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COMMENTARY

Conflicting effect of alcohol on cardiovascular risk: a clue to understand the different etiologies of coronary artery disease, stroke and peripheral artery disease

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The relationship between drinking dose and risk for cardiovascular diseases (CVDs) has been shown to be U-shaped,[1] while a positive linear relationship between drinking dose and blood pressure[2] and a linear relationship between blood pressure and risk for CVDs have also been shown in previous studies on both Westerners[3] and Japanese people.[4] Why does a positive linear relationship between alcohol consumption and blood pressure level turn into a U-shaped relationship between alcohol consumption and risk for CVDs? This inconsistency requires a legitimate and intelligible reason.

The three main lesions included in the term arteriosclerosis are (1) atherosclerosis, (2) Mönckeberg medial calcific sclerosis and (3) arteriocapillary sclerosis.[5] Atherosclerosis is the most common form of arteriosclerosis and involves lipid deposition and thickening of the intimal cell layers within arteries. Mönckeberg medial calcific sclerosis involves thickening and loss of elasticity of arterial walls and calcification of the media of muscular arteries. Arteriocapillary sclerosis involves thickening of the walls of small arteries or arterioles owing to cell proliferation or hyaline deposition.

Dyslipidemia is a strong risk factor for coronary artery diseases (CAD) in any ethnicity. Epidemiological studies and pathological studies have strongly suggested that atherosclerosis has an important role in the development of CAD and that dyslipidemia strongly contributes to an elevated risk for CAD by accelerating atherogenesis. Excessive intimal and medial coronary calcification is frequently found in dialysis patients with CAD and this suggests that Mönckeberg medial calcific sclerosis contributes to the progression of CADs.

Ischemic stroke is classified into three major categories by their main etiologies: (1) large-vessel stroke mainly attributable to atherosclerosis, (2) small-vessel stroke typically associated with leukoaraiosis (lacunar stroke) and (3) embolic stroke. Dyslipidemia contributes to an elevated risk for large-vessel stroke by accelerating atherogenesis, while elevated blood pressure certainly contributes to an elevated risk for lacunar stroke by accelerating arteriocapillary sclerosis.

The main etiology of peripheral artery disease (PAD) has not been fully discussed until now. As strong calcified lesions as well as atherosclerotic lesions are commonly observed in peripheral arteries of patients with PAD, both atherosclerosis and Mönckeberg medial calcific sclerosis certainly contribute to the development of PAD. The high incidence of PAD in dialysis patients and in people who live in areas severely contaminated with arsenic suggests that factors other than elevated blood pressure, such as renal failure, dysfunction of calcium and phosphorus metabolism, abnormally elevated levels of fibroblast growth factor 23 and other unknown risk factors (arsenic, and so on), may contribute to the development of PAD by accelerating Mönckeberg medial calcific sclerosis.

Based on results from epidemiological studies, we can make a speculative hypothesis: each CVD (CAD, stroke and PAD) has a main specific etiology in the development of arteriosclerosis. Table 1 shows a summary of the supposed association between each CVD and its main lesion of arteriosclerosis. The table also shows the main risk factor for each arteriosclerotic pattern and supposed effects of moderate alcohol drinking on each arteriosclerotic pattern and each CVD (CAD, stroke or PAD).

Now, we consider the relationship between alcohol drinking and risk for several arteriosclerotic CVDs. Mild to moderate alcohol drinking certainly increases blood pressure levels both in Westerners and Japanese, and elevated blood pressure secondary to alcohol drinking may contribute to elevated risks for several CVDs, especially hemorrhagic stroke and lacunar stroke. On the other hand, mild to moderate alcohol drinking favorably contributes to alteration of serum lipid profiles, adiponectin level, fibrinogen level, apolipoprotein A1 level and Lp (a) lipoprotein level.[6] Therefore, alcohol drinking contributes to a reduction of CVD risk by attenuating atherosclerosis owing to alteration of these atherogenesis-related factors.

Next, we consider the difference in prevalence and incidence of each CVD between Westerners and Japanese. Japanese people have a very low incidence of CAD and a relatively high incidence of stroke compared with those in Western people.[7] The proportion of patients with lacunar stroke in all ischemic stroke patients is high among Japanese people[8] compared with that in Westerners.[9] Therefore, Japanese people have a low prevalence of atherosclerosis-related CVDs (CAD and large-vessel stroke) and a high prevalence of arteriocapillary sclerosis-related CVD (lacunar stroke) compared with those in Western people.

Moderate alcohol intake may decrease incidence of CAD and large-vessel stroke, especially in Western people, and it may

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Table 1 Supposed association between each CVD and its main lesion of arteriosclerosis, and supposed associations between moderate alcohol drinking and risks for CVDs

Arteriosclerotic CVDs	*Supposed main etiology*	*Which is a stronger contributor: elevated BP, dyslipidemia or others?*	*Much more observed in*	*Supposed effect of alcohol*
Coronary artery disease	Atheosclerosis	Dyslipidemia > > elevated BP	Caucasian	↓ Incidence
	⩛			
	Mönckeberg medial calcific sclerosis	Other unresolved risk factors (RF, DM, Ca/P, FGF23, arsenic, etc.) ⩛ Elevated BP or dyslipidemia	Not revealed	? Incidence
Ischemic stroke				
(A) Large-vessel infarction (atherosclerosis-related small-vessel infarction)	Atheosclerosis	Dyslipidemia > > elevated BP	Caucasian	↓ Incidence
(B) Small-vessel infarction with leukoaraiosis (lacunar stroke)	Arterio(capillary) sclerosis	Elevated BP > > dyslipidemia	Japanese	↑ Incidence
(C) Embolic stroke	Emobolism	Atrial fibrillation, other cardiac disease and atheromatous debris of aorta	Caucasian	↑ Incidence
Peripheral artery disease	Mönckeberg medial calcific sclerosis	Other unresolved risk factors (RF, DM, Ca/P, FGF23, arsenic, etc.) ⩛ Elevated BP or dyslipidemia	Not revealed	? Incidence
	⩛			
	Atherosclerosis	Dyslipidemia > > elevated BP		↓Incidence

Abbreviations: BP, blood pressure; CVDs, cardiovascular diseases; Ca/P, ratio of serum calcium level to serum phosphorus level; DM, diabetes melittus; FGF23, fibrobrast growth factor 23; RF, renal failure.
'A > > B' means that A is a stronger contributor than B.

increase the incidence of lacunar stroke as well as hemorrhagic stroke, especially in Japanese people (Table 1). Excessive intake of alcohol increases the risk for CVDs, and thus the relationship between alcohol drinking dose and a risk for CVDs becomes J- or U-shaped. Among Japanese people, who have a high incidence of lacunar stroke (arteriocapillary-related disease) and a very low incidence of CAD, a favorable effect of alcohol on atherogenesis may be limited to a small number of people. The relationship between alcohol drinking dose and a risk for CVDs in Japanese people would be different from that observed in Westerners.

Higashiyama *et al.*[10] tried to resolve this troublesome issue by stratified analysis using subclassification of hypertension and drinking status. They found a typical U-shaped relationship between drinking dose and a risk for CVDs only in prevalent hypertensive subjects and also found no harmful effect of alcohol on CVD risk in non-hypertensive subjects. A harmful effect of alcohol on risk for stroke was particularly strong among heavy drinkers with prevalent hypertension. Although they could not assess whether future elevation of blood pressure secondary to alcohol drinking contributes to an elevated risk for CVDs, they could show a favorable effect of moderate alcohol drinking on CVD risk in Japanese people excluding prevalent hypertensive subjects.

We expected that Japanese people living in urban areas had characteristics similar to those of Westerners and that the relationship between risk factors and CVD risk is also similar to those in Westerners. On the other hand, Japanese people living in rural areas that have a high incidence of stroke and low incidence of CAD have different patterns of the relationship between risk factors and CVD risk. Most previous cohort studies in Japan were conducted in rural areas, and the relationship between risk factors and CVD risk shown in previous studies in Japan may reflect the relationship in rural Japan. At least, the results of previous studies do not reflect the relationship in Japanese people living in current urban areas. The subjects in the Suita cohort study consisted of people living in an urban area and they had a rather high incidence of CAD and low incidence of stroke compared with those of subjects in previous Japanese cohort studies. The relationship between drinking dose and a risk for stroke in the Suita Cohort study would be a typical U-shaped relationship as shown in Westerners. However, the relationship shown in Higashiyama's paper was not a typical U-shaped relationship.

Recently, Iso and colleagues revealed for the first time that a higher serum cholesterol level was associated with a higher risk for ischemic stroke, especially non-lacunar stroke in Japanese people.[11] This suggested that dyslipidemia was a significant risk factor for total ischemic stroke and that large-vessel stroke became common in Japanese people. However, we do not have sufficient data regarding associations between risk factors and CVD prognosis, including the association between alcohol consumption and CVD risk, in Japanese people.

Higashiyama *et al.* only showed data for people living in an urban area, and their analysis has several limitations. Subclassification by prevalent hypertension should be done to avoid confusion between alcohol consumption and effect of elevated blood pressure on risk for cardiovascular morbidity and mortality; however, a small number of subjects in each category make the statistical power weak. Dose relationship between alcohol consumption and risk for each CVD seems to be vague. Further prospective studies to determine the associations between

several risk factors and risks for cardiovascular morbidity and mortality in Japanese people are needed. More detailed investigations to reveal the disease-specific arteriosclerotic pattern based on results of both epidemiological and pathological studies are also needed.

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