and 88/619 in group D. Compared with group A, the odds ratio (ORs) for newly diagnosed DM (after adjusting for DM-associated factors) was found to increase with casual serum TG level: 1.38 (group B), 1.79 (group C), and 2.36 (group D). Moreover, the OR for newly diagnosed DM was higher in participants with high casual serum TG levels who were also male (OR 2.46), obese (OR 4.18), or had a high serum glucose level (OR 6.96) than in the reference group.
Conclusions Serum TG level ≥150 mg/dL when fasting or nonfasting is a significant predictor of type 2 diabetes in middle-aged Japanese workers.

Keywords Casual serum triglyceride · Type 2 diabetes · Japanese · Cohorts

Introduction

Insulin resistance is a predisposing factor for metabolic syndrome, leading to the development of type 2 diabetes and cardio- and cerebrovascular diseases over a long period [1–4]. Detecting individuals with insulin resistance and modifying their lifestyle accordingly from their early years are very important aims when attempting to prevent type 2 diabetes. Various methods of evaluating individual insulin resistance, such as the homeostatic model assessment of insulin resistance (HOMA-IR), have been developed [5–8]; however, these are expensive and frustratingly complicated. Therefore, a simple alternative method of screening for insulin resistance or monitoring it in medical check-ups is desired [9].

High levels of fasting serum triglycerides (TGs) have been reported to be a marker of insulin resistance [10, 11] and a predictor of type 2 diabetes [12–19]. Ectopic fat deposition in visceral adipose tissues is considered to play an important role in the pathogenesis of insulin resistance

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[20–23]: fatty acid synthesized in visceral adipose tissues is delivered to the liver and promotes the synthesis of very low density lipoprotein (VLDL), which induces hypertriglyceridemia, leading to insulin resistance [20, 24, 25]. Thus, the association between the serum level of TG and the development of type 2 diabetes has been investigated.

Compared with fasting serum TG levels, less attention has been paid to non-fasting serum TG levels, because fasting overnight is recommended before attempting to obtain a lipid profile [26]. A few studies have, however, demonstrated that non-fasting serum TG levels predict the development of type 2 diabetes [13, 27]. Also, in some settings it is unrealistic to require all participants to fast, especially those who visit in the afternoon. Furthermore, in Japan, general screening for CVD risk factors is performed under non-fasting conditions to improve participation rates.

We therefore focused on assessing whether the casual serum TG level, regardless of the content of the meal consumed before the lipid profile is obtained and the time since that last meal, could be used to predict the development of premature diabetes mellitus (DM) in a cohort study of relatively young Japanese workers.

Methods

The cohort consisted of 6045 individuals who underwent medical examination in 2004. These individuals were aged 20–57 years and worked in a retail company in Japan. Among them, 5833 did not have DM at baseline, and 9 of those were pregnant women who were therefore excluded from the study. Of the remaining 5824 subjects, 3271 (2358 females and 913 males; mean age 45.4 years) who underwent a medical examination every year for 8 years were eligible for analysis in the present study. This study was approved by the ethics committee of the Shiga University of Medical Science (24-18).

All of the medical examinations performed included a questionnaire, physical examination, and laboratory tests. Among the results of the annual examinations, those for age, sex, medical history, alcohol intake, smoking history, blood pressure, height, weight, casual serum glucose, total cholesterol (TC), high density lipoprotein cholesterol (HDLC), and TG were used in the present study. Body mass index (BMI) was calculated from height and weight. Obesity was defined as a BMI level of 25.0 kg/m^2 or more. Optimal blood pressure was defined as systolic blood pressure (SBP) <120 mmHg and diastolic blood pressure (DBP) <80 mmHg [28].

Following the classification of the Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus, the participant was considered to have DM if the fasting glucose level was ≥126 mg/dL (7.0 mmol/L); the casual glucose level was ≥200 mg/dL (11.1 mmol/L); or they used antidiabetic agents. Participants with a fasting serum glucose level of <110 mg/dL (6.1 mmol/L) or a casual serum glucose level of <140 mg/dL (7.8 mmol/L) were classified as "normal type". Those who did not have DM and were not normal type were classified as "borderline type". The first development of DM during follow-up was used as the outcome variable. The date of the examination when a new case of DM was identified was considered the date of the first development of DM. The new case of DM was also defined according to the classification of the Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus, or based on the use of antidiabetic agents.

All subjects were divided into 4 groups according to the level of serum TG at baseline (in 2004): <50 mg/dL (group A), 50–100 mg/dL (group B), 100–150 mg/dL (group C), and ≥150 mg/dL (group D). The risk characteristics of each group at the baseline survey were described as means and standard deviations (SDs) for continuous variables and proportions for categorical variables. The odds ratio (OR) of each group for the development of DM during the 8-year monitoring period in comparison with group A was calculated using a multivariate logistic regression model after adjusting for age, sex, blood pressure, casual serum glucose level, total cholesterol, HDL cholesterol, smoking, and alcohol intake. Furthermore, the association between casual serum TG level and the development of DM was evaluated via combinations of casual serum TG level and sex, BMI, and casual serum glucose level, using 150 mg/dL of serum TG as a cutoff point [26, 29]. All statistical analyses were performed with SPSS version 22.0 for Windows (SPSS Inc.). All significance tests were two-tailed, and $p < 0.05$ was considered to indicate significance in all analyses.

Results

Groups A, B, C, and D included 406, 1534, 712, and 619 subjects, respectively (total: 3271 subjects). The baseline characteristics of these 4 groups are presented in Table 1. There was no significant difference in mean age between group A (44.4 ± 6.7 years) and group D (45.0 ± 6.8 years); the male to female ratio was higher in group D than in group A; and the number of typical risk factors for DM in group D was greater than those in the other groups. During the observation period, 222 subjects were newly diagnosed with DM (137 upon fasting and 85 postprandially): 2.5 % ($n = 10$) in group A, 4.3 % ($n = 66$) in group B, 8.1 % ($n = 58$) in group C, and 14.2 % ($n = 88$) in group D. The mean age at which DM developed was 49.8 ± 7.4 years, and the mean time taken to develop DM

Table 1 Baseline characteristics of the participants in groups A–D (i.e., participants were categorized according to their levels of casual serum triglyceride)

	TG < 50	100 > TG ≥ 50	150 > TG ≥ 100	TG ≥ 150	Total
Subjects	406	1535	712	620	3271
Number of males	32 (7.9 %)	280 (18.3 %)	244 (34.3 %)	357 (57.7 %)	913 (27.9 %)
Current smokers	91 (22.4 %)	415 (27.0 %)	223 (31.3 %)	251 (40.5 %)	980 (29.9 %)
Alcohol intake	254 (62.6 %)	899 (58.6 %)	424 (59.6 %)	413 (66.7 %)	1990 (60.8 %)
Age (years)	44.4 ± 6.7	45.6 ± 6.4*	45.9 ± 6.4*	45.0 ± 6.8	45.4 ± 6.5
SBP (mmHg)	120.8 ± 17.9	122.4 ± 15.3	126.0 ± 16.0*	130.9 ± 15.7*	124.6 ± 16.2
DBP (mmHg)	72.4 ± 12.0	73.5 ± 11.2	76.6 ± 11.2*	79.5 ± 11.2*	75.2 ± 11.6
Glucose (mg/dL)	93.5 ± 12.7	95.2 ± 14.7	99.1 ± 18.7*	101.4 ± 18.3*	97.0 ± 16.4
T-chol (mg/dL)	195.6 ± 31.1	204.7 ± 31.8*	213.5 ± 34.2*	222.4 ± 36.8*	208.8 ± 34.3
HDL chol (mg/dL)	79.2 ± 15.6	71.9 ± 15.5*	62.1 ± 15.0*	51.4 ± 12.2*	66.8 ± 17.4
BMI	21.3 ± 3.3	21.9 ± 3.5*	23.5 ± 3.8*	24.9 ± 4.0*	22.8 ± 3.9
Sampling performed while fasting	123 (30.3 %)	326 (21.3 %)	115 (16.2 %)	60 (9.7 %)	624 (19.1 %)

TG casual serum triglyceride level

* $p < 0.05$ when mean value was compared with that of the TG <50 group using Dunnett's *C* test

Table 2 Association of serum triglyceride level with the development of diabetes mellitus

	TG < 50	100 > TG ≥ 50	150 > TG ≥ 100	TG ≥ 150
Development of DM	10	66	58	88
Odds ratio (95 % CI)				
Model1		1.64 (0.83–3.23)	2.92 (1.46–5.85)	4.81 (2.41–9.59)
Model2		1.42 (0.71–2.81)	1.95 (0.96–3.95)	2.85 (1.41–5.77)
Model3		1.38 (0.69–2.74)	1.82 (0.89–3.69)	2.36 (1.15–4.84)

Model 1: adjusted for age and sex

Model 2: as for model 1 but adjusted for blood pressure (<120/80, ≥120/80 mmHg), casual serum glucose (<140, ≥140 mg/dL), BMI (<25 or ≥25), currently smoking, and currently drinking alcohol (more often than sometimes, or not) too

Model 3: as for model 2 but adjusted for total cholesterol (<220, ≥220 mg/dL) and HDL-cholesterol (>40, ≤40 mg/dL) too

after the baseline survey was 4.5 ± 2.1 years. There was no significant difference in the OR for developing DM between the anterior half and the posterior half of the observation period.

The OR for the development of DM increased as the level of casual serum TG at baseline increased; in comparison with group A, the OR after adjusting for age and sex (model 1) was 1.64 (0.83–3.23) in group B, 2.92 (1.46–5.85) in group C, and 4.81 (2.41–9.59) in group D (Table 2). A similar tendency was observed after adjusting for age, sex, blood pressure (<120/80 or ≥120/80 mmHg), casual serum glucose (<140 or ≥140 mg/dL), BMI (<25 or ≥25), currently smoking, and currently drinking alcohol (model 2), and after adjusting for all of these variables plus TC (<220 or ≥220 mg/dL) and HDLC (≥40 or <40 mg/dL) too (model 3).

Table 3 shows the multivariate adjusted ORs for the development of DM for different combinations of casual serum TG level and sex, BMI, or casual serum glucose level. For all three combinations, the ORs for developing DM were higher than for the corresponding reference group (female/lower TG group, lower BMI/lower TG group, and normal casual serum glucose level/lower TG group); a higher casual serum TG level was strongly associated with a higher OR for the development of DM. Even in relatively low-risk groups such as those with female participants, lower BMIs, or normal casual serum glucose levels, a high casual serum TG level was shown to be a risk for the development of DM (fully adjusted ORs: 1.55, 1.84 and 1.57, respectively).

Discussion

This is the first cohort study to clarify the utility of casual serum TG level as a predictor of premature DM, for which the mean age of incidence is about 50 years old. The present study demonstrated that higher casual serum TG

Table 3 Associations of serum triglyceride level in combination with sex, BMI, or casual serum glucose level with the development of diabetes mellitus

	Female and TG <150	Female and TG ≥150	Male and TG <150	Male and TG ≥150
Development of DM	88/2096	27/262	46/556	61/357
Model 1[a]		2.58 (1.64–4.06)	2.14 (1.46–3.14)	4.87 (3.40–6.95)
Model 2[c]		1.78 (1.11–2.86)	1.66 (1.09–2.52)	2.95 (1.97–4.44)
Model 3		1.55 (0.96–2.52)	1.64 (1.07–2.50)	2.46 (1.60–3.78)
	BMI <25 and TG <150	BMI <25 and TG ≥150	BMI ≥25 and TG <150	BMI ≥25 and TG ≥150
Development of DM	73/2150	33/348	61/502	55/271
Model 1[b]		2.36 (1.51–3.68)	3.84 (2.68–5.50)	5.73 (3.84–8.55)
Model 2[d]		2.15 (1.37–3.39)	3.40 (2.34–4.94)	5.15 (3.40–7.79)
Model 3		1.84 (1.16–2.95)	3.23 (2.22–4.71)	4.18 (2.70–6.48)
	Serum glucose <140 and TG <150	Serum glucose <140 and TG ≥150	Serum glucose ≥140 and TG <150	Serum glucose ≥140 and TG ≥ 150
Development of DM	117/2584	78/594	17/68	10/25
Model 1[b]		2.52 (1.82–3.48)	6.20 (3.44–11.15)	10.81 (4.67–24.99)
Model 2[e]		1.84 (1.31–2.57)	6.04 (3.27–11.15)	7.74 (3.24–18.52)
Model 3		1.57 (1.10–2.24)	6.32 (3.41–11.73)	6.96 (2.90–16.67)

[a] Model 1: adjusted for age; model 1b: adjusted for age and sex

[c,d,e] Model 2: as for model 1[a,b] but also adjusted for blood pressure (<120/80, ≥120/80 mmHg), casual serum glucose (<140, ≥140 mg/dL) (but not in [e]), BMI (<25, ≥25) (but not in [d]), currently smoking, and currently drinking alcohol (more often than sometimes, or not)

Model 3: as for model 2[c,d,e] but also adjusted for total cholesterol (<220, ≥220 mg/dL) and HDL-cholesterol (>40, ≤40 mg/dL)

level was a risk for DM development in a healthy and relatively young Asian population. In combination with sex, BMI, and casual serum glucose level, higher casual serum TG level was significantly associated with the development of DM, even after adjusting for the effects of other DM-associated factors.

Although the change in serum TG level after normal food intake is reported to be slight [30–32], the non-fasting state should not be ignored because periods of fasting during the day tend to be very short in most individuals, considering current lifestyles (eating 3 times a day, sometimes with snacks between meals) [33]. In fact, postprandial serum TG levels are considered pro-atherogenic [34, 35], and are strongly associated with future cardiovascular diseases [31, 35–39]. The mechanism of this phenomenon is probably explained by the finding that non-fasting TG levels are associated with remnants from chylomicrons and very low-density lipoproteins [36], and these postprandial triglyceride-rich lipoproteins penetrate the arterial endothelium [35, 40].

The effect of postprandial serum TG level on the development of DM is unclear, although a few cohort studies have suggested that non-fasting serum TG level is a useful predictor of the development of DM [13, 27]. Lipotoxicity—excess lipid accumulation (including TG) in non-adipose tissues—is thought to play an important role in the onset of insulin resistance and β-cell damage [41–43]. As the net whole-body importation of fatty acids occurs in the postprandial state, tissue fatty acid overexposure has been linked to this physiological state [44]. Therefore, postprandial elevation of the serum TG level is a potential candidate for the cause of impaired insulin secretion and insulin impairment [45]. However, the precise mechanism of lipotoxicity is unclear. Further studies are required to determine the effect of postprandial serum TG levels on insulin impairment or the development of DM.

A few cohort studies have reported that higher serum TG level is a risk factor for the development of DM in Japanese [15, 27]. Kametani et al. followed up 7222 (3916 females and 3306 males) normoglycemic subjects who were divided into 2 groups based on the fasting serum TG level at baseline: normotriglyceridemic (TG <150 mg/dL, age; 52.3 ± 10.5 years) and hypertriglyceridemic (TG ≥150 mg/dL, age; 53.3 ± 10.3 years) [15]. During the follow-up period (average: 4.5 years), 114 (1.57 %) subjects developed DM. However, the subjects in that study were slightly older and had a shorter follow-up period on average than ours. Recently, Fujihara et al. followed up 127,176 non-diabetic subjects (87,980 females and 39,196 males), who were divided into fasting and non-fasting groups based on the number of hours since the previous meal [27]. Among these participants, 8867 (4855 females and 4012 males, 6.97 %) developed DM during a mean follow-up of 5.5 years. They found that the fasting and non-fasting TG levels in males and the non-fasting TG

level in females were predictive of future DM among participants with normal BMI (18.5–24.9). However, the mean age of the participants was around 60 years, and serum glucose level was not included in their multivariate adjusted models.

The present study has some advantages. First, it demonstrates that serum TG level is a predictor of DM development during the early years in Asians; the mean age of the participants was 45.4 ± 6.5 years and the time taken to develop DM was 4.5 ± 2.1 years from the baseline examination. Before the present work, in spite of the significance of ethnicity [10, 46–48], the importance of serum TG level in the development of DM in Asians was unclear because only a few cohort studies had been conducted in Asians, and the mean age of the population in each of those studies was relatively high (in their late 40s [18], 50s [15, 27], or 60s [10]). Second, in the present study, the outcome was obtained by evaluating those who underwent consecutive annual medical check-ups including laboratory tests for 8 years. Third, even in subjects with a low serum non-fasting glucose level (<140 mg/dL), a high serum TG level (≥150 mg/dL) independently predicted the development of DM in the present study. Some cohort studies of healthy populations in which blood glucose level was included in the multivariate analysis have shown an association of serum TG level with the development of DM [14, 15, 18, 49]. However, it is very important to evaluate the effect of serum TG level in low serum glucose subjects, because a high normal blood glucose level is known to be associated with the development of DM [14, 49, 50].

The present study also has some limitations. First, this study disregarded any information about the duration of fasting and the content of the last meal, so it was not designed to clarify the effects of these factors. However, this information is not always obtained correctly in a medical check-up; therefore, the present study proposed even the non-fasting serum TG level can be effectively used as a predictor for the development of DM. Second, our research was not conducted to compare the effects of fasting and non-fasting on the development of DM. This study therefore cannot answer the question of whether non-fasting serum TG level is a better predictor of DM than fasting serum TG level. Third, there is a possibility that subjects with impaired glucose tolerance (IGT) were included in the <140 mg/dL category. However, the number of subjects with a fasting serum glucose level ≥110 mg/dL was 32, and similar results were observed when these subjects were excluded. Finally, the participants in the present study were relatively young, but might not be young enough to confirm the effect of serum TG level on the premature development of type 2 DM. A large cohort with a narrow age distribution in young subjects is ideal; however, gathering young subjects is usually a more difficult task than gathering seniors. Utilizing casual blood sampling may facilitate further studies.

Conclusion

The present study demonstrated that a serum TG level of ≥150 mg/dL when fasting or non-fasting is a significant predictor of type 2 diabetes in middle-aged Japanese workers. Monitoring the casual serum TG level, which has frequently been overlooked so far, should contribute to the early detection of individuals at high risk for DM and should indicate suitable diets for young and healthy subjects.

Compliance with ethical standards

Conflict of interest None.

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References

1. Cui R, Iso H, Yamagishi K, Saito I, Kokubo Y, Inoue M, Tsugane S. Diabetes mellitus and risk of stroke and its subtypes among Japanese: the Japan Public Health Center Study. Stroke. 2011;42:2611–4.
2. Ueshima H, Sekikawa A, Miura K, Turin TC, Takashima N, Kita Y, Watanabe M, Kadota A, Okuda N, Kadowaki T, Nakamura Y, Okamura T. Cardiovascular disease and risk factors in Asia: a selected review. Circulation. 2008;118:2702–9.
3. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care. 1991;14:173–94.
4. Katakami N, Kaneto H, Funahashi T, Shimomura I. Type 2 diabetes and atherosclerosis: focusing on metabolic syndrome. Diabetol Int. 2013;4:143–8.
5. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol. 1979;237:E214–23.
6. Avignon A, Boegner C, Mariano-Goulart D, Colette C, Monnier L. Assessment of insulin sensitivity from plasma insulin and glucose in the fasting or post oral glucose-load state. Int J Obes Relat Metab Disord. 1999;23:512–7.
7. Hanson RL, Pratley RE, Bogardus C, Narayan KM, Roumain JM, Imperatore G, Fagot-Campagna A, Pettitt DJ, Bennett PH, Knowler WC. Evaluation of simple indices of insulin sensitivity and insulin secretion for use in epidemiologic studies. Am J Epidemiol. 2000;151:190–8.
8. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28:412–9.

9. Sato A, Iwamoto Y. Diagnostic criteria of diabetes. Diabetol Int. 2013;4:77–80.
10. Lin SX, Berlin I, Younge R, Jin Z, Sibley CT, Schreiner P, Szklo M, Bertoni AG. Does elevated plasma triglyceride level independently predict impaired fasting glucose? The Multi-Ethnic Study of Atherosclerosis (MESA). Diabetes Care. 2013;36:342–7.
11. Schmidt MI, Duncan BB, Bang H, Pankow JS, Ballantyne CM, Golden SH, Folsom AR, Chambless LE. Identifying individuals at high risk for diabetes: the atherosclerosis risk in communities study. Diabetes Care. 2005;28:2013–8.
12. Dotevall A, Johansson S, Wilhelmsen L, Rosengren A. Increased levels of triglycerides, bmi and blood pressure and low physical activity increase the risk of diabetes in Swedish women. A prospective 18-year follow-up of the BEDA study. Diabet Med. 2004;21:615–22.
13. Perry IJ, Wannamethee SG, Walker MK, Thomson AG, Whincup PH, Shaper AG. Prospective study of risk factors for development of non-insulin dependent diabetes in middle aged British men. BMJ. 1995;310:560–4.
14. Wilson PW, Meigs JB, Sullivan L, Fox CS, Nathan DM, D'Agostino RB Sr. Prediction of incident diabetes mellitus in middle-aged adults: the Framingham Offspring Study. Arch Intern Med. 2007;167:1068–74.
15. Kametani T, Koshida H, Nagaoka T, Miyakoshi H. Hypertriglyceridemia is an independent risk factor for development of impaired fasting glucose and diabetes mellitus: a 9-year longitudinal study in Japanese. Intern Med. 2002;41:516–21.
16. Gupta AK, Dahlof B, Dobson J, Sever PS, Wedel H, Poulter NR. Determinants of new-onset diabetes among 19,257 hypertensive patients randomized in the Anglo-Scandinavian Cardiac Outcomes Trial—blood pressure lowering arm and the relative influence of antihypertensive medication. Diabetes Care. 2008;31:982–8.
17. Freeman DJ, Norrie J, Sattar N, Neely RD, Cobbe SM, Ford I, Isles C, Lorimer AR, Macfarlane PW, McKillop JH, Packard CJ, Shepherd J, Gaw A. Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. Circulation. 2001;103:357–62.
18. He S, Wang S, Chen X, Jiang L, Peng Y, Li L, Wan L, Cui K. Higher ratio of triglyceride to high-density lipoprotein cholesterol may predispose to diabetes mellitus: 15-year prospective study in a general population. Metabolism. 2012;61:30–6.
19. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK. Cardiovascular risk factors in confirmed prediabetic individuals. Does the clock for coronary heart disease start ticking before the onset of clinical diabetes? JAMA. 1990;263:2893–8.
20. Iozzo P. Viewpoints on the way to the consensus session: where does insulin resistance start? The adipose tissue. Diabetes Care. 2009;32(Suppl 2):S168–73.
21. Lafontan M, Girard J. Impact of visceral adipose tissue on liver metabolism. Part I: heterogeneity of adipose tissue and functional properties of visceral adipose tissue. Diabetes Metab. 2008;34:317–27.
22. Girard J, Lafontan M. Impact of visceral adipose tissue on liver metabolism and insulin resistance. Part II: visceral adipose tissue production and liver metabolism. Diabetes Metab. 2008;34:439–45.
23. Tatsumi Y, Ohno Y, Morimoto A, Nishigaki Y, Maejima F, Mizuno S, Watanabe S. U-shaped relationship between body mass index and incidence of diabetes. Diabetol Int. 2012;2:92–8.
24. Snel M, Jonker JT, Schoones J, Lamb H, de Roos A, Pijl H, Smit JW, Meinders AE, Jazet IM. Ectopic fat and insulin resistance: pathophysiology and effect of diet and lifestyle interventions. Int J Endocrinol. 2012;2012:983814.
25. Ginsberg HN, Zhang YL, Hernandez-Ono A. Regulation of plasma triglycerides in insulin resistance and diabetes. Arch Med Res. 2005;36:232–40.
26. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA. 2001;285:2486–97.
27. Fujihara K, Sugawara A, Heianza Y, Sairenchi T, Irie F, Iso H, Doi M, Shimano H, Watanabe H, Sone H, Ota H. Utility of the triglyceride level for predicting incident diabetes mellitus according to the fasting status and body mass index category: the Ibaraki Prefectural Health Study. J Atheroscler Thromb. 2014;21:1152–69.
28. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC Jr, Svetkey LP, Taler SJ, Townsend RR, Wright JT Jr, Narva AS, Ortiz E. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311:507–20.
29. Teramoto T, Sasaki J, Ishibashi S, Birou S, Daida H, Dohi S, Egusa G, Hiro T, Hirobe K, Iida M, Kihara S, Kinoshita M, Maruyama C, Ohta T, Okamura T, Yamashita S, Yokode M, Yokote K. Executive summary of the Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in Japan—2012 version. J Atheroscler Thromb. 2013;20:517–23.
30. Dubois C, Armand M, Azais-Braesco V, Portugal H, Pauli AM, Bernard PM, Latge C, Lafont H, Borel P, Lairon D. Effects of moderate amounts of emulsified dietary fat on postprandial lipemia and lipoproteins in normolipidemic adults. Am J Clin Nutr. 1994;60:374–82.
31. Langsted A, Freiberg JJ, Nordestgaard BG. Fasting and nonfasting lipid levels: influence of normal food intake on lipids, lipoproteins, apolipoproteins, and cardiovascular risk prediction. Circulation. 2008;118:2047–56.
32. Sidhu D, Naugler C. Fasting time and lipid levels in a community-based population: a cross-sectional study. Arch Intern Med. 2012;172:1707–10.
33. Branchi A, Torri A, Berra C, Colombo E, Sommariva D. Changes in serum triglycerides and high-density lipoprotein concentration and composition after a low-fat mixed meal. Effects of gender and insulin resistance. Intern Emerg Med. 2006;1:287–95.
34. Zilversmit DB. Atherogenesis: a postprandial phenomenon. Circulation. 1979;60:473–85.
35. Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides and risk of ischemic stroke in the general population. JAMA. 2008;300:2142–52.
36. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. JAMA. 2007;298:299–308.
37. Bansal S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. JAMA. 2007;298:309–16.
38. Groot PH, van Stiphout WA, Krauss XH, Jansen H, van Tol A, van Ramshorst E, Chin-On S, Hofman A, Cresswell SR, Havekes L. Postprandial lipoprotein metabolism in normolipidemic men with and without coronary artery disease. Arterioscler Thromb. 1991;11:653–62.
39. Iso H, Naito Y, Sato S, Kitamura A, Okamura T, Sankai T, Shimamoto T, Iida M, Komachi Y. Serum triglycerides and risk of coronary heart disease among Japanese men and women. Am J Epidemiol. 2001;153:490–9.

40. Shaikh M, Wootton R, Nordestgaard BG, Baskerville P, Lumley JS, La Ville AE, Quiney J, Lewis B. Quantitative studies of transfer in vivo of low density, SF 12–60, and SF 60–400 lipoproteins between plasma and arterial intima in humans. Arterioscler Thromb. 1991;11:569–77.
41. Shulman GI. Cellular mechanisms of insulin resistance. J Clin Invest. 2000;106:171–6.
42. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet. 2005;365:1415–28.
43. Okazaki Y, Eto K, Yamashita T, Okamoto M, Ohsugi M, Noda M, Terauchi Y, Ueki K, Kadowaki T. Decreased insulin secretion and accumulation of triglyceride in beta cells overexpressing a dominant-negative form of amp-activated protein kinase. Endocr J. 2010;57:141–52.
44. Carpentier AC. Postprandial fatty acid metabolism in the development of lipotoxicity and type 2 diabetes. Diabetes Metab. 2008;34:97–107.
45. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. Diabetologia. 2003;46:3–19.
46. Gasevic D, Frohlich J, Mancini GB, Lear SA. The association between triglyceride to high-density-lipoprotein cholesterol ratio and insulin resistance in a multiethnic primary prevention cohort. Metabolism. 2012;61:583–9.
47. Sumner AE, Finley KB, Genovese DJ, Criqui MH, Boston RC. Fasting triglyceride and the triglyceride-HDL cholesterol ratio are not markers of insulin resistance in African Americans. Arch Intern Med. 2005;165:1395–400.
48. Kim-Dorner SJ, Deuster PA, Zeno SA, Remaley AT, Poth M. Should triglycerides and the triglycerides to high-density lipoprotein cholesterol ratio be used as surrogates for insulin resistance? Metabolism. 2010;59:299–304.
49. Kahn HS, Cheng YJ, Thompson TJ, Imperatore G, Gregg EW. Two risk-scoring systems for predicting incident diabetes mellitus in U.S. adults age 45 to 64 years. Ann Intern Med. 2009;150:741–51.
50. Hayashino Y, Fukuhara S, Suzukamo Y, Okamura T, Tanaka T, Ueshima H. Normal fasting plasma glucose levels and type 2 diabetes: the High-risk and Population Strategy for Occupational Health Promotion (HIPOP-OHP) Study. Acta Diabetol. 2007;44:164–6.