Diabetes Mellitus Modifies the Association of Serum Triglycerides with Ischemic Cardiovascular Disease Mortality: The Ibaraki Prefectural Health Study (IPHS)

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Aim: Diabetes mellitus and hypertriglyceridemia may adversely interact with the development of ischemic cardiovascular disease, but epidemiological evidence on this issue is scarce. We hypothesized that the impact of hypertriglyceridemia on ischemic cardiovascular disease (ischemic heart disease and ischemic stroke) would differ according to the presence or absence of diabetes mellitus and tested our a priori hypothesis under a large population-based prospective study.

Methods: A total of 90,468 men and women aged 40–79 years in 1993 were enrolled in the Ibaraki Prefectural Health Study (IPHS), a community-based cohort study of Japanese. The participants’ serum triglyceride levels (mostly nonfasting) were measured every 5 years, and the participants were followed up for mortality from ischemic cardiovascular disease through 2016. Hazard ratios (95% confidence intervals) were calculated according to 5-year updated triglyceride levels (<100, 100–149, 150–199, 200–299, and ≥300 mg/dl).

Results: During 1,795,877 person-years, there were 3,323 deaths from ischemic cardiovascular diseases (1,968 ischemic heart diseases and 1,355 ischemic strokes). We found no association between triglyceride levels and the risk of mortality from ischemic cardiovascular disease after adjustment for known cardiovascular risk factors. However, when stratified by the presence or absence of diabetes mellitus, excess mortality from ischemic cardiovascular disease appeared among participants with diabetes mellitus with triglyceride levels of ≥300 mg/dl. Further adjustment for high-density lipoprotein-cholesterol attenuated the association toward being statistically nonsignificant.

Conclusion: The impact of high serum triglyceride levels on the risk of ischemic cardiovascular disease mortality was confined to participants with diabetes mellitus.

Key words: Epidemiology, Cohort study, Diabetic dyslipidemia, Follow-up study, Risk factor, Cardiovascular disease

Introduction

Postprandial hypertriglyceridemia commonly occurs in patients with diabetes mellitus, accompanied by several clinical findings: increased production and defect in the clearance of very low-density lipoprotein (VLDL) triglycerides1, absence of the acute inhibitory effect of insulin on chylomicron production2, and increased levels of remnant-like lipoprotein particles3, 4. Hypertriglyceridemia and hyperglycemia usually share underlying lifestyle and constitutional factors, such as high carbohydrate intake and visceral fat...
accumulation. Accordingly, these metabolic conditions may adversely interact with the development of ischemic cardiovascular diseases. However, whether the impact of hypertriglyceridemia on ischemic cardiovascular disease, confirmed by previous studies\(^5\)–\(^7\), is modified by diabetes mellitus is uncertain.

We hypothesized that the impact of hypertriglyceridemia on ischemic cardiovascular disease is pronounced in the presence of diabetes mellitus and tested our \textit{a priori} hypothesis under a large population-based prospective study\(^8\). This investigation could provide clinical implications for controlling risk factors among patients with diabetes.

**Materials and Methods**

**Study Cohort**

In 1993, the Ibaraki Prefectural Government initiated a community-based cohort study, the Ibaraki Prefectural Health Study (IPHS), to obtain information on the association between risk factor and disease for the purpose of health education and policy making\(^8\). The cohort included 97,043 individuals (63,912 women and 33,131 men) aged 40–79 years living in Ibaraki Prefecture, Japan, who completed an annual health checkup in 1993. We excluded 5,339 persons from the analyses because of a history of stroke or heart disease at baseline. We further excluded 1,236 persons because of missing baseline triglycerides \((n=891)\) or follow-up data \((n=345)\). Finally, 90,468 individuals (59,880 women and 30,588 men) were enrolled in the study.

**Baseline Measurements**

At the checkups, height was measured with shoes on, and weight was measured with light clothing. Body mass index was calculated dividing weight in kilograms by the square of height in meters. Blood pressure was measured by a trained observer using a standard mercury sphygmomanometer. Blood sampling was done with the participants in a sitting position. Fasting was not required, and approximately 83% of the participants had blood drawn in nonfasting status \((<8 \text{ hours from the last meal})\) at baseline. Serum total cholesterol and triglyceride levels were measured using enzymatic methods, high-density lipoprotein (HDL) cholesterol levels by the phosphotungstic acid magnesium method between 1993 and 1995 and direct methods thereafter, plasma glucose by the glucose oxidase electrode method between 1993 and 1996 and enzymatic methods thereafter, and serum creatinine by the Jaffe methods between 1993 and 2003 and enzymatic methods thereafter. The serum creatinine values were adjusted to the enzymatic method by subtracting 0.2 from the value measured using the Jaffe method. The estimated glomerular filtration rate was calculated using the Japanese version of the Chronic Kidney Disease Epidemiology Collaboration equation\(^9\). Low estimated glomerular filtration rate was defined as < 60 ml/min/1.73 m\(^2\). Face-to-face interviews were conducted to obtain information on smoking status; number of cigarettes smoked per day; weekly intake of alcohol \((\text{in } \text{go unit}, \text{a traditional Japanese unit equivalent to } 23 \text{ g ethanol})\); and history and treatment of stroke, heart disease, hypertension, dyslipidemia, and diabetes mellitus.

**Follow-Up Surveillance**

The dates of death or moving were obtained from local governments. Data regarding deaths were centralized at the Ministry of Health, Labour and Welfare, where the underlying causes of death were coded for the National Vital Statistics according to the International Classification of Diseases and Related Health Problems (ICD), 9th (1993–1994) and 10th (1995–2016) revisions. Deaths from total cardiovascular disease were identified as codes 393–459 in ICD-9 and as codes I00–I99 in ICD-10, ischemic heart disease as codes 410–414 in ICD-9 and as codes I20–I25 in ICD-10, and ischemic stroke as codes 433–434 and 437.7 in ICD-9 and as code I63 and I69.3 in ICD-10. Deaths from ischemic cardiovascular disease were defined as those from ischemic heart disease and ischemic stroke combined.

**Statistical Analysis**

The differences in the age-adjusted baseline characteristics across the triglyceride categories \((<100, 100–149, 150–199, 200–299, \text{ and } \geq 300 \text{ mg/dl})\) were tested using an analysis of covariance. Follow-up started from the 1993 baseline health checkups and ended at the date of death or emigration or at the end of 2016. Hazard ratios (HRs) and 95% confidence intervals (CIs) for cause-specific mortality according to the triglyceride categories were tested using Cox proportional hazards regression models. The linear trend of HR across the categories was...
tested using a continuous value of log-transformed triglycerides. To reduce the impact of misclassification caused by changes on triglyceride status during follow-up, we updated the categories of triglycerides and the confounding factors listed below (except for sex) using the second (1998 ± 2) and third (2003 ± 2) follow-up health checkup data, in which 77% (n=69,814) and 61% (n=55,184) of the baseline (1993) participants participated, respectively\(^{[10]}\). For example, triglycerides from 1993 health checkups were related to the cardiovascular-related disease mortality occurring between 1993 and the second follow-up point, those from the second follow-up point were related to the mortality occurring between the second and third follow-up points, and those from the third checkups were related to the mortality occurring thereafter. For those who had not participated in the second or third follow-ups, values on the 1993 (or the second) follow-up point were used. Of note, the proportions of participants whose blood was drawn in nonfasting status were 83% at baseline, 66% at second follow-up, and 61% at third follow-up points. The following covariates were included: age (continuous), sex (dichotomous), cigarette smoking (never, ex, occasionally, <69 and ≥69 cigarettes/day), alcohol consumption (noncurrent, <20, 20–29, and ≥30 g ethanol/day), body mass index (continuous), systolic blood pressure (continuous), antihypertensive medication use (dichotomous), serum non-HDL cholesterol level (continuous), serum HDL cholesterol level (continuous), antidyslipidemic medication use (dichotomous), diabetes mellitus (dichotomous), body mass index (continuous), systolic blood pressure (continuous), estimated glomerular filtration rate (dichotomous), systolic blood pressure (continuous), antihypertensive medication use (dichotomous), serum non-HDL cholesterol level (continuous), serum HDL cholesterol level (continuous), antidyslipidemic medication use (dichotomous), diabetes mellitus (dichotomous), low estimated glomerular filtration rate (dichotomous), and fasting status (time between the last meal and blood drawing: <8 or ≥8 hours). The analysis was further stratified by baseline diabetic status (excluding 75 participants with missing baseline diabetic status): with diabetes (fasting blood glucose ≥126 mg/dl or nonfasting blood glucose ≥200 mg/dl and/or use of antidiabetic medication) and without diabetes. For missing covariates, we assigned dummy variables and included them in the models. The multiplicative interactions of triglycerides with diabetic status in relation to mortality from each outcome were tested using cross-product terms. All statistical tests were two-sided, and values of \(p<0.05\) were considered statistically significant. All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA).

### Ethics Approval

Informed consent was obtained from community representatives to conduct an epidemiological study. Individual consent was not required for the analysis of this study, since it was conducted as a secondary use of data obtained for public health practice on cardiovascular disease prevention in the local community at that time. Adhering to relevant guidelines and regulations afterward, the participants were retrospectively given the opportunity to withdraw their data from analysis, and the consent was considered to have been obtained if the participant did not decline in this study. The IPHS protocol was approved by the Ethics Committees of Ibaraki Prefecture and University of Tsukuba.

### Results

At baseline, age was inversely correlated with serum triglyceride levels for men but positively correlated with it for women (Table 1). Body mass index, blood pressures, treatments for hypertension and hyperlipidemia, serum non-HDL cholesterol, and diabetes mellitus were positively correlated with triglycerides levels, while HDL cholesterol, the prevalence of current drinkers, and estimated glomerular filtration rate were negatively correlated. In women, the prevalence of current smokers was positively correlated with triglycerides. Of the participants, 66% were women.

During a 23.1-year median follow-up, there were 3,323 deaths from ischemic cardiovascular diseases including 1,968 deaths due to ischemic heart diseases and 1,355 ischemic strokes.

Serum triglyceride levels, as a whole, were positively associated with age and sex-adjusted mortality from ischemic cardiovascular disease (Table 2). Adjustment for potential confounding factors, however, attenuated the associations, and the trend was no longer statistically significant.

Stratifying by the presence of diabetes (Table 2), we found a positive association of serum triglyceride levels with mortality from ischemic cardiovascular disease among persons with diabetes mellitus. After further adjustment for cardiovascular risk factors, the excess risk of ischemic cardiovascular disease associated with triglycerides of ≥300 mg/dl remained (HR=1.56 [95% CI: 1.02–2.39]). Further adjustment for HDL cholesterol attenuated the association toward being statistically nonsignificant (HR=1.32 [95% CI: 0.84–2.09]). Among persons without diabetes mellitus, the associations were weak and not significant after further adjustment for cardiovascular risk factors. The interaction of triglycerides with diabetic status in relation to mortalities from ischemic cardiovascular disease reached statistical significance (\(p=0.003\)). Similar association and interaction were
found for ischemic heart disease (Table 3). No such association or interaction was found for ischemic stroke, although the HRs in the highest category of triglycerides among participants with diabetes were similar between ischemic heart disease (1.67 [95% CI: 0.97–2.87]) and ischemic stroke (1.44 [95% CI: 0.72–2.89]).

When we used only the baseline triglyceride measurement, the excess risk of ischemic cardiovascular disease associated with triglycerides of ≥ 300 mg/dl were slightly attenuated probably due to the misclassification of triglycerides during follow-up: the multivariable HR in the highest category of triglycerides and \( p \) for trend among participants with diabetes was 1.44 (95% CI: 0.93–2.23) and 0.04, respectively (not shown in tables).

### Discussion

In our cohort study, conducted over a median of 23 years and involving 90,468 men and women aged
40–79 years, we found that nonfasting triglyceride levels were not associated with the risk of mortality from ischemic cardiovascular disease. Stratified by diabetic status, excess mortality from ischemic cardiovascular disease appeared among participants with diabetes mellitus with triglyceride levels of ≥ 300 mg/dl. Further adjustment for HDL cholesterol attenuated the association toward being statistically nonsignificant, probably because HDL cholesterol changes in sync with triglycerides.

Our finding of null associations between nonfasting triglyceride levels and mortality from ischemic cardiovascular disease was consistent with a previous pooled analysis from the Emerging Risk Factor Collaboration, which involved 302,430 people from 68 cohort studies of cardiovascular mortality and morbidity mostly in North America and Europe. In their analysis, the HR for ischemic heart disease with one-standard deviation change in log-transformed triglycerides was 1.37 (95% CI: 1.31–1.42) after adjustment for nonlipid risk factors (age, sex, systolic blood pressure, smoking, body mass index, and history of diabetes), but it was reduced to 0.99 (95% CI: 0.94–1.05) after further adjustment for HDL cholesterol and non-HDL cholesterol. A similar pattern was observed for ischemic stroke: the respective HRs were 1.12 (95% CI: 1.05–1.19) and 1.02 (95% CI: 0.94–1.11). In contrast, most cohort studies of Asians (but not all) have shown a positive association of triglycerides with the incidence or mortality from ischemic heart disease or cardiovascular disease after adjustment for HDL cholesterol. For example, the Circulatory Risk in Communities Study, which involved 5,641 Japanese men and women aged 40–69 in 1975–1980 at baseline who were followed up for 15.5 years, showed that the multivariable adjusted HR of incident ischemic heart disease was 3.21 (95% CI: 1.52–6.75) among the highest versus lowest quartiles of nonfasting triglycerides after adjustment for HDL cholesterol. Another study from the same group (1975–1986 baseline and a median of 22 years follow-up) showed similar results for cardiovascular disease, but not for ischemic heart disease; the
The reasons for the effect modification with diabetic status in relation to the triglycerides–ischemic cardiovascular disease association warrant discussion. Postprandial triglycerides include chylomicron remnants, and their concentration reflects delayed clearance of chylomicron remnants\(^1\). In addition, the catabolism of lipoprotein could be interrupted with diabetes mellitus, resulting in the increased levels of chylomicron remnants and VLDL remnants\(^3\).\(^4\)

Multivariable adjusted HR of incident cardiovascular disease was 1.48 (95% CI: 1.08–2.02) among the highest versus lowest quartiles of triglycerides after adjustment for HDL cholesterol\(^3\). The Asia-Pacific Cohort Study, which involved 96,224 men and women from 26 studies in Asia-Pacific region, showed a 70% greater risk of fatal ischemic heart disease and an 80% greater risk of fatal and nonfatal ischemic heart disease among the highest versus lowest quartiles of triglycerides even after adjustment for total-to-HDL cholesterol ratio\(^3\).
Taken together, high triglycerides in participants without diabetes mellitus (mostly under normal insulin state) may reflect short-term postprandial hypertriglyceridemia, which may have less adverse effects, and result in a null or weak association of triglycerides. As for epidemiological studies, a meta-analysis of a maximum of 31 prospective studies from various countries and involving a maximum of 132,044 people with diabetes mellitus showed an association between triglycerides and cardiovascular disease: pooled relative risk = 1.30 (1.16–1.46) for the highest versus the lowest categories of triglycerides from 11 studies (although nonsignificant when further adjusted for other lipid parameters; respective relative risk = 1.39 [0.92–2.10] from three studies) 19). Additionally, some cohort studies of general populations showed that high triglyceride-glucose index (although it was based on fasting triglycerides and glucose) was associated with a higher risk of incidence for ischemic heart disease or myocardial infarction20-22). These findings were partly in line with our observation. On the other hand, a pooling analysis of studies from the Asia-Pacific region showed that the positive association between triglycerides and fatal ischemic heart disease was similarly observed for participants either with or without diabetes mellitus13).

The effect modification by diabetes mellitus was statistically significant for ischemic cardiovascular disease and ischemic heart disease, but not for ischemic stroke, although the HRs of the highest category of triglycerides among participants with diabetes mellitus were similar between ischemic heart disease and ischemic stroke. This may be caused by the small number of ischemic strokes in the stratum of participants with diabetes mellitus. Another reason is that ischemic stroke deaths included not only atherothrombotic stroke but also lacunar and cardioembolic strokes, which are unlikely to be associated with lipid metabolism.

The strengths of the current study include the largest number of study participants from Asia with triglyceride measurement involving persons both with and without diabetes mellitus and a standardized manner of triglyceride measurement at a single laboratory. The repeat measurements of triglycerides and confounding variables approximately every 5 years would be another strength, which allowed us to account for the changes in them over 20 years of follow-up. Some limitations applied, as with other cohort studies, including observational design, residual confounding, and undetermined external validity. Because the participation in the health checkups was voluntary, the healthy participant effect was unavoidable. We did not have data on the incidence of cardiovascular disease, and the association of triglycerides with the incidence of cardiovascular disease may differ from that of mortality from cardiovascular disease.

Based on clinical trials, pharmacological treatment for elevated triglycerides has generally shown to reduce the risk of cardiovascular disease23, 24), although no study have been specifically designed to recruit patients with hypertriglyceridemia so far24). Among patients with diabetes mellitus, the risk reduction by fibrates has been less clear25, 26), but their sub-analyses suggested a potential benefit of treating triglycerides among patients with diabetes with marked (≥ 204 mg/dl) hypertriglyceridemia27) or hypertriglyceridemia accompanied with low HDL cholesterol27, 28).

In conclusion, the impact of high serum triglyceride levels on the risk of ischemic cardiovascular disease mortality was confined to participants with diabetes mellitus. Taken together with currently available findings from clinical trials, the present study underscores the importance of careful triglyceride monitoring among patients with diabetes mellitus.

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Conflict of Interest

The authors declare that there is no conflict of interest.
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