Fasting and non-fasting triglycerides and risk of ischemic cardiovascular disease in Japanese men and women: The Circulatory Risk in Communities Study (CIRCS)

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ARTICLE INFO

ABSTRACT

Background: Non-fasting triglycerides were reported to have a greater impact on risk of ischemic cardiovascular events than fasting triglycerides. However, evidence from Asia, where the prevalence of dyslipidemia is generally lower, has been limited.
Methods: We used 1975–1986 baseline surveys to investigate cohort data of 10,659 (4264 men and 6395 women) residents aged 40–69 years, initially free from ischemic heart disease and stroke, in four Japanese communities. Serum triglyceride concentrations at baseline were obtained for 2424 fasting ($\geq$8 h after meal) and 8235 non-fasting (<8 h after meal) participants.
Results: During the 22-year follow-up, 284 (165 men and 119 women) developed ischemic heart disease and 666 (349 men and 317 women) ischemic stroke. After adjustment for age, sex and known cardiovascular risk factors, multivariable hazard ratios (95%CI) of ischemic cardiovascular disease (ischemic heart disease and ischemic stroke) for the highest versus lowest quartiles of triglycerides were 1.71 (1.14 –2.59), *P* for trend = 0.013, for fasting participants and 1.60 (1.25–2.05), *P* for trend <0.001, for non-fasting participants. The positive associations did not differ between fasting and non-fasting men, while they were strong for non-fasting women. They were stronger for ischemic heart disease than for ischemic stroke. After further adjustment for HDL-cholesterol, these associations were slightly attenuated, but remained statistically significant.
Conclusion: Non-fasting as well as fasting triglycerides are predictive of risk of ischemic cardiovascular disease for Japanese men, as are non-fasting triglycerides for women.

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1. Introduction

Although the impact of total and LDL-cholesterols on ischemic cardiovascular disease has been well established [1], the impact of triglycerides has remained controversial. Large meta-analyses, primarily performed in western countries [2–4], but not all [5], have identified moderate and statistically significant associations between triglycerides and risk of ischemic heart disease, stroke, or cardiovascular events, even after adjustment for cardiovascular risk factors including body mass index, diabetes mellitus and HDL-cholesterol. The evidence for Asian populations is limited, but a previous study of ours [6,7] and a meta-analysis by Asia Pacific Cohort Studies Collaboration [8] detected an independent relationship between triglycerides and risk of coronary heart disease. Furthermore, emerging evidence from western countries supports the notion that non-fasting triglycerides, a postprandial state of lipid profile, is an even better predictor of ischemic cardiovascular disease [9–12].

High levels of non-fasting triglycerides reflect increased residues from chylomicrons and very low density lipoproteins. These cholesterol-containing and triglyceride-rich lipoprotein residues penetrate the arterial intima and are trapped within the arterial wall, leading to the development of atherosclerosis [13–15]. It remains to be determined, however, whether populations such as Japanese, with lower levels of total- or LDL-cholesterol and triglycerides, run a similar potential risk of high postprandial triglyceride levels.

Associations between non-fasting and fasting triglycerides and risk of incident cardiovascular disease in Asian countries have not been investigated systematically in any cohort studies. We hypothesized that non-fasting triglycerides constitute a better predictor for ischemic cardiovascular disease than fasting triglycerides in Asian populations whose prevalence of dyslipidemia is lower than that in western populations. To test our hypothesis, we examined the data of the Circulatory Risk in Communities Study (CIRCS), community-based prospective study of approximately 10,000 middle-aged Japanese men and women.

2. Methods

2.1. Study population

The surveyed population comprised 11,370 residents aged 40–69 years in four communities: Ikawa town (a rural community in Akita Prefecture in northwestern Japan), the Minami-Takayasu district in Yao City (a southwestern suburb in Osaka Prefecture), Noichi town, (a rural community in Kochi Prefecture in southwestern Japan) and Kyowa town (a rural community in Ibaraki Prefecture in central Japan) [16,17]. The baseline surveys were conducted in 1975–1980, 1975–1984, 1975–1980, and 1981–1986, respectively. The total census populations aged 40–69 years old in the four communities were, respectively, 2291 in 1975, 5538 in 1980, 3599 in 1975, and 5408 in 1980. The study participation rate was 65%. After the exclusion of participants with a history of coronary heart disease and/or stroke at baseline, the data for the remaining 10,659 subjects were analyzed. This study was approved by the ethics committees of the Osaka Medical Center for Health Science and Promotion and of Osaka University.

2.2. Follow-up and ascertainment of cases

Follow-up lasted until the end of 2005 for Kyowa and Noichi, 2009 for Ikawa and 2008 for Minami-Takayasu, and was terminated at the first incident of ischemic heart disease and stroke, exit from the community or death. Persons who moved out of the communities during the follow-up numbered 822 (8%), and 3597 (34%) persons died. These were censored at the date of moving out or the date of death. The median follow-up was 22.3 years for coronary heart disease and 22.2 years for ischemic stroke.

The details of endpoint determination have been described in previous CIRCS reports [16,17]. For all the residents, cardiovascular disease end points were ascertained from death certificates, national insurance claims, reports by local physicians, reports by public health nurses and health volunteers, and annual cardiovascular risk surveys. To confirm the diagnosis, all living patients were telephoned, visited or invited to take part in risk factor surveys, or a medical history was obtained from their families. In addition, medical records in the local clinics and hospitals were reviewed. In case of death with certain underlying causes of death (ICD 9 classification codes: 410–414, 428 and 429), histories were obtained from families and/or attending physicians and medical records were reviewed.

The criteria for ischemic heart disease, i.e. definite and probable myocardial infarctions, angina pectoris and sudden cardiac death within 1 h of onset were modified from those of the World Health Organization Expert Committee [1], as previously reported by us [16].

The criterion for incident stroke was a focal neurological disorder with rapid onset and persisting for at least 24 h or until death [17]. The determination of stroke subtypes was performed primarily by using CT/MRI findings, which were available for 81% of the stroke cases. Strokes that were diagnosed clinically but showed no lesion on CT/MRI films were classified based on the clinical criteria. Ischemic stroke was used as an outcome in this study. The final diagnosis for ischemic heart disease and ischemic stroke were made by a panel of 3–4 physicians participating in this study who were blinded to the data from the risk factor survey.

2.3. Baseline examination

Blood was drawn into a plain, siliconized glass tube and the serum was separated immediately after centrifugation. Fasting was not required. The time intervals since the last meal were: 0 − <1 h (3.0%), 1 − <2 h (20.7%), 2 − <3 h (43.7%), 3 − <8 h (9.9%), and ≥8 h (22.7%). Fasting was defined as ≥8 h after the last meal.

Serum triglycerides were measured with the fluorometric method using Autoanalyzer II (Technicon, Tarrytown, NY, U.S.A.) and serum total cholesterol was measured with the direct Lieberman–Burchard method using Autoanalyzer II for the period 1975–1979 and Autoanalyzer SMA-12/60 from 1979 to 1986 at the Osaka Medical Center for Cancer and Cardiovascular Diseases [6,16]. For 55% of the total sample (5880 subjects), HDL-cholesterol after heparin-manganese precipitation was measured at the same laboratory with the direct Liebermann–Burchard method. The Osaka Medical Center laboratory has been standardized by the Lipid Standardization Program, conducted by the Centers for Disease Control (Atlanta, GA), and successfully met the criteria for both reproducibility and accuracy of triglycerides and cholesterol measurements [18].

Serum total cholesterol was measured with the enzymatic method using Olympus AU 2700 at the lipid reference laboratory of the Osaka Medical Center for Health Science and Promotion, which is an international member of the US National Cholesterol Reference Method Laboratory Network. This laboratory has been certified since 1975 by the CDC-NHLBI Lipid Standardization Program conducted by the Centers for Disease Control and Prevention [18] and successfully met the performance criteria for both reproducibility and accuracy of serum triglycerides, total cholesterol and HDL-cholesterol measurements [19].

Blood pressures were measured by trained physicians using standard mercury sphygmomanometers and unified epidemiological methods [20]. Hypertension was defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg and/or use of antihypertensive medication, while normotension was defined as systolic blood pressure <140 mmHg, diastolic blood pressure <90 mmHg and no antihypertensive medication use. All others were classified as borderline hypertension. Height was measured with the subjects in stocking feet and their weight while wearing light clothing. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2).

An interview was conducted to ascertain the number of cigarettes smoked per day, usual weekly intake of ethanol measured in units of *go* (a Japanese traditional unit of volume corresponding to 23 g ethanol), and menopausal status for women.

Serum glucose values were classified into three categories (diabetic, prediabetic and normal types). Diabetic type was defined