Association of arterial stiffness and diabetes with triglycerides-to-HDL cholesterol ratio for Japanese men: The Nagasaki Islands Study

5   Yuji Shimizu,[1,2] Mio Nakazato,[2] Takaharu Sekita,[2] Koichiro Kadota,[1] Hironori Yamasaki,[3] Noboru Takamura,[4] Kiyoshi Aoyagi,[5] Takahiro Maeda[1,2]

1) Department of Community Medicine, Nagasaki University Graduate School of Biomedical Science, Nagasaki, Japan

10   2) Department of Island and Community Medicine, Nagasaki University Graduate School of Biomedical Science, Nagasaki, Japan

3) Center for Health and Community Medicine, Nagasaki University, Nagasaki, Japan

4) Department of Global Health, Medicine and Welfare, Nagasaki University Graduate School of Biomedical Sciences Atomic Bomb Disease Institute, Nagasaki

15   University, Nagasaki, Japan

5) Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Corresponding author and address for reprint requests:

Prof. Takahiro Maeda, MD, PhD

Department of Community Medicine, Nagasaki University Graduate School of

Biomedical Science, Nagasaki-shi, Sakamoto 1-12-4, Nagasaki 852-8523, Japan

5

Tel.: +81-95-819-7578

Fax: +81-95-819-7189

E-mail: tmaeda@nagasaki-u.ac.jp

10   **Full title:** Association of arterial stiffness and diabetes with triglycerides-to-HDL

cholesterol ratio for Japanese men: The Nagasaki Islands Study

Cover title: Cross-sectional study, CAVI, CIMT, atherosclerosis, arterial stiffness,

TG-HDL, diabetes

15   **Number of tables:** 4

Number of figures: 0

Full word count: 3,815 words

Abstract word count: 239 words

5

10

15

ABSTRACT

Objective: Although many studies have reported that elevated serum triglycerides to

high-density lipoprotein cholesterol (TG-HDL) ratios constitute a risk for insulin

resistance and increased arterial stiffness, no study has clarified as yet the association, in

5   terms of the TG-HDL ratio, between diabetes and increased arterial stiffness evaluated

by means of carotid intima-media thickness (CIMT) and cardio-ankle vascular index

(CAVI). To investigate this association, we conducted a cross-sectional study of 1,344

Japanese men aged 36-79 years undergoing a general health check.

Methods: We investigated the associations between atherosclerosis/arterial stiffness,

10   evaluated by means of CIMT and CAVI, and diabetes for all subjects, who were divided

into tertiles according to TG-HDL levels. Diabetes was defined as HbA_{1c} (NGSP)

$\geq$6.5 %, and/or initiation of glucose-lowering medication or insulin therapy.

Results: Of the130 diabetes patients identified in the cohort, 56 patients had high

TG-HDL (high TG-HDL diabetes) and 43 had low TG-HDL (low TG-HDL diabetes).

15   We found that only diabetic patients with high TG-HDL were at a significant risk for

atherosclerosis (diagnosed as CIMT$\geq$1.1 mm) and increased arterial stiffness (diagnosed

as CAVI $\geq$8.0). The multivariable-adjusted odds ratios and 95 % confidence intervals of

atherosclerosis and increased arterial stiffness for diabetes were 2.67 (95%CI:1.35-5.28)

and 2.36 (95%CI:1.01-5.50), for total TG-HDL diabetes 2.57(95%CI:1.32-5.02) and

3.56(95%CI: 1.50-8.46) for high TG-HDL diabetes, and 1.17(95%CI:0.52-2.63) and

0.80(95%CI:0.33-1.90) for low TG-HDL diabetes, respectively.

Conclusion: Diabetes, especially high TG-HDL diabetes, constitutes a significant risk

5   for increased arterial stiffness and atherosclerosis.

10

15

1 Introduction

Technological advances for medical equipment have made noninvasive assessment

of atherosclerosis possible in its early stages [1]. High-resolution B-mode

ultrasonography is a noninvasive procedure for quantifying arterial wall thickening, and

5 it has been shown that carotid intima-media thickness (CIMT) as measured by

high-resolution B-mode ultrasonography is a strong predictor of cardiovascular disease

[2]. Recently the cardio-ankle vascular index (CAVI), which can evaluate arterial

stiffness, was developed in Japan and has been confirmed to reflect the atherosclerotic

status [3]. We reported that the CAVI was suitable for screening general populations for

10 arterial stiffness [4].

On the other hand, elevated insulin concentrations are reportedly inversely

associated with serum high density lipoprotein (HDL) cholesterol concentrations [5]

and positively associated with serum triglyceride (TG) concentrations [6]. Furthermore,

a higher TG-HDL cholesterol ratio (TG-HDL) was found to indicate insulin resistance

15 among general populations [7], among overweight individuals [8,9], and among type2

diabetes [10]. We therefore classified the diabetes of our study population according to

TG-HDL levels on the assumption that the diabetes of patients with high TG-HDL is

mainly caused by insulin resistance with less compensatory β-cell function, while that in

patients with low TG-HDL is mainly caused by absolutely β-cell dysfunction.

Several previous studies have suggested that the TG-HDL ratio is an easily obtainable atherogenic marker [11] and have shown that high TG-HDL correlates independently with the presence of angiographic coronary artery disease (defined as

5   stenosis >50%) for both men and women even after adjustment for traditional risk factors [12], including diabetes [13]. However, no study has reported on the association, in terms of the TG-HDL ratio, between atherosclerosis/arterial stiffness, evaluated by means of CIMT and CAVI, and diabetes.

We therefore investigated the association between atherosclerosis and increased

10   arterial stiffness evaluated by CIMT and/or CAVI on the one hand, and diabetes in terms of TG-HDL levels on the other, among Japanese men who participated in a general medical check-up between 2005 and 2012.

15

2 Subjects and methods

This study was approved by the ethical committee for use of human of Nagasaki

University (project registration number 0501120073).

The survey population included 1,412 men aged 30 to 79 years, all residents of the

5 western rural community of the Goto Islands, who participated in this study between

2005 and 2012. A total of 68 individuals with missing data were excluded, leaving 1,344

men for enrolment in this study. There were no differences in diabetic risk factors

between participants for whom data of serum measurements were available and those

for whom they were not.

10 The mean age of the study population was 64.1 years (±9.8 SD; range 36-79). Body

weight and height were measured with an automatic body composition analyzer

(BF-220; Tanita, Tokyo, Japan) at the time of drawing blood.

Fasting blood samples were obtained and the serum was separated and centrifuged

after blood coagulation. Serum samples were also obtained in a siliconized tube. Serum

15 TG, serum HDL, serum alanine aminotransferase (ALT), serum creatinine, and HbA$_{1c}$

were measured with standard laboratory procedures.

Trained interviewers obtained information on smoking status, drinking status,

medical history, use of antihypertensive agents, use of medication for diabetes mellitus,

and use of medication for dyslipidemia. Hypertension was defined as systolic blood

pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg and/or

antihypertensive medication use. The glomerular filtration rate (GFR) was estimated

with an established method with three variations recently proposed by a working group

5   of the Japanese Chronic Kidney Disease initiative [14]. According to this adaptation,

GFR (mL/min/1.73 m^2) = 194$\times$(serum creatinine (enzyme

method))$^{-1.094}\times$(age)$^{-0.287}\times$(0.739 for women). HbA$_{1c}$ (as defined by NGSP, the National

Glycohemoglobin Standardization Program) was calculated with the following equation,

which was recently proposed by a working group of the Japanese Diabetes Society

10   (JDS): HbA$_{1c}$(NGSP) = HbA$_{1c}$(JDS) + 0.4 % [15]. Presence of diabetes was defined as

HbA$_{1c}$ (NGSP) $\geq$ 6.5%, and/or initiation of glucose-lowering medication or insulin

therapy [16]. We further defined subtypes of diabetes by calculating tertiles of TG-HDL

for all the participants: low-TG-HDL diabetes (median TG-HDL level: 1.00),

intermediate-TG-HDL diabetes (2.08), and high-TG-HDL diabetes (4.33).

15

2.1 Carotid B-mode ultrasound imaging

Measurement of CIMT by ultrasonography of the left and right carotid arteries was

performed by two medical doctors (N.T. and M.N.) using a LOGIQ Book XP with a

10-MHz transducer, GE Healthcare, Milwaukee, WI, USA). The protocol they used has

been described in detail elsewhere [17]. The values of right and left CIMT without

measurement of plaque were calculated and the higher CIMT value was used for

analysis. Since a previous study reported the normal CIMT value as <1.1mm we defined

5   atherosclerosis as CIMT≥1.1mm [18]. Intra-observer variation for CIMT (N.T., n=32)

was 0.91 (p<0.01), and interobserver variation (N.T. vs M.N., n=41) was 0.78 (p<0.01).

2.2 Cardio-Ankle Vascular Index (CAVI)

Brachial-ankle pulse wave velocity (PWV) is generally used to evaluate arterial

10   stiffness. However, since one study has pointed out that PWV measurements can be

strongly affected by blood pressure [19], CAVI was recently developed in Japan to

avoid the susceptibility of PWV measurements to blood pressure [20]. CAVI was

recorded with a Vasera VS-1000 vascular screening system (Fukuda Denshi, Tokyo,

Japan) with the participant resting in a supine position. The underlying principles of

15   CAVI have been described by Yamabe et al [21].

ECG electrodes are placed on both wrists, a microphone for detecting heart sounds

is placed on the sternum, and cuffs are wrapped around both arms and ankles. After

measurements had been obtained automatically, data were analyzed with VSS-10

software (Fukuda Denshi) in order to calculate the values for right and left CAVI and

we used the higher CAVI value for analysis. According to the manufacturer's

recommendations, CAVI should be considered normal at <8, borderline at ≥8 and <9,

and abnormal at ≥9. These categorize were also used by previous study [22][23].

5   Furthermore, Nakamura et al. reported that a cut-off level of 8.81 for CAVI yielded

maximal sensitivity and specificity for coronary artery disease [24]. We therefore

adopted these values for CAVI for diagnosis of increased arterial stiffness (CAVI≥8),

early atherosclerosis (8≤CAVI<9) and atherosclerosis (CAVI≥9).

10   2.3 Statistical analysis

The clinical characteristics in the present study were expressed. We established

TG-HDL categories according to the tertiles of TG-HDL values for all the subjects. For

the diabetic patients, differences in age-adjusted mean values for diabetic risk factors by

TG-HDL category were analyzed by using covariance or general linear models, and

15   logistic regression models were used for calculating odds ratios (ORs) and 95%

confidence intervals (CIs) for the association of diabetes with TG-HDL levels.

Two different approaches were used for making adjustments for confounding

factors. First, the data were adjusted only for age. Second, we included other possible

confounding factors, namely smoking status (never smoker, former smoker, current

smoker), alcohol consumption [non-drinker, current light to moderate drinker (1-6

times/week), current heavy drinker (every day)], hypertension (no, yes), history of

cardiovascular disease (no, yes), antihyperlipidemic medication use (no, yes),

5   antidiabetic medication use (no, yes), ALT (IU/L), and estimated GFR.

All statistical analyses were performed with the SAS system for Windows

(version 9.3; SAS Inc., Cary, NC). All p-values for statistical tests were two-tailed, and

values of <0.05 were regarded as statistically significant.

10   **3 Results**

3.1 Characteristics of the study population.

The clinical characteristics of the study population are summarized in Table1. The

mean age was 64.1 years (±9.8 SD) and mean body mass index 23.8 kg/m^2 (±3.1 SD).

Prevalence of current drinkers and current smokers were 51 % and 26 %, respectively.

15

3.2 Determination of diabetes subtypes according to TG-HDL levels.

Of the total of 1,344 men, 130 were diagnosed with diabetes, 43 of whom had low

TG-HDL, 31 intermediate TG-HDL, and 56 high TG-HDL Table 2 shows the

age-adjusted characteristics of the patients divided into diabetes categories as defined by

tertiles of TG-HDL for all the subjects. Diastolic blood pressure, BMI, TG and serum

creatinine were found to be positively associated with TG-HDL levels and inversely

associated with HDL and anti-diabetic medication use.

5

3.3 Association between atherosclerosis (CIMT≥1.1mm) and diabetes.

Table 3 shows the ORs and 95% CIs for atherosclerosis (CIMT≥1.1mm) according

to diabetes category based on TG-HDL subtypes. We found significant associations for

total and high TG-HDL diabetes with atherosclerosis (CIMT≥1.1mm) but not for low

10   and intermediate TG-HDL diabetes. "No at risk" refers to the total number of

participants with or without diabetes at risk of atherosclerosis, and the former, the total

number of patients and those with low TG-HDL, intermediate TG-HDL, and high

TG-HDL diabetes. "No of cases" refers to the number of participants with

atherosclerosis.

15   The multivariable-adjusted ORs and 95%CIs for atherosclerosis for total and high

TG-HDL diabetes were 2.67(95%CI:1.35-5.28) and 2.57(95%CI:1.32-5.02), whereas

for intermediate and low TG-HDL diabetes they were 1.17(95%CI:0.52-2.63) and

0.76(95%CI:0.29-2.00), respectively.

3.4 Association between increased arterial stiffness (CAVI≥8.0), early atherosclerosis (8≤CAVI<9), atherosclerosis (CAVI≥9) and diabetes.

Table 4 shows the ORs and 95% CIs of an increase in arterial stiffness (CAVI≥8.0), early atherosclerosis (8≤CAVI<9), and atherosclerosis (CAVI≥9) in relation to diabetes and its TG-HDL subtypes. "No of cases" refers to the number of participants with increased arterial stiffness, early atherosclerosis or atherosclerosis.

Multivariable logistic regression analysis showed that diabetes constitutes a significant risk for increased arterial stiffness and atherosclerosis but not for early atherosclerosis. High TG-HDL diabetes constitutes a significant risk for increased arterial stiffness, early atherosclerosis and atherosclerosis. However, no significant associations were observed for low and intermediate TG-HDL diabetes.

4 Discussion

A major finding of the present study was that diabetes, especially with high

TG-HDL, represents a significant risk for atherosclerosis (CIMT≥1.1 mm) and

5   increased arterial stiffness (CAVI≥8.0) in Japanese men.

A previous randomized study reported that diabetes was characterized by a greater

CIMT independently of other established risk factors for atherosclerosis [25]. A

Japanese cross-sectional study reported that CAVI was a useful index of arterial

stiffness and was not influenced by blood pressure changes during measurements [26].

10   In a previous study we found that CAVI was an appropriate screening tool for

atherosclerosis and also correlated with hemoglobin A1c as significantly as did CIMT

[4].

The findings of these studies were compatible with our result that showed diabetes

was a significant risk factor for atherosclerosis (CIMT≥1.1 mm, CAVI≥9) and increased

15   arterial stiffness (CAVI≥8.0). Our TG-HDL subtype analysis showed further evidence

that these associations were confined to diabetic patients with high TG-HDL.

Previous studies have shown that higher TG-HDL indicates insulin resistance, [8,9]

and that high TG-HDL correlates independently with coronary artery disease even after

adjustment for traditional risk factors including diabetes [12,13]. Other previous studies reported that TG-HDL is a strong predictor for risk of myocardial infarction [27], coronary atherosclerosis [12,13], CHD incidence [28], cardiovascular and all causes of death [13,29,30]. Those studies indicate that diabetes with elevated TG-HDL indicates

5   insulin resistance and increased arterial stiffness while diabetes with lower TG-HDL indicates absence of insulin resistance and normal arterial stiffness.

Another previous study reported that early atherosclerosis was independently associated with insulin resistance in diabetic but not in non-diabetic patients [25]. Since TG-HDL is reportedly associated with insulin resistance, this study appears to support

10   our finding that early atherosclerosis diagnosed as CAVI≥8.0 and <9 was independently associated with high TG-HDL but not with low TG-HDL diabetes. Moreover, this association was also observed for atherosclerosis (CIMT≥1.1 mm, CAVI≥9) and increased arterial stiffness (CAVI≥8.0).

The mechanisms accounting for a significant association between diabetes and

15   arterial stiffness for diabetes with high TG-HDL only have not been elucidated. Diabetes may be associated with accelerated atherosclerosis as a result of increasing the conventional risk factors, such as dyslipidemia and high blood pressure, or diabetes-specific risk factors such as advanced glycation end products (AGEs), reactive

oxygen species (ROS) and matrix protein production [31]. Further, the generation of

AGEs may play a key role in diabetes and cardiovascular disease, leading to chronic

hyperglycemia, dyslipidemia and oxidative stress [32]. AGEs are produced when

proteins and lipids undergo prolonged exposure to high glucose concentrations, which

5   leads to loss of collagen elasticity within the walls of blood vessels and subsequent

reduction in arterial flexibility [33]. Furthermore, a cross-sectional study conducted in

Taiwan reported that AGEs correlate more strongly with TG levels and TG/HDL when

compared to glucose or correlation with the degree of insulin resistance [34]. Diabetes

with high TG-HDL levels may thus indicate the presence of diabetes with high AGEs

10   levels, which induce arterial stiffness while diabetes with low TG-HDL levels may

indicate diabetes with low AGEs levels, which do not induce arterial stiffness. To

validate these hypotheses, further investigations using AGEs will be necessary.

Some potential limitations of this study warrant consideration. First, a number of

Japanese adult participants with type1 diabetes were initially diagnosed as having type2

15   diabetes at disease onset [35], and in our study type1 diabetes could not be

differentiated from type2 diabetes, either. However, type1 diabetes is also considered to

be an independent risk factor for atherosclerosis [36]. Furthermore, intermediate

TG-HDL diabetes in our study showed almost the same tendencies as low TG-HDL

diabetes, a result that could not be explained only by the effect of dividing according to

TG-HDL ratio for an effective differentiation between type 1 and type 2 diabetes.

Second, since data on exercise were not available, we could not make adjustments for

the influence of exercise. Third, there may be a difference in patient compliance with

5   treatment between low and high TG-HDL diabetic patients, which may affect the

associations between diabetes and arterial stiffness. However, our study showed such

associations between TG-HDL diabetes subtypes and risk of arterial stiffness remain

significant even after adjustment for use of anti-diabetic medication and

anti-hyperlipidemic medication. Fourth, the small number of diabetes cases limited the

10   robustness of our comparative analysis of the risk of increased arterial stiffness for

participants with high TG-HDL and low TG-HDL diabetes. However the wide

difference in the confidence interval for participants with low and with high TG-HDL

diabetes pointed to a significantly higher risk of increased arterial stiffness (CAVI$\geq$8.0)

for the latter, with a multivariable OR of 6.67(1.21-36.89)(P<0.026). Nevertheless,

15   further investigations with larger numbers of diabetic patients will be necessary.

Finally, because this study was a cross sectional study, we could not establish any

causal relationships.

In conclusion, we found diabetes, especially in association with high TG-HDL,

was a significant risk factor for atherosclerosis (CIMT$\geq$1.1 mm) and increased arterial

stiffness (CAVI$\geq$8.0) for Japanese men.

Disclosure

5   None

Acknowledgements

10

15

References

[1] Vogel RA, Benitez MR. Noninvasive assessment of cardiovascular risk: From

Framingham to the future. Rev Cardiovasc Med 2000; 1:32-42.

5   [2] Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid

intima-media thickness and risk of stroke and myocardial infarction: The Rotterdam

Study. Circulation 1997; 96:1432-1437.

[3] Shirai K, Utino J, Otsuka K, Takata M. A novel blood pressure-independent arterial

wall stiffness parameter; cardio-ankle vascular index (CAVI). J Atherosclerosis

10   Thromb 2006; 13:101-107.

[4] Kadota K, Takamura N, Aoyagi K, Yamasaki H, Usa T, Nakazato M, et al.

Availability of Cardio-Ankle Vascular Index (CAVI) as a Screening Tool for

Atherosclerosis. Circ J 2008; 72:304-308.

[5] Stalder M, Pometta D, Suenram A: Relationship between plasma insulin levels and

15   high density lipoprotein cholesterol levels in healthy men. Diabetologia 1981;

21:544-548.

[6] Farquhar JW, Frank A, Gross RC, Reaven GM. Glucose, insulin and trigryceride

responses to high and low carbohydrate diets in man. J Clin Invest 1966;

45:1648-1656

[7] Antonio G.C, Luis E.S.M, Sandra E.A. Elevated triglycerides /HDL-cholesterol ratio associated with insulin resistnace. Cir Cir 2011; 79:115-119.

[8] McLaughlin T, Abbasi F, Cheal K, Chu J, Lamendola C, Reaven G. Use of metabolic marker to identify overweight individuals who are insulin resistant. Ann Intern Med 2003: 139; 802-809

[9] Karelis AD, Pasternyk SM, Messier L, St-Pierre DH, Lavoie JM, Garrel D, et al. Relationship between insulin sensitivity and the triglyceride-HDL-c ratio in overweight and obese postmenopausal women: a MONET study. Nurt Metab 2007; 32: 1089-1096.

[10] Surapon T, Prapaporn P, Orathai T. Association of serum lipoprotein ratios with insulin resistance in type2 diabetes mellitus. Indian J Med Res 2010; 131:641-648.

[11] Dobiasova M, Frohlich J. The plasma parameter log(TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate in apoB-lipoprotein-depleted plasma (FERHDL). Clinical Biochemistry 2001; 34:583-588.

[12] Frohlich J, Dobiasova M. Fractional esterification rate of cholesterol and ratio of triglycerides to HDL-cholesterol are powerful predictors of positive finding on

coronary angiography. Clin Chem 2003; 49:1873-1880.

[13] Drexel H, Aczel S, Marte T, Benzer W, Langer P, Moll W, et al. Is atherosclerosis in diabetes and impaired fasting glucose driven be elevated LDL cholesterol or by decreased HDL cholesterol? Diabetes Care 2005; 28:108-114.

5   [14] Imai E. Equation for estimating GFR from creatinine in Japan. Nippon Rinsho 2008; 66: 1725-1729.

[15] Kashiwagi A, Kasuga M, Araki E, Oka Y, Hanafusa T, Ito H, et al. International clinical harmonization of glycated hemoglobin in Japan: From Japan Diabetes Society to National Glycohemoglobin Standardization Program values. J of

10   diabetes Invest 2012; 3:39-40

[16] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33:562-569.

[17] Hara T, Takamura N, Akashi S, Nakazato M, Maeda T, Wada M, et al. Evaluation of clinical markers of atherosclerosis in young and elderly Japanese adults. Clin

15   Chem Lab Med 2006;44:824-829.

[18] Kawamori R, Yamasaki Y, Matsushima H, Nishizawa H, Nao K, Hougaku H, et al. Prevalence of carotid atherosclerosis in diabetic patients. Ultrasound high-resolution B-mode imaging on carotid arteries. Diabetes Care 1992;

15:1290-1294.

[19] Yamashina A, Tomiyama H, Arai T, Koji Y, Yambe M, Motobe H, et al. Nomogram

of the relation of brachial-ankle pulse wave velocity with blood pressure.

Hypertens Res 2003; 26: 801-806.

5   [20] Shirai K, Utino J, Otsuka K, Takata M. A novel blood pressure-independent arterial

wall stiffness parameter; cardio-ankle vascular index (CAVI). J atherosclerosis

Thromb 2006; 13: 101-107.

[21] Yambe T, Yoshizawa M, Saijo Y, Yamaguchi T, Shibata M, Konno S, et al.

Brachio-ankle pulse wave velocity and cardio-ankle vascular index (CAVI).

10   Biomed Pharmacother 2004; 58**:** 95– 98.

[22] Korkmaz L, Erkan H, Korkmaz AA, Acar Z, Ağaç MT, Bektaş H, et al.

Relationship of aortic knob width with cardio-ankle vascular stiffness index and

it's value in diagnosis of subclinical atherosclerosis in hypertensive patients: a

study on diagnostic accuracy. Anadolu Kardiyol Derg 2012;12:102-106.

15   [23] Korkmaz L, Adar A, Korkmaz AA, Erkan H, Agac MT, Acar Z, Kurt IH, Akyuz

AR, Celik S. Atherosclerosis burden and coronary artery lesion complexity in acute

coronary syndrome patients. Cardiol J. 2012;19:295-300.

[24] Nakamura K, Tomaru T, Yamamura S, Miyashita Y, Shirai K, Noike H.

Cardio-Ankle Vascular Index is a candidate predictor of coronary atherosclerosis. Circ J 2008;72:598-604.

[25] Bonora E, Tessari R, Micciolo R, Zenere M, Targher G, Padovani R, et al. Intimal-medial thickness of the carotid in nondiabetic and NIDDM patients.

5   Relationship with insulin resistance. Diabetes Care 1997; 20:627-31.

[26] Kubozono T, Miyata M, Ueyama K, Nagaki A, Otsuji Y, Kusano K, et al. Clinical Significance and Reproducibility of New Arterial Distensibility Index. Circ J 2007; 71:89-94.

[27] Gaziano JM, Hennekens CH, O'Donnell CJ, Breslow JL, Buring JE. Fasting

10   triglycerides, high-density lipoprotein, and risk of myocardial infarction. Circulation 1997; 96:2520-2525.

[28] Jeppesen J, Hein HO, Suadicani P, Gyntelberg F. Low triglycerides-high-density lipoprotein cholesterol and risk of ischemic heart disease. Arch Internal Med 2001; 161:361-366.

15 [29] Shishehbor MH, Hoogwerf BJ, Lauer MS. Association of triglyceride-to-HDL cholesterol ratio with heart rate recovery. Diabetes Care 2004; 27:936-941.

[30] Asia Pacific Cohort studies Collaboration. A comparison of lipid variables as predictor of cardiovascular disease in Asia Pacific Resion. Ann Epidemiol 2005;

15:405-413.

[31] Goldberg IJ. Why does diabetes increase atherosclerosis? I don't know! J Clin

Invest 2004; 114:613-615.

[32] Jandeleit-Dahm K, Cooper ME. The role of AGEs in cardiovascular disease. Curr

Pharm Des 2008; 14:979-986.

[33] Aronson D. Cross-linking of glycated collagen in the pathogenesis of arterial and

myocardial stiffening of aging and diabetes. J Hypertens 2003; 21:3-12.

[34] Tahara N, Yamagishi S, Matsui T, Takeuchi M, Nitta Y, Kodama N, et al. Serum

levels of advanced glycation end products (AGEs) are independent correlates of

insulin resistance in nondiabetic subjects. Cardiovasc Ther 2012; 30:42-48.

[35] Kawasaki E, Ide A, Abiru N, Eguchi K. Review article immunogenic heterogeneity

of type 1 diabetes in Japan. Acta medica Nagasakiensia 2002;47:81-88.

[36] Duncan B, Darryl M, Kenneth S, Michel C. Endothelial dysfunction and

pre-symptomatic atherosclerosis in type 1 diabetes-pathogenesis and identification.

Br J Diabetes Vasc Dis 2003;3:27-34.

Table 1. Sex-specific clinical characteristics of the studied population.

Parameters	Men
No. at risk	1,344
Age, years	64.1± 9.8
Hypertension, % (n)	63 (n=855)
Systolic blood pressure, mmHg	142 ± 21
Diastolic blood pressure, mmHg	86 ± 11
Antihypertensive medication use, % (n)☐	28 (n=380)
Serum HDL-cholesterol, mg/dL	55 ± 15
Serum triglycerides, mg/dL	126 ± 85
TG-HDL ratio, traditional units	2.65 ± 2.37
HbA1C, %	5.3 ± 0.7
Antidiabetic medication use, % (n)	6.3 (n=85)
Antihyperlipidemic medication use, % (n)	6.3 (n=85)
History of cardiovascular disease, % (n)	9.1 (n=122)
Body mass index, kg/m^2	23.8 ± 3.1
Current drinker, % (n)	51 (n=688)
Current smoker, % (n)	26 (n=347)
Serum alanine aminotransferase (ALT),IU/L	24 ± 14
Serum creatinine, mg/dL	0.89 ± 0.21
Glomerular filtration rate (GFR), mL/min/1.73	71.1 ± 16.9

Values are given as mean ± standard deviation.

Table 2. Relationship betwwen sex-specific age-adjusted mean values and TG-HDL categories for diabetic patients.

	Categories of TG-HDL ratios			
	Low TG-HDL diabetes	Intermediate TG-HDL diabetes	High TG-HDL diabetes	p
Median value of TG-HDL ratio, traditional units	1.00	2.08	4.33	
No.of cases	43	31	56	
Age, years	68.2	66.7	65.9	
Serum HDL-cholesterol, mg/dL	68	48	44	<0.001
Serum Triglycerides, mg/dL	65	98	233	<0.001
Hypertension, %	66	71	75	0.621
Systolic blood pressure, mmHg	142	144	152	0.083
Diastolic blood pressure, mmHg	81	84	89	0.004
Antihypertensive medication use, %□	30	42	34	0.544
HbA(1c), %	6.3	6.5	6.7	0.176
Antidiabetic medication use, %	74	78	52	0.023
Antihyperlipidemic medication use, %	9	3	20	0.057
History of cardiovascular disease, %	14.5	16.4	15.6	0.974
Body mass index, kg/m^2	22.7	23.7	25.5	<0.001
Current smoker, %	24	26	21	0.844
Current drinker, %	52	38	48	0.453
Serum alanine aminotransferase (ALT),IU/L	25	27	29	0.433
Serum creatinine, mg/dL	0.80	0.90	0.90	0.042
GFR, ml/min/1.73m^2	77.3	69.7	70.9	0.116

Age: mean values of age. ALT:alanine aminotransferase. GFR:Glomerular filtration rate. TG-HDL ratio: Triglycerides / HDL-cholesterol ratio. Categories of TG-HDL ratios were categorized by tertiles of TG-HDL values for all subjects. p: trends of diabetes categories.

Table 3 Sex-specific odd ratios (ORs) and 95% CI for atherosclerosis according to subtypes of diabetes classified by tertiles of TG-HDL.

	Total diabetes			Low TG-HDL diabetes			Intermediate TG-HDL diabetes			High TG-HDL diabetes		
	(-)	(+)	p	(-)	(+)	p	(-)	(+)	p	(-)	(+)	p
Atherosclerosis (CIMT≥1.1 mm)												
No. at risk	1,214	130		1,301	43		1,313	31		1,288	56	
No. of cases (percentages)	248 (20)	44 (34)		279 (21)	13 (30)		284 (22)	8 (26)		269 (21)	23 (41)	
Age-adjusted OR	1.00	1.76 (1.17-2.63)	0.006	1.00	1.26 (0.64-2.49)	0.509	1.00	1.09 (0.47-2.53)	0.849	1.00	2.63 (1.48-4.66)	0.001
Multivariable OR	1.00	2.67 (1.35-5.28)	0.005	1.00	1.17 (0.52-2.63)	0.709	1.00	0.76 (0.29-2.00)	0.575	1.00	2.57 (1.32-5.02)	0.006

Multivariable OR: adjusted further for age and body mass index, smoking, alcohol intake, hypertension, antidiabetic medication use, antihyperlipidemic medication use, history of cardiovascular disease, serum alanine aminotransferase (ALT), and glomerular filtration rate(GFR). Median values of TG-HDL for each types of diabetes are 1.00 for lowest, 2.08 for intermediate, and 4.29 for highest TG-HDL diabetes.

Table 4 Sex-specific odd ratios (ORs) and 95% CI for increased arterial stiffness and atherosclerosis according to subtypes of diabetes classified by TG-

	Total diabetes			Low TG-HDL diabetes			Intermediate TG-HDL diabetes			High TG-HDL diabetes		
	(-)	(+)	p	(-)	(+)	p	(-)	(+)	p	(-)	(+)	p
Increased arterial stiffness (8≤CAVI)												
No. at risk	1,214	130		1,301	43		1,313	31		1,288	56	
No. of cases (percentages)	769 (63)	101 (78)		838 (64)	32 (74)		849 (65)	21 (68)		822 (64)	48 (86)	
Age-adjusted OR	1.00	1.46 (0.93-2.32)	0.104	1.00	0.94 (0.45-1.94)	0.859	1.00	0.82 (0.36-1.89)	0.646	1.00	3.06 (1.38-6.79)	0.006
Multivariable OR	1.00	2.36 (1.01-5.50)	0.047	1.00	0.80 (0.33-1.90)	0.609	1.00	0.68 (0.26-1.78)	0.434	1.00	3.56 (1.50-8.46)	0.004
Early atherosclerosis (8≤CAVI<9)*												
No. at risk	793	63		836	20		838	18		831	25	
No. of cases (percentages)	348 (44)	34 (54)		373 (45)	9 (45)		374 (45)	8 (44)		365 (44)	17 (68)	
Age-adjusted OR	1.00	1.15 (0.68-1.97)	0.602	1.00	0.73 (0.29-1.81)	0.491	1.00	0.77 (0.29-2.05)	0.597	1.00	2.29 (0.95-5.52)	0.064
Multivariable OR	1.00	1.76 (0.68-4.54)	0.244	1.00	0.64 (0.20-1.98)	0.432	1.00	0.76 (0.25-2.36)	0.635	1.00	2.70 (1.05-6.91)	0.039
Atherosclerosis (CAVI≥9)**												
No. at risk	866	96		928	34		939	23		923	39	
No. of cases (percentages)	421 (49)	67 (70)		465 (50)	23 (68)		475 (51)	13 (57)		457 (50)	31 (79)	
Age-adjusted OR	1.00	2.06 (1.21-3.51)	0.008	1.00	1.28 (0.56-2.95)	0.556	1.00	1.29 (0.47-3.50)	0.622	1.00	3.98 (1.60-9.86)	0.008
Multivariable OR	1.00	3.36 (1.24-9.11)	0.017	1.00	0.98 (0.38-2.50)	0.957	1.00	0.89 (0.28-2.84)	0.843	1.00	4.40 (1.52-12.75)	0.006

Multivariable OR: adjusted further for age and body mass index, smoking, alcohol intake, hypertension, antidiabetic medication use, antihyperlipidemic medication use, history of cardiovascular disease, serum alanine aminotransferase (ALT), and glomerular filtration rate(GFR). *Analyses were performed for participants without CAVI≥9. **Analyses were performed for participants without 8≤CAVI<9. Median values of TG-HDL for each types of diabetes are 1.00 for lowest TG-HDL, 2.08 for intermediate, and 4.29 for highest TG-HDL diabetes.