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Association of Chronic Kidney Disease and Diabetes with Triglycerides-to-HDL Cholesterol Ratio for a Japanese Population: The Nagasaki Islands Study

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Abstract

Objective and background

Although a previous study of ours found that diabetes combined with high serum Triglycerides to High-Density Lipoprotein cholesterol (TG-HDL) ratios constitutes a risk factor for atherosclerosis, the association, in terms of TG-HDL ratio, between diabetes and Chronic Kidney Disease (CKD), which is also known to be an independent risk factor for atherosclerosis, has not been clarified yet.

Methods

We conducted a cross-sectional study of 3,069 Japanese (1,153 men and 1,916 women) aged 60-89 years who underwent a general health check. We investigated the associations between CKD and diabetes for all subjects, who were divided into tertiles according to TG-HDL level. Diabetes was defined as HbA1c ≥ 6.5% (reference: the National Glycohemoglobin Standardization Program), and/or initiation of glucose-lowering medication or insulin therapy. CKD was defined as GFR<60mL/min/1.73 m^2.

Results

Of the 246 diabetes participants identified in this study, 102 had high and 74 low TG-HDL diabetes. Even though total diabetes showed no significant association with CKD, high TG-HDL diabetes showed a significant positive association and low TG-HDL diabetes a significant inverse association. Adjusted odds ratios (ORs) of classical cardiovascular risk factors for CKD were 0.92 (0.70-1.23) for total diabetes, 1.52 (1.01-2.29) for high TG-HDL diabetes, and 0.55 (0.31-0.97) for low TG-HDL diabetes.

Conclusion

High but not low TG-HDL diabetes constitutes a significant risk for CKD, suggesting that diabetes categorized by TG-HDL ratio is clinically relevant for estimating the risk of CKD.

Keywords: Chronic kidney disease; TG-HDL ratio; Diabetes; Cross-sectional study

Abbreviations: TG: Triglycerides; HDL: High-Density Lipoprotein Cholesterol; CKD: Chronic Kidney Disease; AST: Aspartate Aminotransferase; GTP: γ-Glutamyltransferase; HbA1c: Hemoglobin A1c; GFR: Glomerular Filtration Rate; NGSP: National Glycohemoglobin Standardization Program; JDS: Japanese Diabetes Society; ORs: Odds Ratios; CIs: Confidence Intervals

Introduction

Asian type 2 diabetes patients are reportedly characterized by lower Body Mass Index (BMI) and lower serum insulin levels than Mexican-American or African-American type 2 diabetes patients [1-3]. Moreover, Asians are thought to possess less compensatory β-cell function and have type2 diabetes at lower BMI than people in Western countries [4]. In a previous study of ours we established that the associations between diabetes and BMI for Japanese subjects are strongly influenced by the status of TG-HDL: high TG-HDL diabetes is positively associated and low TG-HDL diabetes inversely associated with BMI [5]. Classification of diabetes for our entire study population by TG-HDL level tertile (Shimizu's diabetes classification) [5-7] was based on the assumption that, compared to the general population, diabetes with high TG-HDL might have stronger insulin resistance while low diabetes with TG-HDL might have lower serum insulin levels with less insulin resistance. Therefore diabetes of patients with high TG-HDL is mainly caused by insulin resistance accompanied by reduced compensatory β-cell function, while that of patients with low TG-HDL is the result of reduced insulin resistance and mainly caused by complete β-cell dysfunction. A previous study of ours of Japanese men found that high TG-HDL but not low TG-HDL diabetes is significantly associated with arterial stiffness and atherosclerosis [6]. We also found, in connection with a sex-combined study, that hemoglobin levels were positively associated with high TG-HDL diabetes and inversely associated with low TG-HDL diabetes [7]. Furthermore, we reported that hemoglobin levels were significantly positively associated with arterial stiffness in a non-anemic non-overweight Japanese population [8]. These findings suggest that diabetes categorized by TG-HDL level may serve as an effective tool for estimating risk of atherosclerosis for diabetes patients. On the other hand, while Chronic Kidney Disease (CKD) is known to be associated with atherosclerosis [9], no studies reported thus far have examined the association between diabetes categorized according to TG-HDL ratio and CKD. We therefore conducted a cross-sectional study of 3,069 Japanese individuals 60-89 years of age who underwent general health checkups between 2005 and 2012.

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Methods

Participants

The study presented here was approved by the Ethics Committee for Human Use of Nagasaki University (project registration number 0501120073). The survey population consisted of 3,136 residents in the western rural community of the Goto Islands: 1,175 men and 1,961 women, aged 60-89 years, who participated in this study between 2005 and 2012. A total of 67 individuals (22 men and 45 women) with missing data were excluded. The remaining 3,069 subjects (1,153 men and 1,916 women) with a mean age of 69.9 ± 7.0years (70.2 ± 7.0 for men and 69.7 ± 7.1 for women; range 60-89) were enrolled in this study.

Measurements

Systolic and diastolic blood pressures were recorded at rest. Bodyweight and height were measured with an automatic body composition analyzer (BF-220; Tanita, Tokyo, Japan) at the time the blood sample was obtained. Trained interviewers obtained information on smoking status, drinking status, medical history, use of antihypertensive agents and use of medication for diabetes mellitus. Fasting blood samples were obtained with a siliconized tube. The serum was separated and centrifuged after blood coagulation using a sample from the siliconized tube. Serum concentrations of Triglyceride (TG), High Density Lipoprotein- Cholesterol (HDL), Aspartate Aminotransferase (AST), γ- Glutamyl transferase (GTP), creatinine, and Hemoglobin A1c (HbA1c) were measured using standard laboratory procedures. Trained interviewers obtained information on smoking status, drinking status, medical history, use of antihypertensive agents, medication for diabetes mellitus, and medication for dyslipidemia. The Glomerular Filtration Rate (GFR) was estimated by using an established method with three adaptations recently proposed by a working group of the Japanese Chronic Kidney Disease Initiative [10]. According to this adapted version, GFR (mL/min/1.73 m^2)=1.94×(serum creatinine [enzymemethod])$^{-1.094}$×(age)$^{-0.287}$×(0.739 for women). HbA_{1c} (the National Glycohemoglobin Standardization Program: NGSP) was calculated with the following equation, which was recently proposed by a working group of the Japanese Diabetes Society (JDS): HbA1c(NGSP)=HbA_{1c}(JDS)×1.02+0.25 % [11]. Diabetes was defined as HbA_{1c} (NGSP) ≥ 6.5%, and/or initiation of glucose-lowering medication or insulin therapy [12]. Hypertension was defined as systolic blood pressure ≥ 140mmHg and/or diastolic blood pressure ≥ 90 mmHg and /or antihypertensive medication use.

Statistical analysis

Differences in sex-and age-adjusted mean values or prevalence of potentially confounding factors in relation to TG-HDL levels were calculated with ANOVA or logistic regression models. We established TG-HDL categories by means of tertiles of TG-HDL values for all subjects as in previous studies [5-7]. For the diabetic patients, differences in sex-and age-adjusted mean values for cardiovascular risk factors by TG-HDL category were analyzed by means of covariance or general linear models, while 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 sex and 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)], body mass index (BMI: kg/m^2), hypertension (no,yes), antihyperlipidemic medication use (no,yes), history of cardiovascular disease (no,yes), AST, and GTP.

All statistical analyses were performed with SAS systems for Windows (version 9.3; SAS Inc., Cary, NC). All p-values for statistical test were two-tailed, and values of <0.05 were regarded as statistically significant.

Results

Of the 3,069 participants, 246 were diagnosed with diabetes, 102 of whom had high TG-HDL, 70 intermediate TG-HDL, and 74 low TG-HDL.

The clinical characteristics of the study population are summarized in Table 1. Hypertension (systolic blood pressure, diastolic blood pressure, antihypertensive medication use), serum triglycerides, HbA1c,antihyperlipidemic medication use, BMI, GTP, and serum creatinine showed positive associations with TG-HDL levels while HDL-cholesterol, current drinker status and GFR were inversely associated with TG-HDL levels.

Table 2 shows the sex-and age-adjusted characteristics of the patients divided into diabetes categories as defined by TG-HDL tertiles for all the subjects. Systolic blood pressure, diastolic blood pressure, serum triglycerides, HbA1c, BMI, and serum creatinine were found to be positively associated with TG-HDL levels while serum HDL-cholesterol, antidiabetic medication use and GFR were identified as being inversely associated.

Table 3 shows the ORs and 95% CIs for CKD according to diabetes category based on TG-HDL subtypes. We identified a significant positive association for high TG-HDL diabetes with CKD and a significant inverse association for low TG-HDL diabetes. The respective multivariable-adjusted ORs and 95%CIs of CKD for high TG-HDL and low TG-HDL diabetes were 1.52 (1.01-2.29) and 0.55(0.31-0.97). We also investigated the sex-and age-adjusted values of TG-HDL analyzed with a general linear model in relation to CKD status. Compared to participants without CKD, participants with CKD had significantly higher TG-HDL levels, that is, the corresponding values were 2.29 for the former and 2.57 for the latter (P<0.001).

As part of our study, we examined the CAVI (Cardio Ankle Vascular Index) data that were available for 2,959 subjects and found that CKD is a significant risk factor for increased arterial stiffness (CAVI ≥ 8.0). The sex-and age-adjusted OR of increased arterial stiffness for CKD was 1.33 (1.11-1.59) (P=0.002).

Discussion

The major finding of the present study was that high but not low TG-HDL diabetes constitutes a significant risk for CKD for a Japanese elderly population. The mechanisms accounting for such a significant association for diabetes patients with high TG-HDL only have not been elucidated. However, endothelial dysfunction has been recognized as one of the initial mechanisms that lead to glomerular injury [13] and atherosclerosis. Moreover, a previous study of ours of Japanese men demonstrated that high TG-HDL but not intermediate or low TG-HDL diabetes is a significant risk for arterial stiffness and carotid atherosclerosis [6]. This may account for the association of high TG-HDL but not low TG-HDL diabetes with CKD via atherosclerosis. In our study, on the other hand, low TG-HDL diabetes proved to be associated with a significantly lower risk of CKD. In our previous sex-combined study hemoglobin levels was found to be significantly positively associated with high TG-HDL diabetes and significantly

Parameters	TG-HDL ratios			
	T1 (Low)	T2	T3 (high)	P
Median values of TG-HDL ratio, traditional units				
No. at risk	1,024	1,022	1,023	
Men, n (%)	385 (37.6)	384(37.6)	384 (37.5)	
Age, years	69.5 ± 7.1	70.2 ± 7.0	70.0 ± 6.7	
Hypertension, %	64.4	71.0	74.6	<0.001
Systolic blood pressure, mmHg	143	145	148	<0.001
Diastolic blood pressure, mmHg	83	84	85	<0.001
Antihypertensive medication use, %	31.8	40.5	40.9	<0.001
Serum HDL-cholesterol, mg/dL	69	57	47	<0.001
Serum triglycerides, mg/dL	64	103	189	<0.001
HbA1C, %	5.2	5.2	5.4	<0.001
Antidiabetic medication, use, %	5.6	5.2	5.6	0.889
Antihyperlipidemic medication use, %	8.1	12.8	12.3	0.001
History of cardiovascular disease, %	9.8	10.2	10.3	0.211
Body mass index, kg/m^2	22.1	23.5	24.4	<0.001
Current drinker, %	26.4	23.8	19.6	0.001
Current smoker; %.	7.7	9.3	10.3	0.086
Serum aspartate aminotransferase (AST),IU/L	24	23	24	<0.001
Serum γ- glutamyltransferase (GTP), IU/L	27	28	35	<0.001
Serum creatinine, mg/dL	0.74	0.79	0.80	<0.001
Glomerular filtration rate (GFR), mL/min/1.73 m^2	70.0	66.2	65.1	<0.001

Ages are given as mean ± standard deviation. Median values of TG-HDL ratio (traditional units): 1.00, 1.81 and 3.84 for men. 0.93, 1.73, and 3.33 for women.

Table 1: Sex-and age-adjusted mean values of participants characteristics according to tertiles of TG-HDL levels

	Categories of TG-HDL ratios			
Parameters	Low TG-HDL diabetes	Intermediate TG-HDL diabetes	High TG-HDL diabetes	P
No. at risk	74	70	102	
Age, years	71.4 ± 7.0	71.8 ± 6.8	69.8 ± 5.9	
Hypertension, %	68.6	79.6	78.9	0.213
Systolic blood pressure, mmHg	142	150	151	0.011
Distolic blood pressure, mmHg	79	83	86	<0.001
Antihypertensive medication use, %	45.2	53.1	38.7	0.175
Serum HDL-cholesterol, mg/dL	72	54	46	<0.001
Serum triglycerides, mg/dL	65	103	214	<0.001
HbA 1C, %.	6.4	6.3	6.8	<0.001
Antidiabetic mediation use, %.	76.6	76.4	55.7	0.003
Antityperlipidenic medication use, %	12.9	11.7	15.0	0.824
History of cardiovascular disease, %	12.6	16.7	13.7	0.765
Body mass index, kg/m^2	22.6	24.3	25.1	<0.001
Current drinker, %	28.8	26.2	20.9	0.364
Current smoker; %.	12.3	12.9	10.6	0.281
Serum aspartate aminotransferase (AST),IU/L	25	26	25	0.205
Serum γ- glutamyltransferase (GTP), IU/L	35	34	37	0.785
Serum creatinine, mg/dL	0.73	0.78	0.84	0.002
Glomerular filtration rate (GFR), mL/min/1.73 m^2	72.3	70.0	64.7	0.010

Ages are given as mean ± standard deviation. Median values of TG-HDL ratio (traditional units): 1.00, 1.81 and 3.84 for men. 0.93, 1.73, and 3.33 for women.

Table 2: Relationship between sex-and age-adjusted values and TG-HDL categories for diabetic patients

	Total Diabetes			Low TG-HDL diabetes*		Intermediate TG-HDL diabetes*		High TG-HDL diabetes*	
	(-)	(+)	P	(+)	P	(+)	P	(+)	P
CKD(GFR<60 mL/ min/1.73m^2)									
No. at risk	2,823	246		74		70		102	
No. of Cases (percentage)	968 (34.3)	85 (34.6)		17 (23.0)		21 (30.0)		47 (46.1)	
Sex- and age-adjusted OR	1.00	0.98 (0.74-1.30)	0.908	0.54 (0.31-0.93)	0.028	0.74 (0.44-1.25)	0.260	1.71 (1.14-2.55)	0.010
Multivariable OR	1.00	0.92 (0.70-1.23)	0.584	0.55 (0.31-0.97)	0.038	0.69 (0.41-1.17)	0.170	1.52 (1.01-2.29)	0.046

Multivariable OR: adjusted further for sex and age, body mass index, smoking, alcohol intake,hypertension, antihyperlipidemic medication use, history of cardiovascular disease, serum aspartate aminotransferase (AST), and γ- glutamyltransferase (GTP).Median values of TG-HDL for each type of diabetes are 0.96 for lowest, 1.76 for intermediate, and 3.47 for highest TG-HDL diabetes.*: values in comparison with non-diabetes.

Table 3: Odd ratios (ORs) and 95% Confidence Interval (CIs) for CKD according to subtypes of diabetes classified by tertiles of TG-HDL

inversely associated with low TG-HDL diabetes [7]. The same study also reported found that an increase in hemoglobin levels of both men and women was significantly positively associated with an increase in arterial stiffness evaluated by CAVI (Cardio Ankle Vascular Index) [7]. Furthermore other our previous studies with non-anemic Japanese reported hemoglobin levels were significantly associated with arterial stiffness [8] and hypertension [14]. These studies also disclosed that such associations were restricted to participants with BMI<25kg/m^2. In addition, another sex-combined study reported that BMI was positively associated with high TG-HDL diabetes and inversely associated with low TG-HDL diabetes [5]. The fact that diabetes patients with low TG-HDL may therefore be associated with lower BMI suggests they are also characterized by lower risks of atherosclerosis and hypertension, which are also well-known factors associated with CKD. This mechanism may thus also result in diabetes patients with low TG-HDL having lower risk of CKD. Furthermore, CKD itself is also well known as a factor associated with dyslipidemia, which might affect the association between TG-HDL diabetes and CKD. Our additional study found that participants with CKD showed significantly higher TG-HDL values than did those without CKD although CKD is a significant risk factor for increased arterial stiffness (CAVI ≥ 8.0). Furthermore, we also investigated the TG-HDL values in relation to increased arterial stiffness in CKD patients. Patients with increased arterial stiffness showed higher TG-HDL values than did those without increased arterial stiffness, although the difference did not reach significance. Specifically, the sex- and age-adjusted values of TG-HDL were 2.46 for participants without and 2.55 for participants with increased arterial stiffness (P=0.374). The TG-HDL value itself might therefore also indicate that there is an association between CKD and diabetes categorized by TG-HDL value via the presence of increased arterial stiffness such as atherosclerosis. Some possible limitations of this study warrant further consideration. We could not perform any sex-specific analysis because of the limited number of participants. However, essentially the same associations were observed for both men and women. The respective multivariable ORs of high, intermediate and low TG-HDL diabetes were 1.22 (0.65-2.31), 0.87 (0.39-1.96), and 0.34 (0.14-0.84) for men and 1.68 (0.96-2.93), 0.57 (0.28-1.18), and 0.91 (0.42-1.97) for women. Since data regarding exercise were not available, we could not make adjustments for the influence of exercise. As in other epidemiological studies, ours estimated GFR from serum creatinine at a single point in time, and defined CKD in terms of GFR value only without ascertaining the clinical diagnosis [15,16]. However, we found diabetes with high TG-HDL was a significantly higher risk factor of CKD while diabetes with low TG-HDL diabetes constituted a significantly lower risk of CKD. Finally, we could not establish any causal relationships because this was a cross-sectional study.

Conclusion

In conclusion, high but not low TG-HDL diabetes constitutes a significant risk for CKD, suggesting that diabetes categorized by TG-HDL ratio is clinically relevant for estimating the risk of CKD.

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